Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Protocol 27/9/2006

1. Title

Thrombophilia testing

2. TAR team

School of Health and Related Research (ScHARR) Technology Assessment Group, The University of Sheffield
TAR team lead: Dr E. L. Simpson, Research Fellow;
ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA;
Direct line: 0114 2220708; Fax: 0114 2724095; Email: e.l.simpson@sheffield.ac.uk

3. Plain English summary

Arterial and venous thrombophilias are acquired or inherited (genetic) defects in blood coagulation that lead to a predisposition towards arterial or venous thrombosis. A thrombus is a solid mass of blood constituents that can fragment and block vessels downstream (thromboembolism). Depending on the blood vessel occluded, arterial thromboemoboli can lead to coronary artery thrombosis (myocardial infarction) or stroke, and venous thromboemboli can lead to pulmonary embolism, or rarely, stroke.

Venous thrombosis often occurs in normal vessels, with the majority of venous thrombi forming in the deep veins of the leg (deep vein thrombosis, DVT). Venous thrombosis is an important cause of morbidity and mortality; approximately 90% of pulmonary emboli are caused by dislodged fragments from asymptomatic DVTs. The estimated annual incidence of venous thrombosis is 1 in 1000 individuals in the general population.

Arterial thrombosis usually occurs in association with atheroma in areas of turbulent blood flow, such as the bifurcation of arteries.

Inherited (genetic) thrombophilia is caused most commonly by mutations in genes for coagulation factors II and V. Acquired thrombophilia refers to conditions in which individuals without genetic defects in coagulation factors are at increased risk of thrombosis, for example pregnancy, oestrogen therapy from combined oral contraceptives or hormone replacement therapy, obesity, fractures and major orthopaedic surgery.

4. Decision problem

Objective

To appraise the clinical and cost effectiveness of thrombophilia testing in patients with venous thrombotic events, and in patients with arterial thrombotic events, and to provide guidance to the NHS in England and Wales. The appraisal will consider the extent to which a diagnosis of thrombophilia influences the intensity or duration of anticoagulant therapy, and the subsequent impact on outcome.

Intervention

Thrombophilia testing refers to a panel of tests which are performed on individuals who are believed to be at high risk of thrombosis, the purpose being to identify those who may benefit from a more intensive or prolonged course of anticoagulant therapy and to prevent thrombosis. A blood sample is taken and a panel of diagnostic tests are performed to detect deficiencies in blood coagulation.

Diagnostic tests that may be predictive for an increased risk of venous thrombosis include tests for factor V Leiden, prothrombin G20210A, assays of clotting factors and the physiological anticoagulants antithrombin, protein C and protein S. Diagnostic tests that may be predictive for an increased risk of arterial thrombosis include assays of homocysteine and antiphospholipid antibodies.

The intervention for this review will be thrombophilia tests performed on individuals with thrombosis, with the resulting anticoagulation management.

Comparator

The comparator for this review will be individuals with thrombosis who are not subject to thrombophilia testing, and their anticoagulation management.

Population

Two populations will be considered separately:
1. Individuals with venous thrombosis;
2. Individuals with arterial thrombosis.

The following subgroups will be considered: smoking status; sex; age at first event; site of first thrombosis. For the intervention group, the population will be grouped according to whether tested after first event or recurrent thrombosis.

Key factors to be addressed

The review aims to discover whether anticoagulation management and subsequent thrombotic event rates are altered in the light of thrombophilia test results. The review will also investigate adverse events resulting from anticoagulation management, specifically rates of haemorrhage, and affect on health-related quality of life.

Areas outside the scope of this appraisal

Screening of individuals exposed to conditions which increase the susceptibility to acquired thrombophilia (for example major orthopaedic surgery and pregnancy) has been excluded from the scope of this appraisal. Case finding by testing of asymptomatic individuals with a family history of thrombophilia or thrombosis, but no personal history of thrombosis, is outside the scope of this review. These are important issues but it has been agreed that it is not feasible to appraise all these within a single technology assessment report.

5. Report methods for synthesis of evidence of clinical effectiveness

Search strategy

A comprehensive search will be undertaken to systematically identify clinical and cost-effectiveness literature concerning thrombophilia testing of patients with thrombosis and the resulting long-term anticoagulation management.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

Electronic searches

The search will aim to identify all studies relating to thrombophilia testing of patients with thrombosis, with the resulting anticoagulation management. Searches will not be restricted by language, publication date or publication type. An example of the Medline search strategy is shown in Appendix 1.

Citation searches of included studies will be undertaken using the Web of Science citation search facility, and the reference lists of included studies, relevant review articles will also be checked.

Databases

The following electronic databases will be searched from inception: MEDLINE (Ovid); CINAHL; EMBASE; PreMEDLINE, The Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, NHS EED and HTA databases; Science Citation Index (SCI); National Research Register (NRR); Current Controlled Trials; BIOSIS; Centre for Reviews and Dissemination (ongoing reviews database), Research Findings Register, Internet searches, Web of Science.

Inclusion criteria

Intervention

- Thrombophilia testing, using a panel of diagnostic tests, and the resulting anticoagulation management

Examples of thrombophilia tests are:

Factor V Leiden, prothrombin G20210A, activated protein C resistance, protein C, protein S and antithrombin levels, antiphospholipid antibodies and homocysteine levels, dysfibrinogenaemia and levels of Factor VIII, Factor IX, Factor XI and D-Dimer.
Anticoagulation management comprises any prescription of anticoagulants, and follow-up of the patient.

Population
Two populations considered separately

- Individuals with venous thrombosis
- Individuals with arterial thrombosis

Comparator

- Current standard treatments, that is risk assessment based on personal and family history of thrombosis, and the resulting long-term anticoagulation management

Outcomes

- Thromboembolic events (including fatal events) – venous events for population with venous thrombosis including DVT, pulmonary embolism, venous stroke; arterial events for population with arterial thrombosis including arterial stroke and myocardial infarction
- Mortality (death from any cause)
- Adverse effects of anticoagulation treatment (e.g. haemorrhage)
- Health-related quality of life (HRQoL)
- Anticoagulation management measures, including whether or not an anticoagulant is prescribed, frequency of INR testing, INR target, duration of anticoagulant prescription, duration of follow-up of patient

Study types
According to the accepted hierarchy of evidence, randomised controlled trials and meta-analyses from systematic reviews will be searched initially, as they provide the most authoritative forms of evidence. If data is not available from these, the review will accept data from other study types, including cohort and case-control studies.

Exclusion criteria

- Studies considered methodologically unsound
- Publications in languages other than English
- Thrombophilia tests conducted while patient was taking warfarin
- Thrombosis in pregnancy, or pregnancy complications associated with thrombophilia
- Thrombosis related to predisposing factor, such as major surgery or oestrogen therapy
- Case finding by testing individuals with family history of thrombosis or thrombophilia, but no personal experience of thrombosis

Based on the above inclusion/exclusion criteria, study selection will be made by one reviewer, with involvement of a second reviewer when necessary.

Data extraction and critical appraisal

Data will be extracted with no blinding to authors or journal. Data will be extracted by one reviewer using a standardised form. If there are data available from randomised controlled trials, quality will be assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination (see Appendix 2). If other study types are accepted into the review, quality assessment will instead be assessed based on the Downs and Black checklist for randomised and non-randomised studies (see Appendix 2). The purpose of such quality assessment is to provide a narrative account of trial quality for the reader and, where meta-analysis is appropriate, inform potential exclusions from any sensitivity analysis.

Data synthesis

Pre-specified outcomes will be tabulated and discussed within a descriptive synthesis. Where statistical synthesis is appropriate, meta-analysis will be conducted using fixed and random effect models, using RevMan software. If sufficient trials are available, a sensitivity analysis will be undertaken to see if the removal of poor quality trials affects the results.

Methods for estimating qualify of life

Any HRQoL data available from studies accepted into the review will be extracted.

In the absence of such evidence, the mathematical model may use indirect evidence on quality of life from alternative sources. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model.

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

Studies relating to the costs and effects associated with thrombophilia will be identified using an economic search filter, which will be integrated into the search strategy. Studies included within the cost-effectiveness review will be critically appraised using the Drummond checklist (see Appendix 2).

6.2 Methods for estimating costs and cost-effectiveness

A mathematical model will be constructed to estimate the cost-effectiveness of thrombophilia testing in patients with thrombotic events.

The appraisal will consider the extent to which a diagnosis of thrombophilia influences the intensity or duration of anticoagulant therapy, and the subsequent impact on outcome.

Cost-effectiveness analysis will take into account the effectiveness of thrombophilia testing, the sensitivity and specificity of specific diagnostic tests, and changes in the performance characteristics of some tests (due to the effect of thrombus) when thrombophilia testing is performed before, or after anti-coagulant treatment.

Where the evidence allows, consideration will be given to the

- cost-effectiveness of testing with specific tests and combinations of tests
- testing in central vs. local hospital laboratories

Sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the treatments. Multivariate Monte Carlo methods will be undertaken to generate information on the likelihood that each treatment is optimal. The results of this probabilistic sensitivity analysis will be presented as cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

7. Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 6/12/2006. Data arriving after this date will not be considered. The industry dossier will be used as a source of data for published studies that meet the inclusion criteria for both the clinical and cost-effectiveness review.

Any clinical and cost effectiveness information contained in the company submission to NICE, and not otherwise available in published reports, will be assessed for inclusion into the review. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any 'commercial in confidence' data taken from a company submission will be highlighted and underlined in the assessment report (followed by an indication of the relevant company name).

Any economic evaluation included in the company submission that complies with NICE's advice on presentation will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing de-novo modelling.

8. Competing interests of authors

None

9. Appendices

Appendix 1

Draft search terms for Medline

1 clinical trial.pt. (225210)
2 meta$.pt. (11138)
3 review.pt. (683286)
4 exp review literature/ (2443)
5 exp clinical trials/ (87937)
6 meta-analysis/ (4893)
7 exp guidelines/ (47776)
8 health planning guidelines/ (916)
9 or/1-8 (992360)
10 randomized controlled trials/ (36135)
11 controlled clinical trial.pt. (26436)
12 randomized controlled trials/ (36135)
13 random allocation/ (21037)
14 double blind method/ (42876)
15 single blind method/ (7621)
16 or/10-15 (128447)
17 clinical trial.pt. (225210)
18 exp clinical trials/ (87937)
19 (clin$ adj25 trial$).tw. (79059)
20 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw. (41776)
21 placebos/ (7536)
22 placebo$.tw. (52195)
23 random$.tw. (220009)
24 research design/ (23074)
25 or/17-24 (475260)
26 Comparative Study/ (560069)
27 exp evaluation studies/ (279253)
28 follow-up studies/ (157398)
29 prospective studies/ (131914)
30 (control$ or prospectiv$ or volunteer$).tw. (894853)
31 or/26-30 (1600442)
32 16 or 25 or 31 (1758984)
33 animal/ (1390937)
34 human/ (3698913)
35 33 not 34 (936064)
36 32 not 35 (1425207)
37 exp "Sensitivity and Specificity"/ (167664)
38 sensitivity.tw. (151370)
39 specificity.tw. (97754)
40 ((pre-test or pretest) adj probability).tw. (454)
41 post-test probability.tw. (131)
42 predictive value$.tw. (22089)
43 likelihood ratio$.tw. (2584)
44 or/37-43 (331092)
45 exp case-control studies/ (222729)
46 case control stud$.mp. (70352)
47 exp cohort studies/ (323926)
48 cohort analysis.mp. (796)
49 exp longitudinal studies/ (288791)
50 exp prospective studies/ (131914)
51 exp follow-up studies/ (157398)
52 cohort$.tw. (71183)
53 or/45-52 (523656)
54 meta-analysis/ (4893)

55 meta analy$.tw. (12804)
56 metaanaly$.tw. (469)
57 meta analysis.pt. (11138)
58 (systematic adj (review$1 or overview$1)).tw. (8999)
59 exp review literature/ (2443)
60 or/54-59 (27802)
61 cochrane.ab. (6521)
62 embase.ab. (4721)
63 (psychlit or psyclit).ab. (655)
64 (psychinfo or psycinfo).ab. (864)
65 (cinahl or cinal).ab. (1773)
66 science citation index.ab. (556)
67 bids.ab. (168)
68 cancerlit.ab. (312)
69 or/61-68 (9349)
70 reference list$.ab. (2752)
71 bibliograph$.ab. (4046)
72 hand-search$.ab. (1317)
73 relevant journals.ab. (222)
74 manual search$.ab. (664)
75 or/70-74 (7994)
76 selection criteria.ab. (6672)
77 data extraction.ab. (2971)
78 76 or 77 (9084)
79 review.pt. (683286)
80 78 and 79 (6373)
81 comment.pt. (214279)
82 letter.pt. (259780)
83 editorial.pt. (112306)
84 animal/ (1390937)
85 human/ (3698913)
86 84 not (84 and 85) (936064)
87 or/81-83,86 (1328208)
88 60 or 69 or 75 or 78 (38808)
89 88 not 87 (35917)
90 9 or 36 or 44 or 45 or 46 or 53 or 89 (2257794)
91 factor v leiden.mp. (2486)
92 activated protein c resistance.mp. or exp activated protein c resistance/ (1007)
93 apc resistance.mp. (468)
94 exp protein c deficiency/ (565)
95 protein c deficienc$.tw. (410)
96 exp protein s deficiency/ (591)
97 protein s deficienc$.tw. (549)
98 exp antithrombin III deficiency/ (259)
99 anti thrombin deficienc$.tw. (0)
100 antithrombin deficienc$.tw. (200)
101 antiphospholipid antibod$.tw. (2560)
102 antiphospholipid antibodies.mp. or exp Antibodies, Antiphospholipid/ (4074)
103 lupus anticoagulant.mp. or exp lupus coagulation inhibitor/ (1582)
104 anticardiolipin antibodies.mp. or exp Antibodies, Anticardiolipin/ (2015)
105 homocysteine.mp. or exp Homocysteine/ (8131)
106 dysfibrinogenaemia.mp. (13)
107 factor VIII.mp. or exp factor VIII/ (5055)
108 factor 8.mp. (1036)
109 d-dimer.mp. (2315)
110 factor IX.mp. or exp Factor IX/ (1523)
111 factor 9.mp. (323)
112 factor XI.mp. or exp Factor XI/ (450)
113 factor 11.mp. (39)
114 dilute russell viper venom time.mp. (33)

115 prothrombin G20210A.mp. (385)
116 MTHFR C677T.mp. (435)
117 kaolin clotting time.mp. (38)
118 or/91-117 (26120)
119 thrombophilia.mp. or exp Thrombophilia/ (7295)
120 mass screening.mp. or exp Mass Screening/ (43753)
121 screen$.mp. (159255)
122 test$.mp. (765004)
123 exp "diagnostic techniques and procedures"/ or diagnostic tests, routine/ (1024968)
124 (diagnostic test$ and procedure$).mp. (1579)
125 or/120-124 (1629523)
126 119 and 125 (2335)
127 118 or 126 (27217)
128 deep vein thrombosis.mp. or exp Venous Thrombosis/ (14230)
129 dvt.mp. (2271)
130 pulmonary embolism.mp. or exp Pulmonary Embolism/ (9702)
131 pe.mp. (7031)
132 venous thromboembolism.mp. (3551)
133 vte.mp. (1159)
134 stroke.mp. or exp Cerebrovascular Accident/ (58898)
135 cva.mp. (563)
136 peripheral vascular disease$.mp. or exp Peripheral Vascular Diseases/ (5229)
137 pvd.mp. (511)
138 myocardial infarction.mp. or exp Myocardial Infarction/ (50751)
139 mi.mp. (9201)
140 coronary heart disease.mp. or exp Coronary Disease/ (62297)
141 chd.mp. (5642)
142 exp Lateral Sinus Thrombosis/ or exp Hepatic Vein Thrombosis/ or exp Sagittal Sinus Thrombosis/ or exp Thrombosis/ or exp Coronary Thrombosis/ or exp Sinus Thrombosis, Intracranial/ or exp Cavernous Sinus Thrombosis/ or exp "Intracranial Embolism and Thrombosis"/ or exp Carotid Artery Thrombosis/ or exp Venous Thrombosis/ or exp Intracranial Thrombosis/ (37174)
143 exp Embolism/ (20440)
144 exp Thromboembolism/ (10415)
145 thrombo$.mp. (94723)
146 thromboembolism$.mp. (10235)
147 embol$.mp. (32214)
148 occlu$.mp. (57340)
149 or/128-148 (292284)
150 exp Anticoagulants/ (43413)
151 anticoag$.mp. (28066)
152 warfarin.mp. or exp Warfarin/ (6252)
153 blood coagulation test$.mp. or exp Blood Coagulation Tests/ (6685)
154 or/150-153 (55019)
155 90 and 127 and 149 and 154 (3411)
156 *Pregnancy Complications/ (10779)
157 *Pregnancy Outcome/ (5261)
158 *Abortion, Spontaneous/ (1519)
159 *Contraceptives, Oral/ (1495)
160 *Hormone Replacement Therapy/ (2483)
161 *Estrogen Replacement Therapy/ (5519)
162 or/156-161 (25911)
163 pregnancy complication$.ti. (141)
164 pregnancy outcome$.ti. (1336)
165 pregnancy loss$.ti. (437)
166 miscarriage$.ti. (644)
167 foet$.ti. (1044)
168 puerperium$.ti. (257)
169 oral contraceptive$.ti. (1781)
170 oral contraception.ti. (125)

171 hormone replacment therap$.ti. (0)
172 oestrogen therap$.ti. (26)
173 estrogen therap$.ti. (209)
174 oestrogen replacement.ti. (60)
175 estrogen replacement.ti. (606)
176 or/163-175 (6620)
177 162 or 176 (28991)
178 155 not 177 (4908)

Appendix 2

Data extraction

Quality assessment form for use if sufficient evidence is available from RCTs, adapted from NHS CRD Report No. 4. (NHS Centre for reviews and Dissemination. (2001) *Report 4: Undertaking systematic reviews of research on effectiveness; CRD's guidance for those carrying out or commissioning reviews*. York: University of York.)

	Yes/No/ Unclear
Was the method used to assign participants to the treatment groups really random?	
What method of assignment was used?	
Was the allocation of treatment concealed?	
What method was used to conceal treatment allocation?	
Was the number of participants who were randomised stated?	
Were details of baseline comparability presented?	
Was baseline comparability achieved?	
Were the eligibility criteria for study entry specified?	
Were any co-interventions identified that may influence the outcomes for each group?	
Were the outcome assessors blinded to the treatment allocations?	
Was the success of the blinding procedure assessed?	
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	
Were the reasons for withdrawal stated?	
Was an intention-to-treat analysis included?	

Quality assessment form if non-randomised studies are to be included, based on the external validity and internal validity sections of the Downs and Black checklist (from Downs S.H. and Black N. (1998) *J Epidemiol Community Health* 52: 377-384)

External validity
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?
Internal validity – bias
Was an attempt made to blind those measuring the main outcomes of the intervention?
If any of the results of the study were based on "data dredging", was this made clear?
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
Were the statistical tests used to assess the main outcomes appropriate?
Was compliance with the intervention/s reliable?
Were the main outcome measures used accurate valid and reliable?
Internal validity - confounding (selection bias)
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
Were the subjects randomised to intervention groups?
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
Were losses of patients to follow-up taken into account?
Power
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

Data to be extracted includes

Study identifier
Objective
Publication type(s) (i.e. full report or abstract)
Description of intervention or standard care, including thrombophilia tests used where applicable
Length of follow up
Numbers included in the study
Target population with inclusion / exclusion criteria
Characteristics of participants at baseline
Were intervention and control groups comparable?
Definition of primary outcomes
Definition of other outcomes
Statistical techniques used
Intention to treat analysis? Number of participants in analysis
Attrition rates (overall rates) i.e. Loss to follow-up
Compliance with study treatment
Study results Thromboembolic events (number, rate, type)
Study results Mortality/Overall survival
Study results Adverse effects of anticoagulation treatment
Study results Health-related quality of life
Study results Anticoagulation management measures

The Drummond checklist for assessing quality of economic literature (Drummond, M. and Jefferson, T. O. (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 313: 275-283)

1. Was a well-defined question posed in answerable form?
1.1 Did the study examine both costs and effects of the service(s) or programme(s)?
1.2 Did the study involve a comparison of alternatives?
1.3 Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often?
2.1 Were any important alternatives omitted?
2.2 Was (Should) a do-nothing alternative (be) considered?

3. Was the effectiveness of the programmes or services established?
3.1 Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?
3.2 Was effectiveness established through an overview of clinical studies?
3.3 Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?

4. Were all the important and relevant costs and consequences for each alternative identified?
4.1 Was the range wide enough for the research question at hand?
4.2 Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)
4.3 Were capital costs, as well as operating costs, included?

5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life-years)?
5.1 Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
5.2 Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. Were costs and consequences valued credibly?

6.1 Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements).
6.2 Were market values employed for changes involving resources gained or depleted?
6.3 Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinical space donated at a reduced rate), were adjustments made to approximate market values?
6.4 Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility been selected)?

7. Were costs and consequences adjusted for differential timing?
7.1 Were costs and consequences which occur in the future 'discounted' to their present value?
7.2 Was any justification given for the discount rate used?

8. Was an incremental analysis of costs and consequences of alternatives performed?
8.1 Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?

9. Was allowance made for uncertainty in the estimates of costs and consequences?
9.1 If data on costs or consequences were stochastic, were appropriate statistical analyses performed?
9.2 If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?
9.3 Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?

10 Did the presentation and discussion of study results include all issues of concern to users?
10.1 Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?
10.2 Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?
10.3 Did the study discuss the generalisability of the results to other settings and patient/client groups?
10.4 Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or other ethical issues)?

10.5 Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?