
A. This protocol is provisional and subject to change

B. Details of review team

Correspondence to:
Cody, June, Ms.
Research Fellow, Lead Reviewer
Health Services Research Unit
University of Aberdeen, Foresterhill, Polwarth Building
Aberdeen AB25 2ZD
Tel: (01224) 559244
Fax: (01224) 554580; E-mail: j.cody@abdn.ac.uk

Alphabetical List of Other Review Team Members:

Glazener, Cathryn, Dr.
Senior Research Fellow, Systematic Reviewer
Health Services Research Unit
University of Aberdeen, Foresterhill, Polwarth Building
Aberdeen AB25 2ZD
Tel: (01224) 553732
Fax: (01224) 554580; E-mail: c.glazener@abdn.ac.uk

Grant, Adrian, Professor.
Director, Systematic Reviewer
Health Services Research Unit
University of Aberdeen, Foresterhill, Polwarth Building
Aberdeen AB25 2ZD
Tel: (01224) 553909
Fax: (01224) 663087; E-mail: a.grant@abdn.ac.uk

Kilonzo, Mary, Ms.
Research Fellow, Health Economist
Health Economics Research Unit
University of Aberdeen, Foresterhill, Polwarth Building
Aberdeen AB25 2ZD
Tel: (01224) 681818 ext 43314
Fax: (01224) 662994; E-mail: mxk@heru.abdn.ac.uk

Stearn, Sally, Dr.
Senior Research Fellow, Health Economist
Health Economics Research Unit
University of Aberdeen, Foresterhill, Polwarth Building
Aberdeen AB25 2ZD
Tel: (01224) 552494
Fax: (01224) 662994; E-mail: s.c.stearns@abdn.ac.uk
Vale, Luke, Mr.
Research Fellow, Project Coordinator
Health Services Research Unit and Health Economics Research Unit
University of Aberdeen, Foresterhill, Polwarth Building
Aberdeen AB25 2ZD
Tel: (01224) 551127
Fax: (01224) 663087; E-mail: l.vale@abdn.ac.uk

Wallace, Sheila, Ms.
Research Fellow, Information Specialist
Health Services Research Unit
University of Aberdeen, Foresterhill, Polwarth Building
Aberdeen AB25 2ZD
Tel: (01224) 551107
Fax: (01224) 554580; E-mail: s.a.wallace@abdn.ac.uk

Wyness, Laura, Ms.
Research Assistant, Systematic Reviewer
Health Services Research Unit
University of Aberdeen, Foresterhill, Polwarth Building
Aberdeen AB25 2ZD
Tel: (01224) 551126
Fax: (01224) 663087; E-mail: law@ph.abdn.ac.uk

Steering Committee: Mr. John Cairns, Professor Adrian Grant, Professor Peter Fayers,
Professor W. Cairns Smith, Dr Sally Stearns.

B. Full title of research question

Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape (TVT) for treatment of stress incontinence.

C. Clarification of research question and scope

This review will assess whether tension-free vaginal tape (TVT) is more effective and cost-effective than the standard surgical interventions currently used. The alternative treatments to be considered are colposuspension, open suburethral sling procedures and injectables (periurethral bulking agents). However if any studies are found that formally compare TVT with other types of surgical management they will also be included.

The analysis will focus on long term outcomes (> 2 years) of clinical effectiveness (eg cure, improvement rates and quality of life), but will also assess short term outcomes relating to the operative procedure (eg surgical complications, hospital stay) (see section E 2.4 below).

D. Report methods

E.1 Search strategy

Extensive electronic searches of the databases listed below will be conducted to identify both published and unpublished information. These searches will aim to identify existing systematic reviews and primary studies evaluating the effectiveness and cost-effectiveness of TVT compared
with colposuspension, open suburethral sling procedures and injectables (periurethral bulking agents). However if any studies are found that formally compare TVT with other types of surgical management they will also be included.

The search terms will build upon work conducted by the Cochrane Incontinence Review Group and will involve the use of Medical Subject Headings (MeSH) in MEDLINE and other controlled vocabulary in other databases as well as textword searching (Grant et al, 2002).

Below is a table of the search approach that will be taken. All types of evidence will be sought for TVT over a broad range of electronic bibliographic databases. For the other interventions a tiered approach will be taken using a hierarchy of evidence – if insufficient evidence is found in the highest level then evidence from the next level down will be sought. This process will be repeated until sufficient evidence has been found or all levels of evidence have been sought. No limits will be applied to the search. The literature search for TVT will go back to 1990, for the other interventions the search will go back as far as the earliest year covered by the electronic bibliographic databases to be searched.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Types of studies sought</th>
<th>Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVT</td>
<td>All study designs</td>
<td>• Cochrane Incontinence Review Group’s Specialised Register of Trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cochrane Controlled Trials Register</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cochrane database of systematic reviews (CDSR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Database of abstracts of reviews of effectiveness (DARE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HTA database and reports</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NHS EED</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• MEDLINE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EMBASE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CINAHL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HealthSTAR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• BIOSIS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Science Citation Index</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PreMEDLINE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ISTP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• BL Inside</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ICS web-based conference abstracts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• UK National Research Register</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Current controlled trials/metaRegister of Controlled Trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ClinicalTrials.gov</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FDA</td>
</tr>
<tr>
<td>Colposuspension</td>
<td>1. RCTs or systematic reviews of RCTs</td>
<td>For level 1 or 2 evidence a broad search of databases as listed above for TVT would be used. If level 3 evidence is sought then just MEDLINE and EMBASE will be searched.</td>
</tr>
<tr>
<td></td>
<td>2. Systematic reviews of other (non-randomised) evidence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Population based registries</td>
<td></td>
</tr>
<tr>
<td>Open suburethral slings</td>
<td>1. RCTs or systematic reviews of RCTs</td>
<td>For level 1 or 2 evidence a broad search of databases as listed above for TVT would be used. If level 3 evidence is sought then just MEDLINE and EMBASE will be searched.</td>
</tr>
<tr>
<td></td>
<td>For level 1 or 2 evidence a broad search of databases as listed above for TVT would be used. If level 3 evidence is sought then just MEDLINE and EMBASE will be searched.</td>
<td></td>
</tr>
</tbody>
</table>
Two reviewers will screen the abstracts of all papers identified by the search strategy for potential inclusion. Full text copies of all potentially relevant studies will be obtained and formally assessed for inclusion by two reviewers working independently. Any disagreements that cannot be resolved through discussion will be referred to an arbiter.

Further citations will be sought from the reference lists of all relevant studies. Relevant professional and research organisations will be contacted.

**E.2. Inclusion criteria**

**E.2.1 Types of studies**

The review will concentrate on systematic reviews of randomised controlled trials (RCTs) and randomised or quasi-randomised trials. By quasi, we mean where the unit of treatment allocation is, for example, by alternation rather than random. Where no systematic reviews of RCTs or trials are available we shall search for studies from the next level of evidence ie systematic reviews of other evidence and population based registries. As TVT is a relatively new procedure it may be necessary to consider non-randomised evidence to establish the occurrence of rare events which may occur long term. Minimum follow up for these outcomes will be 2 years.

Studies reported in languages other than English will be identified from their abstracts and where time and resources allow translations will be obtained.

**E.2.2 Population**

Women affected by urinary stress incontinence (USI), for whom non-surgical therapies, such as pelvic floor muscle training or oestrogens either (a) have failed or ceased to be effective, or (b) are not suitable, and for whom a surgical intervention is indicated.

Women with symptoms of USI will be included, whether or not USI has been proven by urodynamics. Women who present with prolapse alone without overt urinary incontinence will be excluded.

If the evidence allows the assessment will attempt to identify women for whom TVT may be particularly effective (or ineffective). The following sub-groups will be considered:

- Women undergoing a secondary intervention (after failed previous incontinence surgery).
- Women with co-existing prolapse.
- Women with mixed incontinence (ie USI plus urge incontinence or detrusor instability)
The assessment will exclude pregnant women, or those who plan to have children in future, as TVT and other sling operations are not recommended for this group.

E.2.3 Types of interventions

TVT compared with colposuspension, open suburethral sling procedures and injectables (periurethral bulking agents). However if any studies are found that formally compare TVT with other types of surgical management they will also be included.

E.2.4 Types of outcome measures

The following items will be sought for all included studies: The primary outcomes will be subjective cure rates and quality of life, at least 24 months after the procedure.

1. Subjective measures of cure (based on women's symptoms)
   (a) Subjective cure and improvement rates
   (b) Pad changes over 24 hours (from self-reported number of pads used)
   (c) Incontinent episodes over 24 hours (from self completed bladder chart)
   (d) Urge symptoms or urge incontinence (clinical diagnosis without urodynamics)

2. Objective measures (physical)
   (a) Objective cure rate (using negative cystometrogram &/or pad test)
   (b) Pad tests of quantified leakage (mean volume or weight of urine loss)

3. Surgical outcome measures
   (a) Voiding dysfunction/difficulty after three months (with or without urodynamic confirmation)
   (b) De novo detrusor instability (urodynamic diagnosis)
   (c) New or recurrent prolapse / Entero-rectocele
   (d) Peri-operative surgical complications (e.g. haemorrhage, deep vein thrombosis, urinary tract and visceral injuries, wound infection, urinary retention delaying discharge, bacteriuria, bladder perforation)
   (e) Short and long term complications specifically related to the use of tape in TVT
   (f) Duration of operation
   (g) Blood loss during operation
   (h) Post operative pain
   (i) Length of inpatient stay
   (j) Discharge with indwelling catheter
   (k) Rate of self catheterisation
   (l) Time to return to normal activity level
   (m) Repeat incontinence surgery and/or surgery to remove the tape or correct tape erosion
   (n) Urinary retention
   (o) Later prolapse surgery
   (p) Dyspareunia (pain during sexual intercourse)
   (q) Death

4. Health status measures
   (a) Condition-specific health measures (specific instruments designed to assess incontinence) eg BFLUTS-Q (Jackson et al, 1996)
(b) Generic measures of Quality of Life/General health status measures (e.g. Short Form 36 (Ware et al, 1993))

E.3 Data extraction strategy

A data extraction form will be developed to record details of trial methods, participants, interventions, patient characteristics and outcomes. Two reviewers will extract data independently. Where a difference of opinion exists that cannot be resolved through discussion, an arbiter will be consulted.

E.4 Quality assessment strategy

Two reviewers working independently will assess all studies that meet the selection criteria for methodological quality. Any disagreements that cannot be resolved through discussion will be referred to an arbiter. The assessment will use a check list developed by Downs & Black to assess the quality of studies to be included in a systematic review of surgical studies for stress incontinence (Downs and Black, 1996). A specific quality assessment form devised to assess systematic reviews will also be used (Oxman, 1994).

E.5 Methods of analysis/synthesis

If more than one eligible study is identified, the use of quantitative synthesis will be explored. If possible we shall undertake analyses for the following sub-groups:

1. Women having TVT as a secondary intervention (after failed previous incontinence surgery).
2. Women with co-existing prolapse
3. Women with mixed incontinence.

Where quantitative synthesis is not possible, a narrative synthesis of eligible studies will be undertaken.

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

Existing economic evaluations including the submissions received through NICE will be systematically identified and critically appraised using the BMJ guidelines for reviewers of economic evaluations (Jefferson et al 1996). Strengths and weaknesses of the existing literature will be highlighted and the results summarised. The results of these studies will be considered in the light of the result of the economic model described below.

A model will be developed to estimate the relative cost-effectiveness of TVT compared with colposuspension, open sling procedures and injectables (periurethral bulking agents). This model will combine data on clinical effectiveness with cost data relevant to the UK NHS.

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 treatment options.
Quantities of resources used will be identified from the included studies which form part of the systematic review of economic evaluations, other relevant literature, and advice from health care professionals. We anticipate that unit cost data will be extracted from the literature or obtained from other relevant sources (e.g. manufacturer price lists, NHS reference costs). All cost data will be converted to a single year (2001) in pounds sterling.

The following data will be needed to estimate costs incurred by the NHS for a particular procedure:

- Staff time costs, consumables, overheads and capital associated with the operative procedure;
- Management of any complications that occur during the procedure or before discharge from hospital;
- Management of any complications that occur subsequent to discharge;
- Cost consequences of less than full cure and deterioration in continence requiring a subsequent procedure.

In order to provide a wider societal perspective and to elicit the impact on patients and their families, those costs that fall upon patients and their carers will also be reported where data are available. The range of costs that will be considered will be:

1) Patients’ time and travel costs (reported in natural units of resource use)
2) Changes in productivity of patient/carer due to differences in management strategy

Where appropriate costs will be discounted at 6%, the rate recommended in the NICE guidance to manufacturers and sponsors of submissions.

The model will also require data on the following:

- Cost of the operation and hospital stay
- Risk of complications
- Extent of incontinence after the procedure
- Probability of reoperations
- Outcome data (e.g. health status data in order to estimate QALYs using existing published quality of life figures)
- Mortality rates

E.6.2 Assessment of benefits

The following outcome measures will be elicited:

If at all possible, QALYs will be estimated for the methods of treatment and subsequent changes in health status. The strengths and weaknesses of the sources used to compute these QALY values will be highlighted.

Where appropriate, effectiveness and other measures of benefit will be discounted at 1.5%, the rate recommended in the NICE guidance to manufacturers and sponsors of submissions.

E.6.3 Modelling
A Markov model will be used to estimate costs and effectiveness over the lifetime of cohorts of women who initially receive the interventions. The precise nature of the model will be constrained by the data available. The type of economic evaluation will depend upon the findings.

Ideally, the results would be presented as incremental cost per QALY ratios for TVT compared with the alternatives considered.

E.6.4 Sensitivity analysis

Sensitivity analysis will be applied to the model in order to assess how robust the results are 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 the total NHS cost implications under different scenarios of adoption of TVT based upon the subgroups identified in section E5 above.

F. Handling the company submission(s)

We shall develop the economic model to assess cost-utility and cost-effectiveness, using if necessary data contained in the company submission to inform the estimates of effectiveness, cost-effectiveness, cost-utility. 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 will then be compared with that provided by the model we develop so that differences in results can be highlighted. If the model we 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) 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.

G. Project management

G.1 Timetable/milestones

Draft protocol: Due 18 February 2002

Progress report: 7 June 2002

The progress report will address the following matters:

1) Is the report progressing on schedule?
2) Confirmation of external reviewers, including job title and institution
3) Confirmation of date of receipt of industry submission (or notification if still outstanding)
4) Indication of whether extent of data marked ‘in confidence’ within industry submission is unreasonable i.e. if the whole of the submission is marked ‘in confidence’
5) Optional opportunity to comment on any problems encountered in production of the report
Draft final report: 12 August 2002

G.2 Competing interests

We are involved in the editorial office of the Cochrane Incontinence Review Group, but do not see this as a competing interest.

G.3 External reviewers

The rapid review 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 rapid review encounters particularly challenging methodological issues, we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the rapid review and will understand that their role is part of external quality assurance. We will require peer reviewers to sign a copy of the NICE Confidentiality, Acknowledgement and Undertaking. We will return peer reviewers’ signed copies to NCCHTA. Comments from external reviewers and our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

The names of external reviewers will be supplied with the progress report submitted to NCCHTA.

References


