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TECHNOLOGY ASSESSMENT PROTOCOL FOR THE HTA PROGRAMME

Research Project: 06/28

The clinical and cost effectiveness of testing for cytochrome P450 polymorphisms in patients treated with antipsychotics

CONTENTS:

UNIVERSITY OF LIVERPOOL

Liverpool Reviews & Implementation Group

1. Title of project

The clinical and cost effectiveness of testing for cytochrome P450 polymorphisms in patients treated with antipsychotics.

2. TAR team

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3. Plain English summary

Patient response to drug therapy is highly unpredictable, with some patients experiencing side effects and others not responding to drugs at standard doses. This unpredictability may in part be explained by a patient's genetic makeup. Tests to identify genetic differences might mean that for certain drugs individualised tailoring of drug therapy may be possible.

A group of enzymes know as the cytochrome P450 enzymes have been identified as playing a major role in the way patients respond to drugs. Several tests have been developed to test for genetic differences in specific cytochrome P450 enzymes. Most tests are 'in house' laboratory tests, however one test (the AmpliChip®) has market approval and hence can be used by any hospital laboratory. The AmpliChip® may be of particular value in the field of schizophrenia as many drugs used in this area are metabolised by the P450 enzyme system for which the AmpliChip® tests. Furthermore, there is a large degree of patient variability in terms of response to therapy and it is hoped that testing may assist doctors when prescribing antipsychotics.

This review aims to assess whether cytochrome P450 testing is of clinical value in assessing the response to therapy with antipsychotic drugs. If suitable data are available the review will also determine if cytochrome P450 testing represents good value for money to the NHS.

4. Decision problem

Clarification of research question and scope

At the present time antipsychotics and antidepressants are the two main therapeutic areas where genetic testing has been proposed to be clinically useful and where there is a body of literature.[1, 2] A recent report by the Agency for Healthcare and Research Quality (AHRQ)[3] has attempted to assess the clinical and economic value of cytochrome P450 (CYP450) testing in the area of antidepressants, in particular the selective serotonin reuptake inhibitors (SSRIs).

There are many different types of CYP enzymes; the forms most relevant to the metabolism of drugs used in psychiatry are CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 all of which may be subject to polymorphisms (changes in the structure of the enzymes which can affect its activity). On the basis of these genetic polymorphisms, it has been possible to classify individuals into one of four phenotypes, poor metaboliser (PM), intermediate metaboliser (IM), extensive metaboliser (EM), and ultra-rapid metaboliser (UM). In terms of drug effects; the PM is expected to have higher drug concentrations with the potential for side-effects, the EM is expected to have the anticipated drug concentrations and response, the IM is in between the EM and PM, and finally the UM is expected to have sub-therapeutic drug concentrations with possible non-response.

The AHRQ[3] utilised a five key research question framework in order to assess the value of CYP450 testing for treating patients with SSRIs. The results of this review, presented by research question, are shown below:

- *Question 1:* Does testing for CYP450 polymorphisms in adults entering SSRI treatment for non-psychotic depression lead to improvement in outcomes, or are testing results useful in medical, personal, or public health decision making? (overarching question)

→ The AHRQ did not identify any studies that directly addressed this question.

- *Question 2:* What is the analytic validity of tests that identify key CYP450 polymorphisms?

→ The AHRQ review identified 12 published articles and two documents from the FDA website (on performance of the Roche AmpliChip®) that described methods for genotyping various CYP450 enzymes (nine pertaining to CYP2D6, three to CYP2C19, two to CYP2C8, and one each to CYP2C9 and CYP1A1). Of the studies of CYP450 enzymes most relevant to SSRI metabolism (CYP 2D6, 2C19, and 2C9), only four used the gold standard comparison (DNA sequencing), while others were methods comparisons. Notably, very few of the known polymorphisms of the CYP enzymes were tested. Sensitivity and specificity were high (in the range of 94 to 100 percent) for these studies, but confidence intervals for analytic sensitivity for most genotypes were very wide because of the relatively few samples tested. Gene deletion and duplication studies had lower sensitivity and specificity, further compounded by the limitation that there is no accepted gold standard for such tests.

- *Question 3a:* How well do particular CYP450 genotypes predict metabolism of particular SSRIs? Do factors such as race/ethnicity, diet, or other medications, affect this association?

→ The AHRQ identified 16 studies which met the inclusion criteria, of which five were conducted in healthy adults after a single dose of an SSRI. Of these, three showed that CYP2C19 PMs have significantly higher area under the curve (AUC), longer half-life, and reduced oral clearance of the parent drug, and significantly lower AUC, and lower maximum plasma concentration (C_{max}) of the metabolite of each drug than EMs (drugs studied were sertraline, fluoxetine, and citalopram). Similar results were

found in a study of CYP2D6*10 (associated with PM status) in healthy volunteers after a single dose of paroxetine, while another study of CYP2D6 using multiple doses of paroxetine found no significant difference between PMs and EMs. The remaining 11 studies were in clinical patients in treatment with SSRIs, were heterogeneous, had small sample sizes, and showed mixed results with respect to the association between CYP2D6/CYP2C9/ CYP2C19 polymorphisms and SSRI blood levels.

- *Question 3b:* How well does CYP450 testing predict drug efficacy? Do factors such as race/ethnicity, diet, or other medications, affect this association?

→ The AHRQ review identified only five studies, three of which involved cohorts of depressed patients in antidepressant treatment. Of these, one found no differences in the proportion of responders among CYP2D6 EMs, IMs, and PMs treated with fluvoxamine. The second found that although plasma concentrations varied significantly between groups (with respect to 2D6 and 2C9 metaboliser status), levels above or below the lower limit of presumed therapeutic levels did not predict response. The third found no differences in depression scores between two groups, CYP2D6 UMs + EMs versus PMs + IMs, treated with paroxetine. The other two studies found significantly higher proportions of CYP2D6 PMs in non-responders to CYP2D6 metabolized SSRIs compared to the general population. The studies had several limitations including non-randomized designs, inadequate power, studying several SSRIs together as a group, and not accounting for other genetic factors that may influence SSRI efficacy.

- *Question 3c:* How well does CYP450 testing predict adverse drug reactions? Do factors such as race/ethnicity, diet, or other medications, affect this association?

→ The AHRQ review identified nine studies, three of which reported adverse effects in CYP PMs only as a secondary finding. Of the other six, three reported no differences in rates of adverse effects between CYP2D6 PMs and EMs, while a fourth reported no differences in adverse effects between the combined PM + IM and EM + UM groups. One study found a greater prevalence of gastrointestinal (GI) adverse effects in PMs compared to EMs. This study also found that the combination of CYP2D6 polymorphism and serotonin receptor 5HT2A polymorphism predicted GI adverse effects. Two studies found a significantly higher prevalence of PMs in depressed patients with adverse effects than in the general population. The studies had several limitations including non-randomized design, inadequate power, and not accounting for other genetic factors that may influence SSRI tolerability.

- *Question 4a:* Does CYP450 testing influence depression management decisions by patients and providers in ways that could improve or worsen outcomes?

→ The AHRQ did not identify any studies that directly addressed this question.

- *Question 4b:* Does the identification of the CYP450 genotypes in adults entering SSRI treatment for non-psychotic depression lead to improved clinical outcomes compared to not testing?

→ The AHRQ did not identify any studies that directly addressed this question.

- *Question 4c*: Are the testing results useful in medical, personal or public health decision making?

→ The AHRQ did not identify any studies that directly addressed this question.

- *Question 5:* What are the harms associated with testing for CYP450 polymorphisms and subsequent management options?

→ The AHRQ did not identify any studies that directly addressed this question.

AHRQ[3] *model of treatment for major depression*

As a complement to the AHRQ evidence review, they constructed a basic decision model to consider the circumstances under which testing for CYP polymorphisms could improve clinical outcomes, or favourably impact costs. The review examined four strategies:

(1) use a non-CYP metabolized SSRI without testing;
(2) test and choose a non-CYP or CYP metabolized SSRI based on the result;
(3) test and choose the dose of a CYP metabolized SSRI based on the result;
(4) use a CYP metabolized SSRI without testing.

In no plausible scenario was a testing strategy predicted to improve expected outcomes of treatment at 6 weeks. The efficacy of a test strategy could approach the efficacy of use of a non-CYP metabolized drug, although this required the condition that a high correlation exist between genotype and phenotype (metaboliser status), as well as between phenotype and clinical outcomes. Current evidence does not support the conclusion that such high correlations apply. Moreover, the cost of testing is not offset by treatment savings if treatment duration is less than approximately 9 months.

Overall, the AHRQ concluded that there was a lack of good quality data to address the question of whether CYP450 testing in adults treated with SSRIs for depression leads to improvements in outcomes and / or assists decision makers.

Objectives of the HTA project

Following on from the AHRQ[3] review, we propose that it would be useful to:

1. Use the key research questions outlined in the AHRQ report (see above) in relation to the use of CYP450 testing for antipsychotic agents in order to determine the clinical value of CYP450 testing.

2. Develop a decision model to determine if the AmpliChip or similar CYP450 genotyping technologies are cost effective for prescribing antipsychotics in the UK.

Background

Mental health is recognised as a major challenge in UK clinical practice, and as such it is one of the nine national service frameworks.[4] Depression and schizophrenia are two of the most exigent conditions, as they are complex to diagnose and treat. Treatment of both conditions is especially difficult due to the large amount of inter-individual variability in patient response to therapy. This high degree of heterogeneity is associated with adverse drug reactions (ADRs) or therapeutic failure, which has important implications for both the patient and the NHS.

The inter-individual variability to therapy may in part be explained by differences in the target drug receptors, the transport proteins responsible for transporting the drug to its target and the enzymes responsible for metabolising the drug to its excretable form. A link between drug metabolism and drug response has been widely discussed in the literature.[5-6] A large amount of this literature has focussed on the cytochrome P450 (CYP450) enzyme system, which has been identified as a major metabolic pathway for many drugs and a source of inter-individual variability in patient response.[5-6]

The CYP450 enzyme system is a large superfamily of isoenzymes that metabolise many drugs and chemicals. Of them, CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 are the most crucial accounting for over 90% of drugs metabolised by CYP450. Several studies have shown a link between genetic polymorphisms and response to drugs with regards to CYP2C9, CYP2D6 and CYP2C19.[7-9]

A number of antipsychotics (both typical and atypical) are metabolised by CYP2D6 and CYP3A4, and to a lesser extent CYP1A2, including haloperidol, risperidone and clozapine. Table 1 summarises the P450-mediated metabolism of numerous antipsychotic drugs, split into typical and atypical agents.

The technology

Diagnostic genotyping tests for certain CYP450 enzymes are now available. Many tests are offered as in-house laboratory services, which do not require regulatory approval but which must meet general laboratory quality standards for high complexity testing.

In December 2004, the Food and Drug Administration (FDA) granted market approval for the AmpliChip® CYP450 test (Roche). The test is intended to identify a patient's CYP2D6 and CYP2C19 genotype from genomic DNA extracted from a whole blood sample and provides a predicted metabolic phenotype: poor, intermediate, extensive, or ultra-rapid metaboliser.

As our understanding of pharmacogenetics improves, other genotyping tests will no doubt follow, which may test for a wider array of CYP450 isoforms including CYP1A2 and CYP3A4. It is also possible that the Amplichip platform could be modified to incorporate other P450 gene polymorphisms. However, the current profile in the Amplichip is predicated by the fact that common polymorphisms exist only in CYP2C19 and CYP2D6, while the polymorphisms in CYP1A2 and CYP3A4 are relatively rare and of unknown functional consequence.

Table 1: A summary of common antipsychotics metabolised by the CYP450 enzyme system

Iso-enzyme	Typical antipsychotics[a]	Atypical antipsychotics[b]
CYP1A2	Haloperidol	Clozapine, olanzapine
CYP2D6	Thioridazine, perphenazine, fluphenazine, zuclopenthixol, haloperidol, chlorpromazine	Risperidone, olanzapine
CYP3A4	Haloperidol	Clozapine, risperidone, quetiapine, ziprasidone, olanzapine

[a]The typical antipsychotic agents are older drugs which frequently cause symptoms not dissimilar to Parkinsons disease (extrapyramidal side-effects).

[b]The atypical antipsychotics are newer agents which are generally better tolerated than the typical agents, having fewer extrapyramidal side-effects.

5. Methods for synthesising clinical effectiveness evidence

A systematic review methodology will be utilised to address each of the five research questions developed by AHRQ. [3]

Search strategy

The searching strategy will be composed of two parts:

Part 1 is aimed at addressing the question of the analytic validity of the pharmacogenetic tests and any harms associated with testing

Part 2 is focussed on linking genotype to phenotype and clinical outcome for patients treated with antipsychotics.

The following databases will be searched for relevant published literature for the period from 1995 to April 2007. We believe that this will capture all of the relevant studies as genetic testing for CYP450 is a relatively new area, for example the AmpliChip was only launched in the US in 2003.

- CENTRAL (Cochrane Central Register of Controlled Trials)
- CDSR (Cochrane Database of Systematic Reviews)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment (HTA) database
- ISI Web of Science- Proceedings (Index to Scientific & Technical Proceedings)
- MEDLINE
- ISI Web of Science- Science Citation Index Expanded
- HuGENet Published Literature database (www.cdc.gov/genomics/hugenet)

Details of the search strategy that will be used to explore MEDLINE are available in Appendix I.

The information sources listed below will be examined for relevant information on completed or on-going studies and if data are available, these may be considered for inclusion in the review.

- Trends in Medicine
- ClinicalTrials.gov – National Institutes of Health database
- *meta*Register of Controlled Trials and ISRCTN Register
- National Research Register
- The Cochrane Library
- TRIP Database plus
- Google Scholar
- FDA

Bibliographies of previous reviews and retrieved articles will be searched for further studies. In addition, research groups identified through searches will be contacted for information about ongoing trials.

We will also contact the company (Roche) directly to identify on-going studies and obtain additional data required for analysis.

Study selection

The citations identified by the two search strategies will be assessed for inclusion through two stages. Firstly, two reviewers will independently scan all the titles and abstracts identified by the searching exercise to isolate the potentially relevant articles to be retrieved. Full text copies of the selected studies will subsequently be obtained and assessed independently by two reviewers for inclusion using the inclusion and exclusion criteria outlined below. Any disagreements will be resolved by discussion at each stage, and if necessary a third reviewer will be consulted.

Part 1 Analytic validity of CYP450 pharmacogenetic tests

Inclusion criteria:

Study design	Comparative studies
Patient population	Adults suitable for pharmacogenetic testing
Interventions	Any CYP450 test
Comparators	Gold standard – DNA sequencing
Outcomes	Sensitivity, specificity and harms associated with testing

Exclusion criteria:

- Single case
- Patients aged less than 18 years

Part 2 Linking genotype to phenotype and clinical outcome

Inclusion criteria:

Study design	RCT, non randomised trial, observational study, laboratory based study
Patient population	Adults
Interventions	Antipsychotics
Outcomes[a]	Linking genotype to phenotype Linking phenotype to clinical outcome

[a] Outcomes are split into genotype, phenotype and clinical outcome; where genotype is the specific genetic variant of the enzyme the patient possesses, phenotype is how this genetic variant affects the patients ability to metabolise drugs (i.e PM, IM, EM, UM), and clinical outcome is the response to the drug the patient has i.e adverse event or reduced/no response.

Exclusion criteria:

- Single case
- Patients aged less than 18 years

Data extraction strategy

Data from the selected studies will be extracted as detailed below and will include information listed in Appendix II.

Data relating to study design, findings and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted on pre-tested data extraction forms. Time permitting, authors (and sponsors) of the studies will be contacted for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all other relevant publications listed.

Quality assessment strategy

Quality assessment tools appropriate to the study design will be employed. The quality assessment instruments will be derived from CRD Report No. 4[10] and will be relevant to the study design being evaluated. There are some additional aspects specific to genetic association studies that also need to be considered for quality assessment purposes, and these are summarised in chapter 6 of the HuGENet HUGE Review Handbook[11]. The quality assessment instruments will therefore be expanded to incorporate the additional quality assessments described in the HuGENet handbook. Two reviewers will independently evaluate the quality of the included studies and discuss disagreements where necessary. If required, a third reviewer will be consulted to achieve consensus.

Methods of analysis/synthesis

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. If appropriate, meta-analytic techniques will be utilised (see below for details), however if suitable data are not available a narrative discussion will be presented.

For part 1 meta-analysis methods will be adopted in order to arrive at a pooled estimate of diagnostic odds ratio. This measure takes into account the relationship between the pair of sensitivity and specificity measurements obtained from each study. Forest plots and the I^2 statistic will be examined and in the event of any heterogeneity being evident random-effects methods will be utilised when calculating the pooled estimates. Covariates of interest will also be explored by way of meta-regression in order to determine whether these are accountable for any of the detected heterogeneity. The covariates to be explored will be decided upon after identification of relevant studies but before any analyses are undertaken.

Part 2 will involve meta-analyses of the phenotype and clinical outcomes identified in the systematic review. For this part, guidelines set out in the HuGENet handbook [11] for undertaking meta-analyses of genetic association studies will be followed. In addition to the standard methods of undertaking a meta-analysis mentioned above, the following issues will also be considered in accordance with these guidelines:

- separate pooled estimates for heterozygotes and homozygotes will be presented;
- the genetic model assumed will be that proposed in the first study in the literature, provided that this is clear, and a pooled estimate will be calculated both with and without this first study. A decision will be made prior to analysis as to whether any further genetic models will also be tested and results from all assumed models will be reported;
- an assessment will be made as to how each study addressed possible population stratification in the design or analysis of their studies. Ethnic group-specific estimates will be calculated with these estimates being pooled only if they appear sufficiently similar;
- departure from HWE will be evaluated for each study separately. A sensitivity analysis will be undertaken to assess the impact of any deviations found.

Since the HuGENet guidelines were originally proposed for gene-disease association studies, they will be adapted as appropriate to suit this pharmacogenetic setting.

6. Methods for synthesising cost effectiveness evidence

Systematic review of published economic literature

The search strategy detailed in section 5 will be used to identify studies examining the cost effectiveness of CYP450 testing when prescribing antipsychotics. Other searching activities, including electronic searching of online health economic journals and contacting experts in the field will also be undertaken. Full details of the search process will be presented in the final report.

Titles and abstracts will be examined for inclusion by two reviewers independently. Potentially relevant studies will then be obtained in full text and examined more carefully by two independent reviewers using a pre-specified inclusion / exclusion criteria, details of which will be described in the final report. Any disagreement will be resolved by consensus, and if necessary a third reviewer will be consulted.

Only full economic evaluations (assessing both outcomes and benefits) of CYP450 testing will be included. However, to supplement findings, additional information on costs and benefits will be collated and discussed narratively as appropriate.

Data from the full economic evaluations meeting the inclusion criteria will be extracted into structured tables and will include, but not be limited to, the criteria set out in Appendix III. The quality of the included studies will be assessed using the critical appraisal checklist for economic evaluations proposed by Drummond and colleagues[12] (see Appendix IV).

Development of a *de novo* economic model

If suitable data are available an economic model will be developed. The model will use clinical data from our review of CYP450 testing in patients treated with antipsychotics to determine if CYP450 testing is a cost-effective strategy when prescribing antipsychotics. As there is likely to be a difference, particularly in terms of side-effects, between atypical and typical agents we will split the model into typical and atypical antipsychotic agents, concentrating on defining clear clinical and cost pathways.

Where possible, the results will be presented as incremental cost per QALY ratios. If sufficient data are not available to construct these measures with reasonable precision incremental cost-effectiveness analysis will be undertaken, or failing this a narrative discussion will be presented in place of a formal economic model.

Appropriate sensitivity analyses will be undertaken in order to assess the robustness of model 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 analyse the exact nature of the impact of variations.

Threshold analysis will also be undertaken to determine the threshold of effectiveness required for a genotyping technology to be cost-effective.

Imprecision in the principal model cost-effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question (e.g. multi-way sensitivity analysis, cost-effectiveness acceptability curves etc).

Estimates of the budgetary impact to the NHS will also be explored.

7. Expertise within LRiG

The LRiG team is a multi-disciplinary group of researchers and is well practised in undertaking health technology evaluations. Three members of the team are clinicians (Dundar, Pirmohamed, Walley); Dr Dundar is a full time psychiatric registrar, Professor Pirmohamed is a clinical pharmacologist and the Department of Health Chair in Pharmacogenetics, Professor Walley is a clinical pharmacologist. The remaining team members are specialists in mathematical modelling (Bagust, Beale), health economics (Bagust, Beale, McLeod), systematic reviewing (Dickson, Fleeman) and medical statistics (Jorgensen, Williamson).

In anticipation of carrying out this work, three members of the LRiG team (Beale, Dickson, McLeod) had the opportunity to participate in a seminar funded by the Economics and Social Research Council (ESRC) focusing on Economic Evaluation in Genetic Testing (23-24 November 2006, Oxford). As a result we have established collaborative links with researchers from the UK and the USA conducting research in this area.

Following on from referee comments, the LRiG team has been further reinforced by the addition of Dr Katherine Payne. Katherine is a Senior Research Fellow in Health Economics with a specialist interest in the economic evaluation of genetic technologies, as well as a member of the research team at the North West Genetics Knowledge Park.

Furthermore, in order to ensure the views of patients are considered, user groups will be contacted as necessary.

8. Timetable/milestones

Dates (estimated)	Activity
1st November 2007	Begin review
November – December 2007	Literature searching and assessment of papers for inclusion in the review
January 2008	Data extraction
February – March 2008	Data synthesis and economic modelling
April 2008	Draft report for internal and external advisors
Mid May 2008	Full report produced

9. References

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10. Appendices

Appendix I Details of MEDLINE search strategy

The searching strategy will be comprised of two parts:

Part 1 is aimed at addressing the question of the analytic validity of the pharmacogenetic tests and any harms of associated with testing

Part 2 is focussed on linking genotype to phenotype and clinical outcome for patients treated with antipsychotics.

Part 1:

1. Cytochrome P-450 Enzyme System/
2. cytochrome.tw.
3. (pharmacogenetic$ adj test$).tw.
4. Pharmacogenetics/mt
5. amplichip$.tw.
6. validity.tw.
7. "Sensitivity and Specificity"/
8. "Reproducibility of Results"/
9. *Polymerase Chain Reaction/
10. or/1-5
11. or/6-9
12. 10 and 11
13. animal/ not human/
14. 12 not 13
15. limit 14 to english language

Part 2:

1. genotyp$.tw. or Genotype/
2. phenotyp$.tw. or Phenotype/
3. antipsychotic$.tw. or Antipsychotic Agents/
4. (risperidone or olanzapine or thioridazine or perphenazine or fluphenazine or zuclopenthixol or haloperidol or chlorpromazine or clozapine or quetiapine or ziprasidone).af.
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. animal/ not human/
9. 7 not 8
10. limit 9 to english language

Full details of the searching process will be recorded.

Appendix II Details of clinical data extraction

Data extraction will be split into two parts.

Part 1 is aimed at addressing the question of the analytic validity of the pharmacogenetic tests and any harms associated with testing. The data to be extracted will include, but not be limited to:

- Test evaluated
- Test comparator
- Genotype specific sensitivity
- Genotype specific specificity
- Phenotype specific sensitivity
- Phenotype specific specificity
- Test for homogeneity
- Harms associated with testing
- Details of funding

Part 2 is focussed on linking genotype to phenotype and clinical outcome for patients treated with antipsychotics. The data to be extracted will include, but not be limited to:

Study characteristics
- Study bibliographic data
- Type of report (abstract, full manuscript, interim report)
- Type of study
- Methodological details of study
- Details of funding

Participants
- Number in study
- Sex
- Age
- Ethnicity
- Condition
- Treatment

Results (data for all outcomes specified will be extracted as available)
- Genotype and alleles of interest
- Predicted phenotype
- Clinical outcome

Appendix III Details of economic data extraction

Cost effectiveness data extraction will include, but not be limited to:

Study characteristics
- Type of evaluation and synthesis
- Intervention
- Study population/disease
- Time period of study

Cost data and cost data sources
- Cost items
- Cost data sources
- Country, currency year

Outcome data and data sources
- Range of outcomes
- Efficiency data sources
- Modelling method and data sources
- Probabilities and assumptions of models

Cost effectiveness
- Cost effectiveness ratios
- Subgroup analysis and results
- Sensitivity analysis and results
- Authors conclusions

Appendix IV Details of economic quality assessment

Studies of cost effectiveness will be assessed using the following criteria, which is an updated version of the checklist developed by Drummond.[12]

- Study question
- Selection of alternatives
- Form of evaluation
- Effectiveness data
- Costs
- Benefit measurement and valuation
- Decision modelling
- Discounting
- Allowance for uncertainty
- Presentation and generalisability of results

All items will be graded as either ✔ **yes** (item adequately addressed), ✘ no (item not adequately addressed), **?** **unclear** or not enough information, **NA** not applicable or **NS** not stated.