SUPPLEMENT

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Single Technology Appraisals

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NIHR HTA programme
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Health Technology Assessment

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy makers. TARs bring together evidence on the value of specific technologies.

This supplement to the Journal series contains a collection of summaries based on Evidence Review Group reports (ERGs), produced as part of NICE's Single Technology Appraisal (STA) process. The reports are mainly based on data submissions from manufacturers and do not undergo the standard peer-review process.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

Criteria for inclusion in the HTA Journal series and Supplements

Reports are published in the Journal series and Supplements if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the supplement was commissioned and funded by the HTA programme on behalf of NICE. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report. The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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Introduction

We are delighted to present the first Supplement to the journal series *Health Technology Assessment*. The series is now over 10 years old and has published more than 400 titles, covering a wide range of health technologies in a diverse set of applications. In general, the series publishes each technology assessment as a separate issue within each annual volume. This Supplement departs from that format by containing a series of shorter articles. These are all products from a 'call-off contract' which the HTA programme holds with a range of academic centres around the UK, at the universities of Aberdeen, Birmingham, Exeter, Liverpool, Sheffield, Southampton and York. These centres are retained to provide a highly responsive resource which meets the needs of national policy makers, notably the National Institute for Health and Clinical Excellence (NICE).

Until recently, these HTA Technology Assessment Review (TAR) centres provided academic input to policy making through independent analyses of the impact and value of health technologies. As many readers will be aware, the perception that the advice NICE provides to the NHS could be made more timely has led to the development of the 'Single Technology Appraisal' process. In this approach, manufacturers of technologies, which are, in general, pharmaceuticals close to the time of launch, submit a dossier of evidence aiming to demonstrate effectiveness and cost-effectiveness. The independent academic input to NICE's process, which continues to be supported by the TAR centres around the UK under contract to the HTA programme, is to scrutinise, critique and explore this dossier of evidence.

The papers included in this Supplement report on the first tranche of this HTA programme funded work which, with only one exception, relates to the potential use of new drugs for cancer within the NHS.

We hope that the summaries of the work carried out to inform the development of NICE guidance for these technologies will be of interest and value to readers. Further details of each of the NICE Appraisals are available on the NICE website (www.nice.org.uk) and we welcome comments on the summaries via the HTA website.

Prof. Tom Walley
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Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal

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Declared competing interests of authors: none

Abstract

This paper presents a summary of the evidence review group (ERG) report into the the clinical and cost-effectiveness of trastuzumab for the treatment of primary breast cancer in human epidermal growth factor 2 (HER2)-positive women based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The manufacturer's scope restricts the intervention to intravenous trastuzumab given for 1 year after surgery and after the completion of standard adjuvant chemotherapy, and the comparator to standard therapy without trastuzumab. The clinical rationale for the duration of treatment in the scope is open to question and leads to the exclsuion of one potentially relevant trial. The submitted evidence reports that the 3-weekly regimen of trastuzumab produced a relative reduction in all-cause mortality of 24–33%. Meta-analysis of all available studies based on 12 months of trastuzumab showed that there was a statistically significant 30% relative improvement in overall survival using the 3-weekly regimen. A study looking at weekly cycles of trastuzumab, excluded in the manufacturer's submission, produced a relative reduction in all-cause mortality of 59%, which was not statistically significant. All included studies showed a statistically significant difference in the risk of recurrence or death from any cause (disease-free survival), favouring trastuzumab. There was a statistically significant increase in the relative risk of a serious adverse event in women treated with 3-weekly cycles of trastuzumab, with no excess toxicity in the study evaluating weekly cycles. Estimates of cost-effectiveness provided by the

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The research reported in this article of the journal supplement was commissioned and funded by the HTA programme on behalf of NICE as project number 05/51/01. The assessment report began editorial review in July 2007 and was accepted for publication in November 2008. See the HTA programme website (www.hta.ac.uk) for further project information. This summary of the ERG report was compiled after the Appraisal Committee's review.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

manufacturer were based on data from the HERA trial using the 3-weekly regimen of trastuzumab. The economic model was a state-transition model that compared the lifetime impact of adding 1 year of trastuzumab therapy to standard care with standard care alone. The initial cost-effectiveness estimate was £5687 per additional quality-adjusted life-year (QALY) gained, rising to a maximum of £8689 upon one-way sensitivity analysis. The base-case estimate of cost-effectiveness was subsequently revised by the manufacturer, resulting in an estimated incremental cost per additional QALY gained of £2387. A number of assumptions behind the manufacturer's model may be optimistic and could mean that the incremental costs per QALY gained were underestimated. Additional analysis carried out by the evidence review group concluded that the incremental cost-effectiveness ratio (ICER) is expected to be around £20,000 to £30,000. The addition of potential long-term cardiac events could push the ICER above £30,000, although there is no long-term evidence to date surrounding this issue. In addition, the small study excluded from the manufacturer's submission raises the possibility of an equally effective but shorter regimen, incurring lower cost and toxicity and with greater patient convenience. The guidance issued by NICE in June 2006 as a result of the STA states that trastuzumab, given at 3-week intervals for 1 year or until disease recurrence, is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy and radiotherapy.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of trastuzumab for the treatment of primary breast cancer in HER2-positive women.[2]

Description of the underlying health problem

HER2-positive breast cancer is a breast cancer that tests positive for human epidermal growth factor receptor 2 (HER2). This protein promotes cancer cell growth. Cancer cells produce an excess of HER2 as a result of gene mutation in about one-third of cases of breast cancer. HER2-positive breast cancers are more aggressive than other types of breast cancer and are less responsive to hormone treatment.

Scope of the ERG report

No scoping exercise was undertaken by NICE for this STA. The scope as defined by Roche (the manufacturer of trastuzumab), restricts the intervention to intravenous trastuzumab given for 1 year after surgery and after the completion of standard adjuvant chemotherapy. It restricts the comparator to standard therapy without trastuzumab, which by implication is NICE's recommended four to eight cycles of anthracycline-containing chemotherapy postsurgery and 5 years of hormonal therapy. The primary outcome is defined as disease-free survival (cancer recurrence or death from any cause); secondary outcomes include overall survival, breast cancer recurrence and cardiotoxicity. Economic outcomes include cost per life-year gained (LYG) and cost per quality-adjusted life-year (QALY) gained.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process. In addition, the ERG carried out a meta-analysis of trials to derive a more precise estimate of treatment effect in terms of overall survival, disease-free survival, distant recurrence and cardiac toxicity. The ERG also critically evaluated the role of a study excluded in the manufacturer's submission (FinHER study[3]) in decision-making. Sensitivity analysis was also carried out to evaluate the robustness of the

manufacturer's model, as well as the impact of the ERG's revised base-case assumptions.

Results

Summary of submitted clinical evidence

Five relevant phase III trials were identified by systematic review: HERA ($n = 3387$),[4] BCIRG-006 ($n = 2148$),[5] NCCTG N9831 ($n = 1615$),[6] NSABP B-31 ($n = 1736$),[6] and FinHER ($n = 229$).[3] The published evidence reports that 18×3-weekly cycles of trastuzumab produced a relative reduction in the hazard of all-cause mortality from 24% [hazard ratio (HR) 0.76, 95% CI 0.47–1.23; absolute risk reduction 0.5%) at a median follow-up of 1 year in the HERA trial to 33% (HR 0.67, 95% CI 0.48–0.93; absolute risk reduction 1.8%) at a median follow-up of 2 years in the combined B-31 and N9831 analysis. When all studies with available data were meta-analysed there was a 30% relative improvement in overall survival and this was statistically significant at the 5% level (HR 0.70, 95% CI 0.53–0.92, $p = 0.010$). The excluded study,[4] which looked at nine weekly cycles of trastuzumab, given concurrently with three cycles of docetaxel or eight cycles of vinorelbine, produced a relative reduction in the hazard of all-cause mortality of 59% (HR 0.41, 95% CI 0.16–1.08; absolute risk reduction 6.9%) at a median follow-up of 3 years (the longest follow-up available for any trastuzumab schedule). This study had a small sample size and was not statistically significant at the 5% level.

All included studies, at whatever schedule or length of follow-up, showed a statistically significant difference in the risk of recurrence or death from any cause (disease-free survival), favouring trastuzumab. The combined HR for 18×3-weekly cycles was 0.50 (95% CI 0.44–0.57, $p < 0.00001$). In the study evaluating nine weekly cycles the HR was 0.42 (95% CI 0.21–0.83, $p = 0.01$). There was a statistically significant (almost sixfold) increase in the relative risk (5.54, 95% CI 2.07–14.82, $p = 0.0007$) of a serious life-threatening or fatal cardiac event in women treated with 18 three-weekly cycles of trastuzumab, although this represents an absolute risk increase of just 1.6% (*Figure 1*). In the FinHER study evaluating nine weekly cycles there was no excess toxicity.[3]

Summary of submitted cost-effectiveness evidence

Roche have developed a state-transition cohort model to compare the lifetime impact of 1 year of adjuvant trastuzumab therapy with no trastuzumab following standard chemotherapy. The main data source for the model is the Herceptin Adjuvant (HERA) trial, an international, multicentre, randomised trial on women with HER2-positive primary breast cancer, with a median of 1 year of follow-up. Outcomes from the HERA trial are extrapolated over a lifetime horizon to assess the long-term benefits and costs of trastuzumab. The model takes into account cardiac toxicity but does not consider other adverse events. The health states used within the model are considered to be appropriate for the required analysis. The cost of trastuzumab has been underestimated in the Roche submission, along with the cost of monitoring for cardiac toxicity. The costs and utilities associated with each health state were based upon studies carried out by the MEDTAP (Medical Technology Assessment and Policy) research centre specifically

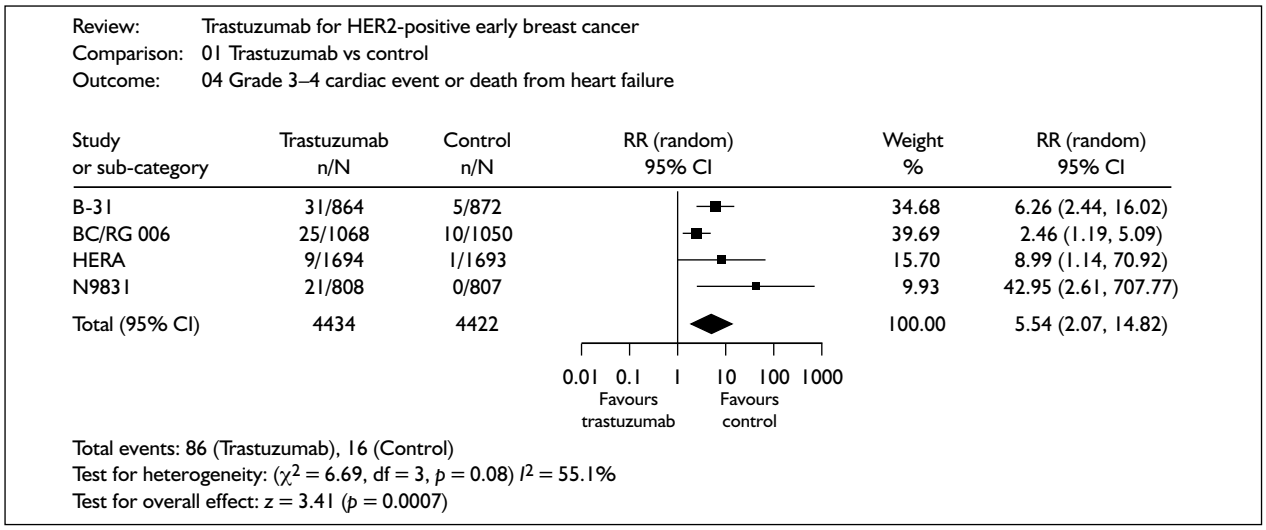

FIGURE 1 *Cardiac toxicity.*

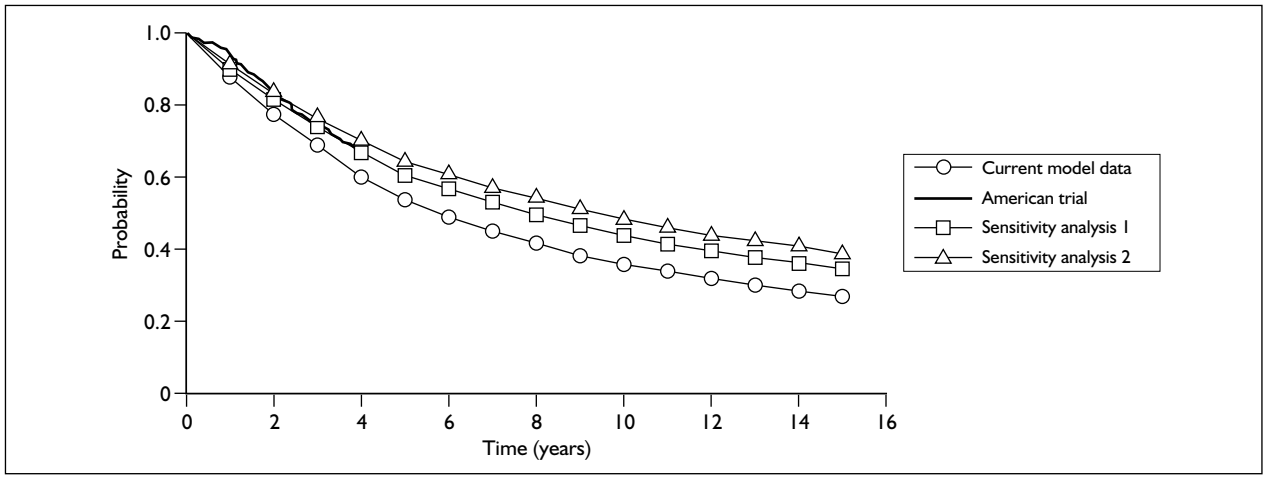

FIGURE 2 *Sensitivity analysis around rate of recurrence over time in comparator arm.*

for the model. These costs appear high relative to other recent breast cancer models.[8,9]

The Roche model estimated that the base-case incremental cost-effectiveness ratio (ICER) of chemotherapy plus trastuzumab versus chemotherapy is £5687 per QALY gained, rising to a maximum of £8689 upon one-way sensitivity analysis of the parameters. However, in the view of the ERG several of the baseline costs were underestimated and some of the upper or lower parameter values tested within the sensitivity analysis were not sufficiently extreme. In addition, there was no sensitivity analysis around the extrapolation of rate of recurrence in the comparator arm and limited sensitivity analysis around the relative risk of recurrence for trastuzumab. With respect to the probabilistic sensitivity analysis the description of uncertainty surrounding the mean values of many of the model parameters was considered to be insufficient or incomplete. However, following responses from Roche to queries raised by the ERG in a letter dated 8 March 2006 a revised base case of £2387 was presented by Roche (section 6 of ERG report[2]). This included a correction to an error in the original model, which reduced the ICER. Based on further sensitivity analysis carried out by the ERG (e.g. *Figure 2*) the ERG conclude that the ICER presented by Roche is too low. The combined effect of the uncertainties has the potential to increase the central estimate of the ICER to around £20,000–£30,000 (*Figure 3*). The addition of potential long-term cardiac events could push the ICER above £30,000, although the ICER is not expected to rise above £35,000–£50,000.

Commentary on the robustness of submitted evidence

The model structure is appropriate and allows sensitivity analysis to be carried out easily. One-way sensitivity analysis suggests that variations in the majority of the parameters do not have a large effect upon the ICER. The baseline ICER is relatively modest, such that potential parameter

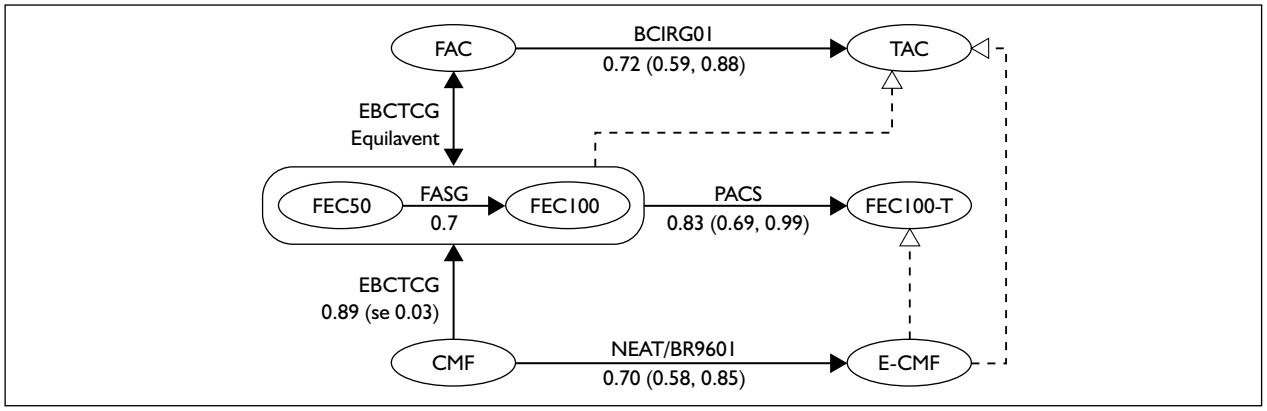

FIGURE 3 *Evidence review group's base case – cost-effectiveness acceptability curve. QALY, quality-adjusted life-year.*

variations are unlikely to increase the ICER beyond the currently accepted threshold values. However, no sensitivity analysis has been undertaken to explore the impact of uncertainty surrounding the comparator arm on the ICER. Little sensitivity analysis has been carried out around the long-term benefits of trastuzumab. Confidence intervals of some of the parameters do not adequately describe the uncertainty. For instance, the upper values of the cost of trastuzumab and cardiac monitoring were considered to be unrealistic.

There are a number of major areas of uncertainty. Disease-free and overall survival may differ from the comparator arm in the model, depending on the chemotherapy regimens being used in the UK. The benefits of trastuzumab regarding rates of recurrence are unknown beyond 3–4 years. There is little evidence to date on the effects of trastuzumab upon overall survival. There is no evidence on the effects of trastuzumab upon long-term cardiac dysfunction.

Conclusions

The following issues have the potential to impact on the cost-effectiveness results: the uncertainty surrounding the long-term benefits of trastuzumab in terms of reduction in the risk of recurrence; the extent to which reductions in the rate of recurrence will translate into benefits in overall survival; the extent to which patients in both the comparator arm and the trastuzumab arm are likely to receive trastuzumab in the metastatic setting; and the uncertainty generated by long-term extrapolation of the comparator arm. The combined effect of these uncertainties has the potential to increase the ICER from below £5000 to around £20,000–£30,000. The addition of potential long-term cardiac events could push the ICER above £30,000 although there is no long-term evidence to date surrounding this issue.

There are also a number of other important issues that are not explicitly taken into account in the economic modelling. A small study (the FinHER trial,[3] $n = 229$), excluded from the manufacturer's submission, raises the possibility of an equally effective but shorter regimen, incurring lower cost and toxicity and with greater patient convenience. Finally, there are a number of capacity issues for the NHS: HER2 testing, the preparation and administration of trastuzumab and cardiac monitoring will all require the augmentation of currently available facilities.

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in June 2006 states that:

Trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).

Cardiac function should be assessed prior to the commencement of therapy and trastuzumab treatment should not be offered to women who have a left ventricular ejection fraction (LVEF) of 55% or less, or who have any of the following:

- a history of documented congestive heart failure
- high-risk uncontrolled arrhythmias
- angina pectoris requiring medication
- clinically significant valvular disease
- evidence of transmural infarction on electrocardiograph
- poorly controlled hypertension.

Cardiac functional assessments should be repeated every 3 months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from from baseline and to below 50% then trastuzumab treatment should be suspended. A decision to resume trastuzumab therapy should be based on a further cardiac assessment and a fully informed discussion of the risks and benefits between the individual patient and their clinician.

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Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal

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Declared competing interests of authors: none

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of docetaxel for the adjuvant treatment of early node-positive breast cancer based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The manufacturer's scope restricts the intervention to docetaxel in combination with doxorubicin and cyclophosphamide (TAC), and the comparator to anthracycline-based chemotherapy. Based on the BCIRG 001 trial, the submitted evidence shows that TAC is associated with superior disease-free and overall survival at 5 years compared with the anthracycline-based regimen FAC. The absolute risk reduction in patients treated with TAC compared with those treated with FAC was 7% for disease-free survival and 6% for overall survival. However, TAC was associated with significantly greater toxicity than FAC. There is also evidence that docetaxel, in an unlicensed sequential regimen FEC100-T, is associated with superior disease-free and overall survival at 5 years compared with FEC100. An economic model was developed by the manufacturer based on the BCIRG 001 trial. This generated central estimates of the cost per life-year gained and cost per quality-adjusted life-year (QALY) gained of TAC compared with FAC of £7900 and £9800 respectively. The manufacturer's submission predicts a cost-effectiveness of £15,000–£20,000 per QALY gained for TAC compared with E-CMF (epirubicin in sequential therapy with cyclophosphamide, methotrexate, and

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

fluorouracil), and estimates the cost-effectiveness of FEC100-T to be £8200 per QALY compared with FEC100. Taking into account a number of issues identified by the ERG this may generate higher estimates of cost-effectiveness, but these are unlikely to exceed £35,000 per QALY gained. Importantly, FAC is not commonly used in clinical practice in the UK and, therefore, the submitted evidence does not indicate whether TAC is superior to the anthracycline-based regimens that are in common use (FEC or E-CMF). The indirect comparisons presented suggest that the economic case for TAC in comparison to current UK practice may not be proven. The manufacturer's submission failed to record evidence of three serious adverse events in patients receiving docetaxel with doxorubicin or to mention the concern of the European Medicines Agency regarding TAC's long-term adverse events. The guidance issued by NICE in June 2006 as a result of the STA states that docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen), is recommended as an option for the adjuvant treatment of women with early node-positive breast cancer.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of docetaxel for the adjuvant treatment of early node-positive breast cancer.[2]

Description of the underlying health problem

Breast cancer is the most common cancer among women in England and Wales. Around one in nine women will be diagnosed with breast cancer at some time in their lives. In 2002, 37,134 new cases of breast cancer were diagnosed in women in England and Wales.[3] The risk of breast cancer increases with age; over 80% of cases occur in women aged over 50.[3]

In breast cancer, prognosis is related to a number of factors, including the extent of disease progression identified at diagnosis or initial surgery.

Scope of the decision problem

The scope of the manufacturer's submission was limited to docetaxel in combination with doxorubicin and cyclophosphamide (TAC) for the adjuvant treatment of women diagnosed with operable node-positive breast cancer (i.e. the relevant licensed application), compared with anthracycline-based chemotherapy. It thus excludes women with high-risk node-negative cancers. Such women, who are at intermediate risk of recurrence, would, in clinical practice, be considered for adjuvant chemotherapy. The scope also excludes docetaxel used in sequential therapy (i.e. following or preceding several cycles of other cytotoxic drugs), although current clinical opinion appears to favour such regimens rather than combination regimens such as TAC. The anthracycline-based regimens in common use in the UK at the time of the assessment were FEC and E-CMF. The limitation of the comparators to anthracycline-based regimens excludes paclitaxel, another taxane, which, like docetaxel, is licensed for use in the UK as adjuvant therapy for operable node-positive breast cancer in sequential therapy following treatment with doxorubicin and cyclophosphamide.

Methods

The ERG report comprised a critical review of the evidence for the clinical and cost-effectiveness of the technology, based upon the manufacturer's/sponsor's initial submission to NICE and subsequent clarification of issues raised by the ERG early in the STA process. A narrative critique of the

submitted evidence was presented. The economic model submitted by the manufacturer was analysed to investigate the impact of different assumptions regarding potential indirect comparisons with UK comparator therapies.

Results

Summary of submitted clinical evidence

There is evidence from a randomised controlled trial (RCT) that, compared with the anthracycline-based regimen FAC, TAC is associated with superior disease-free and overall survival at 5 years (HR 0.72, 95% CI 0.59–0.88, $p = 0.001$ versus HR 0.70, 95% CI 0.53–0.91, $p = 0.008$).[4] The absolute risk reduction at 5 years in patients treated with TAC compared with those treated with FAC was 7% for disease-free survival and 6% for overall survival, and the number of patients who had to be treated with TAC rather than FAC for one additional patient to benefit was 14 for disease-free survival and 17 for overall survival. However, TAC was associated with significantly greater toxicity than FAC.

There is also RCT evidence that a sequential regimen, FEC100-T, in which docetaxel is used after the anthracycline-based regimen FEC100, is associated with superior disease-free and overall survival at 5 years (adjusted HR 0.83, 95% CI 0.69–0.99, $p = 0.041$ versus HR 0.77, 95% CI 0.59–1.00, $p = 0.05$) compared with FEC100.[5] The estimated absolute risk reduction at 5 years in patients treated with FEC100-T compared with those treated with FEC100 was 5.1% for disease-free survival and 4.0% for overall survival, and the number of patients who had to be treated with FEC100-T rather than FEC100 for one additional patient to benefit was 20 for disease-free survival and 25 for overall survival.

Summary of submitted cost-effectiveness evidence

An economic model was developed by the manufacturer, based primarily on the single trial BCIRG 001.[4] This submission model generates central estimates of the cost per life-year gained and cost per quality-adjusted life-year (QALY) gained of TAC compared with FAC of £7900 and £9800 respectively.

The manufacturer's submission predicts a cost-effectiveness of £15,000–£20,000 per QALY gained for TAC compared with E-CMF (epirubicin in sequential therapy with cyclophosphamide, methotrexate, and fluorouracil). This estimate was based upon an indirect comparison of absolute disease-free survival rates.

Based upon the RCT of FEC100-T compared with FEC100, the manufacturer's submission estimates the cost-effectiveness of FEC100-T to be £8200 (£3500–£56,000) per QALY compared with FEC100. Only four of the six potentially relevant studies reported overall survival and/or disease-free survival (*Table 1*).

Commentary on the robustness of submitted evidence

The ERG identified four other potentially relevant studies that do not meet the inclusion criteria in full, which were missed by the manufacturer in their literature search. These are the ECOG 2197,[6] GEICAM 9805,[7] USO 9735[8] and RAPP 01[9] studies.

The submitted clinical evidence depends primarily on an interim analysis from one trial, BCIRG 001, which uses docetaxel in its licensed regimen (TAC).[4] This is a large study carried out in a population that appears to be representative of the population for whom adjuvant docetaxel is licensed and who are expected to be eligible to receive it. However, there is no evidence that the study outcome assessors were blinded to treatment allocation, although the US Food and Drug Administration (FDA) recommends such blinding when disease-free survival is measured and considers it necessary to minimise bias in the assessment of drug toxicity. FAC, the anthracycline-based regimen used as the comparator in the trial, is not in common use in the UK, where FEC and E-CMF predominate. The submitted evidence does not therefore indicate whether TAC is superior to the anthracycline-based regimens that are in common use.

No evidence of systematic bias has been found in the primary economic analysis of TAC compared with FAC presented within the manufacturer's submission. It is the ERG's opinion that a revised model taking into account a number of modelling issues identified by the ERG may generate higher estimates of cost-effectiveness (*Table 2*), but it is unlikely that these estimates would exceed £35,000 per QALY gained. The manufacturer's submission presents a probabilistic sensitivity analysis of uncertainty in the economic estimates; the certainty in the cost-effectiveness estimates is overestimated.

TABLE 1 *Docetaxel in women with node-positive or high-risk node-negative breast cancer: studies reporting survival or disease recurrence*

Study Intervention/ comparator	Population	Median follow-up	Number of patients	Outcome	Intervention	Comparator	Hazard ratio (95% CI)	Absolute risk reduction
BCIRG 001, six cycles of TAC, six cycles of FAC	Node-positive	55 months	1491	Recurrence of breast cancer within 5 years	19%	26%	0.72 (0.59–0.88), $p = 0.001$	7%
PACS 01, three cycles of FEC100 followed by three cycles of docetaxel, six cycles of FEC100	Node-positive	60 months	1999	Recurrence of breast cancer within 5 years	22%	27%	0.83 (0.69–0.99), $p = 0.041$	5%
ECOG 2197, four cycles of AT, four cycles of AC	Node-positive and high-risk node negative	53 months	2952	4-year disease-free survival	87%	87%	1.08 (0.89–1.31), $p = 0.43$	0%
				4-year overall survival	93%	93%	1.09 (0.84–1.43), $p = 0.48$	0%
USO 9735, four cycles of TC, four cycles of AC	Node-positive and high-risk node-negative	66 months	1016	Estimated 5-year disease-free survival	86%	80%	0.67 (0.50–0.94), $p = 0.015$	6%
				Estimated 5-year overall survival	90%	87%	0.76, $p = 0.131$	3%

AC, doxorubicin and cyclophosphamide; AT, doxorubicin and docetaxel; FAC, fluorouracil, doxorubicin and cyclophosphamide; FEC100, fluorouracil, epirubicin 100 mg/m2 and cyclophosphamide; TAC, docetaxel, doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide.

TABLE 2 *Economic results for TAC compared with FAC from an adjusted model*

(a) Estimates of costs and outcomes

	TAC	FAC	Incremental
Costs (deterministic mean per patient)			
Cost of chemotherapy and administration	£7173	£1263	£5910
Cost of supportive G-CSF	£963	£353	£609
Cost of managing adverse events	£1521	£749	£772
Monitoring cost for patients in remission	£769	£737	£32
Cost of treatment for relapsing patients	£5482	£6042	–£561
Total expected cost	£15,908	£9145	£6763
Outcomes (deterministic)			
Patients discontinuing because of adverse events (%)	6.04	1.07	4.97
Life-years (mean per patient)	11.238	10.501	0.736
QALYs (mean per patient)	8.798	8.223	0.575

FAC, fluorouracil, doxorubicin and cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; QALYs, quality-adjusted life-years; TAC, docetaxel with doxorubicin and cyclophosphamide.

(b) Incremental cost-effectiveness ratio (ICER) estimates

	Point estimate of mean		95% Confidence interval	
	Deterministic	Probabilistic[a]	Lower	Upper
Incremental cost/LYG	£9187	£7932	£7289	£8641
Incremental cost/QALY	£11,760	£9760	£7805	£15,561

LYG, life-years gained; QALY, quality-adjusted life-year.
a The probabilistic results reflect the most recent run of the probabilistic simulation. If alternative analyses have been made without rerunning the probabilistic model they will not reflect the current analysis.

Conclusions

Docetaxel has been licensed for use in combination with doxorubicin and cyclophosphamide (TAC) for the adjuvant treatment of women diagnosed with operable node-positive breast cancer. Evidence from a large RCT demonstrates that TAC is superior to the anthracycline-based FAC regimen in terms of disease-free and overall survival at 5 years. However, the same evidence suggests that TAC is associated with significantly greater toxicity than FAC. Importantly, FAC is not commonly used in clinical practice in the UK. The most common adjuvant chemotherapy regimens currently in use in the UK are FEC, using an epirubicin dose of 75 mg/m^2 or greater, or E-CMF. FAC has not been demonstrated to be superior to these anthracycline regimens.

The manufacturer's submission to NICE failed to record the premature termination of the French RAPP 01 trial following three fatal or life-threatening adverse events in patients receiving docetaxel with doxorubicin. Furthermore, the submission does not mention the concern of the European Medicines Agency (EMEA) regarding TAC's long-term adverse events, as a result of which intensive monitoring for cardiotoxicity, secondary leukaemia and serious gastrointestinal toxicity is ongoing.

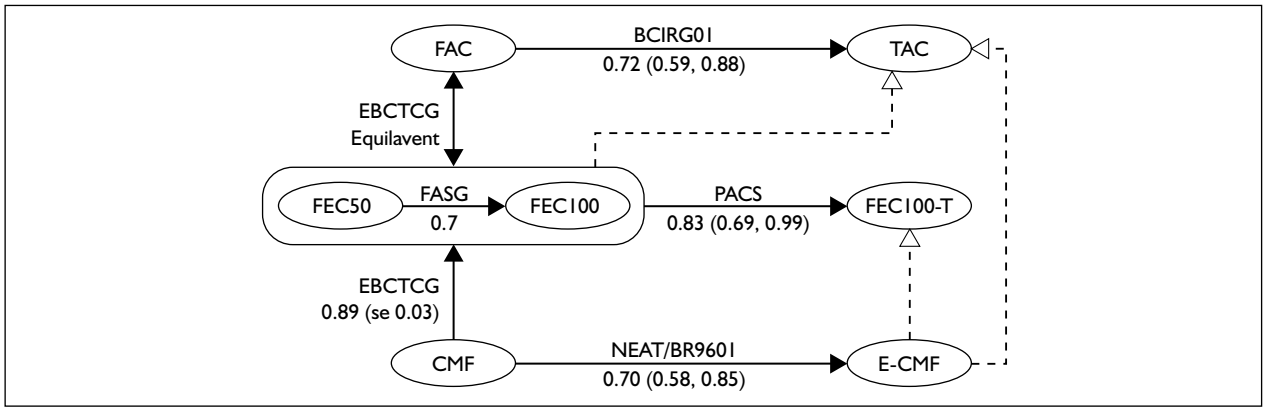

FIGURE 1 *Indirect comparisons. CMF, cyclophosphamide, methotrexate and fluorouracil; E-CMF, epirubicin with cyclophosphamide, methotrexate and fluorouracil; FAC, fluorouracil, doxorubicin and cyclophosphamide; TAC, docetaxel with doxorubicin and cyclophosphamide.*

There also exists RCT evidence that docetaxel, in an unlicensed sequential regimen FEC100-T, is associated with superior disease-free and overall survival at 5 years compared with FEC100.

The health economic model submitted by Sanofi-aventis estimates that TAC has a cost-effectiveness in the order of £10,000 per QALY gained compared with FAC. Indirect comparisons presented within this review (*Figure 1*) suggest that the economic case for TAC in comparison to current UK practice is not proven. As part of the unlicensed FEC100-T regimen, the manufacturer's submission estimates that the cost-effectiveness for docetaxel is in the order of £10,000 per QALY gained compared with FEC100, a comparator that is currently used in the UK.

The relevance of the cost-effectiveness estimates put forward in the manufacturer's submission depends on subjective judgments regarding the likely superiority of TAC over FEC75–100 or E-CMF (*Table 3*).

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in June 2006 states that:

Docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) as per its licensed indication, is recommended as an option for the adjuvant treatment of women with early node-positive breast cancer.

TABLE 3 *Relative risk of disease-free survival, TAC versus E-CMF, for a range of ICER/QALY values*

ICER threshold (£/QALY)	% Responders in E-CMF arm	Average relative monthly hazard of relapse over 5 years
£10,000	87.9	0.75
£20,000	92.3	0.84
£30,000	93.8	0.88
£40,000	94.7	0.90
£50,000	95.2	0.91
£60,000	95.5	0.92
£70,000	95.8	0.93
£100,000	96.2	0.95
E-CMF indirect estimate		0.92

E-CMF, epirubicin with cyclophosphamide, methotrexate and fluorouracil; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TAC, docetaxel with doxorubicin and cyclophosphamide.

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The use of paclitaxel in the management of early stage breast cancer

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of paclitaxel in the management of early stage breast cancer based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The scope was not clearly defined in the manufacturer's submission. Two of the three clinical trials included in the submission report showed that the addition of four cycles of paclitaxel to four cycles of doxorubicin and cyclophosphamide (AC-P) resulted in modest improvements in the two end points of disease-free survival (DFS) and overall survival (OS). The third unpublished study evaluating four cycles of AC followed by paclitaxel or docetaxel in breast cancer did not show any statistically significant differences in DFS or OS between any group. The economic evaluation of paclitaxel for adjuvant therapy in early breast cancer was based on two of the three trials submitted as clinical evidence and used a probabilistic Markov state-transition model. The measure of health benefit was quality-adjusted life-years (QALYs) and the model included direct costs using a UK NHS perspective. The primary analysis compared AC-P with four cycles of AC. The reported incremental cost-effectiveness ratio (ICER) for this comparison was £4726 per additional QALY for AC-P compared with four cycles of AC. The submission did not include a

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

systematic review for clinical or cost-effectiveness evidence. As a result, potentially relevant trials and previously published studies were omitted. The main comparator used did not represent standard care in the UK NHS and a large number of relevant comparators were omitted, including docetaxel. The manufacturer did not consider potentially important patient subgroups defined by baseline risk, and the cost-effectiveness result in the average overall patient population may conceal important variation between subgroups. Overall, although the economic model may have indicated that the addition of four cycles of paclitaxel to four cycles of AC may be cost-effective compared with providing four cycles of AC only, this comparison is not informative to current clinical practice in the UK NHS. In the context of this review it is not possible for the ERG to predict the cost-effectiveness of paclitaxel compared with more appropriate, and potentially more effective, relevant comparators. The guidance issued by NICE in July 2006 as a result of the STA states that paclitaxel is not recommended as an option for the adjuvant treatment of women with early node-positive breast cancer.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

The single technology appraisal (STA) process of NICE is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA on the use of paclitaxel in the management of early stage breast cancer.[2]

Description of the underlying health problem

In England and Wales breast cancer is the most common malignancy and cause of cancer mortality in women,[3–5] with 39,175 new cases of breast cancer registered in 2003,[4–6] representing a crude incidence rate of 74 per 100,000 population. In the same year over 11,000 women died of breast cancer.[3–6] This is a cancer that affects predominantly middle-aged to older women. The incidence of new cases in 2003 in women younger than 30 years was less than 0.4% and the incidence in men represented less than 1% of all new cases.[4–6] More than 80% of new cases are diagnosed in women aged 50 and over,[3,4,6] with the peak age range for diagnosis in women being 55–59 years (5395 out of 38,864 new cases in 2003).[4,6]

The 5-year age-standardised relative survival rate up to the end of 2001 for adult female patients (15–99 years) diagnosed with breast cancer between 1996 and 1999 in England and Wales was 77.5%, with a trend towards increasing rates of survival over the years.[7]

An invasive breast cancer is one in which there is dissemination of cancer cells outside the basement membrane of the ducts and lobules into the surrounding adjacent normal tissue.[8] The presence or absence of involved axillary lymph nodes is the single best predictor of survival in breast cancer, and important treatment decisions are based on it. Both the number of involved nodes and the level of nodal involvement predict survival from breast cancer.[9] When invasive breast cancer is diagnosed the extent of the disease should be assessed and the tumour staged. The two staging classifications in current use are the tumour node metastases (TNM) system and the International Union Against Cancer (UICC) system, which incorporates the TNM classification. Prognosis in breast cancer relates to the stage of the disease at presentation.[8]

Data published in 2003[10] indicated a prevalence of early stage node-positive breast cancer (T1–3, N+, M0) in two regional UK populations ($n = 559$) of approximately 21% of all presenting breast cancers; the same study reported a pan-European ($n = 4478$) incidence rate of 31%. An earlier (1997) UK study ($n = 1440$) reported that 49.8% of all presenting breast cancers were node positive at the time of diagnosis.[11]

When surgery is considered appropriate treatment for breast cancer, a number of options are available, with differing levels of breast tissue conservation. When chemotherapy is administered after surgery of any type it is known as adjuvant chemotherapy. When chemotherapy is administered before surgery it is known as neoadjuvant chemotherapy.[12]

Ensuring that adjuvant therapy is always offered to women with primary breast cancer when appropriate could reduce recurrence and improve survival rates.[13] In 2002, NICE recommended that almost all patients with invasive breast cancer should be offered adjuvant systemic therapy (hormone therapy and/or chemotherapy).[13] Women at intermediate or high risk of recurrence, dictated by primary tumour size, extent of nodal involvement and tumour grade, who have not had neoadjuvant chemotherapy should normally be offered four to eight cycles of multiple-agent chemotherapy that includes an anthracycline.[13]

Scope of the ERG report

The ERG report critically evaluated the evidence submission from Bristol-Myers Squibb Pharmaceuticals (BMS) on the clinical and cost-effectiveness of paclitaxel (Taxol®) for adjuvant treatment of early breast cancer.[14] The perceived aim of the BMS submission was to evaluate the clinical and cost-effectiveness of paclitaxel for the licensed indication of the treatment of early stage, operable, node-positive breast cancer following four cycles of anthracycline and cyclophosphamide therapy. The licensed dose is 175 mg/m^2 every 3 weeks for four courses. Additionally, paclitaxel is licensed for treating ovarian cancer, advanced non-small cell lung cancer and AIDS-related Kaposi's sarcoma. Paclitaxel is manufactured in the UK as Taxol (BMS) and is now also available generically (from Mayne Pharma). The list prices at time of writing are comparable, with prices of the generic drug being £112.20, £336.60 and £1009.80 and prices of Taxol being £116.05, £347.82 and £1043.46 for the 5-ml, 16.7-ml and 50-ml vials respectively.[15]

Methods

The ERG report comprised a critical review of the evidence for the clinical and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

This report identifies the submission's strengths and weaknesses, supplemented, where appropriate, with the ERG's own analysis. Clinical experts were asked to advise the ERG to help inform the review.

As the scope for this STA was not clearly defined in the BMS submission, and BMS did not summarise the decision problem, the ERG made the decision to look at the scope based on the licensed indication, that is, the use of paclitaxel for the treatment of node-positive breast cancer following anthracycline and cyclophosphamide therapy.

In view of the lack of a systematic review in the manufacturer's submission, a full detailed search needed to be undertaken as part of the ERG report. Thus, the ERG report included a detailed systematic search for studies and a critical analysis of relevant trials, regardless of whether the BMS submission had included them or not. It included a summary of the main points from any systematic reviews found, and a review of the main points from three sets of international guidelines included in the BMS submission.

The economic model included in the submission was reviewed on the basis of the manufacturer's report and by direct examination of the electronic model. The critical appraisal was conducted with the aid of a checklist for assessing the quality of economic evaluations[16] and a narrative review to highlight key assumptions and possible limitations.

This was a pilot STA and processes were not in place to give the manufacturer the opportunity to provide revised analyses to address limitations identified by the ERG during the course of the review process. Therefore, additional analyses were undertaken by the ERG to provide further information on areas that the ERG considered were not sufficiently dealt with in the manufacturer's submission. The additional work undertaken by the ERG was intended to provide additional information on the qualitative impact of identified limitations. Given the restricted nature of these additional analyses only three areas were considered:

- subgroup analysis
- sensitivity analysis
- additional comparator.

It should be noted that the analyses into these areas were selective and that the revised economic analyses were undertaken to examine the robustness of the manufacturer's own model

to alternative assumptions. These analyses are clearly subject to the same major limitations as the economic model. The results should therefore be taken only as indicative of the potential impact of these gaps in the manufacturer's submission.

Results

Summary of submitted clinical evidence

Of the three clinical trials included in the submission report two were fully published.[17,18] These trials aimed to determine whether four cycles of paclitaxel following four cycles of doxorubicin and cyclophosphamide (AC-P) would prolong disease-free survival (DFS) and overall survival (OS). Improvements of 5% [hazard ratio (HR) 0.83, 95% CI 0.73–0.94] and 4.2% (HR 0.83, 95% CI 0.72–0.95) in DFS and 4% (HR 0.82, 95% CI 0.71–0.95) and 0.8% (HR 0.93, 95% CI 0.78–1.12) in OS were seen in the two published trials. Both showed that the addition of four cycles of paclitaxel to four cycles of AC chemotherapy resulted in modest improvements in these two end points. The unpublished study[19] evaluated four cycles of AC followed by paclitaxel or docetaxel in breast cancer. This trial had insufficient data presented to fully assess the validity of the study, but it did show that there were no statistically significant differences in DFS or OS between any group.

Summary of submitted cost-effectiveness evidence

The submission included a de novo economic evaluation of paclitaxel for adjuvant therapy in early breast cancer, which the manufacturer's stated was based on two[17,19] of the three trials submitted as clinical evidence. Of the explicitly included trials, one was fully published and the other was unpublished. A probabilistic Markov state-transition model was used to compare the cost-effectiveness of the treatment strategies included in the two clinical trials (*Figure 1*). The measure of health benefit was quality-adjusted life-years (QALYs) and the model included direct costs using a UK NHS perspective. The primary analysis compared AC-P with four cycles of AC. The reported incremental cost-effectiveness ratio (ICER) for this comparison was £4726 per additional QALY for AC-P compared with four cycles of AC. A summary of the manufacturer's economic evaluation is provided in *Table 1*.

Commentary on the robustness of submitted evidence

The sections containing descriptions of individual studies did accurately reflect the data presented within the clinical trials that were considered in the manufacturer's submission. The overall economic model structure was appropriate for the decision problem, and the data sources used to inform the model were appropriate from a UK NHS perspective.

The ERG felt that the BMS submission was generally of poor quality with key omissions. The major flaw in the submission was the absence of a systematic literature review, as instructed by NICE in the draft guidance.[20] BMS limited the clinical effectiveness review in the submission to three studies, and it was unclear without the ERG undertaking a full systematic review whether they had considered all of the relevant literature. This same selective use of available evidence was

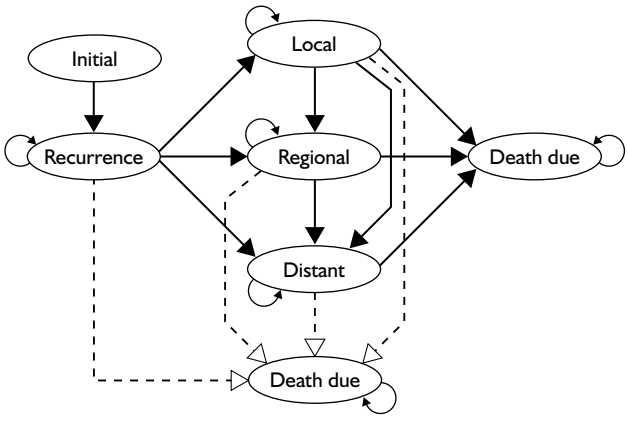

FIGURE 1 *Schematic of Markov model submitted by Bristol-Myers Squibb Pharmaceuticals.*

TABLE 1 *Summary of manufacturer's economic evaluation*

	Assumption	Source/justification
Model	Markov state-transition model with lifetime horizon, cycle length of 1 year	None provided
Natural history	Equivalent to AC arm of single randomised trial. Baseline risk assumed constant after year 7 (maximum follow-up in trial)	Baseline data taken from CALGB 9344.[17] Justification for constant risk after year 7 based on Bonadonna *et al*.,[23] who compared CMF with no treatment, but no corresponding statements found in original paper
Treatment effect on DFS	Lifetime treatment effect	Probability of recurrence based on CALGB 9344[17] and NABCI E1199.[19] No justification provided for lifetime treatment effect
Treatment effect on OS	Location of recurrence based on excluded clinical trial NSABP-B28	Mamounas *et al.*[18]
	Risk of progression following a recurrence independent of treatment received and based on a previous economic study rather than OS in included trials	Johnston.[24] Manufacturers state belief that OS from trials would overestimate survival and would not allow recognition of costs and quality of life implications associated with progression
Adverse events	Only considers the costs of managing neutropenia. All febrile neutropenia is hospitalised and treated with 14-day course of G-CSF. All neutropenia assumed to occur in first cycle of treatment and be prevented in subsequent cycles by G-CSF. No attempt to quantify the potential impact of side effects on quality of life	Probability of neutropenia based on CALGB 9344[17] and NABCI E1199.[19] No justification for inclusion or exclusion of adverse events
Health-related quality of life	External utility estimates assigned to acute-phase period and the main health states. Utility during acute phase assumed to be the same for all chemotherapies. Utility for distant recurrence assumes that it is treated with second-line chemotherapy	Abstract by Sorensen *et al.*[25] No justification provided for selection of data source
Treatment costs	Average patient weighs 70 kg with body surface area of 1.7 m^2. Cost of 1-hour chemotherapy administration assumed equal to one outpatient visit. Cost of additional hours required for administration adjusted on the basis of US costs	BNF 50.[15] No justification provided for approach used to cost of administration
Health state costs	Primary surgery based on that received in CALGB 9344. Death due to breast cancer incurs palliative care cost but death due to other causes does not	Johnston[24]
Discount rates	3.5% for health outcomes and costs	In accordance with NICE guidance[26]

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate and fluorouracil; DFS, disease-free survival; G-CSF, granulocyte colony-stimulating factor; OS, overall survival.

apparent in the economic evaluation. There was a tendency throughout the trials section to refer to relative risk rather than absolute risk, and relevant *p*-values were not quoted. This had the effect of exaggerating any possible benefits of treatment. Although the trial evidence around paclitaxel appears to show modest benefit, the trials themselves may not be directly applicable to the clinical situation that these patients are likely to face.

A further shortcoming of the submission was in not clearly defining the choice of comparator(s). This is important in determining relative efficacy and, if not clearly stated, affects the underlying discussions throughout the document. The comparators that were included in the cost-effectiveness analysis were not considered by the ERG to represent current treatment in the UK NHS or relevant licensed alternatives, and four cycles of AC may be regarded as a weak comparator in this patient population.

The submission did not consider identifiable subgroups of patients defined by prognostic factors that strongly influence the baseline risk of future events. Instead, the results were presented for the average patient recruited to the clinical trials included in the analysis, and this may conceal wide variation in the cost-effectiveness of paclitaxel according to baseline risk. The ERG attempted to highlight the potential impact of different patient characteristics on both DFS and the improvement in outcomes from different treatment options. They used data from Adjuvant! Online, a web-based decision aid that predicts 10-year breast cancer outcomes with and without adjuvant therapy.[21,22] *Table 2* presents a comparison of 10-year DFS rates from the manufacturer's model with those from Adjuvant! Online.

There were a number of typographical errors, minor discrepancies in data and modelling errors in the submission report and a number of statements throughout that were not supported by valid references. Overall, the submission report was not of a high quality. See *Table 3* for a comparison of the submission model with a NICE reference case. Consequently, parts of the submission needed to be repeated by the ERG and a lot more time was spent on areas that should have been appropriately completed by BMS.

Conclusions

The submission did not include a systematic review for clinical or cost-effectiveness evidence. As a result, potentially relevant trials and previously published studies were omitted. The main comparator used did not represent standard care in the UK NHS and a large number of relevant comparators were omitted, including docetaxel, another taxane, as licensed for the same indication. The manufacturer did not consider potentially important patient subgroups defined by baseline risk, and the cost-effectiveness result in the average overall patient population may conceal important variation between subgroups.

Overall, although the economic model may have indicated that the addition of four cycles of paclitaxel to four cycles of AC may be cost-effective compared with providing four cycles of AC only, this comparison is not informative to current clinical practice in the UK NHS. In the context of this review it is not possible for the ERG to predict the cost-effectiveness of paclitaxel compared with more appropriate, and potentially more effective, relevant comparators such as six cycles of FAC or the licensed indication of docetaxel. It is therefore impossible for the ERG to predict what effect including these comparators would have on the cost-effectiveness of paclitaxel for adjuvant treatment of early breast cancer.

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in July 2006 states that:

Paclitaxel is not recommended as an option for the adjuvant treatment of women with early node-positive breast cancer.[27]

TABLE 2 *Percentage of patients without recurrence after 10 years: comparison of manufacturer's model and Adjuvant! Online*

		AC/first generation (%)	AC-P3/second generation (%)	Percentage point difference between treatment
Manufacturer's model		47	53	6
Adjuvant! Online	ERG base case	48.1	55.2	7.1
	ER status negative	39.9	47.5	7.6
	Grade 3	41.9	49.4	7.5
	Size > 5.0 cm	35.7	43.5	7.8
	> Nine positive nodes	31.2	39.1	7.9
	Low risk	82.9	85.3	2.4
	High risk	9.8	15.7	5.9

AC, doxorubicin and cyclophosphamide; AC-P, paclitaxel with doxorubicin and cyclophosphamide; ER, oestrogen receptor; ERG, evidence review group.

TABLE 3 *Comparison of manufacturer's submission with NICE reference case*

Element of assessment	Reference case	Manufacturers submission
Defining the decision problem	N/A for STA	Treatment of interest was the licensed form of paclitaxel. Model considers a hypothetical cohort of women aged 50 years with operable node-positive breast cancer (based on patients recruited to Henderson *et al*[17])
Comparator	Alternative therapies routinely used in the NHS	No. Four cycles of AC used as the comparator. This is unlikely to represent standard treatment in the UK for this high-risk patient population
Perspective on costs	NHS and PSS	Yes. However, some relevant categories of cost are omitted from the analysis (e.g. premedication)
Perspective on outcomes	All health effects on individuals	Yes. However, model does not include differential utility impact related to toxicity while receiving treatment
Types of economic evaluation	Cost-effectiveness analysis	Yes
Synthesis of evidence on outcomes	Based on a systematic review	No
Measure of health benefits	Quality-adjusted life-years (QALYs)	Yes
Description of health states for calculation of QALYs	Health states described using a standardised and validated generic instrument	No. Utilities based on standard gamble methodology. Health state descriptions not publicly available
Methods of preference elicitation for health state valuation	Choice-based method, for example time trade-off, standard gamble (not rating scale)	Yes
Source of preference data	Representative sample of the public	No. Sample consisted of patients: 67 postmenopausal women aged 55–70 years in the UK ($n = 23$) and US ($n = 44$) who had a history of stage 1 or 2 operable early breast cancer
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity provision	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

AC, doxorubicin and cyclophosphamide; N/A, not applicable; PSS, personal and social services.

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Rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma (FNHL) based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The manufacturer's scope restricts the intervention to rituximab in combination with CVP (cyclophosphamide, vincristine and prednisolone) (R-CVP); the only comparator used was CVP alone. The evidence from the one included randomised controlled trial (RCT) suggests that the addition of rituximab to a CVP chemotherapy regimen has a positive effect on the outcomes of time to treatment failure, disease progression, overall tumour response, duration of response and time to new lymphoma treatment in patients with stage III/IV FNHL compared with CVP alone. Adverse events were comparable between the two arms. This study was confirmed as the only relevant RCT. The economic analyses provided by the manufacturer were modelled using a three-state Markov model with with the health states being defined as progression-free survival (PFS), progressed (in which patients have relapsed) and death (which is an absorbing state). The model generated results for a cohort of patients with an initial age of 53 and makes no distinction between men and women. The model is basic in design, with several serious design flaws and key parameter values that are probably incompatible. Attempting

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

to rectify the identified errors and limitations of the model did not increase the incremental cost-effectiveness ratio (ICER) above £30,000. Although the cost-effectiveness results obtained appear to be compelling in support of R-CVP compared with CVP for the trial population the results may not be so convincing for a more representative population. The results of the ERG analysis on the impact of age suggest that ICERs increase steadily with age, as the proportion of PFS that can be converted to overall survival (OS) is diminished by rising mortality rates in the general population. For the most extreme scenario (no OS gain) the ICER appears to remain below £30,000 per QALY gained. On balance the evidence indicates that R-CVP is more cost-effective than CVP. The guidance issued by NICE in July 2006 as a result of the STA states that rituximab within its licensed indication (in combination with cyclophosphamide, vincristine and prednisolone) is recommended as an option for the treatment of symptomatic stage III/IV follicular non-Hodgkin's lymphoma in previously untreated patients.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma (FNHL).

Description of the underlying health problem

In the UK non-Hodgkin's lymphoma (NHL) represents about 3% of all diagnosed cancers. In 2002 the incidence of NHL was 16 per 100,000 population and 15.6 per 100,000 population in England and Wales respectively. The overall rate of NHL is increasing by 3–4% annually. This is greater than expected when considering the ageing population and improvements in diagnosis. Follicular lymphoma (FL) is the second most common form of NHL in the UK with an incidence of approximately 4 per 100,000 population. It is considered incurable and the aim of treatment is to induce periods of remission, to lengthen remission and to improve survival and quality of life. There is no single accepted therapy for first-line treatment of stage III/IV FNHL, with current treatment options falling into four main categories: alkylator-, anthracycline-, fludarabine- and R-CVP-(rituximab plus cyclophosphamide, vincristine and prednisolone)-based therapies. Guidelines from the British Committee for Standards in Haematology (BCSH)[2] recommend CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), an anthracycline-based therapy, for treatment of grade III FNHL, although no guidance for the treatment of grade IV FNHL is given. There is currently no consensus as to whether combination therapy provides additional treatment benefits over monotherapy. However, recent published clinical guidelines[3] suggest that trials have shown advantages for combination therapy or extended chemotherapy with more frequent and longer lasting remissions and improvements to quality of life.

Scope of the ERG report

The ERG report presented the results of the assessment of the manufacturer's report regarding the use of rituximab (within the context of the licensed indication) in combination with CVP for the first-line treatment of stage III/IV FNHL.[4] The scope of the appraisal is presented in *Table 1*. The report included an assessment of both the clinical and cost-effectiveness evidence submitted by the manufacturer (Roche) of rituximab (MabThera®), indicated for the treatment of previously untreated patients with stage III/IV FNHL in combination with CVP chemotherapy.

TABLE 1 *Scope of the appraisal*

	Clinical effectiveness	Cost-effectiveness
Population	Adults with stage III/IV non-Hodgkin's lymphoma who have not received any previous treatment	
Intervention	Rituximab in combination with CVP (cyclophosphamide, vincristine and prednisolone)	
Comparators	CVP	
	CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone)	
	CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisolone)	
	MCP (mitoxantrone, chlorambucil and prednisolone)	
	Chlorambucil	
Outcomes	Time to treatment failure	Incremental cost per quality-adjusted life-year
	Tumour response (complete response, unconfirmed complete response, partial response, progressive disease)	*From the draft scope*: Details of the time horizon for the economic evaluation based on the time period over which costs and benefits can reasonably be expected given the progression of the disease
	Duration of response	
	Overall survival	
	Disease-free survival	
	Adverse effects of treatment	
	Health-related quality of life	
Study design	Randomised controlled trial	Economic analysis
Inclusion criteria	Main focus of follicular lymphoma	Main focus of follicular lymphoma
	Clinical trial data publications	Full economic evaluation
Exclusion criteria	Clinical trials in previously treated patients	No attempt to synthesis costs and benefits
	Reviews	Letters, editorials, commentaries or methodological papers
	Animal studies or in vitro research work	

Methods

The ERG report comprised a critical review of the evidence for the clinical and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

As part of their critical review the ERG repeated the searches for studies of clinical and cost-effectiveness. An accepted tool[5] relating to rigour of the review process and clarity of reporting was used to assess the methodological quality of the manufacturer's literature review. The ERG assessed whether each paper reported in the manufacturer's submission met the inclusion criteria according to: publication date; language; type of study (whether a full economic evaluation was included); intervention; and subjects. They conducted a detailed critique of the single efficacy trial included in the manufacturer's submission. They critiqued the manufacturer's economic model and the model was rerun after correcting for errors relating to costs and life-years gained; a Weibull survival curve was used to estimate survival.

In addition, because the submitted model is based on a cohort of patients with an unrealistically low average age (53 years), the ERG explored this further. It was observed that it was possible that at higher ages the apparently promising cost-effectiveness ratios may not be so attractive and could become unacceptable. It proved to be impossible to modify the model to allow accurate adjustment of age because of inherent structural problems and inherent inconsistencies in the model structures and, therefore, the ERG attempted a supplementary analysis. These results are necessarily imprecise approximations and should not be viewed as more than a general indication of the types of variations that may be expected if the ERG's assumptions prove to be valid.

Results

Summary of submitted clinical evidence

The submitted clinical evidence includes one randomised controlled trial (RCT), M30921, comparing CVP chemotherapy alone with CVP in combination with rituximab and involving a total study population of 322 patients with stage III or IV FNHL. The evidence from this trial suggests that the addition of rituximab to a CVP chemotherapy regimen has a positive effect on the primary outcome of time to treatment failure; it is reported to increase from 6.6 months in patients receiving CVP to 27 months in patients in the R-CVP arm with a risk reduction of 66% (95% CI 55%–74%). Other positive outcomes were measured for disease progression, overall tumour response, duration of response and time to new lymphoma treatment. Overall survival (OS) was not estimable at 42 months and the 38% risk reduction had not reached statistical significance. Adverse events were comparable between the two arms for the proportion of patients experiencing at least one adverse event, although the proportion experiencing an adverse event in the first 24 hours was greater for the R-CVP arm (71% versus 51%). These are primarily represented by infusion-related events. Similar proportions of patients in each arm experienced grade 3–4 haematological toxicity and infection except for neutropenia (14.5% CVP versus 24.1% R-CVP).

Summary of submitted cost-effectiveness evidence

The submitted review of economic studies included 15 studies, only eight of which actually met the inclusion criteria established for the review. None of these studies, however, compared R-CVP with CVP. The data extraction of the economic literature undertaken by the manufacturer was lacking in depth and no quality assessment of the included studies was provided. However, given the fact that these studies do not compare the same health-care technologies as the manufacturer's own economic evaluation, this is of limited importance.

The economic model included in the manufacturer's submission is a three-state Markov model, with the health states being defined as:

- progression-free survival (PFS)
- progressed (in which patients have relapsed)
- death (which is an absorbing state).

Patients begin in the PFS state and at the end of each cycle (cycle length 1 month) can either stay within this health state or move to the progressed health state or death state. Once in the progressed health state patients either move to the death state or continue in the progressed health state; once in the progressed health state they cannot return to PFS (*Figure 1*). However, the progressed state has been adjusted (in terms of utility) to account for periods of PFS. Movement between health states is governed by transition probabilities. The probabilities applied to the PFS health state vary over time but are generally similar between the two arms. The probabilities applied to the progressed health state are constant and do not differ between the two arms. The submitted model generates results for a cohort of patients with an initial age of 53 and makes no distinction between men and women.

Commentary on the robustness of submitted evidence

The single study included in the manufacturer's submission was confirmed as the only relevant RCT. In the manufacturer's submission the only comparator used was CVP alone. A wide range of treatment options are used in the UK for the treatment of FNHL, but currently there is no consensus on the most effective treatment. These include alkylator-based regimens (e.g. CVP, chlorambucil) or anthracycline-based regimens

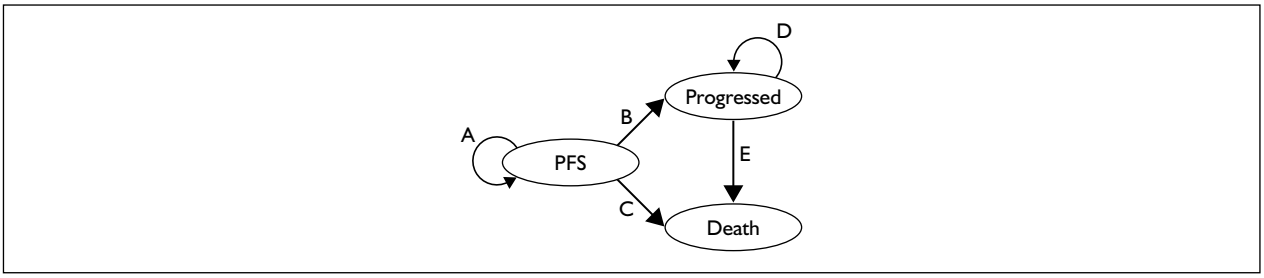

FIGURE 1 *Structure of the Markov model (adapted from the manufacturer's submission). PFS, progression-free survival.*

(e.g. CHOP, CNOP, MCP) used either alone or in combination with rituximab. Clinical guidelines, however, note a lack of data directly comparing outcomes with alternative therapeutic strategies. There is mention in the manufacturer's submission of other studies using a variety of treatments; however, no analyses were carried out comparing the results with R-CVP. Preliminary findings of a meta-analysis, available only as a conference abstract, are discussed descriptively.

There is an issue relating to the rationale for the outcomes used, including an explanation of the reasons for using time to treatment failure as the primary outcome instead of OS as is usual for oncology clinical trials. However, although OS is a preferred outcome measure, in the case of FNHL the submission presents a persuasive rationale for the use of time to treatment failure.

The model submitted in support of the manufacturer's submission is basic in design. It suffers from several serious design flaws and key parameter values are probably incompatible. The ERG attempted to rectify the identified errors and limitations of the model, none of which increased the incremental cost-effectiveness ratio (ICER) above the conventional threshold of £30,000. However, because of design flaws within the model as outlined in the report it was impossible for the ERG to simultaneously correct all of the errors and limitations within it. Although the

TABLE 2 *Results of analysis on impact of age on cost-effectiveness indices. Illustrative age-related model results, based on simple assumptions*

(a)

	Age						
	All	**All**	**All**	**All**	**All**	**All**	**All**
Proportion PFS gain is OS gain	0%	10%	20%	30%	40%	50%	60%
Incremental cost	£5944	£6459	£6975	£7491	£8007	£8522	£9038
Incremental life-years	0.000	0.190	0.381	0.571	0.762	0.952	1.143
Incremental QALYs	0.215	0.347	0.479	0.611	0.742	0.874	1.006
Incremental cost per life-year	N/A	£33,917	£18,312	£13,111	£10,510	£8950	£7910
Incremental cost per QALY	£27,619	£18,615	£14,568	£12,269	£10,785	£9749	£8985

OS, overall survival; PFS, progression-free survival; QALY(s), quality-adjusted life-year(s).

(b)

	Age				
	50	**53**	**60**	**70**	**75**
Max proportion of PFS gain is OS gain	67.0%	65.5%	59.4%	36.8%	12.5%
Incremental cost	£9401	£9322	£9007	£7843	£6588
Incremental life-years	1.277	1.248	1.131	0.701	0.238
Incremental QALYs	1.099	1.079	0.998	0.700	0.380
Incremental cost per life-year	£7364	£7472	£7962	£11,185	£27,686
Incremental cost per QALY	£8577	£8643	£9025	£11,197	£17,343

OS, overall survival; PFS, progression-free survival; QALY(s), quality-adjusted life-year(s).

cost-effectiveness results obtained appear to be compelling in support of R-CVP compared with CVP for the trial population, it could be argued that the results would not be so convincing for a more representative population.

The results of the ERG analysis on the impact of age (*Table 2*) suggest that ICERs increase steadily with age, as the proportion of PFS that can be converted to OS is diminished by rising mortality rates in the general population. For the most extreme scenario (no OS gain) the ICER appears to remain below £30,000 per quality-adjusted life-year gained.

Conclusions

On balance the evidence indicates that R-CVP is more cost-effective than CVP.

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in July 2006 states that:

Rituximab within its licensed indication (that is in combination with cyclophosphamide, vincristine and prednisolone) is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients.

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Bortezomib for the treatment of multiple myeloma patients

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of bortezomib for the treatment of multiple myeloma patients at first relapse and beyond, in accordance with the licensed indication, based upon the evidence submission from Ortho Biotech to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The outcomes stated in the manufacturer's definition of the decision problem were time to disease progression, response rate, survival and quality of life. The literature searches for clinical and cost-effectiveness studies were adequate and the one randomised controlled trial (RCT) included was of reasonable quality. Results from the RCT suggest that bortezomib increases survival and time to disease progression compared with high-dose dexamethasone (HDD) in multiple myeloma patients who have had a relapse after one to three treatments. Cost-effectiveness analysis based on the same trial and an observational study was reasonable and gave an estimated cost per life-year gained of £30,750, which ranged from £27,957 to £36,747 on sensitivity analysis. An attempt was made to replicate the results of the manufacturer's model and to compare the results to the Kaplan–Meier survival curve presented in the manufacturer's submission. In addition, a one-way sensitivity analysis and a probabilistic sensitivity analysis were undertaken, as well as additional scenario analyses. Based on these analyses the ERG suggests that the cost-effectiveness results

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

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presented in the manufacturer's submission may underestimate the cost per life-year gained for bortezomib therapy (versus high-dose dexamethasone) when potential UK practice and scenarios are considered. The guidance issued by NICE in June 2006 as a result of the STA states that bortezomib monotherapy for the treatment of relapsed multiple myeloma is clinically effective compared with HDD but has not been shown to be cost-effective and is not recommended for the treatment of progressive multiple myeloma in patients who have received at least one previous therapy and who have undergone, or are unsuitable for, bone marrow transplantation.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of bortezomib for the treatment of multiple myeloma patients.

Description of the underlying health problem

Multiple myeloma is a haematological cancer that progresses rapidly and is incurable. As well as reducing life expectancy it causes significant morbidity with painful symptoms including lytic bone lesions. These lead to pathological fractures of the long bones and vertebral collapse. Patients may also suffer renal failure, anaemia and neutropenia leading to infections. In the UK the median age at diagnosis is 65 years, with 1-year survival rates of approximately 60% and 5-year survival rates of approximately 25%.[2,3] Multiple myeloma is more common in men than women[3,4] and the incidence rate among Afro-Caribbean populations is higher than for Caucasians of European descent.[5]

Scope of the ERG report

The ERG critically evaluated the evidence submission from Ortho Biotech for the use of bortezomib monotherapy for the treatment of multiple myeloma patients at first relapse and beyond, in accordance with the licensed indication.[6] Bortezomib is a proteasome inhibitor and works by disrupting normal intracellular protein regulation, leading to programmed cell death (apoptosis).

Bortezomib was licensed for the treatment of people with relapsed and refractory multiple myeloma in 2004. The marketing authorisation was extended in April 2005 to allow use as a monotherapy for the treatment of progressive multiple myeloma in patients who have received at least one previous therapy (at first relapse) and who have already undergone (or who are unsuitable for) bone marrow transplantation.

The outcomes stated in the manufacturer's definition of the decision problem were time to disease progression, response rate, survival and quality of life.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process. The ERG checked the literature searches and applied the NICE critical appraisal checklist to the included studies. In addition, the ERG attempted to replicate the results of the manufacturer's model and also compared the model's results to the Kaplan–Meier survival curve presented in the manufacturer's submission (*Figure 1*). A one-way sensitivity analysis and a probabilistic sensitivity analysis (*Figure 2*) were undertaken by the ERG, as well as additional scenario analyses.

Results

Summary of submitted clinical evidence

The manufacturer based the submission on one randomised controlled trial (RCT) comparing bortezomib with high-dose dexamethasone (HDD) in multiple myeloma patients who have had a relapse after one to three treatments. Results of the RCT suggest that bortezomib increases survival and time to disease progression compared with high-dose dexamethasone in these patients.

Summary of submitted cost-effectiveness evidence

The manufacturer submitted a cost-effectiveness analysis that used a decision-analytic model (quasi-Markov) to estimate the treatment effect with bortezomib compared with high-dose dexamethasone. The model used clinical effectiveness data from the RCT supplemented with data from an observational study. Primary analysis presented an estimated cost per life-year gained of £30,750. Cost per life-year gained ranged from £27,957 to £36,747 from sensitivity analyses.

Commentary on the robustness of submitted evidence

The literature searches for clinical and cost-effectiveness studies were adequate and all available evidence was included. The RCT was of reasonable quality when assessed according to NICE internal validity criteria. However, the reporting of the trial lacked detail and clarity making interpretation of clinical effectiveness results difficult. Furthermore, the included RCT does not reflect current UK clinical practice, calling into question its external

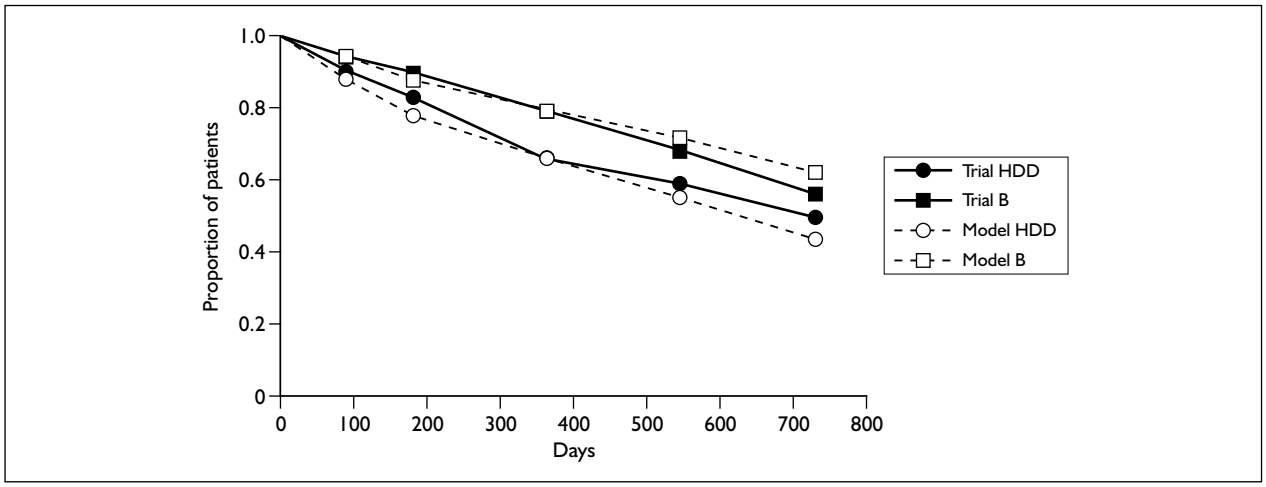

FIGURE 1 *Patient survival for high-dose dexamethasone (HDD) and bortezomib for the APEX trial and model results.*

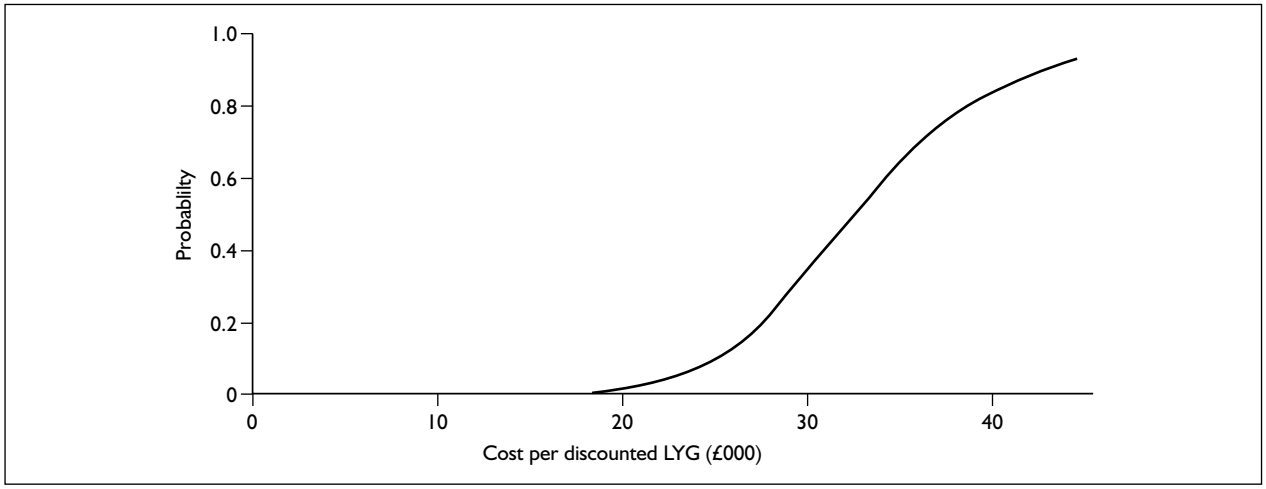

FIGURE 2 *Cost-effectiveness acceptability curve from the evidence review group probabilistic sensitivity analyses. LYG, life-years gained.*

validity. However, the lack of standardisation in the clinical management of relapsed myeloma suggests that the impact of this on the generalisability of the economic model in terms of patient group and comparator may be minimal.

The manufacturer's approach taken to model disease progression and cost-effectiveness in this patient group seemed reasonable. However, the manufacturer's submission did not originally present quality of life issues in the economic model, although an additional analysis on cost per QALY was subsequently submitted.

The ERG considered that the economic model in the manufacturer's submission may overestimate the treatment effect from the trial for a UK setting (*Figure 1*). Furthermore, sensitivity analyses undertaken in the economic evaluation were considered to be limited. Using what the ERG considered to be appropriate ranges for the one-way sensitivity analysis (*Table 1*), the most influential variables were the time to (disease) progression (TTP) hazard ratio and the cost of bortezomib. A sensitivity analysis was run in which each of the hazard ratios [TTP and overall survival (OS)] were varied in the same direction at the same time (low and high scenarios) and the cost-effectiveness ratios ranged from £23,287 to £46,814. A sensitivity analysis in which the cost of bortezomib was varied by ±50% gave a cost-effectiveness ratio ranging from £18,311 to £43,850.

The ERG also ran an additional scenario analysis, which was a combination of the three scenarios run in the original submission (limiting the number of cycles of treatment from eight to three; assuming 40% of patients were treated at first relapse, with the remaining 60% at second relapse and beyond; and using a combination of bortezomib and HDD as treatment). The results of the ERG scenario are summarised in *Table 2*.

The ERG probabilistic sensitivity analysis used the 95% confidence intervals for the hazard ratios and has estimated a range of ±25% for the costs. A cost of £470 has been used for the 'other care costs'. The baseline scenario is shown in *Figure 2* with more appropriate ranges for the probabilistic sensitivity analysis. The results of the probabilistic sensitivity analysis show that the fifth percentile is £22,693 and the 95th percentile is £46,751 (cost per life-year gained). A probabilistic sensitivity analysis in which the cost of bortezomib varies by ±50% had a fifth percentile of £20,364 and 95th percentile of £49,876.

The ERG identified that adverse events had not been included in the manufacturer's model, either in terms of loss of quality of life or increased resource use.

TABLE 1 *Amended one-way sensitivity analyses*

		Inputs		Cost-effectiveness ratios		
Variable	**Base case**	**Left**	**Right**	**Left**	**Right**	**Range**
Hazard ratio – TTP	0.56	0.44	0.69	£25,339	£39,141	£13,802
Cost of bortezomib per course	£21,035	£15,776	£26,294	£24,365	£37,136	£12,770
Duration of treatment effect (years)	3	4	2	£27,957	£36,747	£8790
Cost of other care – bortezomib preprogression	£470	£352	£588	£28,266	£33,892	£5627
Hazard ratio – OS (year 1)	0.42	0.30	0.60	£29,317	£33,175	£3858
Cost of other care – pre- and postprogression	£470	£352	£588	£29,682	£32,476	£2795
Cost of HDD per course	£82	£103	£62	£30,725	£30,774	£50

HDD, high-dose dexamethasone; OS, overall survival; TTP, time to progression.

TABLE 2 *Cost-effectiveness results for additional scenario analysis*

Patient group	Cost per life-year gained
All patients treated at first relapse	£27,334
80% of patients treated at first, 20% at second relapse	£30,219
60% of patients treated at first, 30% at second, 10% at third relapse	£35,783
40% of patients treated at first, 40% at second, 20% at third relapse	£44,602

Note: Intervention is bortezomib plus high-dose dexamethasone (HDD) vs HDD alone; the number of cycles of treatment is limited in non-responding patients; mix of patients by stage of treatment.

Conclusions

The ERG suggests that the cost-effectiveness results presented in the manufacturer's submission may underestimate the cost per life-year gained for bortezomib therapy (versus HDD) when potential UK practice and scenarios are considered.

There is no standard treatment for relapsed multiple myeloma patients, which makes assessing the effectiveness and cost-effectiveness of new treatments problematic in terms of the individuality of treatment protocols and which comparators to use. It would be useful for future trials to reflect current practice but this may be difficult as it is a quickly developing area in which clinicians are eager to have new treatments options for patients who do not easily fit into stereotypical groups.

Summary of NICE guidance issued as a result of the STA

The following guidance was issued by NICE in October 2007:

> 1.1 Bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances:
> – the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) **and**
> – the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response (as defined above).
>
> 1.2 People currently receiving bortezomib monotherapy who do not meet the criteria in paragraph 1.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

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Fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of fludarabine phosphate or fludarabine plus cyclophosphamide for the first-line treatment of chronic lymphocytic leukaemia, based upon the evidence submission from Schering Health Care (SHC) to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submission was of good quality with no major errors or omissions in the clinical evidence. Two published studies and seven abstracts were included in the company submission, which showed improvements in overall response and progression-free survival (PFS) and a higher complete response rate in the fludarabine-containing arms; however, until the complete data are made available for evaluation these results must be interpreted with caution. The manufacturer's decision-analytic Markov model to estimate the cost-effectiveness of treatment with fludarabine monotherapy, fludarabine plus cyclophosphamide and chlorambucil was considered to be the most relevant source for informing this STA; it was appropriate for the decision problem and the data sources used to inform the model were appropriate from a UK NHS perspective. The incremental cost-effectiveness ratio of fludarabine plus cyclophosphamide compared with chlorambucil from the revised model presented in the manufacturer's addendum was £3244 per additional quality-adjusted life-year. The results were robust to a range of subgroup

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and sensitivity analyses. Additional sensitivity and survival analyses were carried by the ERG to investigate possible bias in the results. This brought into question the validity of the assumptions underpinning the extrapolation of data over a lifetime time horizon and showed *t*hat the ICER estimates submitted by the manufacturer were not calculated correctly and uncertainty surrounding the decision problems was not expressed fully. Based on these analyses the ERG suggests that further evidence is needed to enable an accurate assessment to be made of the clinical and cost-effectiveness of fludarabine as first-line treatment for chronic lymphocytic leukaemia. The guidance issued by NICE in December 2006 as a result of the STA states that fludarabine monotherapy, within its licensed indication, is not recommended for the first-line treatment of chronic lymphocytic leukaemia; no recommendations have been made with respect to fludarabine plus cyclophosphamide combination therapy because the current marketing authorisation does not specifically provide a recommendation that fludarabine should be used concurrently with other drugs for the treatment of chronic lymphocytic leukaemia.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia.[2]

Description of the underlying health problem

Chronic lymphocytic leukaemia (CLL) is defined as a slow progressive form of leukaemia characterised by an increased number of lymphocytes,[3] mostly of small or medium size, with clumped nuclear material (chromatin), an indistinct or absent nucleoli and little cytoplasm.[4] The other type of lymphocyte commonly observed in approximately 15% of patients is a prolymphocyte, which appears large with a prominent nucleolus.[4,5] The general symptoms of CLL are tiredness, night sweats, weight loss, anaemia and associated symptoms, and increased susceptibility to infection.[4] The lymphocytes may also accumulate in the lymph nodes and spleen resulting in lymphadenopathy, splenomegaly and other abdominal masses.[4,5] Frequently the condition is identified by chance during a routine blood test in the absence of specific symptoms or physical signs. At the point of diagnosis CLL is usually widespread and with some degree of bone marrow involvement. With the exception of blood and marrow transplantation, the condition is inherently incurable with treatment emphasis on maintaining an acceptable state of health and inducing remission when required.[5]

B-cell CLL is reported to be the most common leukaemia, representing approximately 25% of all cases of leukaemia.[6] In England and Wales in 2003 there were 6198 cases of leukaemia;[7,8] assuming that 25% of these are B-cell CLL means that there were approximately 1550 new cases of B-cell CLL diagnosed in 2003. This indicates a crude incidence in this population of approximately 3 per 100,000 population per year;[7–9] however, this belies the demographics of its incidence. CLL is rare below the age of 30 years with 20–30% of patients presenting under the age of 55 years.[4] The peak incidence is between 60 and 80 years, with the incidence increasing up to almost 50 per 100,000 population per year after the age of 70 years.[6] It is male dominant, occurring with a male–female ratio of 2:1.[4,10]

Scope of the ERG report

The report critically evaluates the evidence submission from Schering Health Care (SHC) on the clinical and cost-effectiveness of fludarabine phosphate (Fludara®) or fludarabine plus cyclophosphamide for the first-line treatment of chronic lymphocytic leukaemia.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The ERG undertook additional work to examine the potential robustness of the base-case results to several of the assumptions made in the manufacturer's model and also to identify possible sources of bias. This work was performed on the revised model presented in the manufacturer's addendum and was separated into three main areas: (1) additional one-way sensitivity analyses to examine the robustness of the base-case incremental cost-effectiveness ratio (ICER) to alternative assumptions related to the response rate for retreatment and the duration of this response; (2) a more appropriate presentation of the probabilistic sensitivity analysis results from the submission; and (3) formal survival analysis of the individual patient data from the CLL4 trial to explore the appropriateness of assuming constant transition probabilities to extrapolate over a lifetime time horizon. These were selective analyses and the revised economic analyses were undertaken to examine the robustness of the manufacturer's own model to alternative assumptions. These analyses were thus subject to potential limitations regarding the structural assumptions, the general approach used to estimate transition probabilities and issues related to the modelling of second-line treatments. The results should, therefore, be taken as indicative of the potential impact on the cost-effectiveness estimates.

Results

Summary of submitted clinical evidence

Two published studies[11,12] and seven abstracts were included in the company submission. Fludarabine or fludarabine plus cyclophosphamide were compared with chlorambucil (Chl) in five studies[12–16] and two studies[11,17] compared fludarabine with fludarabine plus cyclophosphamide. Only one study compared all three regimens.[13,18]

All studies, with one exception,[16] showed an improvement in overall response (OR) in those patients receiving fludarabine compared with those receiving Chl.[11–15,17] In all but one[15] of the studies comparing fludarabine or fludarabine plus cyclophosphamide with Chl there was a higher complete response (CR) rate for the fludarabine-containing arms.[12–14,16] Although progression-free survival (PFS) was stated as a primary outcome measure in five studies,[11–14,17] this outcome was fully reported in only three.[11,12,17] In one study comparing differences in median PFS between the fludarabine and Chl regimens there was a significantly longer duration of response in the fludarabine arm.[12] Two studies demonstrated a significantly longer duration of response with the fludarabine plus cyclophosphamide combination compared with fludarabine alone.[11,17] At present, the follow-up periods of the studies included in the submission are too short to demonstrate any significant improvement in overall survival (OS). Therefore, fully matured survival data are necessary to ascertain whether any improvement in PFS translates into an increase in OS. Three studies included quality of life (QoL) analyses; however, only limited data from the CLL4 study are presented.[18] In this study QoL was the same for each treatment group at baseline and at 12 months and correlated with the quality of response. It is anticipated that the results of further QoL analyses are likely to become available within the next year. Because five of the studies included in the submission are not fully published and report only preliminary results in abstract form there are insufficient data presented to fully assess the validity of these studies.[13–16] Although the unpublished CLL4 study[13] is supplemented with additional patient-level data[18] provided by the manufacturer to support the health economic analyses, these supplemental data are not in the public domain and therefore cannot be verified externally. Until these studies are fully published and the complete data made available for evaluation, these results must be interpreted with caution.

Summary of submitted cost-effectiveness evidence

Two papers were identified in both the manufacturer's submission and the ERG searches that reported on the cost-effectiveness of fludarabine monotherapy compared with Chl in the management of CLL in previously untreated patients.[19,20] Neither of the studies was considered particularly relevant because of the limited clinical and economic evidence on which the studies were based (mainly because of the limited evidence available at the time that these studies were undertaken) and the restricted range of comparators considered. Neither of these studies considered the cost-effectiveness of fludarabine

combined with cyclophosphamide as a first-line treatment for CLL. Consequently, the submission by the manufacturer was considered to comprise the most relevant evidence for the purposes of this STA.

The manufacturer's submission included a de novo decision-analytic Markov model to estimate the cost-effectiveness of treatment with (1) fludarabine monotherapy, (2) fludarabine in combination with cyclophosphamide and (3) Chl. The model used individual patient data from the CLL4 trial to model transition probabilities related to first-line treatment with these therapies. The costs of first-line treatment were derived from an audit of UK patients from the CLL4 trial. The model was based on a lifetime time horizon and included the costs and consequences of further treatments required after first-line treatment had failed. Data on the costs and effects of further treatment (including retreatment and second-line and salvage therapies) were derived from a combination of secondary sources and assumptions by the manufacturer. Results were presented in terms of the incremental cost per quality-adjusted life-year (QALY) gained, with QoL estimates informed by a separate systematic review. In the original submission by the manufacturer, the incremental cost-effectiveness (ICER) of fludarabine in combination with cyclophosphamide compared with Chl was £2602 per additional QALY. Fludarabine in combination with cyclophosphamide was reported to dominate fludarabine (i.e. was less costly and more effective). These results were based on an approach which assumed that median (as opposed to mean) survival was equal in all treatments. An addendum was submitted by the manufacturer, which presented similar results based on an approach that equalised mean survival. This latter approach was considered by the ERG to be a more appropriate assumption. The results presented in the addendum increased the ICER of fludarabine in combination with cyclophosphamide compared with Chl to £3244 per additional QALY. Fludarabine plus cyclophosphamide continued to dominate fludarabine. The results of the subgroup analysis presented by age and Binet stage did not substantially alter these results. Similarly, the results were reported to be robust to a wide range of sensitivity analyses undertaken by the manufacturer. The results were most sensitive to the time horizon of the model, such that fludarabine plus cyclophosphamide did not appear cost-effective at a time horizon of 5 years.

Commentary on the robustness of submitted evidence

Strengths

The ERG felt that the SHC submission was generally of good quality. There were no major errors or omissions in the clinical evidence. The majority of the data quoted within the submission was a fair and accurate representation of the original reference data. The ERG noted the limitations of existing cost-effectiveness studies in this area and considered the economic model submitted by the manufacturer to be the most relevant source for the purpose of informing this STA. The economic model structure (including the comparators) was considered appropriate for the decision problem, and the data sources used to inform the model were deemed appropriate from a UK NHS perspective. A range of subgroups was considered and uncertainty in parameter estimates was addressed using probabilistic approaches.

Weaknesses

The majority of the reference data presented in the submission was not fully published and was only available in abstract form. Therefore, the ERG felt that, until these studies are fully published and the complete data made available for evaluation, these results must be interpreted with caution. The ERG identified a number of potential sources of weakness in the manufacturer's economic submission. In particular, a number of issues were identified that may have introduced possible bias into the results. Most of these issues appeared to act in favour of the fludarabine plus cyclophosphamide regimen such that it is likely that the manufacturer's results are overly optimistic towards this regimen. The robustness of the manufacturer's results to some of these issues was explored in additional work undertaken by the ERG. The cost-effectiveness of fludarabine in combination with cyclophosphamide appeared relatively robust to wide variation in several of the key assumptions made by the manufacturer. The ERG was concerned with the approach that the manufacturer used to estimate a number of key probabilities derived from the CLL4 trial data. Because of the structure of the model it was not possible to fully explore the potential robustness of the manufacturer's results to alternative assumptions. However, work undertaken by the ERG brought into question the validity of the assumptions underpinning the extrapolation of data over a lifetime time horizon. In addition, the ERG noted that the ICER estimates submitted by the manufacturer were not calculated correctly and

uncertainty surrounding the decision problems was not expressed fully. The revised ICER results are presented in *Table 1*, with the associated cost-effectiveness acceptability curves given in *Figure 1*.

Areas of uncertainty

The fludarabine summary of product characteristics (SPC) does not mention the use of fludarabine in combination with other chemotherapeutic agents. The dose for oral therapy in combination with cyclophosphamide does not appear to be a licensed dose and is not mentioned in the SPC. The SPC for cyclophosphamide states that it is frequently used in combination chemotherapy regimens involving other cytotoxic drugs and that it is recommended that the calculated dose be reduced at the discretion of the clinician when it is given in combination with other antineoplastic agents or radiotherapy and in patients with bone marrow suppression. However, the ERG feels that the efficacy of the fludarabine plus cyclophosphamide regimen is still under investigation and that the recommendations outlined in the British Committee for Standards in Haematology (BCSH) guidelines are expected to be revised following the outcomes of the CLL4 study. Therefore, the ERG sought clarification on this matter from the manufacturer. The manufacturer believes that the proposed regimen falls within the current licenses and states that they are not, therefore, considering an extension to the fludarabine license. The dosing 11 regimen for the fludarabine plus cyclophosphamide combination was agreed by expert clinicians within the MRC/LRF UK-CLL group. However, independent expert advice given to the ERG confirms that the fludarabine plus cyclophosphamide regimen is increasingly used for the first-line treatment of CLL and that the dosing regimen chosen also reflects current practice.

Conclusions

To enable an accurate assessment to be made of the clinical and cost-effectiveness of fludarabine as first-line treatment for chronic lymphocytic leukaemia there is a need for further evidence to clarify areas of uncertainty.

TABLE 1 *Probabilistic sensitivity analysis results*

Comparator	Mean costs	Mean QALYs	ICER (compared with Chl)	Probability cost-effective at willingness to pay		
				£20,000	£30,000	£40,000
Chl	£11,836	5.48	–	0.047	0.032	0.028
F	£17,840	5.70	Dominated by FC	0.04	0.067	0.09
FC	£13,291	6.13	£3213	0.913	0.901	0.882

Chl, chlorambucil; F, fludarabine; FC, fludarabine with cyclophosphamide; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

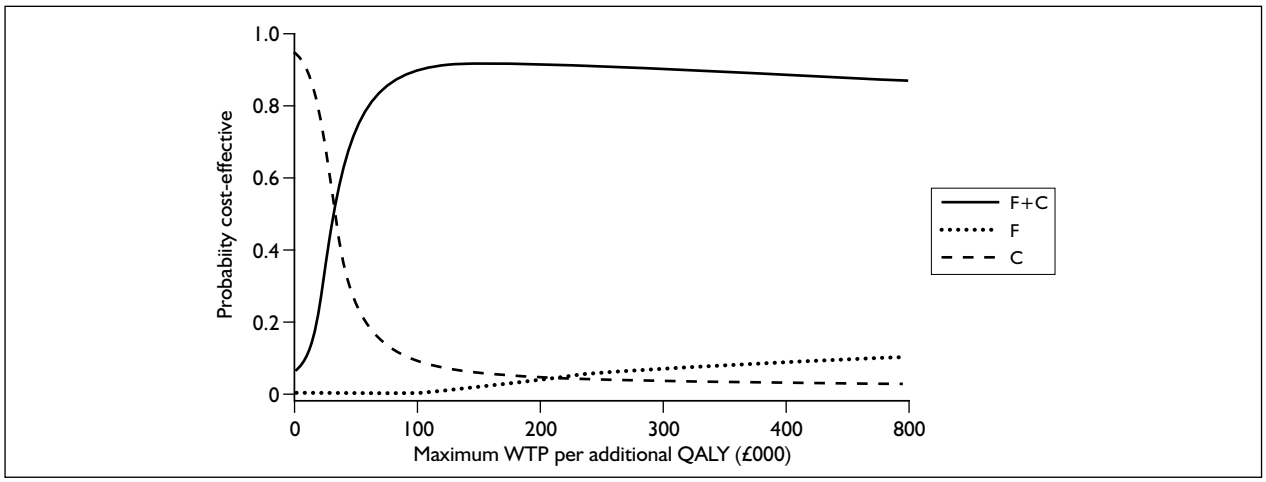

FIGURE 1 *Cost-effectiveness acceptability curves – revised by the ERG. QALY, quality-adjusted life-year; WTP, willingness to pay.*

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in December 2006 states that:

Fludarabine monotherapy, within its licensed indication, is not recommended for the first-line treatment of chronic lymphocytic leukaemia. No recommendations have been made with respect to fludarabine plus cyclophosphamide combination therapy because the current marketing authorisation does not specifically provide a recommendation that fludarabine should be used concurrently with other drugs for the treatment of chronic lymphocytic leukaemia.

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Erlotinib for the treatment of relapsed non-small cell lung cancer

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of erlotinib for the treatment of relapsed non-small cell lung cancer (NSCLC), according to its licensed indication, based upon the evidence submission from Roche Products to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submitted clinical evidence includes one randomised controlled trial (RCT) (BR21) investigating the effect of erlotinib versus placebo, which demonstrates that erlotinib significantly increases median overall survival, progression-free survival and response rate compared with placebo. The majority of patients in the trial experienced non-haematological drug-related adverse effects. Currently there are no trials that directly compare erlotinib with any other second-line chemotherapy agent. For the purposes of indirect comparison, the manufacturer's submission provides a narrative discussion of data from 11 RCTs investigating the use of docetaxel. From these data the manufacturer concludes that erlotinib has similar clinical efficacy levels to docetaxel but results in fewer serious haematological adverse events; however, it is difficult to compare the results of BR21 with those of the docetaxel trials or with current UK clinical practice because, for example, the BR21 patient population is younger than that expected to present in UK clinical practice and almost half of the BR21 participants received erlotinib as third-

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line chemotherapy, with third-line chemotherapy being rare in the UK. The manufacturer's submission included a three-state model comparing erlotinib with docetaxel, reporting an incremental cost-effectiveness ratio (ICER) of –£1764 per quality-adjusted life-year (QALY) gained for erlotinib compared with docetaxel. Rerunning the manufacturer's economic model with varied parameters and assumptions increases the ICER to in excess of £52,000 per QALY gained. There is still a large amount of unquantifiable uncertainty in the model and it is unlikely that erlotinib could be considered to be cost-effective compared with docetaxel at a willingness to pay of £30,000 and there may even be the potential for docetaxel to dominate erlotinib. Because of the limitations of the indirect analysis undertaken by the manufacturer and the subsequent economic modelling exercise there is a need for a head-to-head trial comparing erlotinib with docetaxel. The guidance issued by NICE in February 2007 as a result of the STA states that erlotinib is not recommended for the treatment of locally advanced or metastatic NSCLC.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of erlotinib for the treatment of relapsed non-small cell lung cancer (NSCLC).[2]

Description of the underlying health problem

Lung cancer is the most common cause of cancer-related death in men and the second most common cause of cancer-related death after breast cancer in women.[3] In 2002, 37,700 patients were newly diagnosed with lung cancer in the UK, accounting for one in seven new cancer cases, with an incidence of about 62–65 per 100,000 population; the incidence of NSCLC is approximately 52 per 100,000 population.[4] Lung cancer is rarely diagnosed in people under 40 years of age, but the incidence rises steeply with age thereafter, peaking in people aged 75–84 years.[4] The male–female ratio for lung cancer cases is 3:2.[4] There is a strong association between incidence and mortality rates and levels of deprivation.[4]

Scope of the ERG report

The ERG report presents the results of the assessment of the manufacturer's (Roche Products) evidence submission regarding the use of erlotinib for the second-line treatment of patients with locally advanced or metastatic (stage III/IV) NSCLC. The report includes an assessment of both the clinical and cost-effectiveness evidence submitted by the manufacturer. Erlotinib (Tarceva®) is an orally active inhibitor of epidermal growth factor receptor/human epidermal growth factor receptor 1 (EGFR/HER1) tyrosine kinase inhibitor. In 2004, pemetrexed (Alimta®; Lilly) received a licence for use 'as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy'. The licensing submission for pemetrexed was supported by a phase III study comparing pemetrexed and docetaxel.[5] In 2005, erlotinib was licensed 'for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen'. The licensing submission for erlotinib was supported by a phase III study comparing erlotinib with placebo.[6]

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE

as part of the STA process. The ERG assessed the quality of the clinical effectiveness review using a checklist and conducted a literature search. The group fitted exponential curves to the manufacturer's Kaplan–Meier plots to calculate overall survival (OS) and also reran the manufacturer's economic model after correcting for an inherent error and altered some of the assumptions and parameter values to recalculate the cost–utility ratios, quality-adjusted life-years (QALYs) and estimates of benefits.

Results

Summary of submitted clinical evidence

The submitted clinical evidence includes one randomised, placebo-controlled, double-blind trial (BR21)[6] that investigates the effect of erlotinib within its licensed indication (treatment of relapsed NSCLC) versus placebo. The BR21 trial demonstrates that erlotinib significantly increases median OS by 42.5% compared with placebo (6.7 months versus 4.7 months respectively; $p < 0.001$, hazard ratio 0.70). Progression-free survival (PFS) is significantly longer in the erlotinib arm compared with the placebo arm (2.2 months versus 1.8 months respectively; $p < 0.001$, hazard ratio 0.61) and the overall response rate is significantly higher (8.9% versus 0.9%; $p < 0.001$).

The majority of patients in the BR21 trial experienced non-haematological drug-related adverse effects (AEs). The most commonly reported AEs attributed to erlotinib were rash (76%) and diarrhoea (55%), leading to a dose reduction in 12% and 5% of patients respectively. Currently there are no trials that directly compare erlotinib with any other second-line chemotherapy agent. For the purposes of indirect comparison, the manufacturer's submission provides a narrative discussion of data from 11 randomised controlled trials (RCTs) investigating the use of docetaxel at a dose of 75 mg/m^2. The manufacturer extracted detailed data from two of the 11 trials involving docetaxel: docetaxel versus best supportive care (TAX317)[7] and docetaxel versus pemetrexed (JMEI)[5]. In these trials docetaxel showed similar efficacy levels to those of erlotinib as reported in the BR21 trial. Median OS was 7.5 months (docetaxel, TAX317), 7.9 months (docetaxel, JMEI) and 6.7 months (erlotinib, BR21). Median PFS was reported as 2.9 months (docetaxel, JMEI) and 2.2 months (erlotinib, BR21) and overall response rates were reported as 8.9% (docetaxel, JMEI) and 8.8% (erlotinib, BR21). Analyses of TAX317 and JMEI in relation to the BR21 study demonstrated the lower rates of haematological toxicities experienced by patients receiving erlotinib compared with those receiving docetaxel, particularly incidences of febrile neutropenia. The manufacturer's submission therefore concludes that erlotinib has similar clinical efficacy levels to docetaxel but results in fewer serious haematological adverse events. When interpreting the results of BR21 a number of issues relating to the patient population must be considered. For example, the BR21 patient population is younger than that expected to present in UK clinical practice. Almost half of the trial participants received erlotinib as third-line chemotherapy, with third-line chemotherapy being rare in the UK. Furthermore, a large number of participants in the BR21 trial had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2–3; typically patients receiving chemotherapy in UK clinical practice have a PS of 0–1. For these reasons it is difficult to compare the results of BR21 with those of TAX317 and JMEI or with current UK clinical practice.

Summary of submitted cost-effectiveness evidence

The economic model submitted in support of the manufacturer's submission is a basic three-state model comparing erlotinib with docetaxel, furnished with clinical data from the TAX317 and BR21 trials. The manufacturer reports an incremental cost-effectiveness ratio (ICER) of –£2941 per QALY for erlotinib compared with docetaxel, with a 68% probability that erlotinib is cost-effective at a willingness to pay (WTP) of £30,000 per QALY gained. After adjustment for the double counting of half-cycle correction, the manufacturer's model yields a corrected ICER of –£1764. However, a number of key assumptions and parameters in the model do not seem to be clinically and/or economically justified, particularly in terms of costs. For example, the manufacturer underestimates the acquisition cost of erlotinib and overestimates the acquisition cost of docetaxel. Once these assumptions are adjusted to reflect more realistic estimates, the ICER increases to £52,098 per QALY as shown in *Table 1*, with a 44% probability that erlotinib is cost effective at a WTP of £30,000. A modified cost-acceptability curve using manufacturer probabilistic sensitivity analysis (PSA) results adjusted for average incremental cost and outcome alterations and a modified cost-effectiveness uncertainty scatter plot using manufacturer PSA results adjusted for average incremental cost and outcome alterations are shown in *Figures 1* and *2* respectively.

TABLE 1 *Cost-effectiveness summary table updated for identified corrections and amendments to the manufacturer's model*

	Erlotinib	Docetaxel	Increment
Costs per patient			
Drug acquisition	£7164	£5022	£2142
Drug administration and monitoring	£473	£839	–£365
Adverse event treatment	£113	£374	–£261
Other preprogression care	£1034	£859	£175
Postprogression care	£4699	£5444	–£745
Total cost	£13,482	£12,536	£946
Outcomes per patient			
Overall mean survival (months)	9.03	9.03	0.00
PFS (months)	4.11	3.33	0.78
PPS (months)	4.92	5.70	–0.78
PFS QALYs	0.1591	0.1139	0.0452
PPS QALYs	0.0953	0.1224	–0.0271
Total QALYs	0.2544	0.2362	0.0182
Incremental cost per QALY			£52,098

PFS, progression-free survival; PPS, post-progression survival; QALY(s), quality-adjusted life-year(s).

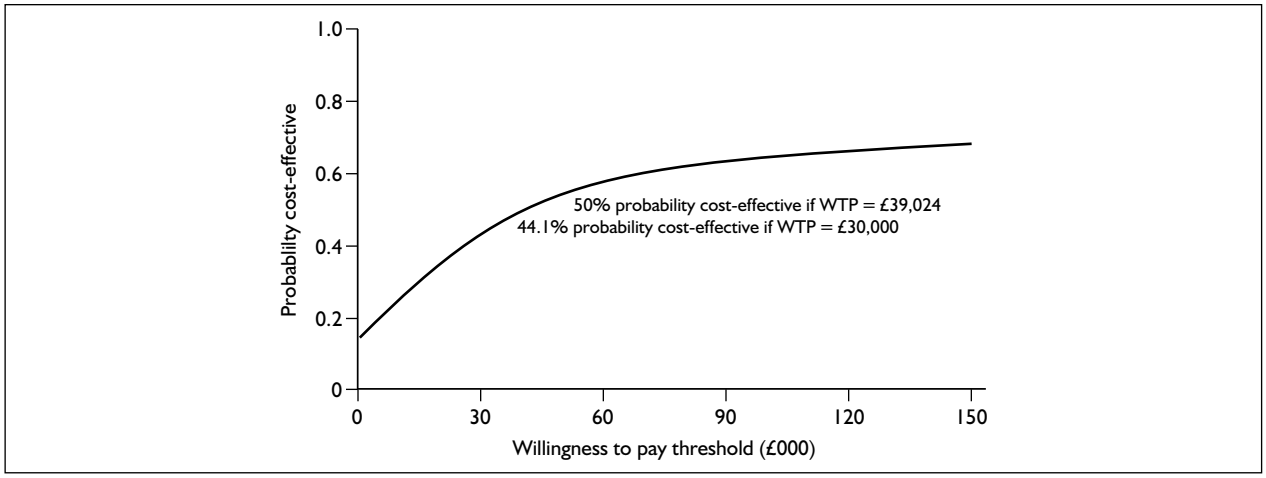

FIGURE 1 *Modified cost-effectiveness curve using manufacturer probabilistic sensitivity analyses results adjusted for average incremental cost and outcome alterations. WTP, willingness to pay.*

In terms of health outcomes a further issue is the use of visual analogue scale (VAS) scores from the Oxford Outcomes study; the scores were not adjusted to zero for death and conflict with the tariff values calculated using responses from the same sample of healthy volunteers. As presented in *Table 2*, reanalysis of the model rescaling the VAS PFS utility scores to ensure that death has zero utility further increased the ICER (£68,673 per QALY gained). Similarly, reanalysis using tariff PFS utility values led to an ICER slightly above the WTP threshold of £30,000 (£31,261 per QALY gained). Joint exploration of uncertainty in the cost of docetaxel and the degree of variation in dosing introduced by clinical judgement yields a range of ICER estimates between £41,943 and £70,418 per QALY gained.

There is also a large amount of unquantifiable uncertainty in the model relating to AEs, postprogression survival and PFS health state costs, and the length of PFS. These areas of ambiguity

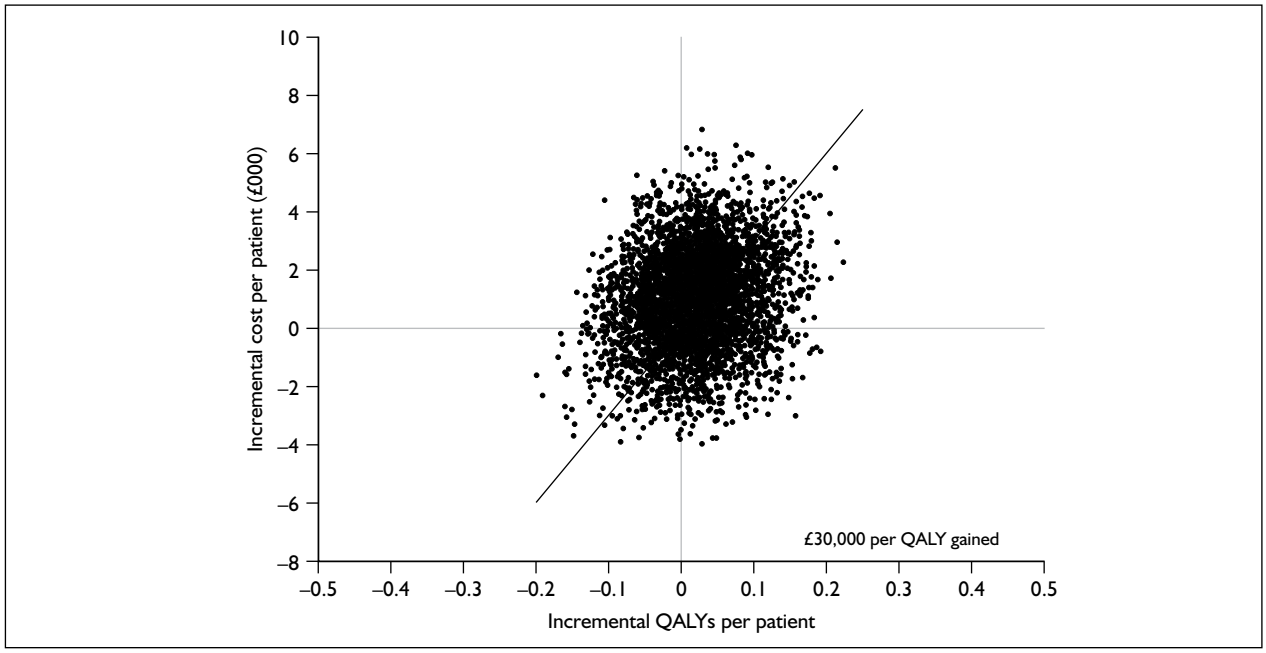

FIGURE 2 *Modified cost-effectiveness uncertainty scatter plot using manufacturer probabilistic sensitivity analyses results adjusted for average incremental cost and outcome alterations. QALY(s), quality-adjusted life-year(s).*

TABLE 2 *Sensitivity analyses – alternative methods to estimate utility in preprogression period*

	Erlotinib	Docetaxel	Increment
Using rescaled VAS values in PFS			
PFS QALYs (rescaled VAS)	0.1292	0.0883	0.0409
PPS QALYs (the ERG estimate)	0.0953	0.1224	–0.0271
Total QALYs	0.2245	0.2107	0.0138
Incremental cost per QALY			£68,673
Using tariff values in PFS			
PFS QALYs (tariff)	0.1337	0.0763	0.0573
PPS QALYs (the ERG estimate)	0.0953	0.1224	–0.0271
Total QALYs	0.2289	0.1987	0.0303
Incremental cost per QALY			£31,261

ERG, evidence review group; PFS, progression-free survival; PPS, post-progression survival; QALY(s), quality-adjusted life-year(s); VAS, visual analogue scale.

could potentially further increase the ICER and may even result in docetaxel dominating erlotinib.

Commentary on the robustness of submitted evidence

A major limitation in the manufacturer's submission is the reliance on the BR21 trial (currently the only available erlotinib study) which compares erlotinib with placebo, rather than an accepted chemotherapy regimen. As a consequence, the manufacturer's submission is forced to compare erlotinib and docetaxel indirectly; such comparisons have inherent difficulties and are subject to biases.

Further to this, there are a number of differences between the patient population in the BR21 trial and the TAX317 study, of which the most important are the number of prior chemotherapy regimens and the performance status of patients.

TABLE 3 *Main elements of monthly postprogression costs per patient*

Component	Cost per month	Proportion
Hospital episodes	£547.97	55.4%
Health professionals	£331.54	33.5%
Medications	£39.46	4.0%
Tests	£69.83	7.1%
Total	£988.80	100.0%

In addition, the best supportive care component of treatment may not be comparable between the trials, which could potentially inflate a treatment response in one of the trials unjustifiably. This confounding issue was not discussed in the manufacturer's submission, but should have been considered when the indirect comparison was undertaken.

A number of unquantifiable areas of uncertainty were found and relate to AEs, pre- and post-progression health state costs and progression-free survival. There is a note in the manufacturer's table of event probabilities for AEs, which seems to imply that the model does not allow patients to suffer multiple adverse events. If this is so it is a severe and unrealistic constraint, as individual patients frequently suffer multiple events either concurrently (e.g. rash with diarrhoea) or serially. In addition, the resources assumed to be incurred each month for patients before and after disease progression were exclusively determined by five clinical experts without use of any observational data. The main elements contributing to the increase in such costs postprogression are shown in *Table 3*. Clearly hospital episodes constitute the dominant component in these estimates. It seems disappointing that no attempt has been made to sample routine hospital records and statistics to validate the expert opinion in this respect. The ERG raised issues about the validity of the claims of equivalence in overall survival and of improved PFS with erlotinib. These are of profound importance to the economic evaluation of erlotinib as if either of these assertions proves to be untenable then most of the modest outcome gains claimed for erlotinib will disappear, other than the very small short-term quality of life benefits associated with oral administration and reduced AEs. In the context of important increases in drug acquisition costs this would mean that erlotinib could not be considered cost-effective and might in fact be dominated by docetaxel (more expensive and less effective).

Conclusions

The manufacturer's submission presents a case for the replacement of docetaxel by erlotinib as second-line chemotherapy for NSCLC patients with advanced or metastatic disease. However, there is a proportion of NSCLC patients whose poor health status precludes them from receiving docetaxel; for these patients best supportive care is currently the only treatment option available. It may be argued that some of these patients could be considered for erlotinib instead of docetaxel as it is a less demanding oral regimen.

The ERG attempted to rectify several of the limitations in the clinical and cost-effectiveness evidence submitted, generating much higher incremental cost-effectiveness ratios than those generated in the manufacturer's submission (in excess of £52,000). This extreme sensitivity is due to the very small value of incremental benefit, which renders the ICER highly unstable to small changes. There is still a large amount of unquantifiable uncertainty, however at the current price it is unlikely that erlotinib could be considered to be cost effective compared with docetaxel at a WTP of £30,000. There may even be the potential for docetaxel to dominate erlotinib (i.e. be more effective yet less expensive). This means that adoption of erlotinib would need to be justified on grounds out with the factors included in the model (for example, patient preference for oral self-medication and service pressures to limit or reduce demand for hospital administered chemotherapy).

Given the limitations of the indirect analysis undertaken by the manufacturer and the subsequent economic modelling exercise there is a need for a head-to-head trial comparing erlotinib with docetaxel.

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in February 2007 states that:

> 1.1 Erlotinib is recommended, within its licensed indication, as an alternative to docetaxel as a second-line treatment option for patients with non-small-cell lung cancer (NSCLC) only on the basis that it is provided by the manufacturer at an overall treatment cost (including administration, adverse events and monitoring costs) equal to that of docetaxel.
> 1.2 The decision to use erlotinib or docetaxel (as outlined in section 1.1) should be made after a discussion between the responsible clinician and the individual about the potential benefits and adverse effects of each treatment.
> 1.3 Erlotinib is not recommended for the second-line treatment of locally advanced or metastatic NSCLC in patients for whom docetaxel is unsuitable (that is, where there is intolerance of or contraindications to docetaxel) or for third-line treatment after docetaxel therapy.
> 1.4 People currently receiving treatment with erlotinib, but for whom treatment would not be recommended according to section 1.3, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

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Cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck

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Declared competing interests of authors: none

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) considered inappropriate for chemoradiotherapy but appropriate for radiotherapy, based upon the evidence submission from Merck Pharmaceuticals to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The manufacturer's submission was generally of good quality and was an accurate representation of the original reference data. One good-quality randomised controlled trial comparing radiotherapy plus cetuximab with radiotherapy alone in patients with stage III or IV non-metastatic LA SCCHN was included, demonstrating that the duration of locoregional control was significantly longer with radiotherapy plus cetuximab than with radiotherapy alone; also, overall and progression-free survival were significantly longer and the overall response rate was significantly better with the combination therapy. Cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck. No supporting evidence for these findings are available. The patient population in the trial included a high proportion of patients who would be expected to be suitable for chemoradiotherapy and therefore does not

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match the population described in the submission's decision problem. Also, the radiotherapy regimens used in the trial are not typical of current UK practice. The ERG considered the manufacturer's economic evaluation to comprise the only relevant evidence to consider for the purposes of this STA. The economic model was considered appropriate for the decision problem. The results suggested that cetuximab plus radiotherapy was cost-effective compared with radiotherapy alone under a broad range of different assumptions on the basis of a cost-effectiveness threshold of £20,000. In the base case the incremental cost-effectiveness ratio of cetuximab plus radiotherapy compared with radiotherapy alone in the treatment of patients with LA SCCHN was £6390 per additional QALY. Simple sensitivity analyses to examine the robustness of the results were undertaken, suggesting that areas of uncertainty that emerged in the modelling are unlikely to have a material effect on the conclusions. The guidance issued by NICE in May 2007 as a result of the STA states that cetuximab in combination with radiotherapy is not recommended for patients with LA SCCHN.

Introduction

The National Institute of Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck (LA SCCHN).[2]

Description of the underlying health problem

Head and neck cancer is a broad term for any cancer from the base of the neck upwards,[3] excluding tumours of the brain and related tissues and malignant melanomas.[4,5] The most common histological type of head and neck cancer is a squamous cell carcinoma, particularly affecting the oral cavity and larynx, although patients may present with more than one primary cancer.[3,5,6] In 2003 there were over 5000 new cases of cancer of the oral cavity, oropharynx, hypopharynx and larynx in England. Male prevalence dominates (70%), possibly because of lifestyle factors (smoking, drinking), as does increasing age (median 60–64 years). Only 1965 of the above new cases related specifically to cancer of the oropharynx, hypopharynx and larynx.[7] A recent audit of head and neck cancer treatment, specifically that of the oral cavity and larynx, indicated that 51% of all patients present with early-stage disease, although these figures may be skewed by the fact that laryngeal cancer is often detected early because of patients presenting with voice alteration.[5]

Prognosis is dependent on many factors, not least the origin of the cancer and stage at diagnosis.[3] There is considerable variation in the severity of the cancer at diagnosis or presentation. Laryngeal cancers have higher 5-year survival rates than oral cancers because an obvious symptom of the cancer is voice alteration, which often prompts patients to consult a doctor earlier than do patients with oral cancers, which may only manifest as painless ulcers. Ultimately, patients with cancer diagnosed and treated at an earlier stage have a much better prognosis.[3] Treatment usually consists of a combination of surgery and radiotherapy and may include chemotherapy.[3]

Scope of the ERG report

The ERG report critically evaluated the evidence submission from Merck Pharmaceuticals on the clinical and cost-effectiveness of cetuximab (Erbitux®) in combination with radiotherapy relative to radiotherapy alone in patients with LA SCCHN who are considered inappropriate for chemoradiotherapy but appropriate for radiotherapy.

Cetuximab in combination with radiotherapy is specifically licensed only for the treatment of LA SCCHN.[8]

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process. The report identified the strengths and weaknesses of the manufacturer's submission and presented additional work to address issues and uncertainties identified during the structured critique of the manufacturer's submission. Simple sensitivity analyses to examine the robustness of the results were undertaken by (1) examining what change in the average utility value for patients in the cetuximab plus radiotherapy arm would be required to increase the incremental cost per quality-adjusted life-year (QALY) gained of cetuximab plus radiotherapy to levels that may not be considered cost-effective; the base-case average utility in the two groups was identified (ignoring discounting) by dividing the estimated QALYs in each group by the estimated life-years (*Figure 1*); and (2) examining what change in total average costs for the cetuximab plus radiotherapy arm would be required, *ceteris paribus*, for cetuximab plus radiotherapy not to be considered cost-effective (*Figure 2*).

Results

Summary of submitted clinical evidence

One study was included in the submission.[9] This study was a fully published and well-designed and -conducted randomised controlled trial that compared radiotherapy plus cetuximab with radiotherapy alone in patients with stage III or IV non-metastatic squamous cell carcinoma of the oropharynx, hypopharynx or larynx. Efficacy was evaluated on an intention to treat basis and included all randomised patients. Safety was evaluated in all patients who received treatment. The trial demonstrated that the duration of locoregional control (the primary end point) was significantly longer with radiotherapy plus cetuximab than with radiotherapy alone. With respect to secondary end points both overall and progression-free survival were significantly longer and the overall response rate was significantly better with the combination therapy than with radiotherapy alone (*Table 1*). Cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck. Severe (grade 3–5) acneiform rash and infusion reaction occurred more frequently with radiotherapy plus cetuximab than with radiotherapy alone, whereas the converse applied to severe anaemia.

Summary of submitted cost-effectiveness evidence

No previous studies were identified by the manufacturer or by the ERG that would help inform this STA. Therefore, the manufacturer's economic evaluation is considered by the ERG to comprise the only relevant evidence to consider for the purposes of this STA.

The manufacturer's submission included a de novo economic evaluation to estimate the cost-effectiveness of treatment with (1) cetuximab plus radiotherapy and (2) radiotherapy alone. The economic model (including the comparator)

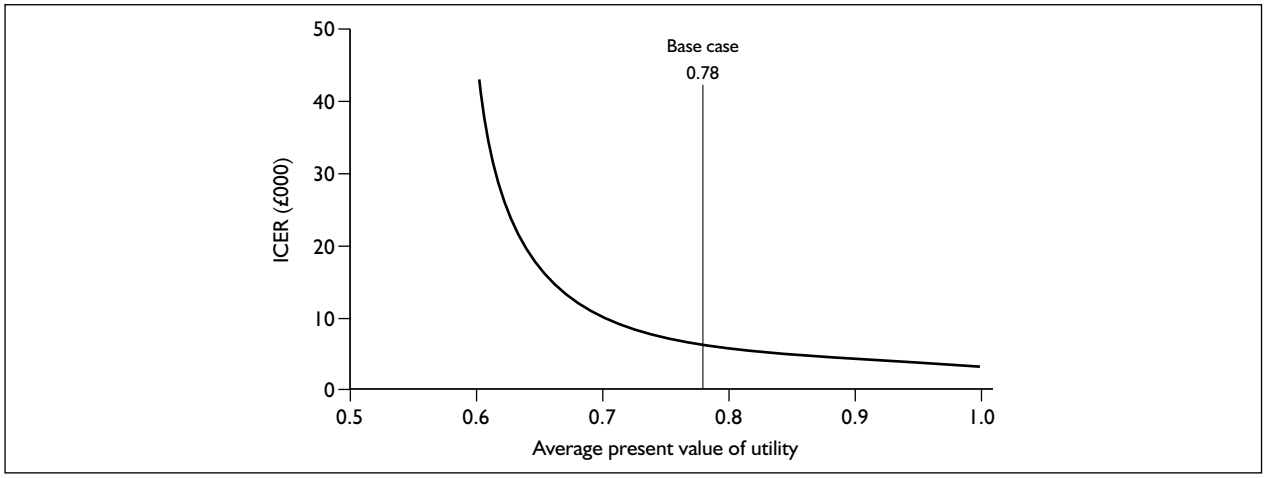

FIGURE 1 *Average utility with cetuximab plus radiotherapy and its impact on the incremental cost per quality-adjusted life-year gained for the combination therapy. The average utility with radiotherapy alone remains at 0.69.*

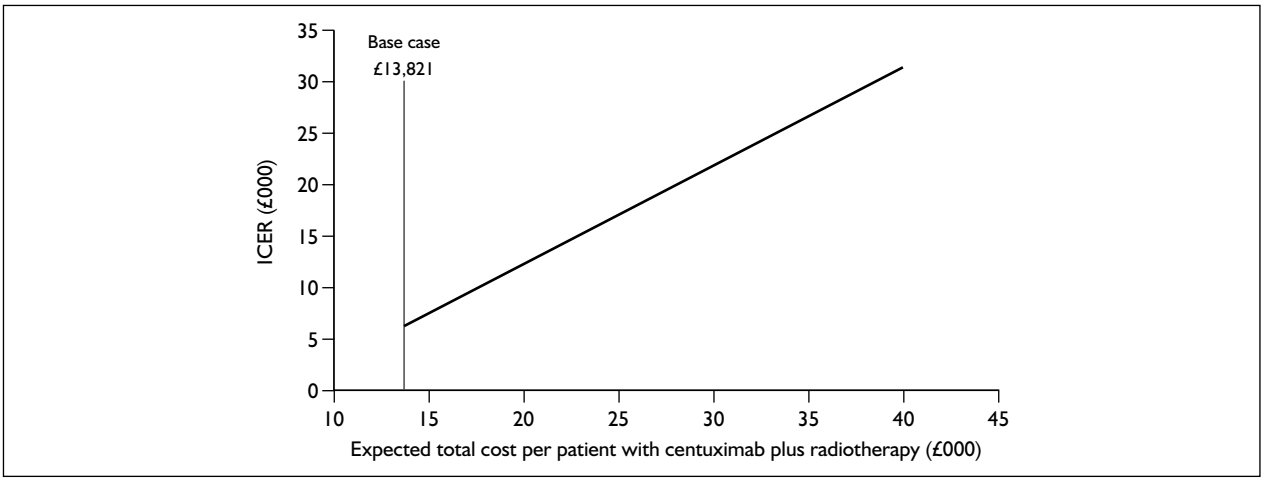

FIGURE 2 *Average total cost with cetuximab plus radiotherapy and its impact on the incremental cost per quality-adjusted life-year gained for the combination therapy. The average cost with radiotherapy alone remains at £7195. ICER, incremental cost-effectiveness ratio.*

TABLE 1 *Efficacy outcomes for the intention to treat (ITT) trial population*

Variable	Radiotherapy alone (ITT population *n* = 213)	Radiotherapy plus cetuximab (ITT population *n* = 211)
Locoregional control, median duration in months	14.9	24.4
Progression-free survival, median duration in months	12.4	17.1
Overall survival, median duration in months	29.3	49.0
Response rate (complete response + partial response) total number (%)	137 (64%)	155 (74%)

was considered appropriate for the decision problem. The results suggested that cetuximab plus radiotherapy was cost-effective compared with radiotherapy alone under a broad range of different assumptions on the basis of a cost-effectiveness threshold of £20,000. In the base case the incremental cost-effectiveness ratio of cetuximab plus radiotherapy compared with radiotherapy alone in the treatment of patients with LA SCCHN was £6390 per additional QALY (*Table 2*).

Commentary on the robustness of submitted evidence

The ERG felt that the manufacturer's submission was generally of good quality. There were no major errors or omissions and the majority of the data quoted within the submission were a fair and accurate representation of the original reference data.

The main weakness of the submission was that the evidence for the clinical effectiveness of cetuximab plus radiotherapy is based on a single clinical trial. Therefore, no supporting evidence for the findings is available.

The ERG felt that there were two major areas of uncertainty:

1. The patient population in the pivotal trial by Bonner *et al.*[9] included a high proportion of patients who would be expected to be suitable for chemoradiotherapy and therefore it does not match the population that is the focus of the submission's decision problem, i.e. patients who are considered inappropriate for chemoradiotherapy. No data are available regarding the number of patients in the trial who would be considered inappropriate for radiotherapy and hence no subgroup analysis on the population specified in the decision

TABLE 2 *Incremental cost per quality-adjusted life-year (QALY)*

	Incremental cost	Incremental QALYs	Incremental cost per QALY
Cetuximab plus radiotherapy vs radiotherapy alone	£6626	1.26	£6390

problem has been carried out. Therefore, the trial results may not be directly applicable to the target population. However, the clinical experts consulted by the ERG were of the opinion that the Bonner *et al*. trial is a good source for the comparison of radiotherapy plus cetuximab with radiotherapy alone and use of the whole trial population is appropriate because the factors that would lead to chemotherapy being inappropriate are highly variable.

2. The radiotherapy regimens used in the trial are not typical of current UK practice. Once-daily radiotherapy is the regimen most representative of current UK practice (used in about 80% of patients according to a survey by the Royal College of Radiologists). In the Bonner *et al*. trial, however, altered fractionation regimens (twice daily and concomitant boost) were selected for 18% and 56% of patients respectively (74% in total).

Another possible area of uncertainty was whether there are subgroups of patients who may derive more benefit than others from cetuximab with radiotherapy. The Bonner *et al*. trial was not powered to detect treatment-related differences for subgroups, such as patients who received once-daily radiotherapy or those with laryngeal or hypopharyngeal cancer,[10] but some results for subgroups are presented in the published paper, although with no confidence intervals or *p*-values. In view of the lack of power of the trial, caution needs to be exercised in drawing conclusions; however, the results presented raise questions as to whether there are subgroups of patients who may derive more benefit than others from the combination therapy. In patients with oropharyngeal cancer, locoregional control and overall survival durations appeared to be longer than those in patients with laryngeal or hypopharyngeal cancer. Furthermore, the once-daily radiotherapy regimen may have been less effective in terms of overall survival than the two altered fractionation regimens, and overall survival appeared to be longer with radiotherapy plus cetuximab than with radiotherapy alone in patients who received the concomitant boost regimen. Further clinical trials are needed to resolve these issues. Details of these subgroup analyses are included in the structured critical appraisal of the Bonner *et al*. trial presented in Appendix 3 of the full ERG report.[2]

Conclusions

A number of areas of uncertainty emerged in the manufacturer's cost-effectiveness modelling. These relate mainly to the extrapolation methods and the assumptions used to derive the utility and cost estimates. However, based on the sensitivity analyses undertaken by the manufacturer and some additional ERG analyses, these areas of uncertainty are unlikely to have a material effect on the conclusions of the cost-effectiveness analysis.

Future research into establishing which patients are likely to derive most benefit from cetuximab in conjunction with radiotherapy would be useful, as would further research on the clinical effectiveness of cetuximab plus radiotherapy in those patients with locally advanced SCCHN who are considered inappropriate for chemoradiotherapy. Setting up a patient register to collect post-treatment observational data of patients treated with cetuximab may be useful.

Summary of NICE guidance issued as a result of the STA

The following guidance was issued by NICE in May 2007:

This guidance on the use of cetixumab in combination with radiotherapy, for patients with locally advanced squamous cell cancer of the head and neck, is based on evidence submitted by the manufacturer. The evidence submitted was insufficient to enable a recommendation to be made on the use of cetuximab in combination with radiotherapy, as an alternative in patients for whom chemoradiotherapy is inappropriate. Cetuximab in combination with radiotherapy is not recommended for patients with locally advanced squamous cell cancer of the head and neck. People currently receiving cetuximab should have the

option to continue therapy until they and their clinicians consider it appropriate to stop.

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Infliximab for the treatment of adults with psoriasis

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of infliximab for the treatment of moderate to severe plaque psoriasis, in accordance with the licensed indication, based on the evidence submission from Schering-Plough to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The outcomes stated in the manufacturer's definition of the decision problem were severity [Psoriasis Area and Severity Index (PASI) score], remission rates, relapse rates and health-related quality of life. The main evidence in the submission comes from four randomised controlled trials (RCT) comparing infliximab with placebo and eight RCTs comparing either etanercept or efalizumab with placebo. At week 10, patients on infliximab had a significantly higher likelihood of attaining a reduction in PASI score than placebo patients. There were also statistically significant differences between infliximab and placebo in the secondary outcomes. In the comparator trials both the efalizumab and etanercept arms included a significantly higher proportion of patients who achieved a reduction in PASI score at week 12 than the placebo arms. No head-to-head studies were identified directly comparing infliximab with etanercept or efalizumab. The manufacturer carried out an indirect comparison, but the ERG had reservations about the comparison because of the lack of information presented and areas of uncertainty in relation to the included data. The economic model presented by the manufacturer was appropriate for the disease area and given the available data. The cost-effectiveness analysis estimates the mean length of time that an individual would respond to infliximab compared

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

with continuous etanercept and the utility gains associated with this response. The base-case incremental cost-effectiveness ratio (ICER) for infliximab compared with continuous etanercept for patients with severe psoriasis was £26,095 per quality-adjusted life-year. A one-way sensitivity analysis, a scenario analysis and a probabilistic sensitivity analysis were undertaken by the ERG. The ICER is highly sensitive to assumptions about the costs and frequency of inpatient stays for non-responders of infliximab. The guidance issued by NICE in August 2007 as a result of the STA states that infliximab within its licensed indication is recommended for the treatment of adults with very severe plaque psoriasis, or with psoriasis that has failed to respond to standard systematic therapies. Infliximab treatment should be continued beyond 10 weeks in people whose psoriasis has shown an adequate response to treatment within 10 weeks. In addition, when using the Dermatology Life Quality Index (DLQI), care should be taken to take into account the patient's disabilities, to ensure DLQI continues to be an accurate measure.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of infliximab for the treatment of moderate to severe plaque psoriasis in adults.

Description of the underlying health problem

Plaque psoriasis is the most common type of psoriasis and is characterised by exacerbations of thickened, erythematous, scaly patches of skin that can occur anywhere on the body. The disease impacts on health-related quality of life. The severity of plaque psoriasis can differ in individuals; it can be split into mild, moderate and severe psoriasis.

Clinical opinion is that the prevalence of moderate to severe psoriasis in the UK is around 2%, which the ERG would estimate to mean that approximately 267,000 people in England and Wales have moderate to severe disease.

The accepted system for classifying the severity of psoriasis is the Psoriasis Area and Severity Index (PASI). The PASI is not an ideal measure of the severity of psoriasis; the limits of PASI are well documented,[2] but it is the measure used in most clinical trials. The guidance for the use of biological therapies in psoriasis issued by NICE in July 2006 defines severe psoriasis as a PASI of ≥ 10 combined with a Dermatology Life Quality Index (DLQI) of > 10.[3] A 2005 review of the PASI as an instrument for determining the severity of chronic plaque-type psoriasis defines severe psoriasis as a PASI of > 12 and moderate psoriasis as a PASI ranging from 7 to 12.[4] Body surface area (BSA) and the DLQI are also commonly used as systems for classifying the severity of psoriasis.

Scope of the ERG report

The ERG critically evaluated the evidence submission from Schering-Plough for the use of infliximab for the treatment of moderate to severe plaque psoriasis, in accordance with the licensed indication (see below). Infliximab is a tumour necrosis factor-alpha (TNF-α) inhibitor which affects T-cell functions that involve the release of TNF-α and which binds to free TNF-α receptors on cell surfaces.

Infliximab is licensed for the treatment of adults with moderate to severe psoriasis who have not responded to (or who are intolerant of) other systemic therapies.

The outcomes stated in the manufacturer's definition of the decision problem were severity, remission rates, relapse rates and health-related quality of life.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's submission to NICE as part of the STA process. The ERG checked the literature searches and applied the NICE critical appraisal checklist to the included studies, and checked the quality of the manufacturer's submission with the Centre for Reviews and Dissemination (CRD) quality assessment criteria for a systematic review. In addition, the ERG checked and provided commentary on the manufacturer's model using standard checklists. A one-way sensitivity analysis, a scenario analysis and a probabilistic sensitivity analysis (*Figure 1*) were undertaken by the ERG.

Results

Summary of submitted clinical evidence

- The main evidence in the submission comes from four international randomised controlled trials (RCTs) comparing infliximab with placebo.[5–8] A further eight RCTs were also included: four comparing etanercept with placebo[9–12] and four comparing efalizumab with placebo.[13–16]
- Evidence in trials was presented as changes in baseline PASI scores, i.e. a PASI 75 refers to an individual who had a 75% reduction in their baseline PASI score.
- At week 10, patients on infliximab had a significantly higher likelihood of attaining a PASI 75 than placebo patients (range 75–88% versus 2–18% respectively) (four trials). It should be noted that there were wide confidence intervals around all four point estimates. There was also a statistically significant difference at 10 weeks in favour of infliximab for the proportion of patients achieving a PASI 50 and 90 (three trials).
- For both efalizumab and etanercept a significantly higher proportion of patients achieved a PASI 75 at week 12 compared with patients receiving placebo.
- In terms of secondary outcomes there were statistically significant differences between infliximab and placebo in Physician's Global Assessment (PGA) score, DLQI and Nail Psoriasis Severity Index (NAPSI). The incidence of any adverse event was slightly higher in those receiving infliximab compared with those receiving placebo, although this was not tested statistically.

Summary of submitted cost-effectiveness evidence

- The cost-effectiveness analysis estimates the mean length of time that an individual would respond to treatment and the utility gains associated with this response. The model is based closely upon the model reported in the study by Woolacott and colleagues.[2] The results are presented for infliximab compared with continuous etanercept based upon utility values for fourth quartile DLQI patients and also for all patients.

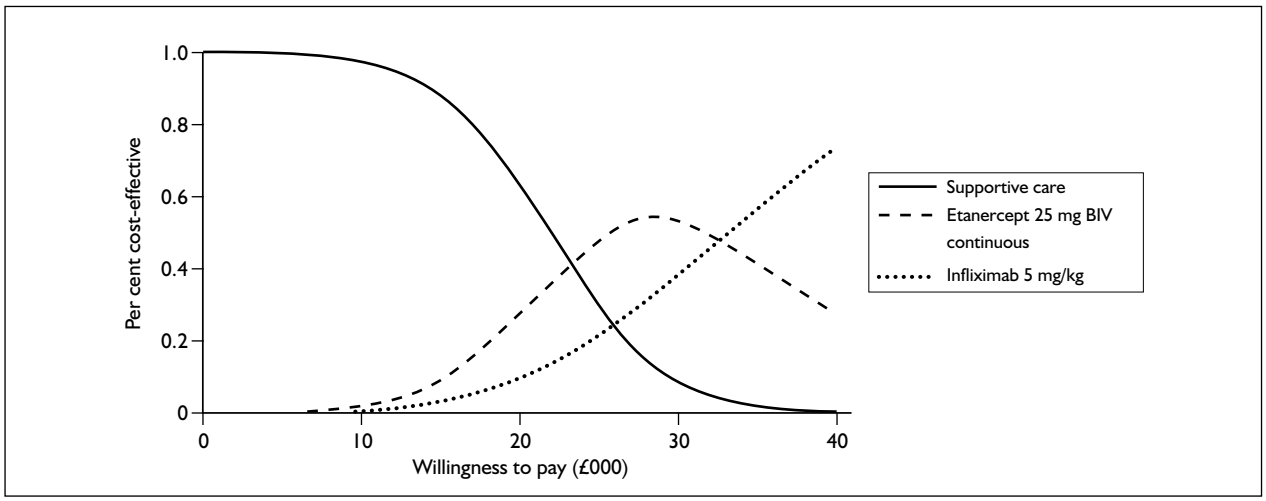

FIGURE 1 *Cost-effectiveness acceptability curve with the inclusion of uncertainty on variables previously assumed certain. BIV, twice weekly.*

- The model is generally internally consistent and appropriate to psoriasis in terms of structural assumptions. The cost-effectiveness analysis generally conforms to the NICE reference case and the scope/decision problem.
- Treatment effectiveness is reported in terms of the numbers of patients achieving PASI 50, 75 and 90 goals at 10–12 weeks and is estimated by an indirect comparison using a random-effects model.
- Patients who achieve improvements in PASI were assigned an associated improvement in quality of life with the higher responses associated with larger improvements in quality of life. These utility values have been taken from a previous report and no information was included in the manufacturer's submission on the characteristics of the individuals or the methodology used to obtain these values.
- The base-case incremental cost-effectiveness ratio (ICER) for infliximab compared with continuous etanercept for patients with severe psoriasis was £26,095 per quality-adjusted life-year (QALY).

Commentary on the robustness of submitted evidence

Strengths

- The manufacturer conducted a systematic search for clinical effectiveness and cost-effectiveness studies of infliximab. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include other databases.
- The four identified infliximab trials were of reasonable methodological quality (with some limitations) and measured a range of outcomes that are as appropriate and clinically relevant as possible.
- Overall, the manufacturer's submission presents an unbiased estimate of treatment efficacy for infliximab based on the results of the placebo-controlled trials.
- The economic model presented with the manufacturer's submission used an appropriate approach for the disease area and given the available data.

Weaknesses

- The processes undertaken by the manufacturer for screening studies, extracting data and applying quality criteria to included studies are not detailed in the submission. In addition, details relating to the searches were not always thorough and were recorded inconsistently. These factors limit the robustness of the systematic review.
- The manufacturer's submission reported very limited data on the comparator trials and did not undertake a systematic review of these.
- Combining the four infliximab trials in a meta-analysis was not appropriate given the statistically significant heterogeneity between studies. Similarly, pooling data in the indirect comparison was also inappropriate given the known heterogeneity. The resulting pooled mean values should therefore be treated with caution.
- The base-case results for the economic model have been presented for fourth quartile DLQI patients. It is unclear precisely what this definition means and how representative this is of severe psoriasis patients.

Conclusions

Areas of uncertainty

- The short intervention period of 10 weeks provides limited information about the longer-term efficacy of infliximab.
- The relative risks calculated by the manufacturer have wide confidence intervals around all four point estimates for the primary outcome of PASI 75 achievement (and other outcomes), indicating a lack of certainty regarding the true effect.
- No description of the principles, assumptions or methodology behind the indirect comparison was provided, making it difficult for the ERG to check either the model or the data. Despite asking the manufacturer for clarification, a number of areas remain unclear, such as where the data come from, which trials were included and which placebo groups were included for the pooled estimates.
- A definition of moderate psoriasis was not provided in the manufacturer's submission and neither were there any inclusion/exclusion criteria for the rating of the severity of psoriasis to ensure that patients were moderate to severe. The populations of the included infliximab trials were predominantly those with severe psoriasis. In addition, it is unclear what proportion of trial participants had previously been treated with systemic therapy. This causes concern over whether the participants included in the trials reflect those in the scope.
- The PASI is not an ideal measure of the severity of psoriasis in terms of measuring the impact on patients, but it is often the best

available outcome and is the measure used most in clinical trials. This raises questions regarding the relevance of the PASI outcome to patient experience in practice.
- There is uncertainty over the appropriate group to use in terms of QALY values. The base case presents values for fourth quartile DLQI patients. It is unclear precisely what the characteristics of patients were in this group.
- It was unclear how values for the number of inpatient days per year for a non-responder were derived. There was also uncertainty over the costs associated with inpatient care and the number of outpatient stays required for an individual on supportive care.
- There may be greater variability in the cost-effectiveness of treatment than is presented in the sensitivity analyses in the manufacturer's submission.
- The dropout rate for patients who no longer respond may be underestimated in the model.

Key issues

- The trials of infliximab efficacy presented in the manufacturer's submission were placebo-controlled trials. No head-to-head studies were identified that directly compared infliximab with etanercept or efalizumab, the comparators stated in the scope. The manufacturer carried out an indirect comparison but the ERG has reservations about the comparison because of the lack of information presented and areas of uncertainty in relation to the included data. In addition, the ERG question the appropriateness of pooling data that is statistically heterogeneous.
- The ICER is highly sensitive to assumptions about the costs and frequency of inpatient stays for non-responders of infliximab.
- It is unclear what severity of psoriasis was represented by the utility values presented in the manufacturer's submission. It is also unclear to what extent moderate psoriasis would be represented in the analysis presented in the submission.

Summary of NICE guidance issued as a result of the STA

NICE issued an appraisal consultation document in August 2007 which states that:

> 1.1 Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met.
> – The disease is very severe as defined by a total Psoriasis Area Severity Index (PASI) of 20 or more **and** a Dermatology Life Quality Index (DLQI) of more than 18.
> – The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate **or** PUVA (psoralen and long-wave ultraviolet radiation), **or** the person is intolerant to or has a contraindication to these treatments.
>
> 1.2 Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to 0 treatment within 10 weeks. An adequate response is defined as either:
> – a 75% reduction in the PASI score from when treatment started (PASI 75) **or**
> – a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started.
>
> 1.3 When using the DLQI healthcare professionals should take care to ensure that they take account of a patient's disabilities (such as physical impairments) or linguistic or other communication difficulties, in reaching conclusions on the severity of plaque psoriasis. In such cases healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with section 1.2.

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No. 7
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al*.

No. 8
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

No. 9
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

No. 11
Newborn screening for inborn errors of metabolism: a systematic review.
By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al*.

No. 12
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

No. 13
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

No. 14
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.
A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al*.

No. 4
A cost–utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al*.

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.
By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

No. 15
Ethical issues in the design and conduct of randomised controlled trials.
A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16
Qualitative research methods in health technology assessment: a review of the literature.
By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17
The costs and benefits of paramedic skills in pre-hospital trauma care.
By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18
Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.
By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al*.

No. 19
Systematic reviews of trials and other studies.
By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20
Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.
A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al*.

Volume 3, 1999

No. 1
Informed decision making: an annotated bibliography and systematic review.
By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al*.

No. 2
Handling uncertainty when performing economic evaluation of healthcare interventions.
A review by Briggs AH, Gray AM.

No. 3
The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

No. 4
A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.
By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al*.

No. 5
Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6
Assessing the costs of healthcare technologies in clinical trials.
A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7
Cooperatives and their primary care emergency centres: organisation and impact.
By Hallam L, Henthorne K.

No. 8
Screening for cystic fibrosis.
A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9
A review of the use of health status measures in economic evaluation.
By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10
Methods for the analysis of quality-of-life and survival data in health technology assessment.
A review by Billingham LJ, Abrams KR, Jones DR.

No. 11
Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12
Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.
A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al*.

No. 13
'Early warning systems' for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

No. 14
A systematic review of the role of human papillomavirus testing within a cervical screening programme.
By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al*.

No. 15
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

No. 17 (Pt 1)
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)
Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18
A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.
By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al*.

No. 19
What role for statins? A review and economic model.
By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al*.

No. 20
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al*.

No. 21
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenny AM, Song F.

No. 22
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.
By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al*.

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.
By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al*.

No. 8
An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.
By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al*.

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

No. 16
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.
By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al*.

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

No. 19
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.
By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al*.

No. 20
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

No. 21
Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O'Meara S, Cullum N, Majid M, Sheldon T.

No. 22
Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

No. 23
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

No. 24
Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, *et al*.

No. 25
A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

No. 26
Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
By Parkes J, Bryant J, Milne R.

No. 27
Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

No. 28
Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.
By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, *et al*.

No. 29
Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

No. 30
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

No. 31
A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32
Intrathecal pumps for giving opioids in chronic pain: a systematic review.
By Williams JE, Louw G, Towlerton G.

No. 33
Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

No. 34
A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35
Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al*.

No. 36
A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37
Systematic review of treatments for atopic eczema.
By Hoare C, Li Wan Po A, Williams H.

No. 38
Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39
The management of dyspepsia: a systematic review.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*.

No. 40
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1
Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*.

No. 2
The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al*.

No. 3
Equity and the economic evaluation of healthcare.
By Sassi F, Archard L, Le Grand J.

No. 4
Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

No. 5
Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al*.

No. 6
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8
Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al*.

No. 9
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al*.

No. 11
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15
Home treatment for mental health problems: a systematic review.
By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al*.

No. 16
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

No. 18
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al*.

No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz- Serrano A, Creed F, Sledge W, Kluiter H, *et al*.

No. 22
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al*.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al*.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al*.

No. 36
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*.

No. 4
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al*.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*.

No. 8
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*.

No. 19
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al*.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al*.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al*.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al*.

No. 28
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al*.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al*.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al*.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al*.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al*.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al*.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al*.

No. 6
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.
By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al*.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.
By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al*.

No. 9
Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.
By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al*.

No. 11
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.
By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al.*

No. 14
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al*.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.
By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al*.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21
Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.
By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al*.

No. 22
The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allsup S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.
By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.
By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al*.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.
By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al*.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33
Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

No. 35
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.
By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.
By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al*.

No. 38
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39
Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al*.

No. 40
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Hunn A, Wight J.

No. 41
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.
By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, *et al*.

Volume 8, 2004

No. 1
What is the best imaging strategy for acute stroke?
By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al*.

No. 2
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al*.

No. 3
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4
A systematic review of the role of bisphosphonates in metastatic disease.
By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al*.

No. 5
Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6
Effectiveness and efficiency of guideline dissemination and implementation strategies.
By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al*.

No. 7
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.
By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al*.

No. 11
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.
By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12
Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14
Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.
By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al*.

No. 15
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.
By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al*.

No. 16
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.
By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al*.

No. 17
Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al*.

No. 18
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.

No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*.

No. 20
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al*.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al*.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al*.

No. 27
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al*.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al*.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al*.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, *et al.*

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al*.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al*.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al*.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al*.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al*.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al*.

No. 4
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*.

No. 8
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al*.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al*.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al*.

No. 12
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al*.

No. 15
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al*.

No. 16
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al*.

No. 17
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al*.

No. 18
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*.

No. 22
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.
By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al*.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.
By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al*.

No. 25
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.
By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*.

No. 26
Indirect comparisons of competing interventions.
By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al*.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.
By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al*.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.
By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.
By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al*.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.
By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.
By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al*.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.
By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al*.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.
By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al*.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.
By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al*.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.
By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al*.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.
By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.
By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*.

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al*.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al*.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al*.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*.

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al*.

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al*.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al*.

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, *et al*.

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*.

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al*.

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al*.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al*.

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al*.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al*.

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al.*

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al*.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al*.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al*.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al*.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al*.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al*.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al*.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*.

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al*.

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al*.

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38
A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, et al.

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al*.

No. 41
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al*.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.
By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*.

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al*.

No. 48
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*.

No. 49
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.
By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al*.

No. 50
Amniocentesis results: investigation of anxiety. The ARIA trial.
By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al*.

Volume 11, 2007

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.
By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al*.

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.
By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al*.

No. 3
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.
By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al*.

No. 4
The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.
By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al*.

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.
By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al*.

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.
By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al*.

No. 9
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.
By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al*.

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.
By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al*.

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.
By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al*.

No. 14
A systematic review and economic evaluation of statins for the prevention of coronary events.
By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.
By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al*.

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17
Screening for type 2 diabetes: literature review and economic modelling.
By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al*.

No. 18
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al*.

No. 19
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.
By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al*.

No. 21
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.
By Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al*.

No. 23
Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.
By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al*.

No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.
By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al*.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.
By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.
By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al*.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.
By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al*.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.
By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al*.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.
By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al*.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.
By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Homebased compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.
By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al*.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.
By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al*.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.
By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al*.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.
By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al*.

No. 39
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.
By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al*.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.
By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.
By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al*.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, *et al*.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.
By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, *et al*.

No. 47
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.
By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al*.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al*.

No. 49
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.
By Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, *et al*.

No. 50
Evaluation of diagnostic tests when there is no gold standard. A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.
By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, *et al*.

No. 52
A review and critique of modelling in prioritising and designing screening programmes.
By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, *et al*.

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.
By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, *et al*.

No. 2
'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.
By Thornton J, Ashcroft D, O'Neill T, Elliott R, Adams J, Roberts C, *et al*.

No. 4
Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.
By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

No. 5
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.
By Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, *et al*.

No. 6
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al*.

No. 7
The use of economic evaluations in NHS decision-making: a review and empirical investigation.
By Williams I, McIver S, Moore D, Bryan S.

No. 8
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.
By Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, *et al*.

No. 9
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
By Loveman E, Frampton GK, Clegg AJ.

No. 10
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.
By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al*.

No. 12
The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.
By Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y, *et al*.

No. 13
Stepped treatment of older adults on laxatives. The STOOL trial.
By Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, *et al*.

No. 14
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.
By Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, *et al*.

No. 15
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

No. 16
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.
By Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A.

No. 17
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.
By Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, *et al*.

No. 18
Structural neuroimaging in psychosis: a systematic review and economic evaluation.
By Albon E, Tsourapas A, Frew E, Davenport C, Oyebode F, Bayliss S, *et al*.

No. 19
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
By Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, *et al*.

No. 20
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years.
By Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, *et al*.

No. 21
Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.
By Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, *et al*.

No. 22
Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.
By Underwood M, Ashby D, Carnes D, Castelnuovo E, Cross P, Harding G, *et al*.

No. 23
A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.
By George S, Pockney P, Primrose J, Smith H, Little P, Kinley H, *et al*.

No. 24
A review and critical appraisal of measures of therapist–patient interactions in mental health settings.
By Cahill J, Barkham M, Hardy G, Gilbody S, Richards D, Bower P, *et al*.

No. 25
The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.
By Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

No. 26
A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.
By de Verteuil R, Imamura M, Zhu S, Glazener C, Fraser C, Munro N, *et al*.

No. 27
A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.
By Karnon J, Czoski-Murray C, Smith K, Brand C, Chakravarthy U, Davis S, *et al*.

No. 28
Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.
By Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A.

No. 29
Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.
By Fader M, Cottenden A, Getliffe K, Gage H, Clarke-O'Neill S, Jamieson K, *et al*.

No. 30
A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.
By French B, Leathley M, Sutton C, McAdam J, Thomas L, Forster A, *et al*.

No. 31
The effectiveness and cost-effectivness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.
By Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, *et al*.

No. 32
Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.
By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

No. 33
Performance of screening tests for child physical abuse in accident and emergency departments.
By Woodman J, Pitt M, Wentz R, Taylor B, Hodes D, Gilbert RE.

No. 34
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.
By Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, *et al*.

No. 35
Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.
By Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R, *et al*.

No. 36
Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.
By Wang D, Cummins C, Bayliss S, Sandercock J, Burls A.

Volume 13, 2009

No. 1
Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.
By McLeod C, Fleeman N, Kirkham J, Bagust A, Boland A, Chu P, *et al*.

No. 2
Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.
By Simpson EL, Stevenson MD, Rawdin A, Papaioannou D.

No. 3
Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.
By Main C, Liu Z, Welch K, Weiner G, Quentin Jones S, Stein K.

No. 4
Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis.
By McDaid C, Griffin S, Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, *et al*.

No. 5
Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.
By Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al*.

No. 6
The harmful health effects of recreational ecstasy: a systematic review of observational evidence.
By Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, *et al*.

No. 7
Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.
By Mowatt G, Houston G, Hernández R, de Verteuil R, Fraser C, Cuthbertson B, *et al*.

No. 8
The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports.
By Taylor RS, Elston J.

No. 9
Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial.
By Potter J, Mistri A, Brodie F, Chernova J, Wilson E, Jagger C, *et al*.

No. 10
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.
By Pilgrim H, Lloyd-Jones M, Rees A.

No. 11
Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation.
By Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R, *et al.*

No. 12
Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.
By Hobart J, Cano S.

No. 13
Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial.
By Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL, *et al.*, on behalf of the CAST trial group.

No. 14
Non-occupational postexposure prophylaxis for HIV: a systematic review.
By Bryant J, Baxter L, Hird S.

No. 15
Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial.
By Farmer AJ, Wade AN, French DP, Simon J, Yudkin P, Gray A, *et al*.

No. 16
How far does screening women for domestic (partner) violence in different health-care settings meet criteria for a screening programme? Systematic reviews of nine UK National Screening Committee criteria.
By Feder G, Ramsay J, Dunne D, Rose M, Arsene C, Norman R, *et al*.

No. 17
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation.
By Simpson, EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J.

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The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history.
By Fortnum H, O'Neill C, Taylor R, Lenthall R, Nikolopoulos T, Lightfoot G, *et al.*

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Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study.
By Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA, *et al.*

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Systematic review of respite care in the frail elderly.
By Shaw C, McNamara R, Abrams K, Cannings-John R, Hood K, Longo M, *et al.*

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Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID).
By Tyrer P, Oliver-Africano P, Romeo R, Knapp M, Dickens S, Bouras N, *et al.*

No. 22
Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study.
By Kendrick T, Chatwin J, Dowrick C, Tylee A, Morriss R, Peveler R, *et al.*

No. 23
Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation.
By Bryant J, Cooper K, Picot J, Clegg A, Roderick P, Rosenberg W, *et al.*

No. 24
Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis.
By McKenna C, McDaid C, Suekarran S, Hawkins N, Claxton K, Light K, *et al*.

No. 25
Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE).
By Donnan PT, McLernon D, Dillon JF, Ryder S, Roderick P, Sullivan F, *et al*.

No. 26
A systematic review of presumed consent systems for deceased organ donation.
By Rithalia A, McDaid C, Suekarran S, Norman G, Myers L, Sowden A.

No. 27
Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial.
By Hay AD, Redmond NM, Costelloe C, Montgomery AA, Fletcher M, Hollinghurst S, *et al*.

No. 28
A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE).
By Newman SP, Cooke D, Casbard A, Walker S, Meredith S, Nunn A, *et al*.

No. 29
Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making.
By Andronis L, Barton P, Bryan S.

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We look forward to hearing from you.

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