TECHNOLOGY ASSESSMENT REPORTS FOR THE HTA PROGRAMME

An updated review of the clinical and cost-effectiveness of liquid-based cytology in cervical screening.

DRAFT PROTOCOL

A. **This protocol is provisional and subject to change**

B. **Details of review team**

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C. **Full title of research question**

A review of the clinical and cost-effectiveness of liquid-based cytology in cervical screening.

D. **Clarification of research question and scope**

The overall aim of this review will be to consider the evidence regarding the clinical and cost-effectiveness of liquid-based cytology as a screening test for cervical cancer compared with conventional pap smear testing. A major component of the review will involve the assessment and incorporation of the results from the liquid-based cytology screening pilot sites, including the identification of any implementation issues.

The review will assess differences between liquid-based cytology and conventional pap smear testing with respect to:

- Test outcomes, including sensitivity, specificity, and smear inadequacy,
- Impact of the test, such as the levels of inconvenience and anxiety caused,
- Clinical outcomes, including incidence of cervical cancer, morbidity and mortality, and
- Expected utility associated with each test, combining the lifetime profile of the respective populations.

More specifically, the data obtained from the review will be synthesised in order to:

1. estimate the effect on overall survival and quality-of-life adjusted survival
2. estimate the incremental cost effectiveness of the drug in comparison to conventional therapy
3. estimate the possible overall cost in England and Wales.

E. **Report Methods**

Search strategy:
This review will update the original HTA rapid review of liquid-based cytology (Payne et al 2000) to reflect any new evidence, including the results of the pilot studies implemented as a result of the previous review.

The search will aim to identify all studies relating to liquid-based cytology in cervical screening. Results of searches will be restricted to those published or made available since the publication of the original HTA review (Payne et al 2000). Search strategies will include the terms cervix neoplasms, cervical intraepithelial neoplasia, cervix dysplasia vaginal smears, cytodiagnosis, liquid, monolayer and thin preparation. The following databases will be searched: Medline, Embase, Science Citation Index (SCI), Cochrane Library, NHS CRD DARE, NHS EED and HTA, OHE HEED and Pre-Medline. Searches will not be restricted by publication type or by study design as studies that do not meet the review inclusion criteria may be important in identifying further relevant papers and current research. Current research registers will also be searched and relevant professional and research organisations contacted. Citation searches of included studies will be undertaken using the SCI citation search facility, and the reference lists of included studies, of sponsor submissions and of relevant review articles will also be checked.

In addition, the report on the evaluation of liquid-based cytology in cervical screening at the pilot sites established since the original HTA report will be included in the review.

Inclusion criteria:

Population:
Women between 20-64 years of age (i.e. those currently eligible for a free cervical smear test every three to five years)

Intervention:
Liquid based cytology

Comparators:
Pap smear

Outcome measures:
- sensitivity;
- specificity;
- smear adequacy;
- cervical cancer incidence;
- cervical cancer-related morbidity;
- mortality;
- quality of life.

Research Design:
- systematic reviews,
- any primary study that attempts to measure an outcome of importance relating to the comparison of liquid-based cytology with conventional pap smears, such as assessments of sensitivity or specificity, categorisation of specimens, or percentage of inadequate or unsatisfactory specimens, and
- economic evaluations.

Data extraction strategy

All abstracts (or titles, where abstracts are unavailable) identified through the literature searches, will be double read and disagreements resolved by discussion. All articles selected will be double read to determine suitability for inclusion as evidence on clinical effectiveness, with disagreements resolved by thorough discussion. For those included, data will be extracted by one researcher, and checked by a second, using a standardised data extraction form; any disagreements will be resolved by discussion.

Quality assessment strategy

Published papers will be assessed according to the accepted hierarchy of evidence, whereby meta-analyses of randomised controlled trials are taken to be the most authoritative forms of evidence, with uncontrolled observational studies the least authoritative. The quality of systematic reviews and meta-analyses will be assessed using the guidelines from the Centre for Health Evidence based upon the Users Guides to Evidence-based Medicine (JAMA 1994; 272 17: 1367-1371).

The quality of randomised controlled trials will be assessed using the Jadad scale which addresses randomisation, blinding and the handling of withdrawals and dropouts (Jadad et al, Controlled Clinical Trials 1996;17:1-12. In addition all included clinical studies will be assessed according to checklists developed specifically for assessing the quality of diagnostic accuracy evaluations (Deeks, Systematic reviews of evaluations of diagnostic and screening tests, IN Systematic reviews in Health Care: Meta-Analysis in Context, 2001)

The quality of the general economic literature will be assessed according to the "Guidelines for authors and peer reviewers of economic submissions to the BMJ" (Drummond & Jefferson, BMJ 1996; 313: 275-283), whilst any identified modelling studies will be assessed using published principles of good practice for such studies (Eddy, Technology assessment: the role of mathematical modelling, IN Assessing Medical Technology, 1985; Anonymous, Pharmacoeconomics 2000, vol. 17,no. 5, pp. 443-444).

Methods of analysis/synthesis

The precise methods of any analysis and synthesis will be determined by the availability, volume and homogeneity of appropriate studies reported in the literature. Meta-analysis will be undertaken where appropriate.

Methods for estimating qualify of life, costs and cost-effectiveness and/or cost/QALY

The mathematical model developed for the original rapid review of liquid-based cytology will be adapted to synthesise the updated data to estimate costs, survival and quality adjusted survival of patients tested using liquid-based cytology, and using pap smear testing.

Cost data from published sources, if available, or derived from published or other sources of resource and cost data will be incorporated into the above model in order to allow economic, as well as clinical, implications of treatment to be assessed. The final outcome measures used will depend on the literature retrieved but are likely to include:

- Cost per life year gained and
- Cost per quality of adjusted life year gained.

A sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the treatments, with the objective of identifying how robust the results of the economic analysis are, given the current level of evidence.

F. **Handling the company submission(s)**

Any published cost-effectiveness and cost-utility studies of relevant comparator groups and interventions will be reviewed systematically.

Where appropriate the review group will develop its own economic model to estimate cost-effectiveness or cost-utility.

The industry dossier will be used as a source of data, looking for studies that meet the inclusion criteria (RCTs/other effectiveness as well as cost effectiveness and cost utility studies). A critical appraisal of any industry models submitted, including the strengths and weaknesses and the implications of different assumptions will be undertaken.

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) so that the NICE secretariat can negotiate (before and during the Institute's consultation process) with industry the subsequent inclusion of such data in the HTA monograph publication or subsequent peer-review publications. A separate version of the HTA report

will also be provided with all 'commercial in confidence' data excluded.

G. **Project Management**

a. **Timetable/milestones** - submission of:

Draft protocol: 14 October 2002
Finalised protocol: 28 October 2002
Progress report: 28 November 2002
Final Draft report to external reviewers – 20 December 2002
Assessment report: 29 January 2003

b. **Competing Interests**

None

c. **External reviewers**:

The Technology Assessment Report will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the TAR encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All reviewers are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will send external reviewers' signed copies to NCCHTA. Comments from external reviewers and the Technical lead, together with our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

H. **Appendices (optional)**

None

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