



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/43321/>

---

**Article:**

Whyte, S., Pandor, A., Stevenson, M. et al. (2010) Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer. *Health Technology Assessment* , 14 (2). pp. 47-53. ISSN: 1366-5278

<https://doi.org/10.3310/hta14suppl2/07>

---

**Reuse**

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.

## Single Technology Appraisals

A supplement to *Health Technology Assessment Journal*

### *In this issue*

Certolizumab pegol for rheumatoid arthritis

Capecitabine for advanced gastric cancer

Rituximab for relapsed/refractory chronic lymphocytic leukaemia

Rituximab for chronic lymphocytic leukaemia

Pemetrexed for locally advanced or metastatic non-small cell lung cancer

Everolimus for advanced and/or metastatic renal cell cancer

Bevacizumab in combination with fluoropyrimidine-based chemotherapy for metastatic colorectal cancer

Dronedarone for atrial fibrillation and atrial flutter

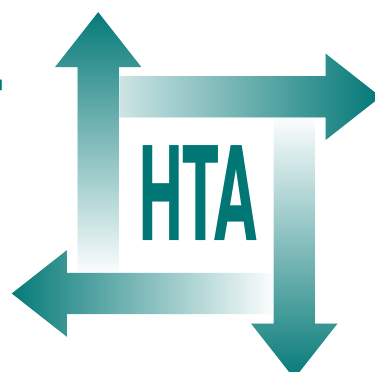
Imatinib as adjuvant treatment following resection of KIT-positive gastrointestinal stromal tumours

Gefitinib for locally advanced or metastatic non-small cell lung cancer



October 2010

**Health Technology Assessment**  
**NIHR HTA programme**  
[www.hta.ac.uk](http://www.hta.ac.uk)





### **How to obtain copies of this and other HTA programme reports**

An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website ([www.hta.ac.uk](http://www.hta.ac.uk)). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

- fax (with **credit card** or **official purchase order**)
- post (with **credit card** or **official purchase order** or **cheque**)
- phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

### **Contact details are as follows:**

HTA Despatch  
c/o Direct Mail Works Ltd  
4 Oakwood Business Centre  
Downley, HAVANT PO9 2NP, UK

Email: [orders@hta.ac.uk](mailto:orders@hta.ac.uk)  
Tel: 02392 492 000  
Fax: 02392 478 555  
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

### **Payment methods**

#### *Paying by cheque*

If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

#### *Paying by credit card*

The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

#### *Paying by official purchase order*

You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

### **How do I get a copy of HTA on CD?**

Please use the form on the HTA website ([www.hta.ac.uk/htacd.htm](http://www.hta.ac.uk/htacd.htm)). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge world-wide.

---

The website also provides information about the HTA programme and lists the membership of the various committees.

# Health Technology Assessment

Volume 14: Supplement 2, October 2010

---

## iii Supplement introduction

- I** Certolizumab pegol (CIMZIA®) for the treatment of rheumatoid arthritis  
*M Connock, S Tubeuf, K Malotki, A Uthman, J Round, S Bayliss, C Meads and D Moore*
- 11** Capecitabine for the treatment of advanced gastric cancer  
*G Norman, M Soares, P Peura, S Rice, D Suh, K Wright, M Sculpher and A Eastwood*
- 19** Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia  
*J Dretzke, P Barton, B Kaambwa, M Connock, O Uthman, S Bayliss and C Meads*
- 27** The clinical effectiveness and cost-effectiveness of rituximab for the first-line treatment of chronic lymphocytic leukaemia: an evidence review of the submission from Roche  
*C Main, M Pitt, T Moxham and K Stein*
- 33** Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer  
*J Greenhalgh, C McLeod, A Bagust, A Boland, N Fleeman, Y Dundar, J Oyee, R Dickson, H Davis, J Green, E McKenna and M Pearson*
- 41** Everolimus for the second-line treatment of advanced and/or metastatic renal cell cancer: a critique of the submission from Novartis  
*M Pitt, L Crathorne, T Moxham, M Bond and C Hyde*
- 47** Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer  
*S Whyte, A Pandor, M Stevenson and A Rees*
- 55** Dronedarone for the treatment of atrial fibrillation and atrial flutter  
*E Maund, C McKenna, M Sarowar, D Fox, M Stevenson, C Pepper, S Palmer and N Woolacott*
- 63** Imatinib as adjuvant treatment following resection of KIT-positive gastrointestinal stromal tumours  
*J Dretzke, J Round, M Connock, S Tubeuf, M Pennant, A Fry-Smith, C Hulme, C McCabe and C Meads*
- 71** Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer  
*T Brown, A Boland, A Bagust, J Oyee, J Hockenhill, Y Dundar, R Dickson, VS Ramani and C Proudlove*

# 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 needed 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.

Editor-in-Chief: Professor Tom Walley CBE  
Series Editors: Dr Martin Ashton-Key, Professor Aileen Clarke, Professor Chris Hyde,  
Dr Tom Marshall, Dr John Powell, Dr Rob Riemsma and Professor Ken Stein  
Editorial Contact: edit@southampton.ac.uk

ISSN 1366-5278

© 2010 Queen's Printer and Controller of HMSO

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (<http://www.publicationethics.org/>). This journal may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by Prepress Projects Ltd, Perth, Scotland ([www.prepress-projects.co.uk](http://www.prepress-projects.co.uk)), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorest Press, Dorchester.



## Supplement introduction

Welcome to the fifth Supplement to the *Health Technology Assessment* journal series. The series is now over 10 years old and has published more than 500 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.

The Supplements depart 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 this HTA programme funded work, and 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.

The papers included here contain reports of the position that the NICE guidance had reached at the time of submission to *Health Technology Assessment* for inclusion in this supplement. As we collect a series of papers together for an issue, the process of developing NICE guidance may have moved on further for some topics than others. Further details on the current position regarding each of the NICE Appraisals are available on the NICE website ([www.nice.org.uk](http://www.nice.org.uk)) and we welcome comments on the summaries via the HTA website ([www.hta.ac.uk/correspond/](http://www.hta.ac.uk/correspond/)).

Professor Tom Walley  
Director, NIHR HTA programme  
Editor-In-Chief, *Health Technology Assessment*

Professor Ken Stein  
Chair, Editorial Board, *Health Technology Assessment*







# Certolizumab pegol (CIMZIA®) for the treatment of rheumatoid arthritis

M Connock,<sup>1</sup> S Tubeuf,<sup>2</sup> K Malottki,<sup>1</sup> A Uthman,<sup>1</sup> J Round,<sup>2</sup>  
S Bayliss,<sup>1</sup> C Meads<sup>1</sup> and D Moore<sup>1\*</sup>

<sup>1</sup>Unit of Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, UK

<sup>2</sup>Leeds Institute of Health Sciences, University of Leeds, Leeds, UK

\*Corresponding author

**Declared competing interests of authors:** none

## Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of certolizumab pegol (CZP) for adults with active rheumatoid arthritis (RA) that have not responded adequately to treatment with conventional disease modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX), in accordance with the licensed indication, based upon the evidence submission from the manufacturer to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The outcome measures included American College of Rheumatology (ACR) 20, 50 and 70 response rates and quality of life measures after 3 months and 6 months of treatment. The ERG examined the submission's search strategies and considered they appeared comprehensive and that it was unlikely that relevant studies would have been missed. Only English language studies were considered in the submission and non-English language studies relevant to the decision problem may possibly have been ignored. The ERG analysed the first submitted economic model so as to itemise in detail clarification points that were brought to the attention of the manufacturer. In response the manufacturer submitted a modified cost-effectiveness analysis. The ERG undertook further analysis of this second model and other additional submitted evidence. The clinical evidence was derived from two multicentre blinded randomised controlled trials (RCTs) comparing CZP + MTX to placebo + MTX (the RAPID 1 and RAPID 2 trials). RAPID 1 lasted 52 weeks with 982

## HTA 07/13/01

### Date of ERG submission:

1 August 2009

### TAR Centre(s):

West Midlands Health Technology Assessment Collaboration

### List of authors:

M Connock, S Tubeuf, K Malottki, A Uthman, J Round, S Bayliss, C Meads and D Moore

### Contact details:

David Moore, Unit of Public Health, Epidemiology and Biostatistics, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

E-mail: [D.J.Moore@bham.ac.uk](mailto:D.J.Moore@bham.ac.uk)

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 07/13/01. The assessment report began editorial review in December 2009 and was accepted for publication in January 2010. See the HTA programme website for further project information ([www.hta.ac.uk](http://www.hta.ac.uk)). 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](http://www.hta.ac.uk/correspond)).

patients and RAPID 2 24 weeks with 619 patients. Evidence for clinical effectiveness of CZP in monotherapy came from the 24-week FAST4WARD trial with 220 patients that compared CZP (400 mg every 4 weeks) versus placebo. The three key RCTs demonstrated statistically significant superiority of CZP + MTX versus placebo + MTX and of CZP versus placebo with respect to a variety of outcomes including ACR 20, ACR 50 and ACR 70 measures and quality of life measures at 3 and 6 months. On the basis of results from the indirect comparison meta-analyses, the manufacturer suggested that CZP may be at least as effective as other 'biological' DMARD (bDMARD) comparators and, in a few ACR measures at 3 and 6 months, more effective. CZP is an effective therapy for adult RA patients whose disease has failed to respond adequately to cDMARDs including MTX or who are intolerant of MTX. The cost-effectiveness of CZP relative to other bDMARDs is unclear because the economic modelling undertaken may have ignored relevant effectiveness data and potential differences between trial populations, and so may have included effectiveness results that were biased in favour of CZP; underestimated uncertainty in the relative effectiveness of compared DMARDs; and ignored the potential influence of differences between bDMARDs with regard to adverse events and their related costs and health impacts. The NICE guidance issued in October 2009 states that: the Committee is minded not to recommend certolizumab pegol as a treatment option for people with RA; and the Committee recommends that NICE asks the manufacturer of CZP for more information on the clinical effectiveness and cost-effectiveness of CZP for the treatment of people with RA. On receipt of this information and details of a patient access scheme NICE issued final guidance recommending CZP, under certain criteria, as a treatment option for people with RA.

## 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, where most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> 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 the Institute.

This paper presents a summary of the ERG report for the STA submission that considered the clinical effectiveness and cost-effectiveness of certolizumab pegol (CZP) for adults with active rheumatoid arthritis (RA) that has not responded adequately to treatment with conventional disease modifying anti-rheumatic drugs (cDMARDs) including methotrexate (MTX).<sup>2</sup> CZP is a 'biological' DMARD (bDMARD) whose effectiveness could be compared to cDMARDs or to other bDMARDs administered within their licensed indications.

## Description of the underlying health problem

This section is taken from the NICE scope for this STA.

Rheumatoid arthritis is a chronic, disabling autoimmune disease characterised by inflammation of the synovial tissue of the peripheral joints, which causes swelling, stiffness, pain and progressive joint destruction. For a small proportion of people, inflammatory disease outside the joints (e.g. eye and lung disease, vasculitis) can also pose a significant problem. RA is heterogeneous, it is usually a chronic relapsing condition which has a pattern of flare-ups followed by periods of lower disease activity, but in a minority of cases the disease is constantly progressive. Most patients with RA develop damage to affected joints, with the amount of damage ranging from mild to severe. RA has a severe impact on quality of life and it is estimated that 40% of people with RA will stop working within 5 years of diagnosis.

Rheumatoid arthritis is three times more prevalent in women than in men. It can develop at any age, but usually starts between 40 and 60 years of age. RA affects 1% of the population, or approximately 400,000 people in England and Wales. Of these, approximately 15% have severe disease.

People with RA are usually treated in an outpatient setting rather than in primary care. There is no cure, and treatment aims to improve quality of life and to prevent or reduce joint damage.

Treatment for RA usually includes: non-steroidal anti-inflammatory agents (NSAIDs) which reduce pain, fever and joint swelling/inflammation; and DMARDs which slow the disease process and reduce joint damage. Corticosteroids may also be used to control inflammation. DMARDs are usually started soon after diagnosis. MTX and sulfasalazine are two commonly used DMARDs. NICE guidance recommends the use of a TNF (tumour necrosis factor)- $\alpha$  inhibitor (adalimumab, etanercept and infliximab; types of bDMARD) after the failure of two cDMARDs such as MTX and sulfasalazine. NICE guidance recommends the use of rituximab (a bDMARD that depletes B cells) after the failure of a TNF inhibitor, but does not recommend the use of abatacept after the failure of a TNF inhibitor.

### Scope of the evidence review group report

The scope for this STA was to address the clinical effectiveness and cost-effectiveness of CZP relative to cDMARDs and to bDMARDs for the treatment of adults with active RA whose disease had not responded adequately to cDMARDs including MTX. The STA was initiated prior to the granting of formal marketing authorisation. The anticipated marketing authorisation for CZP specified a dose regimen of 400 mg administered subcutaneously on weeks 0, 2 and 4, followed by 200 mg every other week. CZP is indicated for use in 'combination' therapy with MTX or as 'monotherapy' (without MTX) for patients intolerant of MTX. The acquisition cost of CZP is £357.50 per 200-mg syringe, excluding VAT (value added tax).

The key sources of evidence on clinical effectiveness of CZP in combination therapy came from two multicentre blinded randomised controlled trials (RCTs) comparing CZP + MTX to placebo + MTX [the RA Prevention of Structural Damage (RAPID) 1<sup>3</sup> and RAPID 2<sup>4</sup> trials]. RAPID 1 lasted 52 weeks with 982 patients and RAPID 2 24 weeks with 619 patients. Evidence for clinical effectiveness of CZP in mono-therapy came from the 24-week FAST4WARD trial<sup>5</sup> with 220 patients that compared CZP (400 mg every 4 weeks) versus placebo. There were no head-to-head trials that compared the effectiveness of CZP to the other bDMARDs. To estimate the relative clinical effectiveness between bDMARDs the manufacturer undertook indirect comparison meta-analyses (ICMs)<sup>6</sup> using the results from various placebo-controlled trials of bDMARDs.

The manufacturer submitted a de novo economic model that was used to estimate the cost per

quality-adjusted life-year (QALY) gained from CZP in comparison with anti-TNF agents (adalimumab, etanercept and infliximab) or with rituximab. Model inputs for clinical effectiveness of the different bDMARDs were derived from results from ICMs and based on the American College of Rheumatology (ACR) 20, 50 and 70 response rates<sup>7</sup> after 3 months and 6 months of treatment. The estimated ACR response rates in the absence of bDMARD treatment were single point values (no associated uncertainty) and were obtained by simple aggregation of the rates reported across the control arms of the included trials.

Health-related quality of life (HRQoL) utilities for the first 6 months of treatment were obtained by regression analysis of the relationship between ACR response and European Quality of Life-5 Dimensions (EQ-5D) scores observed for European patients participating in CZP trials. Utilities while continuing on treatment and utility after cessation of treatment were obtained by converting Health Assessment Questionnaire measures using a published algorithm proposed by Brennan *et al.*<sup>8</sup> Costs were mainly obtained from standard sources.

## 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.

Owing to the central importance of the RAPID 1, RAPID 2 and FAST4WARD studies, these were formally fully appraised by the ERG, taking advantage of responses to requests for clarification from the manufacturer.

The ERG examined the submission's search strategies and considered they appeared comprehensive and that it was unlikely that relevant studies would have been missed. Only English language studies were considered in the submission and non-English language studies relevant to the decision problem may possibly have been ignored.

The ERG critically appraised the submitted ICM with focus on the validity of selection of studies for inclusion, the reproducibility of results and the exploration of heterogeneity. The ERG considered the relative merits of alternative approaches to the ICM submitted.

The ERG analysed the first submitted economic model so as to itemise in detail clarification points that were brought to the attention of the manufacturer. In response the manufacturer submitted a modified cost-effectiveness analysis. The ERG undertook further analysis of this second model and other additional submitted evidence.

## Results

### Summary of submitted clinical evidence

The three key RCTs demonstrated statistically significant superiority of CZP + MTX versus placebo + MTX and of CZP versus placebo with respect to a variety of outcomes including ACR 20, ACR 50 and ACR 70 measures and quality of life measures at 3 and 6 months.

On the basis of results from the ICMs, the manufacturer suggested that CZP may be at least as effective as other bDMARD comparators and, in a few ACR measures at 3 and 6 months, more effective. These ICM estimates were associated with considerable uncertainty. Some evidence was presented that CZP inhibits progression of structural damage to joints.

### Summary of submitted cost-effectiveness evidence

The inputs for the first model were modified in the second model submitted. Some modifications were introduced in response to NICE's requests

for clarification, others depended on new results obtained from unprompted reanalyses of trial data undertaken by the manufacturer. The main changes made were exclusion of adverse events, exact calculation of discontinuation rates and modified annual utility decrement upon cessation of bDMARD treatment. The main results from the second model are shown in *Table 1*. The submission also included an economic analysis encompassing a proposed patient access scheme. At the time, this scheme was not approved by the Department of Health (DoH) and as such it was not considered in the first appraisal meeting.

### Commentary on the robustness of submitted evidence

In the three CZP trials there were large numbers of early patient withdrawals from the control arms that were imposed for lack of a rapidly established clinical effectiveness response.

In the RAPID 1 trial, of 199 patients receiving placebo + MTX, 63% had withdrawn by week 16 and 78% by the end of the trial; this compared to 21% and 35%, respectively, of patients receiving CZP. In RAPID 2, 87% of patients in the placebo + MTX arm had withdrawn by the end of the trial (week 24). In the FAST4WARD monotherapy trial, 54% of control arm patients had withdrawn by week 12 and 74% by the end of the trial at 24 weeks.

The high withdrawal rates at early phases of the CZP trials, especially seen in the control arms,

**TABLE 1** Base-case results from the manufacturer's second economic model using indirect comparison effectiveness analysis

	Mean cost (£)	Mean QALYs	ICER
<b>Combination therapy</b>			
CZP+MTX	89,158	6.654	–
Etanercept + MTX	86,165	6.589	46,192
Adalimumab + MTX	86,034	6.412	12,937
Rituximab + MTX	82,940	6.362	21,345
Infliximab + MTX	95,599	6.196	CZP dominates
<b>Monotherapy</b>			
CZP	85,424	6.305	–
Etanercept	85,941	6.435	(3991) <sup>a</sup>
Adalimumab	84,201	6.09	5687

CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life-years.  
a ICER for etanercept compared with CZP.

necessitated that estimates of effectiveness at later time points required many 'last observations' to be carried forward, and somewhat compromised the robustness of these estimates.

Owing to a lack of head-to-head trials of different bDMARDs, the manufacturer undertook random effects ICMs to gain an estimate of their relative clinical effectiveness.

The effectiveness of CZP relative to other bDMARDs was based on ACR 20, ACR 50 and ACR 70 outcomes measured at 12 and 24 weeks in various trials analysed by ICM. The robustness of these comparisons was potentially compromised by the high withdrawal rates in the CZP trials relative to those observed in the other included trials.

For combination therapy ACR responses at 24 weeks, the ICM included 10 trials [two with CZP (RAPID 1 and 2), three with adalimumab, two with infliximab and one each with etanercept, rituximab and tocilizumab]. Seven trials were used for responses at 12 weeks [two with CZP (RAPID trials), two with etanercept and one each with adalimumab, infliximab and tocilizumab]. For monotherapy ACR responses at 12 and 24 weeks, the ICM included four trials (two with adalimumab and one each with CZP and etanercept).

The reported results from the ICMs (odds ratios) were associated with considerable uncertainty and there were some errors in the reported values for ACR 70. Of the 85 indirect comparisons made between pairs of bDMARDs, only four reached statistical significance. Two of these were for superiority of CZP at 24 weeks in the ACR 20 outcome.

Several aspects of the ICMs reported by the manufacturer were a cause of concern:

- (a) The inclusion and exclusion of studies for the ICM did not appear to be systematic.
- (b) The inclusion of data from the included studies lacked some consistency.
- (c) There was a possibility that relevant information from several excluded studies, including an unpublished industry sponsored randomised trial of CZP + MTX versus MTX + placebo (study C87014), could have been used in the ICM.
- (d) There was insufficient consideration and exploration of underlying heterogeneity amongst the studies included for ICM.

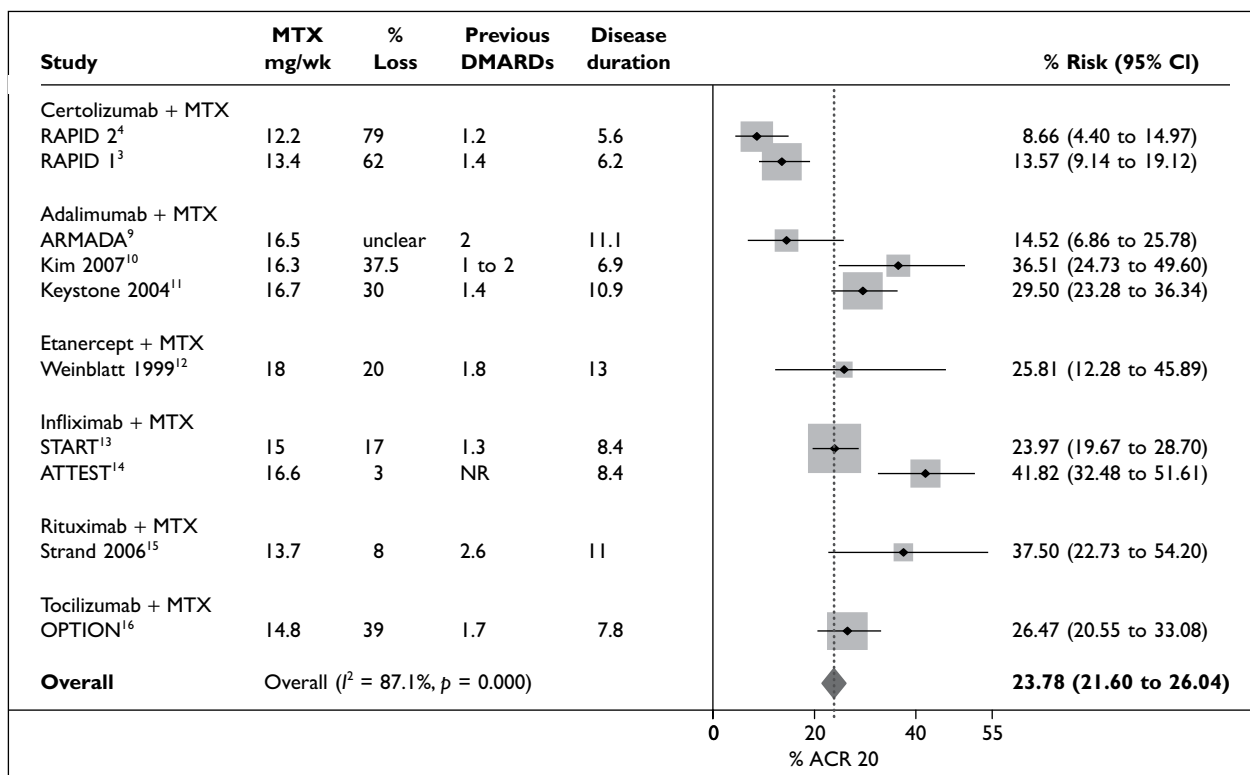
- (e) The development of effectiveness input for the economic analysis included data for a bDMARD comparator omitted from the subsequent economic analysis, raising the issue of whether data for other omitted bDMARDs should also have been included.
- (f) The development of clinical effectiveness input for the economic analysis used a point estimate derived by aggregation across trial control arms and sacrificed some of the strengths of randomisation and underestimated associated uncertainty.

The validity of ICM rests on an assumption of exchangeability between trials such that the placebo arms of the trials are interchangeable. The submission lacked an assessment or discussion of clinical or statistical heterogeneity amongst the trials used for ICM and did not comment on whether baseline characteristics of participants were similar across these RCTs. As such there was no consideration of potential sources of non-comparability of the placebo-controlled arms of the trials.

The ERG undertook an analysis of the heterogeneity amongst the control arms of the studies used in the estimation of effectiveness for the 24-week ACR 20 outcome for combination therapy. This choice was made because it involved the largest number of studies and the largest number of events. The results are shown in *Figure 1*. Data for four study level variables (chosen by the ERG) are also included in the figure.

The control rate in the two CZP RCTs was the lowest amongst the 10 trials, and the  $I^2$  statistic indicated considerable heterogeneity. When the two CZP studies were omitted from the analysis, the  $I^2$  statistic was reduced to 70% and the pooled estimate increased to 28%.

The four study level variables that were looked at as potential contributors to the observed heterogeneity were: entry level MTX dose as a potential indicator of treatment intensity and population differences; percentage withdrawals for the ACR 20 outcome as indicator of completeness of data; duration of RA; and number of previous DMARDs trialed as indicators of possible population differences. For each of these variables the two CZP RCTs were at the extreme of the distributions. The brief examination of heterogeneity amongst the studies used for ICMs indicated that an indirect comparison or mixed-



**FIGURE 1** Risk of ACR 20 in placebo plus MTX arms of trials used for ICM at 6 months. ACR, American College of Rheumatology; CI, confidence interval; DMARDs, disease modifying anti-rheumatic drugs; MTX, methotrexate.

treatment analysis with methods that allow for differences in control rate or baseline risk (similar to the Bayesian analyses undertaken by Nixon *et al.*<sup>17</sup>) probably represents the preferred choice of methodology for the decision problem.

Regarding the economic model, the robustness of quality of life and health-utility inputs was difficult to determine through lack of detail of how many patients were given HRQoL questionnaires and what response rates were elicited. It was not clear how this uncertainty might affect the estimates of cost-effectiveness generated by the model.

Adverse event costs as well as their related health outcomes were not included in the revised model although they were included in the original submission. There was a lack of information to justify this revision, so it was unclear what sources of data were used in this exercise. An assumption of no difference in adverse effects between drugs (CZP, infliximab, adalimumab, etanercept, rituximab) may on average be shown to be reasonable, but on the basis of the submitted information the assumption cannot be considered to be evidence based.

## Conclusions

Certolizumab pegol is an effective therapy for adult RA patients whose disease has failed to respond adequately to cDMARDs including MTX or who are intolerant of MTX.

A reasonable interpretation of the results is that there is little convincing evidence that CZP is more or less effective than the comparators examined.

Patients with RA may respond differently to different bDMARDs and effectiveness of a bDMARD for a specific patient is currently unpredictable; an increase in the variety of available bDMARDs might potentially increase the overall proportion of patients responsive to these drugs.

The cost-effectiveness of CZP relative to other bDMARD is unclear because the economic modelling undertaken may have ignored relevant effectiveness data and potential differences between trial populations, and so may have included effectiveness results that were biased in favour of CZP; underestimated uncertainty in

the relative effectiveness of compared DMARDs; and ignored the potential influence of differences between bDMARDs with regard to adverse events and their related costs and health impacts.

### Summary of NICE guidance issued as a result of the STA

At the time of drafting this report, the guidance appraisal consultation document issued by NICE in October 2009 states that:

1.1 The Committee is minded not to recommend certolizumab pegol as a treatment option for people with rheumatoid arthritis (RA).

1.2 The Committee recommends that NICE asks the manufacturer of certolizumab pegol for more information on the clinical effectiveness and cost-effectiveness of certolizumab pegol for the treatment of people with RA. This information should be made available for the second Appraisal Committee meeting, and should cover the following issues:

Estimation of the clinical effectiveness of certolizumab pegol relative to other TNF- $\alpha$  inhibitors for the treatment of RA, including consideration of uncertainty around the estimate. In order to clarify this issue the Committee requests:

- provision of a mixed-treatment comparison (MTC) analysis, rather than an indirect comparison meta-analysis
- details of potentially relevant studies, including study C87014, that were excluded from the analysis
- provision of data from the C87014 trial and an assessment of the impact on the incremental cost-effectiveness ratios (ICERs) when the American College of Rheumatology (ACR) response for certolizumab pegol in combination with methotrexate is calculated using data from the C87014 plus the RAPID 1 and 2 trials.

Clarification of how the original economic model was revised:

- further justification of why a utility decrease of 0.037 per year after assessment of clinical response at 6 months was assumed in the original model, but a utility increase of 0.0402 per year was assumed in the revised model

- further details of how the assumed utility decrease of 0.0025 per year when treatment is discontinued was derived
- clarification and a full breakdown of the direct and indirect costs included in the model, including an explanation of why the mean cost for the intervention and comparators differed between the original and revised models, and an explanation of how these changes relate to costs associated with adverse events
- clarification of how incorporating an estimated relationship between ACR 20, 50 and 70 would affect cost effectiveness in the revised model.

Provision of an incremental cost-effectiveness analysis:

- comparing certolizumab pegol with other TNF- $\alpha$  inhibitors (that is, not including rituximab)
- including univariate sensitivity analysis exploring the effect of lowering the estimate for the cost of administering infliximab in line with the range of costs used in previous appraisals
- including a comparison of all treatments with full reporting of results of probabilistic sensitivity analysis, including but not limited to presentation of cost-effectiveness acceptability curves, with all treatments plotted and a scatter plot of all treatments on the same cost-effectiveness plane.

The manufacturer responded to the ACD with a new submission that incorporated a MTC that included the industry sponsored CZP study C87014 and two additional studies previously excluded from the ICMEs. The major change to the economic analysis was the introduction of a DOH-approved patient access scheme (PAS) that considerably reduced the initial cost of CZP treatment by making early treatment syringes free of charge.

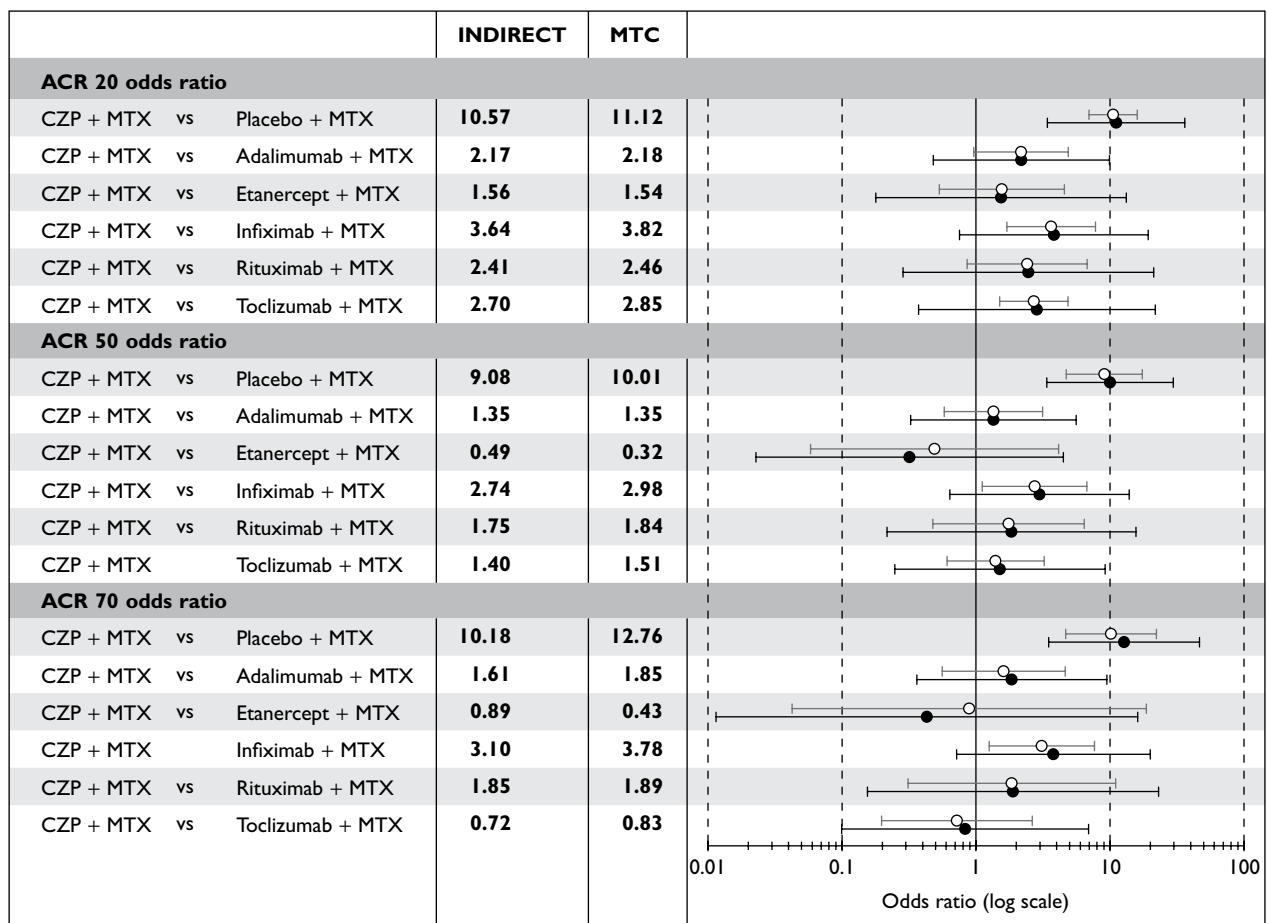
The MTC more faithfully reflected the inherent uncertainty in the estimates of relative effectiveness of the compared DMARDs (*Figure 2*) and the PAS improved the cost-effectiveness of CZP treatment. The main new cost-effectiveness results submitted are summarised in *Table 2*.

The final appraisal document for this technology was issued by NICE shortly before this article was sent to press. The appraisal document states:

**TABLE 2** Manufacturer's revised cost effectiveness results incorporating mixed-treatment comparison of effectiveness and DOH-approved patient access scheme

	Mean cost (£)	Mean QALYs	ICER
<b>Combination therapy</b>			
CZP + MTX	85,583	6.654	–
Etanercept + MTX	86,165	6.589	CZP dominates
Adalimumab + MTX	86,034	6.412	CZP dominates
Rituximab + MTX	82,940	6.362	9072
Infliximab + MTX	95,599	6.196	CZP dominates
<b>Monotherapy</b>			
CZP	81,849	6.305	–
Etanercept	85,941	6.435	(31,582) <sup>a</sup>
Adalimumab	84,201	6.09	CZP dominates

CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life-years.  
 a ICER for etanercept compared with CZP.



**FIGURE 2** Manufacturer's results for ICM (hollow symbol) and MTC (solid symbol) with associated uncertainty: ACR 20, 50, 70 outcomes. ACR, American College of Rheumatology; CZP, certolizumab pegol; MTC, mixed-treatment comparison; MTX, methotrexate.

Certolizumab pegol is recommended as an option for the treatment of people with rheumatoid arthritis only if:

- certolizumab pegol is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 130) and
- the manufacturer provides the first 12 weeks of certolizumab pegol (10 pre-loaded 200-mg syringes) free of charge to all patients starting treatment.

## Key references

1. NICE. *Guide to single technology (STA) process*. 2006. URL: [www.nice.org.uk/page.aspx?o=STAProcessguide](http://www.nice.org.uk/page.aspx?o=STAProcessguide).
2. Connock MJ, Tubeuf S, Malottki K, Uthman A, Round J, Bayliss S, *et al.* *Certolizumab pegol (CIMZIA®) for the treatment of Rheumatoid Arthritis*. URL: [www.nice.org.uk/guidance/index.jsp?action=download&o=45795](http://www.nice.org.uk/guidance/index.jsp?action=download&o=45795).
3. Keystone E, Heijde DV, Mason D, Jr., Landewe R, Vollenhoven RV, Combe B, *et al.* Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: Findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008;**58**:3319–29.
4. Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijckens K, *et al.* Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009;**68**:797–804.
5. Fleischmann R, Vencovsky J, van Vollenhoven RE, Borenstein D, Box J, Coteur G, *et al.* Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis* 2009;**68**:805–11.
6. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;**50**:683–91.
7. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, *et al.* American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:727–35.
8. Brennan A, Bansback N, Nixon R. *Modelling the cost effectiveness of TNF- $\alpha$  inhibitors in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry*. University of Sheffield ScHARR; 2006. Report No.: 06/12.
9. Weinblatt M, Keystone E, Furst D, Moreland L, Weisman M, Birbara C, *et al.* Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADA Trial. *Arthritis Rheum* 2003;**48**:35–45.
10. Kim H-Y. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. *APLAR Journal of Rheumatology* 2007;**10**:9–16.
11. Keystone E, Kavanaugh A, Sharp J, Tannenbaum H, Hua Y, Teoh L, *et al.* Radiographic, Clinical, and Functional Outcomes of Treatment with Adalimumab (a human anti-tumour necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled 52-week trial. *Arthritis Rheum* 2004;**50**:1400–11.
12. Weinblatt M, Kremer J, Bankhurst A, Bulpitt K, Fleischmann R, Fox R, *et al.* A Trial of Etanercept, a Recombinant Tumor Necrosis Factor Receptor: Fc fusion protein, in patients with Rheumatoid Arthritis receiving Methotrexate. *N Engl J Med* 1999;**340**:253–9.
13. Westhovens R, Yocum D, Han J. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. *Arthritis Rheum* 2006;**54**:1075–86.
14. Schiff M, Keiserman M. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008;**67**:1096–103.
15. Strand V, Balbir-Gurman A, Pavelka K. Sustained benefit in rheumatoid arthritis following one

- course of rituximab: improvements in physical function over 2 years. *Rheumatology (Oxford)* 2006;**45**:1505–13.
16. Smolen JSB. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008;**371**:987–97.
17. Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. *Stat Med* 2007;**26**:1237–54.



# Capecitabine for the treatment of advanced gastric cancer

G Norman,\* M Soares, P Peura, S Rice, D Suh, K Wright, M Sculpher and A Eastwood

Centre for Reviews and Dissemination, University of York, York, UK

\*Corresponding author

**Declared competing interests of authors:** M Sculpher has a minority shareholding in a consulting company that has undertaken work for Roche during the last 3 years, but not in the clinical area of gastric cancer. He did not participate personally in this consultancy. M Seymour is a co-investigator in a trial ('321GO'), which includes capecitabine as treatment for patients with advanced gastroesophageal cancer. The trial is peer reviewed and funded by Cancer Research UK, but also receives some supplementary financial support from Roche (£50k over 2 years). M Seymour also attended the ASCO Oncology Conference last year as a guest of Roche. D Suh is also a co-investigator on the '321GO' study. Roche have also offered to sponsor his trip to ASCO this year. Stephen Kelly accepted financial support from Roche in 2008 and 2009 to attend the British Oncology Pharmacists Association Annual Symposium on behalf of the Leeds Teaching Hospitals NHS Trust Pharmacy Department.

## Abstract

This paper presents a summary of the evidence review group (ERG) report into capecitabine for advanced gastric cancer (aGC). Capecitabine is an oral prodrug of 5-fluorouracil (5-FU). The decision problem addressed was the use of capecitabine (X) compared to 5-FU (F), in combination regimens with platinum agents [cisplatin (C) or oxaliplatin (O)] with or without epirubicin (E), in patients with inoperable aGC. Approximately 7000 new cases of gastric cancer are diagnosed in England and Wales every year. Of these, 80% are candidates for palliative chemotherapy and around 2900 receive such treatment. The standard UK practice for patients with aGC who are considered fit enough has consisted of a triplet regimen comprising intravenous 5-FU in combination with a platinum agent (capecitabine or oxaliplatin) and epirubicin. The manufacturer's submission (MS) focused on direct evidence from two phase III non-inferiority randomised controlled trials (RCTs), REAL-2 (Randomized ECF for Advanced and Locally advanced oesophagogastric cancer-2;  $n = 1002$ ) and ML17032 ( $n = 316$ ). REAL-2 randomised patients to four regimens (ECF, ECX, EOF and EOX) to compare 5-FU with capecitabine and cisplatin with oxaliplatin, whereas ML17032 compared CX with CF. Efficacy outcomes from these trials were

## HTA 08/85/01

### Date of ERG submission:

16 February 2010

### TAR Centre(s):

CRD and CHE Technology Assessment Group

### List of authors:

G Norman, M Soares, P Peura, S Rice, D Suh, K Wright, M Sculpher and A Eastwood

### Contact details:

Gill Norman, Centre for Reviews and Dissemination, University of York, York YO10 5DD, UK

E-mail: gn5@york.ac.uk

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 08/95/01. The assessment report began editorial review in June 2010 and was accepted for publication in July 2010. See the HTA programme website for further project information ([www.hta.ac.uk](http://www.hta.ac.uk)). 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](http://www.hta.ac.uk/correspond)).

pooled in an individual patient data (IPD) meta-analysis. Both RCTs demonstrated statistically significant non-inferiority of capecitabine on the outcome of overall survival (OS) assessed in the per-protocol population; equivalent results were also demonstrated for progression-free survival (PFS). The IPD meta-analysis found a statistically significant benefit in OS for capecitabine compared with 5-FU [unadjusted hazard ratio (HR): 0.87; 95% confidence interval (CI) 0.77 to 0.98,  $p = 0.027$ ]. There was no evidence of a poorer safety profile for capecitabine overall, nor of any difference in quality of life (QoL) between the two fluoropyrimidines. The MS included a de novo economic evaluation based on a cost-minimisation analysis (CMA), where the costs of capecitabine-based regimens were compared with their equivalent 5-FU-based regimens in aGC. A time horizon of 5.5 cycles (each lasting for 21 days) was used in the base-case analysis, representing the duration of treatment. The results of the manufacturer's base-case analysis showed that capecitabine regimens are associated with mean net cost savings of £1620 (ECX vs ECF), £1572 (EOX vs EOF) and £4210 (CX vs CF). The manufacturer failed to comment explicitly on the uncertainty around the estimates of efficacy and on the fact that the IPD meta-analysis suggests that capecitabine may actually be more effective on average. Further analyses exploring additional costs incurred by the UK NHS from extending survival duration showed that these are unlikely to have a material effect on conclusions. A full probabilistic analysis was not performed; however, the evidence explored by the MS and ERG is consistent in suggesting that capecitabine has a lower mean cost than 5-FU-based regimens. The submission was considered to contain convincing evidence of the non-inferiority of capecitabine to 5-FU on survival; this evidence was considered to be applicable to UK practice. Although some uncertainty remains, the ERG deemed CMA to be an appropriate framework with which to analyse this decision problem. Overall cost estimates for the CMA were generated appropriately and were robust to uncertainties regarding assumptions and sources. At the time of writing, the guidance document issued by NICE on 28 July 2010 states that capecitabine in combination with a platinum-based regimen is recommended for the first-line treatment of inoperable advanced gastric 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<sup>1</sup> is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor (Roche). 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 prepared by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled '*Capecitabine for the treatment of advanced gastric cancer*'.<sup>2</sup>

## Description of the underlying health problem

Gastric cancer is the 10th most commonly diagnosed cancer in the UK, with approximately 7000 new cases diagnosed in England and Wales every year. Of these, some 80% of patients are unsuitable for curative treatment and are candidates for palliative chemotherapy. It is estimated that just over one-half (around 2900) of these patients with advanced gastric cancer (aGC) receive such treatment.

The standard UK practice for patients with aGC, who are considered fit enough, has consisted of a triplet regimen comprising a fluoropyrimidine, intravenous 5-fluorouracil (5-FU) in combination with a platinum agent (cisplatin or oxaliplatin) and an anthracycline (epirubicin).

## Scope of the ERG report

The decision problem addressed was the use of capecitabine (Xeloda) in combination with platinum-based chemotherapy regimens (cisplatin or oxaliplatin) with or without epirubicin, compared with 5-FU in combination with such

regimens, in patients with inoperable aGC. Capecitabine is an oral prodrug of 5-FU, and is licensed for the first-line treatment of aGC in combination with a platinum-based regimen. Oral chemotherapies are usually considered to be preferred by patients and may have fewer associated costs and/or adverse events.

The outcome measures considered were overall survival (OS), progression-free survival (PFS), response rates, adverse effects of treatment and health-related quality of life (QoL). These were assessed in direct comparisons by two open-label non-inferiority randomised controlled trials (RCTs), assessing doublet or triplet regimens.<sup>3,4</sup>

Economic outcomes included cost per life-year gained (LYG) and cost per quality-adjusted life-year (QALY) gained. The manufacturer proposed evaluating the cost-effectiveness of capecitabine-based regimens compared with 5-FU-based regimens by using cost-minimisation analyses (CMAs).

## 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 (MS) to NICE as part of the STA process. The ERG checked the literature searches and carried out a search for ongoing trials. The review methodology including inclusion criteria was appraised. The validity assessments of the included RCTs were critiqued and the ERG carried out its own assessment using the CRD guidelines for the critical appraisal of RCTs.

In evaluating the cost effectiveness of capecitabine, the manufacturer used a cost-minimisation approach. The ERG has thus first commented on the appropriateness of using such methodology, within this specific decision problem, taking into consideration NICE's reference case methods.<sup>5</sup> Next, the ERG assessed the manufacturer's de novo economic evaluation using Drummond *et al.*'s checklist.<sup>6</sup> In response to the ERG's points of clarification regarding the initial submission, the manufacturer provided additional evidence on the costs of adverse events, drug acquisition inputs and costs of additional survival. The ERG considered this evidence throughout. Based on the identified limitations in the MS, the ERG revisited the base case according to drug use, unit costs of treatments and pharmacy drug preparation costs. The ERG

also undertook additional sensitivity analyses based on the revised base case, and conducted a threshold analysis, evaluating the maximum costs that the NHS would be willing to pay for the extension of survival time implied by prespecified cost-effectiveness thresholds.

## Results

### Summary of submitted clinical evidence

The MS focused on direct evidence from two phase III non-inferiority RCTs.<sup>3,4</sup>

Efficacy outcomes from these trials were pooled in an individual patient data (IPD) meta-analysis.<sup>7</sup> REAL-2 (Randomized ECF for Advanced and Locally advanced oesophagogastric cancer-2) was a 2×2 factorial trial that compared 5-FU with capecitabine and cisplatin with oxaliplatin.<sup>3</sup> The following regimens were used: epirubicin + cisplatin + 5-FU (ECF); epirubicin + cisplatin + capecitabine (ECX); epirubicin + oxaliplatin + 5-FU (EOF); and epirubicin + oxaliplatin + capecitabine (EOX). A second trial, ML17032, compared cisplatin + capecitabine (CX) with cisplatin + 5-FU (CF).<sup>4</sup>

REAL-2 found statistically significant non-inferiority of capecitabine on the primary outcome of OS assessed in the per-protocol population adjusted [hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.77 to 1.02]. ML17032 found statistically significant non-inferiority of capecitabine on the primary outcome of PFS in the per-protocol population (adjusted HR 0.85, 95% CI 0.65 to 1.11). Statistically significant non-inferiority on OS (unadjusted HR 0.85, 95% CI 0.64 to 1.13) was also demonstrated.

The IPD meta-analysis of the intention-to-treat (ITT) populations of the REAL-2 and ML17032 trials found a statistically significant benefit in OS for capecitabine compared with 5-FU (unadjusted HR 0.87, 95% CI 0.77 to 0.98,  $p = 0.027$ ).<sup>7</sup>

There was minimal QoL data reported in the MS. The REAL-2 trial was reported as assessing QoL using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-30), version 3,<sup>8</sup> administered at baseline, and after 3, 6, 9 and 12 months. The manufacturer subsequently provided the levels of compliance, data on the baseline scores for all

subscales, and changes from baseline at 12 weeks and 24 weeks for the REAL-2 trial. These showed few statistically significant differences between the individual trial arms.

Safety analyses showed some significant differences in adverse events profiles between capecitabine and 5-FU regimens. However, in the REAL-2 trial, all statistical analyses were pairwise comparisons with the ECF arm, which the trial was not powered to assess. Of particular note was grade 3 or 4 neutropenia, which occurred significantly more often in the ECX arm ( $p < 0.05$ ) and significantly less often in the EOX and EOF arms ( $p < 0.01$ ) compared with the ECF arm; grade 3 or 4 diarrhoea, which occurred significantly more often in the EOX and EOF arms compared with the ECF arm ( $p < 0.05$ ); and grade 3 or 4 hand-foot syndrome, which occurred significantly more often in the ECX arm compared with the ECF arm ( $p < 0.05$ ). In the ML17032 trial, stomatitis occurred more often, and with greater severity, in the CF arm, while hand-foot syndrome was more common in the CX arm.

### Summary of submitted cost-effectiveness evidence

The manufacturer's literature search identified one economic evaluation relevant to this decision problem. This was Roche's 2007 submission to the Scottish Medicines Consortium for capecitabine in this indication. The methods and results reported are consistent with the current submission.

The MS included a de novo economic evaluation based on a CMA, where the costs of capecitabine-based regimens were compared with their equivalent 5-FU-based regimens (ECX vs ECF, EOX vs EOF, CX vs CF) in the treatment of advanced gastric cancer. A time horizon of 5.5 cycles (each lasting for 21 days) was used in the base-case analysis, representing the duration of treatment of the alternative regimens.

The cost-minimisation approach was based on evidence from two clinical trials – REAL-2 and ML17032 – reporting that capecitabine is at least as effective as intravenous 5-FU (see above). The calculations considered costs relating to drug acquisition and to drug administration. The drug administration costs comprised the costs of

**TABLE 1** Drug administration activities costed for each cycle of a treatment regimen and the days in each cycle (of 21 days) during which the activity takes place

Activity/component	Activity cost (£)	ECF and EOF	ECX and EOX	CF	CX
Line insertion	445.77	Day 1 <sup>a</sup>		Day 1 <sup>a</sup>	
Drug delivery, 1st attendance; outpatient/day case	281.45	Day 1	Day 1	Day 1 <sup>b</sup>	Day 1
Drug delivery, subsequent attendances; nurse cost to flush central line a change pump	36.83	Days 7, 14			
Drug delivery, subsequent attendances; outpatient/day case	198.72			Days 2–4 <sup>b</sup>	
Drug delivery; inpatient stay 5 days	1435.64			Days 1–5 <sup>c</sup>	
Pump cost	38.50	Days 1, 7, 14			
Transport cost (20% of patients)	28.43	Days 1, 7, 14	Day 1	Days 1–5	
Pharmacy preparation	'Complex' (intravenous): 41.87 'Simple' (oral): 25.34	Days 7, 14 'Complex'	Day 1 'Simple'	Days 1–5 'Complex'	Day 1 'Simple'

CF, cisplatin + 5-FU; CX, cisplatin + capecitabine; ECF, epirubicin + cisplatin + 5-FU; ECX, epirubicin + cisplatin + capecitabine; EOF, epirubicin + oxaliplatin + 5-FU; EOX, epirubicin + oxaliplatin + capecitabine; 5-FU, 5-fluorouracil.  
a Line insertion was only considered at the start of the first cycle.  
b Base-case activity.  
c Activity in scenario analysis, which replaces the outpatient/day case drug-delivery activities.  
Shaded cells indicate that the activity was not costed for the regimen.

hospital visits (central line insertion, delivery of chemotherapy, and subsequent care by a nurse to flush central line and change the pump), pharmacy drug preparation costs, ambulatory pump costs and NHS transport costs (Table 1). The manufacturer assumed that there were no significant economically important differences in the incidence or severity of adverse events between capecitabine and 5-FU-based regimens, and therefore the costs of treatment-related adverse events were not included in the analysis. After a request for clarifications, the manufacturer presented the expected costs associated with the relevant adverse events.

The results of the manufacturer's base-case analysis showed that capecitabine regimens are cost saving compared with their equivalent 5-FU-based regimens. The total net cost savings for capecitabine-based regimens were £1620 (ECX vs ECF), £1572 (EOX vs EOF), and £4210 (CX vs CF). Capecitabine remained cost saving in the manufacturer's one-way sensitivity analysis, scenario analysis and worst-case analysis. The manufacturer did not conduct probabilistic sensitivity analysis or subgroup analysis. The submission also included a threshold analysis that explored the additional effectiveness (in terms of QALYs) needed for 5-FU to be considered cost-effective.

### Commentary on the robustness of submitted evidence

The MS appears to include all relevant evidence from completed RCTs with respect to the question of efficacy; the ERG's search revealed no additional completed RCTs, although one additional ongoing trial was located.

The ERG identified a number of issues and errors in the review process, which had the potential to exclude relevant studies. However, it did not appear that this had impacted on the results of the review.

Two RCTs that directly addressed the comparison between capecitabine and 5-FU in combination with platinum in the licensed population were included.

The REAL-2 trial was large ( $n = 1002$ ), adequately powered, and closely reflective of UK standard practice. The patient population was also representative of those UK patients who were considered fit enough for standard chemotherapy,

although these patients are significantly younger than the UK aGC patient population as a whole. The trial included a majority of patients who are outside the licensed indication, having advanced inoperable cancer of the oesophagus or gastroesophageal junction. The ERG's clinical experts confirmed that treatment for each of these cancers would follow the same course as that for advanced inoperable gastric cancer. There was also no evidence of a statistically significant difference in prognosis based on primary tumour location.<sup>9</sup>

The ML17032 ( $n = 316$ ) trial assessed doublet therapy, which the ERG's clinical advisors indicated would be used in patients who were considered unable to tolerate triplet therapy. However, such doublets would be given at a lower dose than was used in the trial. The trial population was also unrepresentative of UK patients, being younger and having a different ethnic composition. When the non-inferiority analyses of efficacy outcomes were performed using a margin of 1.25 relative to the efficacy of 5-FU, rather than 1.40 as the protocol had specified, the trial had only 50% power to detect statistically significant non-inferiority.

Both trials were necessarily open-label, and REAL-2 was unblinded for all outcomes, whereas for ML1703 the MS reported blinded outcome assessment only for the primary outcome of PFS. The ERG requested these independently assessed data for the outcomes of tumour response and adverse events. The manufacturer subsequently supplied these data for response rates and, although differences in the data sets were present, there was no indication of systematic bias.

The primary weakness of the initial MS was the limited QoL data. This is of particular importance where the decision problem centres on an issue of clinical non-inferiority and patient preference.

With respect to economic evaluation, the ERG deems CMA to be an appropriate framework with which to analyse the decision problem. However, it should be noted that the appropriateness of using such an approach is dependent not only on clinical evidence from the REAL-2 and ML17032 trials, but also on evidence relating to QoL and adverse events. The weaknesses identified above regarding the evidence presented by the manufacturer are therefore relevant. The manufacturer has also failed fully to consider uncertainty when justifying the use of CMA.

**TABLE 2** Estimated overall NHS incremental costs reported in the manufacturer's (MS) base-case and worst-case scenario analysis, and results from the ERG's additional analysis

	Cost (£)		
	ECX vs ECF	EOX vs EOF	CX vs CF
<b>Base case</b>			
MS	-1620	-1572	-4210
ERG	-1585	-1538	-4060
<b>Worst-case scenario</b>			
MS	-74	-41	-1175
ERG	-213	-180	-965

CF, cisplatin + 5-FU; CX, cisplatin + capecitabine; ECF, epirubicin + cisplatin + 5-FU; ECX, epirubicin + cisplatin + capecitabine; EOF, epirubicin + oxaliplatin + 5-FU; EOX, epirubicin + oxaliplatin + capecitabine; ERG, evidence review group; MS, manufacturer's submission.

Overall, cost estimates for the CMA were generated appropriately. The ERG identified a number of shortcomings and potential uncertainties related to resource utilisation, unit costs, utilities and sensitivity analysis in the MS. However, these were considered minor, and additional analysis provided by the manufacturer, and further evaluations by the ERG, showed no impact on the overall conclusions. Results from the MS and ERG's additional analysis are compared in *Table 2*.

A full probabilistic analysis was not performed, so the probabilities that capecitabine is less and more costly than its comparators have not been formally quantified. However, the mean estimates, sensitivity analyses and worst-case scenario are consistent in suggesting that capecitabine has a lower mean cost than 5-FU-based regimens. Further analyses exploring the additional costs incurred by the NHS resulting from extending survival duration show that these are unlikely to have a material effect on decision-making regarding capecitabine.

## Conclusions

The submission was considered to contain convincing evidence of the non-inferiority of capecitabine to 5-FU on the outcomes of OS and PFS; this evidence was considered to be applicable to UK practice. There was evidence of some differences in adverse event profiles, but there was no evidence of a poorer safety

profile for capecitabine overall. There was also no evidence of any difference in QoL between the two fluoropyrimidines.

Although some uncertainty remains over the issues identified above, the ERG deems CMA to be an appropriate framework with which to analyse the current decision problem. Overall, cost estimates for the CMA were generated appropriately and were robust to uncertainties regarding assumptions and sources.

## Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance document issued by NICE on 28 July 2010 states that:

Capecitabine in combination with a platinum-based regimen is recommended for the first-line treatment of inoperable advanced gastric cancer.

## Acknowledgements

**Matthew Seymour**, Professor of Gastrointestinal Cancer Medicine, Cancer Research UK Clinical Centre, University of Leeds, Leeds, UK.

**Daniel Swinson**, Medical Oncologist, St James's Institute of Oncology, St James's University Hospital, Leeds, UK.

**Stephen Kelly**, Advanced Clinical Pharmacist for Oncology & Oncology/Haematology Clinical Trials, St James's Institute for Oncology, St James's University Hospital, Leeds, UK.

## Key references

1. National Institute for Health and Clinical Excellence (NICE). *Guide to the single technology (STA) process*. London: NICE; 2006. URL: [www.nice.org.uk/page.aspx?o=STAprcessguide](http://www.nice.org.uk/page.aspx?o=STAprcessguide).
2. Centre for Reviews & Dissemination and Centre for Health Economics Technology Assessment Group. *Capecitabine for the treatment of advanced gastric cancer: a single technology appraisal*. York: University of York, CRD; 2010.
3. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, *et al*. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;**358**:36–46.

4. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, *et al.* Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009;**20**:666–73.
5. National Institute for Health and Clinical Excellence (NICE). *Guide to the methods of technology appraisal*. London: NICE; 2008.
6. Drummond M, Sculpher M, Torrance G, O'Brien BJ, Stoddart G. *Methods for the economic evaluation of health care programmes*. 3rd edn. Oxford: Oxford University Press; 2005.
7. Okines AFC, Norman AR, McCloud P, Kang YK, Cunningham D. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. *Ann Oncol* 2009;**20**:1529–34.
8. Aaronson N, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez N, *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–76.
9. Chau I, Norman AR, Cunningham D, Oates J, Hawkins R, Iveson T, *et al.* The impact of primary tumour origins in patients with advanced oesophageal, oesophago-gastric junction and gastric adenocarcinoma: individual patient data from 1775 patients in four randomised controlled trials. *Ann Oncol* 2009;**20**:885–91.





# Rituximab for the treatment of relapsed/ refractory chronic lymphocytic leukaemia

J Dretzke,<sup>1\*</sup> P Barton,<sup>2</sup> B Kaambwa,<sup>2</sup> M Connock,<sup>1</sup>  
O Uthman,<sup>1</sup> S Bayliss<sup>1</sup> and C Meads<sup>1</sup>

<sup>1</sup>Unit of Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, UK

<sup>2</sup>Unit of Health Economics, University of Birmingham, Birmingham, UK

\*Corresponding author

**Declared competing interests of authors:** none

## Abstract

This paper presents a summary of the evidence review group (ERG) report on the clinical effectiveness and cost-effectiveness of rituximab with chemotherapy compared to chemotherapy only for the treatment of relapsed/refractory chronic lymphocytic leukaemia (CLL) based on the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Evidence was available in the form of one open-label, ongoing, unpublished randomised controlled trial (RCT), REACH (Rituximab in the Study of Relapsed Chronic Lymphocytic Leukemia), conducted by the manufacturer, which compared rituximab with a fludarabine and cyclophosphamide combination (R-FC) to fludarabine and cyclophosphamide (FC) only. REACH was scheduled to run for 8 years; however, the data provided were immature, with a median observation time at the time of data analysis of 2.1 years. REACH provided evidence of prolonged progression free survival with R-FC compared to FC (10 months, investigators' data), but no evidence of an overall survival benefit with R-FC. Patients refractory to fludarabine and with prior rituximab exposure were excluded from REACH and no controlled studies were identified by the ERG for these patient groups. The ERG had concerns about the structure of the economic model submitted by the manufacturer, which did not allow

## HTA 08/94/01

### Date of ERG submission:

14 September 2009

### TAR Centre(s):

West Midlands Health Technology Assessment Collaboration

### List of authors:

J Dretzke, P Barton, B Kaambwa, M Connock, O Uthman, S Bayliss and C Meads

### Contact details:

Janine Dretzke, Unit of Public Health, Epidemiology and Biostatistics, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

E-mail: [j.dretzke@bham.ac.uk](mailto:j.dretzke@bham.ac.uk)

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 08/94/01. The assessment report began editorial review in October 2009 and was accepted for publication in November 2009. See the HTA programme website for further project information ([www.hta.ac.uk](http://www.hta.ac.uk)). 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](http://www.hta.ac.uk/correspond)).

improvement in quality of life from treatment while in a progressed state. The manufacturer's model further assumed a divergence in cumulative deaths between the R-FC and FC treatment arms from the outset, which did not accord with observed data from REACH. When the survival advantage was removed, the manufacturer's base-case incremental cost-effectiveness ratio (ICER) changed from £15,593 to between £40,000 and £42,000 per quality-adjusted life-year (QALY). With no survival advantage, the ICER became sensitive to changes in utility. There was no good empirical evidence on the utility of CLL patients in different states. Allowing for the possibility of a survival advantage with rituximab (although not supported by current evidence), the ERG performed further modelling, which found that rituximab would be cost-effective at £20,000/QALY (£30,000/QALY) if a reduction in survival advantage relative to the manufacturer's base case of 40% (80%) was assumed. The guidance issued by NICE in July 2010 as a result of the STA recommends rituximab with FC for people with relapsed or refractory chronic lymphocytic leukaemia, except when the condition is refractory to fludarabine or where there has been previous treatment with rituximab.

## 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<sup>1</sup> is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor (here, Roche Products Ltd). 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 entitled '*Rituximab for relapsed/refractory chronic lymphocytic leukaemia*'.<sup>2</sup>

## Description of the underlying health problem

The underlying health problem is relapsed/ progressed and refractory chronic lymphocytic leukaemia (CLL). CLL is defined as relapsed in a patient who has previously achieved the criteria for a complete or partial response, but after a period of 6 or more months demonstrates evidence of disease progression. Refractory disease is defined as treatment failure (stable disease or non-response) or disease progression within 6 months of the last therapy.<sup>3</sup> Median age at diagnosis lies between 65 and 70 years, so will be higher for relapse, and the incidence rate at diagnosis is 3/100,000. The proportion of patients that progress in a 1-year period is estimated at 30–40% (Dr Jim Murray, University Hospitals Birmingham, personal communication). Prognosis can vary depending on the presence or absence of various cytogenetic abnormalities. Loss or mutation in the p-arm of chromosome 17 (del 17) is associated with decreased survival.

Treatment of CLL is with cytotoxic drugs/drug combinations (chemotherapy) including alkylating agents (chlorambucil, cyclophosphamide, bendamustine) or antimetabolites/purine analogues (fludarabine, cladripline). Drug combinations are also used, such as FC (fludarabine and cyclophosphamide), CHOP [cyclophosphamide, doxorubicin hydrochloride, vincristine (also called oncovin), prednisolone] and CVP [cyclophosphamide, vincristine (also called oncovin), prednisolone]. Monoclonal antibodies (biological therapy, immunotherapy) such as rituximab or alemtuzumab are also used, with rituximab (+FC) recently approved for first-line treatment by NICE [technology appraisal (TA) 174<sup>4</sup>].

In UK practice, most patients receive fludarabine or FC as first-line treatment then on progression may receive F(C) again, CVP, CHOP or CVP/CHOP with (off-licence) rituximab. Chlorambucil is predominantly reserved for patients unable to tolerate fludarabine or FC. Testing for genetic markers for tailoring treatment is not routinely undertaken but is being investigated in clinical trials. The choice of first and second-line treatment, and the decision about the stage of disease at which to (re-)initiate treatment is made on a patient-by-patient basis and varies according to regional treatment policies, previous treatment(s) and fitness of the patient. The British Committee for Standards in Haematology 2004

guidelines<sup>5</sup> are in the process of being updated to reflect findings of recent trials.

### Scope of the evidence review group report

The key research question was the clinical effectiveness and cost-effectiveness of rituximab plus chemotherapy compared to chemotherapy only in the treatment of patients with relapsed/refractory CLL, including patients with a del 17p mutation. Rituximab (MabThera<sup>®</sup>; Roche Products Ltd, Welwyn Garden City, UK) in combination with chemotherapy has been licensed for use in relapsed/refractory chronic lymphocytic leukaemia.<sup>6</sup>

The bulk of the clinical effectiveness data submitted by the manufacturer was based on one ongoing, open-label, 8-year randomised controlled trial (RCT) [REACH (Rituximab in the Study of Relapsed Chronic Lymphocytic Leukemia),  $n = 552$ ], which compared rituximab with a fludarabine and cyclophosphamide combination (R-FC) versus FC alone. At the time of data analysis (on which this report is based) median observation time was 2.1 years. Refractory patients included in the trial were those refractory to alkylators (CHOP, CVP, chlorambucil). The trial was not representative of all UK rituximab eligible patients as it excluded those refractory to fludarabine and those with prior rituximab exposure. Outcome measures in REACH were progression-free survival (PFS), overall survival (OS), event-free survival and response rates. Quality of life (QoL) measurements were based on the Functional Assessment of Cancer Therapy-General and measured for 1 year only and only up to the time of a patient experiencing an event.

Further (unpublished) evidence was submitted by the manufacturer in the form of uncontrolled studies to support evidence of effectiveness of rituximab in fludarabine refractory patients and for rituximab in combination with other chemotherapy regimens.

The manufacturer submitted an economic model to assess the cost per quality-adjusted life-year (QALY) of R-FC compared to FC. Clinical effectiveness parameters were based mainly on the REACH trial. QoL in REACH was not measured in a way that allowed conversion into utility values. Estimated

(non-preference based) utility values were obtained from the literature.<sup>7</sup>

### 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 reran the searches for RCTs using slightly modified versions of the search strategies employed by the manufacturer and independently assessed the validity of the REACH trial. The ERG also looked at commercial-in-confidence (CIC) results based on an independent (blinded) assessment of progression (as well as the investigators' assessment); summary data (rather than individual patient data) on the independent analysis were supplied by the manufacturer in a separate document.

The main results on PFS and OS in the submission were presented in Kaplan–Meier plots. These plots were modelled using a variety of parametric distributions (exponential, lognormal, log logistic, Weibull, Gompertz and gamma) to identify the best fitting function according to Akaike's information criteria. For economic modelling, the fits were extrapolated beyond observed data to a time horizon of 25 years. The ERG would have liked to independently obtain their own parametric fits in order to (a) test the biological plausibility of all the PFS extrapolations used in the manufacturer's economic modelling, (b) make a comparison of the relative advantage of R-FC versus FC delivered by the various parametric models and (c) effectively compare the investigator and independent assessments of PFS. This was not possible as individual patient data were not made available, and furthermore not all the requested parameters were supplied by the manufacturer.

The model structure and internal model validity were analysed by the ERG, and model parameters were assessed for their appropriateness. A number of additional sensitivity analyses were run based on varying assumptions set out in the submission, and the effect on the incremental cost-effectiveness ratio (ICER) was assessed.

## Results

### Summary of submitted clinical evidence

#### Progression-free survival

*Investigators' assessment* The curves for the FC and R-FC arm were similar in slope for most of the time represented but separated from each other especially during a 3-month period between 15 and 18 months. There was a statistically significant difference in median time to progression of 10.2 months in favour of R-FC. At the time of this analysis, an event had occurred in 53% of patients, the remainder were censored.

*Independent assessment* An independent, blinded assessment of progression, which is less likely to be susceptible to bias, was performed as part of REACH. The results are CIC.

#### Overall survival

At the time of data analysis, 75% (FC arm) and 78% (R-FC arm) of patients were still alive. Median survival could not be estimated for the R-FC arm. The curves were the same for both arms up to 2.5 years, after which they separated (*Figure 1*). There was no statistically significant difference between the curves (hazard ratio 0.83; 95% confidence interval 0.59 to 1.17).

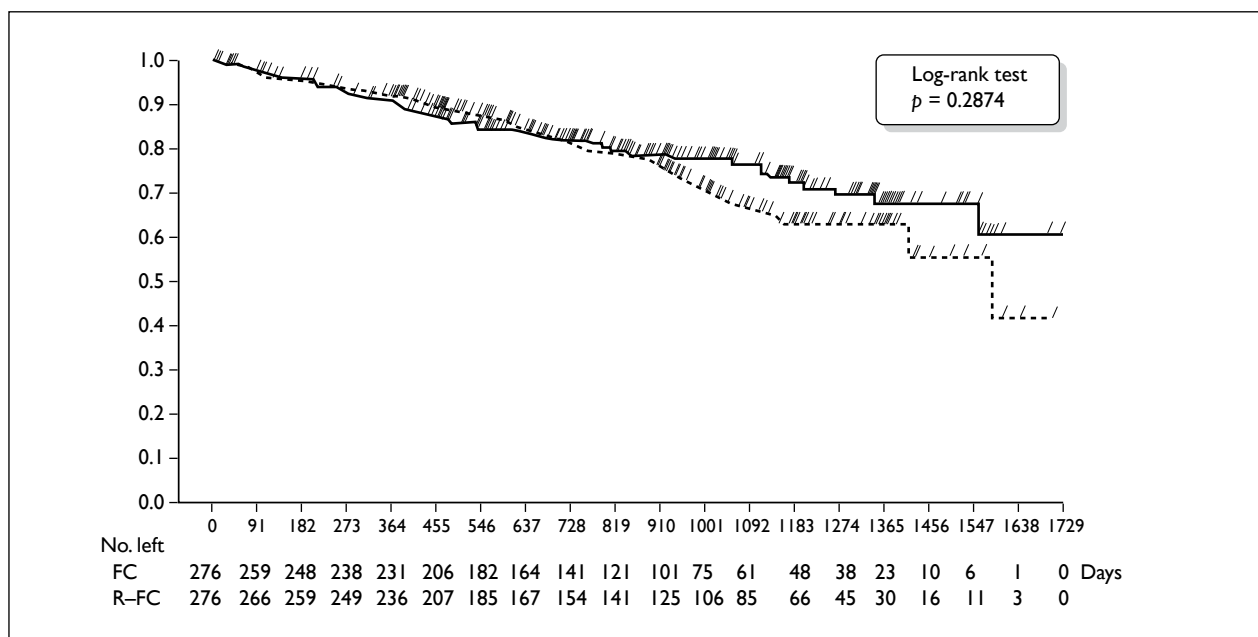
### Non-randomised studies

The manufacturer provided data from one uncontrolled study on salvage therapy with R-FC in sub-groups of patients with and without prior fludarabine exposure, and with and without prior rituximab exposure. These confidential results were provided ahead of publication, and the ERG were unable to identify data in the public domain.

### Summary of submitted cost-effectiveness evidence

The cost per QALY for the base case (manufacturer's calculation) was £15,593. This was based on utility values of 0.8 for PFS and 0.6 for progression, and on a difference in mean life-years between the R-FC arm and FC arm of 0.671, and a difference in mean QALYs of 0.585. The results for a number of one-way sensitivity analyses varied between £13,017 and £23,790. Parameters that were varied in the submission include the utility values, type of curve fit, rituximab costs, adverse event costs and supportive care costs.

A number of alternative analyses were carried out by the ERG in order to test the effect of changes to various assumptions within the manufacturer's submission. The effects on the ICER can be found in *Table 1*.



**FIGURE 1** Kaplan–Meier plot of overall survival (intention to treat) (from manufacturer's submission). FC, fludarabine and cyclophosphamide; R-FC, rituximab, fludarabine and cyclophosphamide.

**TABLE 1** Sensitivity analyses around ICER (performed by the ERG)

General issue	Details for this submission	Effect on ICER (£)
(Roche base case following clarification questions)		15,593
Model structure	Alternative choice of curves for PFS	13,140–17,317
	Correction of minor errors of logic	15,584
Measurement of effectiveness	Removal of overall survival benefit from rituximab	31,009–47,963
	Use of PFS curves based on independent assessment of progression	16,911–17,467
Measurement of utility	Halving and doubling difference between utilities for PFS and progressed states	13,017–17,306
Adverse events	Doubling costs for rituximab arm only	16,455
Rituximab costs	One fewer or one more 100-mg vial per cycle	13,803–17,383
	Retiming of rituximab costs	15,277–20,110
Assessment of progression	Independent (blinded) assessment rather than investigators' assessment (Weibull)	17,507
Survival	No OS benefit	40,568–42,444
Combination	Independent assessment of progression combined with no OS benefit	44,669–48,385
Combination	No OS benefit and utilities: PFS=0.9; progressed=0.5	20,284–21,222
Combination	No OS benefit and utilities: PFS=0.75; progressed=0.65	81,135–84,889

ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival.

Removing the survival effect had the most substantial impact on the ICER and results were subsequently more sensitive to changes in utilities.

Intermediate results can be obtained by taking a weighted average of the two survival curves. This

makes it possible to consider any desired fraction of the modelled advantage in overall survival from rituximab. *Table 2* shows the effect of such changes, using a Weibull curve for PFS. Similar patterns could be expected for other curve options.

**TABLE 2** Effect of reducing overall survival advantage (modelled by ERG)

Case considered	ICER (£)	
	Amended 1 <sup>a</sup>	Amended 2 <sup>b</sup>
0 (as base case)	15,593	15,593
10	16,457	16,478
20	17,453	17,508
30	18,615	18,721
40	19,991	20,169
50	21,647	21,925
60	23,681	24,098
70	26,242	26,852
80	29,573	30,455
90	34,088	35,365
100 (no OS advantage)	40,568	42,444

ICER, incremental cost-effectiveness ratio; OS, overall survival.

a The cumulative probability of death calculated in the comparator arm of the model was applied also to the rituximab arm.

b The cumulative probability of death calculated for the rituximab arm was applied also to the comparator arm.

**Commentary on the robustness of submitted evidence**

The analysis relies on the results of a single open-label, unpublished, ongoing RCT with immature data (median observation time of only 2.1 years at the time of analysis).

There was evidence that treatment with R-FC compared to FC alone results in a statistically significantly longer period of progression-free survival (10 months investigators' assessment; independent assessment results CIC) in both patients with and without the del 17 mutation. It is likely that this delay was associated with QoL gains, although there was a lack of suitable empirical evidence.

For OS, the median had not yet been reached in the R-FC arm and 75% and 78% of patients were still alive in the FC and R-FC arms respectively. There was no convincing evidence that there was a survival benefit in the R-FC arm. The Kaplan-Meier curves separate out after 2.5 years (see *Figure 1*), and the ERG was unsure whether there was a biologically plausible reason for why this might happen. Because of crossover from the FC to the R-FC arm over time, the curves are likely to become increasingly susceptible to bias.

The patients in REACH do not appear representative of a general relapsed CLL population, but may be representative of those eligible for treatment with FC. The median age in REACH was 63 years at relapse compared to a median age of 65–70 years at diagnosis in the general population. Ten per cent of included

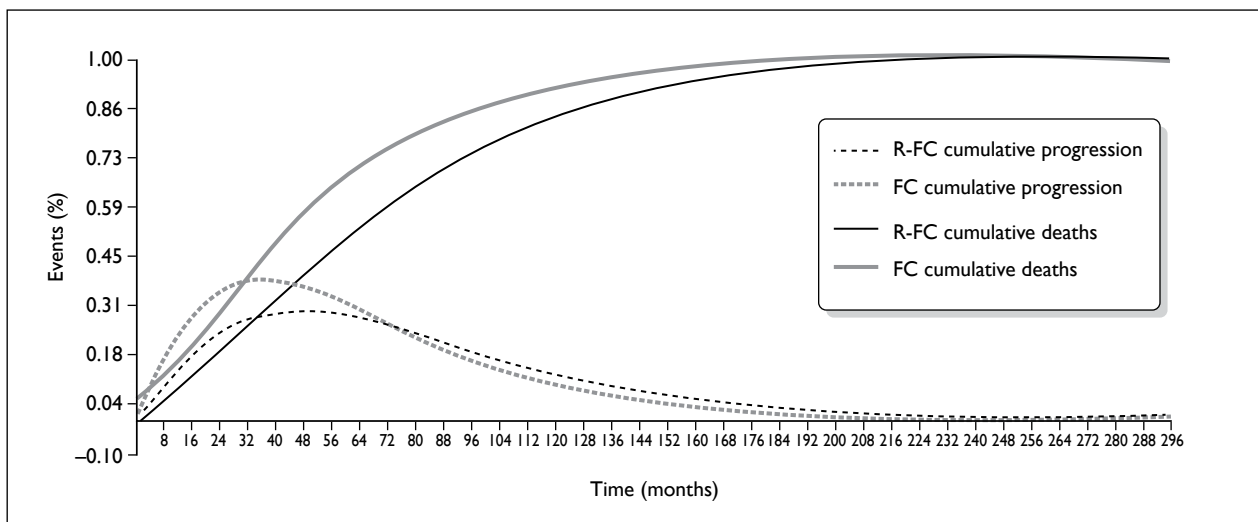
relapsed patients were at Binet stage A, which appears high. Younger and/or healthier patients are less likely to drop out due to side effects.

In REACH, fludarabine and cyclophosphamide were given as an infusion. These drugs are usually given orally in the UK. It is unclear whether this would have an impact on the effectiveness of the drugs.

There was no evidence on the effectiveness of R-FC compared to another treatment in fludarabine refractory patients or patients with prior rituximab exposure.

The model submitted by Roche follows the same structure as that used in the assessment of rituximab for first line treatment of CLL. There are three states in the model: PFS, progressed and death. No transition from progressed to PFS is possible. We share the concerns of the Peninsula Technology Assessment Group (PenTAG) about this structure. In summary, this has the effect of combining all patients post-progression into a single state. It is therefore not possible to improve QoL from treatment while in the progressed state.

There was considerable uncertainty associated with estimates of OS in the economic model. OS has been modelled by applying death rates to the PFS and progressed states in each arm of the model separately. The cumulative deaths modelled show a divergence between the two arms of the model from the start (*Figure 2*): this is not in accord with the observed pattern of deaths in the trial (see *Figure 1*). When the survival advantage is removed,



**FIGURE 2** Cumulative time to progression and death (from manufacturer's submission). FC, fludarabine and cyclophosphamide; R-FC, rituximab, fludarabine and cyclophosphamide.

the base-case ICER changes from £15,593 to between £40,000 and £42,000/QALY.

With no OS advantage for the rituximab arm, the economic model output becomes sensitive to the differential in utility between the non-progressed and the progressed state. There is a lack of empirical evidence about the utility of patients in these states.

While a range of different parametric curves have been applied to the data for PFS, none of them is a particularly good fit to the data, and there are doubts about the long term extrapolation of these curves.

The model assumes that the costs of rituximab are incurred throughout a cycle, so a patient progressing after half a cycle incurs only half of that cycle's cost. As rituximab is given as a one-off infusion at the start of each cycle, this assumption does not seem appropriate.

The model uses the investigators' assessment of progression rather than the independent (blinded) assessments, which are likely to give less biased results. However, when parametric fits were made to the independent analysis results, only small differences in the resulting ICERs were observed and the direction of change was not consistent.

An area of uncertainty is the difference in the cost of relapse therapy with rituximab (£9128) compared to the cost of first line therapy (£11,617) as given in the recent submission on rituximab in CLL.<sup>8</sup>

## Conclusions

The ERG found evidence that R-FC delays progression by 10 months (investigators' assessment) compared to treatment with FC alone in patients who have previously received alkylator-containing chemotherapy or fludarabine alone, are fludarabine sensitive and are considered suitable for treatment with FC. There was no evidence from current data to show that R-FC prolongs survival compared to FC. With no survival benefit assumed in the economic model, the base-case ICER changes from £15,593 to between £40,000 and £42,000/QALY and becomes sensitive to changes in utility. Further modelling around a hypothetical survival benefit found that rituximab would be cost-effective at a threshold of around £20,000/QALY (£30,000/QALY) when a 40% (80%) reduction in

survival benefit relative to the manufacturer's base case was assumed. Further evidence is needed on whether there is a survival benefit, the extent of this benefit and the associated utilities. Robust evidence is lacking on (a) the effectiveness of R-FC in patients who have previously received FC, R-FC or R-chemotherapy (other) as first-line therapy and (b) the effectiveness of R-chemotherapy (other) as treatment for relapsed CLL.

## Summary of NICE guidance issued as a result of the STA

NICE guidance from July 2010 recommends rituximab in combination with fludarabine and cyclophosphamide for people with relapsed or refractory chronic lymphocytic leukaemia, but not when there has been previous treatment with rituximab. Exceptions to the previous treatment with rituximab rule apply where this was in the context of a clinical trial (with any chemotherapy), or at a dose lower than the dose currently licensed for chronic lymphocytic leukaemia.

People who are currently receiving rituximab in combination with fludarabine and cyclophosphamide should have the option to continue treatment until they and their clinicians consider it appropriate to stop. The guidance is due to be reviewed in December 2010.

## Key references

1. NICE. *Guide to single technology (STA) process*. URL: [www.nice.org.uk/media/42D/B3/STAGuideLrFinal.pdf](http://www.nice.org.uk/media/42D/B3/STAGuideLrFinal.pdf) (accessed 24 September 2010).
2. Dretzke J, Barton P, Kaambwa B, Connock M, Uthman O, Bayliss S, Meads C. *Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia*. Birmingham, West Midlands Health Technology Assessment Collaboration, University of Birmingham, September 2009. URL: <http://www.nice.org.uk/nicemedia/live/12042/46063/46063.pdf>.
3. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, *et al*. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 guidelines. *Blood* 2008;**111**:5446–56.
4. Technology Appraisal 174. *Rituximab for first line treatment of chronic lymphocytic leukaemia*. URL: [www.nice.org.uk/TA174](http://www.nice.org.uk/TA174) (accessed October 2010).

5. Oscier D, Fegan C, Hillmen P, Illidge T, Johnson S, Maguire P, *et al.* Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. *Br J Haematol* 2004;**125**:294–317.
6. European Medicines Agency. *Summary of product characteristics*. 2010. URL: [www.emea.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_Product\\_Information/human/000165/WC500025821.pdf/](http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000165/WC500025821.pdf/)
7. Hancock S, Wake B, Hyde C, Doorduyn A. *Fludarabine as first line therapy for chronic lymphocytic leukaemia*. 2009. A West Midlands Health Technology Assessment Collaboration Report 2002. Birmingham, University of Birmingham.
8. Roche Products Limited. *Rituximab for the 1st line treatment of Chronic Lymphocytic Leukaemia*. 2009. URL: [www.nice.org.uk/nicemedia/pdf/RituximabSubmissionFinalCICAIC.pdf](http://www.nice.org.uk/nicemedia/pdf/RituximabSubmissionFinalCICAIC.pdf).



# The clinical effectiveness and cost-effectiveness of rituximab for the first-line treatment of chronic lymphocytic leukaemia: an evidence review of the submission from Roche

C Main,\* M Pitt, T Moxham and K Stein

Peninsula Technology Assessment Group (PenTAG), Exeter, UK

\*Corresponding author

**Declared competing interests of authors:** none

## Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of rituximab for the first-line treatment of chronic lymphocytic leukaemia (CLL) 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 searches for clinical effectiveness and cost-effectiveness data were appropriate and included all relevant studies. The submission's evidence came from a single, unpublished, well-conducted randomised controlled trial (RCT) comparing rituximab in combination with fludarabine and cyclophosphamide (R-FC) with fludarabine and cyclophosphamide (FC) alone for the first-line treatment of CLL. There was a statistically significant increase in progression-free survival (PFS) with R-FC compared with FC alone {median 39.8 months vs 32.2 months; hazard ratio [HR] 0.56 [95% confidence interval (CI) 0.43 to 0.72]}. However, the initial significant treatment benefit for R-FC compared with FC for overall survival was not maintained at a slightly longer follow-up time [median 25.4 months; adjusted HR 0.72 (95% CI 0.48 to 1.09)]. Response rates, numbers of patients with event-free survival and duration of response all favoured treatment with R-FC. Additional evidence from a mixed-treatment comparison model indicated R-FC to be significantly superior to chlorambucil alone for both PFS and overall

## HTA 08/95/01

### Date of ERG submission:

30 January 2009

### TAR Centre(s):

Peninsula Technology Assessment Group (PenTAG)

### List of authors:

C Main, M Pitt, T Moxham and K Stein

### Contact details:

Caroline Main, Peninsula Technology Assessment Group (PenTAG), Noy Scott House, Barrack Road, Exeter, UK

E-mail: [caroline.main@pms.ac.uk](mailto:caroline.main@pms.ac.uk)

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 08/95/01. The assessment report began editorial review in April 2009 and was accepted for publication in May 2009. See the HTA programme website for further project information ([www.hta.ac.uk](http://www.hta.ac.uk)). 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](http://www.hta.ac.uk/correspond)).

and complete response rates. The incidence of grade 3 or 4 adverse events was higher in the R-FC arm (77%) than in the FC arm (62%). Dose modifications were also more frequent in this arm, but this did not lead to differences in treatment discontinuation. Roche used a three-state Markov model (PFS, progressed and death) to model the cost-effectiveness of R-FC compared with FC and chlorambucil alone. The model used a cycle length of 1 month and a lifetime time horizon. The approach taken to modelling was reasonable and the sources and justification of estimates were generally sound. The base-case analysis produced an incremental cost-effectiveness ratio (ICER) of £13,189 per quality-adjusted life-year (QALY) for R-FC versus FC, and £6422 per QALY for the comparison of R-FC versus chlorambucil, suggesting that R-FC is cost-effective at normal willingness-to-pay thresholds. One-way sensitivity analyses produced a range of ICERs from £10,249 to £22,661 per QALY for R-FC versus FC, and £5612 and £6921 per QALY for R-FC versus chlorambucil. Probabilistic sensitivity analysis results matched the deterministic results very closely. However, the sensitivity analysis did not fully investigate the uncertainty associated with differential values across arms or with the structural assumptions of the model, and utility values were not drawn from an empirical study. The NICE guidance issued as a result of the STA states that: Rituximab in combination with fludarabine and cyclophosphamide (R-FC) is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia in people for whom fludarabine in combination with cyclophosphamide (FC) is considered appropriate. Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line 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 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, for a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> 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 the clinical effectiveness and cost-effectiveness of rituximab for the first-line treatment of chronic lymphocytic leukaemia.<sup>2</sup>

## Description of the underlying health problem

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia, comprising approximately 30% of all adult leukaemias. The incidence is about 3 per 100,000, but this varies with age and sex. The median age of diagnosis is between 65 and 70 years, and men are twice as likely to be affected as women. Incidence increases significantly with age, with a rate of almost 50 per 100,000 in patients over 70 years.

The exact causes of CLL remain unknown; however, a combination of genetic and environmental factors is thought to be involved. The presentation of patients with CLL to health-care providers is typically heterogeneous, with about 70–80% of patients diagnosed as an incidental finding following a full blood count test for some other reason. A definitive diagnosis of CLL has a characteristic lymphocyte morphology on blood film, with a specific immunophenotype (as shown by flow cytometry), and requires an absolute B-cell lymphocytosis of at least  $5 \times 10^9/l$ .

Two methods have been devised to stage CLL: the Binet and Rai systems. The Binet system is more commonly used in Europe and comprises three stages: stage A, less than three lymphoid areas involved; stage B, more than three lymphoid areas involved; and stage C, haemoglobin  $< 10$  g/dl or platelets  $100 \times 10^9/l$ . The course of CLL is heterogeneous and it is generally anticipated that approximately one-third of patients (usually with Binet stage A disease) will never need any form of treatment and will die with, rather than of, their disease.<sup>3</sup> For the remaining majority of patients (usually with Binet stage B or C disease) CLL is incurable and has a median life expectancy

of between 5 and 10 years. Standard criteria from the International Workshop on Chronic Lymphocytic Leukaemia are used to guide whether patients should start treatment with a first-line chemotherapeutic regimen.<sup>4</sup>

As CLL is characterised by periods of active disease, during which patients are symptomatic, separated by chemotherapy-induced remissions, once patients have started treatment the main aim of therapy is to induce durable remissions during which patients are free of disease symptoms, the psychological burden of active life-threatening illness and the toxicity of chemotherapy.

## Scope of the ERG report

### Research question

What is the clinical effectiveness and cost-effectiveness of rituximab in combination with fludarabine therapies versus fludarabine therapies alone or chlorambucil for the first-line treatment of CLL?

### Intervention

- Brand name: MabThera®.
- Approved name: rituximab.
- Therapeutic class: antineoplastic agents.
- Product licence holder: Roche Products.

### Outcomes

Clinical effectiveness outcomes were progression-free survival (PFS), overall survival (OS), event-free survival, disease-free survival, response rates, duration of response, time to new CLL treatment, health-related quality of life and adverse effects of treatment. Cost-effectiveness outcomes were incremental cost per quality-adjusted life-year (QALY), resource utilisation and the cost of treating adverse events (blood transfusions and bone marrow transplants).

### Type of clinical effectiveness/cost-effectiveness data used

For clinical effectiveness, 'time to event' data were used, reported as median time in either days or months with the point estimates expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). For cost-effectiveness, Roche built a three-state Markov model. For the comparison of rituximab (R) in combination with fludarabine

and cyclophosphamide (R-FC) versus fludarabine and cyclophosphamide (FC) alone the model was parameterised by effectiveness data from the German Chronic Lymphocytic Leukaemia trial (CLL-8).<sup>5</sup> For the comparison of R-FC versus chlorambucil monotherapy, HRs for PFS were derived using a mixed-treatment comparison (MTC) model. Health-state utility values were taken from a report by Hancock and colleagues<sup>6</sup> on the use of fludarabine as first-line treatment for CLL; these values were estimated by the report authors. Costs were based on an NHS and Personal Social Services perspective.

### Stated potential health effects

Rituximab is a chimeric murine/human monoclonal antibody that binds selectively to the CD20 cell antigen expressed on the surface of mature B lymphocytes and any tumour cell that expresses CD20, including B-cell CLL. It causes depletion of normal and malignant B cells. Although its mechanism of action is not precisely defined, antibody-directed cytotoxicity, complement-dependent cytotoxicity, induction of apoptosis and sensitisation of cells to conventional cytotoxic drugs are all likely to be important.<sup>7-9</sup>

### Stated costs

Rituximab is available in two vials sizes: 10-ml vial (minus VAT) = £174.63; 50-ml vial (minus VAT) = £873.15.

## 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 manufacturer's search strategy was reviewed by an information scientist and the searches were rerun with text words and a full clinical trials filter to see if any relevant trials had been omitted. The methods used by the manufacturer to report clinical effectiveness were critiqued using the principles advocated in the Centre for Reviews and Dissemination's (CRD) guidance for undertaking reviews in health care.<sup>10</sup> Roche's economic evaluation was assessed against the following study quality checklists: NICE reference case,<sup>11</sup> Drummond and colleagues<sup>12</sup> and Philips and

colleagues<sup>13</sup> for decision model-based economic evaluations. The model was extensively checked and rerun to check for wiring and parameterisation errors.

## Results

### Summary of submitted clinical evidence

The evidence for the submission was based on one phase III randomised controlled trial (RCT) comparing R-FC with FC for the first-line treatment of people with CLL (the CLL-8 trial;<sup>5</sup>  $n = 810$ ). Additional evidence was provided in the form of an MTC model based on PFS hazards from five trials allowing for an indirect comparison of R-FC with chlorambucil monotherapy.<sup>5,14-17</sup> Chlorambucil had been included as a comparator in two of the five trials.<sup>15,16</sup>

The CLL-8 trial was a randomised, parallel-group, multicentre trial; however, blinding of both patients and outcome assessors to treatment allocation was not attained, which may have introduced bias into the results. The trial was stopped early (median follow-up 20.7 months) at the time of the planned interim analysis because of significant differences in PFS between treatment arms. Data from four different sets of analyses of the trial are presented: (1) interim analysis (median follow-up 20.7 months); (2) snapshot analysis 1 (median follow-up 25.4 months); (3) snapshot analysis 2 (median follow-up 25.5 months); and (4) economic analyses snapshot (median follow-up 26.4 months).

At 20.7 months follow-up there was a statistically significant increase in PFS with R-FC compared with FC alone [median 39.8 months vs 32.2 months; HR 0.56 (95% CI 0.43 to 0.72)]. However, for OS, the initial treatment benefit for the R-FC regimen noted at the time of the interim analysis was no longer maintained at slightly longer follow-up (snapshot analysis 1) [HR 0.72 (95% CI 0.48 to 1.09)]. Patients in the R-FC arm remained event free (disease progression, relapse, death or start of new CLL treatment) significantly longer than those in the FC-arm [39.8 months vs 31.1 months; HR 0.55 (95% CI 0.43 to 0.70)]. Response rates also significantly favoured treatment with R-FC, with 36.0% of patients in this arm achieving complete response compared with 17.2% in the FC arm. Partial response rates were not significantly different between trial arms at 50.1% for R-FC and 55.5% for FC respectively.

The incidence of grade 3 or 4 adverse events was higher in the R-FC arm (77%) than in the FC arm (62%), mostly because of a higher incidence of blood and lymphatic system disorders (57% versus 41%). Dose modifications were also more frequent in this arm. However, this did not lead to differences in treatment discontinuation. There were also no difference between arms in the rate of deaths considered related to therapy (2%).

### Mixed-treatment comparison model

Based on results of the five trials included in the MTC<sup>5,14-17</sup> (with chlorambucil used as the reference treatment), R-FC significantly increased PFS compared with chlorambucil alone [mean HR 0.24 (lower bound 0.17, upper bound 0.34)].

### Summary of submitted cost-effectiveness evidence

Roche used a Markov model with a three-state structure (PFS, progressed and death) to model the cost-effectiveness of R-FC compared with FC and chlorambucil alone. The model used a cycle length of 1 month and a lifetime time horizon (equating to 15 years).

Roche's base-case analysis produced an incremental cost-effectiveness ratio (ICER) of £13,189 per QALY for R-FC versus FC, and an ICER of £6422 per QALY for the comparison of R-FC versus chlorambucil. One-way sensitivity analyses produced a range of ICERs from £10,249 per QALY to £22,661 per QALY for the comparison of R-FC versus FC, and £5612 per QALY and £6921 per QALY for R-FC versus chlorambucil. Results from further probabilistic sensitivity analysis matched the deterministic results very closely.

## Commentary on the robustness of submitted evidence

### Strengths

The searches for clinical effectiveness and cost-effectiveness data were appropriate and included all relevant studies. The identified RCT was well conducted and the findings were likely to be reasonably robust.

The approach taken to modelling was reasonable and the sources and justification of estimates were generally sound.

## Weaknesses

The evidence was based on only one completed and unpublished RCT.

The sensitivity analysis was limited and did not fully investigate the uncertainty associated with differential values across arms or with the structural assumptions of the model. Utility values were not drawn from an empirical study.

## Conclusions

There was a statistically significant increase in PFS with R-FC compared with FC alone [median 39.8 months vs 32.2 months; HR 0.56 (95% CI 0.43 to 0.72)]. However, the initial significant treatment benefit for R-FC compared with FC for OS was not maintained at a slightly longer follow-up time [median 25.4 months; adjusted HR 0.72 (95% CI 0.48 to 1.09)]. Response rates, numbers of patients with event-free survival and duration of response all favoured treatment with R-FC.

The MTC model indicated R-FC to be significantly superior to chlorambucil alone for both PFS and overall and complete response rates.

With an ICER of £13,189 per QALY for R-FC versus FC, and £6422 for R-FC versus chlorambucil alone, there is a strong probability that R-FC is cost-effective at normal willingness-to-pay thresholds.

## Areas of uncertainty

It was unclear whether the observed treatment benefit for use of rituximab combination therapy for PFS was associated with longer-term gains in OS and how plausible it was to extrapolate any PFS benefits in the longer term.

## Key issues

Almost all data parameters for effectiveness were drawn from the CLL-8 trial. Although this trial was of reasonable quality, there are inherent limitations in an analysis that relies on data from a single clinical trial.

The issue of structural uncertainty in the model relating to the treatment of OS rates between the trial arms was not adequately explored in sensitivity analyses. This relates specifically to the assumption of aggregation in the post-relapse state. The ERG

felt that this was likely to be clinically unrealistic as patients will receive further treatment at progression that may then result in further periods of PFS. The relapsing nature of CLL means that subsequent periods of progression are less likely to respond to further treatment, implying that later periods of progression in the course of disease are likely to be associated with higher disease-related mortality. This casts doubts over the simplifying assumption of a constant hazard of death after progression as modelled by Roche.

Additionally, it should be noted that once any assumed benefit for OS is removed, model outputs become highly sensitive to the utility parameters assumed for the PFS and progressed states, and these values are not currently available from an appropriate source.

## Summary of NICE guidance issued as a result of the STA

At the time of writing, the Appraisal Consultation Document issued by NICE on 26 March 2009 states that:

Rituximab in combination with fludarabine and cyclophosphamide (R-FC) is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia in people for whom fludarabine in combination with cyclophosphamide (FC) is considered appropriate. Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of chronic lymphocytic leukaemia.

## References

1. National Institute for Health and Clinical Excellence. *Guide to the single technology (STA) process*. 19 September 2006. URL: [www.nice.org.uk/page.aspx?o=STAprcessguide](http://www.nice.org.uk/page.aspx?o=STAprcessguide).
2. Main C, Pitt M, Moxham T, Stein K. *The clinical and cost-effectiveness of rituximab for the first-line treatment of chronic lymphocytic leukaemia: an evidence review of the submission from Roche*. London: NICE; 2009. URL: [www.nice.org.uk](http://www.nice.org.uk).
3. Dighiero G. Unsolved issues in CLL biology and management. *Leukemia* 2003;**17**:2385–91.
4. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, *et al.*

- Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008;**111**:5446–56.
5. Roche. *CLL8 final clinical study report ML17102*. 2008.
  6. Hancock S, Wake B, Hyde C. *Fludarabine as first-line therapy for chronic lymphocytic leukaemia*. West Midlands Health Technology Assessment Collaboration Report 42. Birmingham: University of Birmingham, Department of Public Health and Epidemiology; 2002.
  7. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, *et al*. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood* 1994;**83**:435–45.
  8. Demidem A, Lam T, Alas S, Hariharan K, Hanna N, Bonavida B. Chimeric anti-CD20 (IDEC-C2B8) monoclonal antibody sensitizes a B cell lymphoma cell line to cell killing by cytotoxic drugs. *Cancer Biother Radiopharm* 1997;**12**:177–86.
  9. Anderson DR, Grillo-Lopez A, Varns CEA. Targeting cytotoxic immunotherapy. *Biochem Soc Trans* 1997;**25**:705–8.
  10. NHS Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. Report No. 4 update. York: CRD, University of York; 2009.
  11. National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal*. 2008. URL: [www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459](http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459).
  12. Drummond M, O'Brien B, Stoddart G, Torrance G. *Methods for the economic evaluation of health care programmes 47*. Oxford, UK: Oxford University Press; 1997.
  13. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *Pharmacoeconomics* 2006;**24**:355–71.
  14. Eichhorst BF, Busch R, Hopfinger G, Pasold R, Hensel M, Steinbrecher C, *et al*. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood* 2006;**107**:885–91.
  15. Catovsky D, Richards S, Matutes E, Oscier D, Dyer MJ, Bezares RF, *et al*. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. *Lancet* 2007;**370**:230–9.
  16. Hillmen P, Skotnicki AB, Robak T, Jaksic B, Dmoszynska A, Wu J, *et al*. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol* 2007;**25**:5616–23.
  17. Flinn IW, Neuberger DS, Grever MR, Dewald GW, Bennett JM, Paietta EM, *et al*. Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. *J Clin Oncol* 2007;**25**:793–8.



# Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer

J Greenhalgh,\* C McLeod, A Bagust, A Boland, N Fleeman, Y Dundar, J Oyee, R Dickson, H Davis, J Green, E McKenna and M Pearson

Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool, UK

\*Corresponding author

**Declared competing interests of authors:** none

## Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), in accordance with the licensed indication, based upon the evidence submission from the manufacturer (Eli Lilly) to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The primary clinical outcome measure was progression free survival (PFS). Secondary outcomes included overall survival (OS), time to worsening of symptoms, objective tumour response rate, adverse events and changes in lung cancer symptom scale. Data for two populations were presented: patients with non-squamous NSCLC histology and patients with adenocarcinoma histology. The clinical evidence was derived from a double-blind, placebo-controlled randomised controlled trial (RCT), the JMEN trial. The trial compared the use of pemetrexed + best supportive care (BSC) as maintenance therapy, with placebo + BSC in patients with NSCLC ( $n = 663$ ) who had received four cycles of platinum-based chemotherapy (CTX) and whose disease had not progressed. In the licensed population (patients with non-squamous histology), the trial demonstrated greater median PFS for patients treated with

## HTA 08/207/01

### Date of ERG submission:

12 October 2009

### TAR Centre(s):

Liverpool Reviews and Implementation Group

### List of authors:

J Greenhalgh, C McLeod, A Bagust, A Boland, N Fleeman, Y Dundar, J Oyee, R Dickson, H Davis, J Green, E McKenna and M Pearson

### Contact details:

Janette Greenhalgh, Liverpool Reviews and Implementation Group, University of Liverpool, Room 2.21, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB, UK

E-mail: [janette.greenhalgh@liverpool.ac.uk](mailto:janette.greenhalgh@liverpool.ac.uk)

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 08/207/01. The assessment report began editorial review in November 2009 and was accepted for publication in February 2010. See the HTA programme website for further project information ([www.hta.ac.uk](http://www.hta.ac.uk)). 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](http://www.hta.ac.uk/correspond)).

pemetrexed than for patients in the placebo arm [4.5 vs 2.6 months; hazard ratio (HR) 0.44; 95% confidence interval (CI) 0.36 to 0.55,  $p < 0.00001$ ]. Median OS was also greater for the pemetrexed-treated patients (15.5 vs 10.3 months; HR 0.70; 95% CI 0.56 to 0.88,  $p = 0.002$ ). In addition, tumour response and disease control rates were statistically significantly greater for patients who received pemetrexed. Patient survival rates at 1 year and 2 years were higher in the pemetrexed arm. The incremental cost-effectiveness ratios (ICERs) estimated by the manufacturer's model were £33,732 per quality adjusted life-year (QALY) for the licensed nonsquamous population, and £39,364 per QALY for the adenocarcinoma subgroup. Both of these ICERs were above the standard NICE willingness-to-pay range (£20,000–£30,000 per QALY). The manufacturer also presented a case for pemetrexed to be considered as an end of life treatment. The ERG identified a number of problems in the economic model presented by the manufacturer; after correction, the base case ICER was re-estimated as £51,192 per QALY gained and likely to exceed NICE's willingness-to-pay thresholds. Following a revised economic analysis submitted by the manufacturer, the AC accepted that an ICER of £47,000 per QALY gained was most plausible. The AC also considered that maintenance treatment with pemetrexed fulfilled the end of life criteria. The guidance issued by NICE, on 20 June 2010, in TA190 as a result of the STA states that: People who have received pemetrexed in combination with cisplatin as first-line chemotherapy cannot receive pemetrexed maintenance treatment.

1.1 Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.

## 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, where most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> 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 entitled '*Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)*'.

## Description of the underlying health problem

Lung cancer is the second most common cancer diagnosed in the UK, with over 33,000 new cases diagnosed in England and Wales in 2006, and the leading cause of cancer death.<sup>2</sup> Lung cancer is the second most common cancer in men after prostate cancer, and the third most common cancer in women after breast and bowel cancer.

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers diagnosed. The main subtypes of NSCLC are squamous cell carcinoma (33%), adenocarcinoma (25%), large cell carcinoma (4%), and NSCLC 'not-otherwise specified' (NOS; 36%).<sup>3</sup> A further 1% are 'carcinoma in situ' and 1% are broncho-alveolar cell carcinoma. While cigarette smoking has been linked to all four types of lung cancer, the incidence of adenocarcinoma has been steadily increasing worldwide, and modifications to cigarette design are thought to be responsible for this shift in pathologic diagnosis pattern.<sup>4</sup>

Survival in patients with lung cancer is poor. It was responsible for approximately 29,600 deaths in England and Wales in 2007.<sup>2</sup> For patients with stage IIIB, only 7–9% may live for 5 years and for patients with stage IV (metastatic) cancer, only about 2–13% survive for 5 years.<sup>2</sup>

One reason for this poor prognosis is the late identification of the disease. Lung cancer is asymptomatic in the early stages and advanced disease is not amenable to curative treatment. Another reason, which explains the UK's relatively poor performance in comparison with other

developed countries, is low active anti-cancer treatment rates. The National Lung Cancer Audit states that only 23.2% of NSCLC patients in England and Wales received first-line CTX in 2006.<sup>5</sup>

Maintenance treatment is a new treatment paradigm and is proposed as an alternative for the 'watch and wait' phase of the current treatment pathway, for patients with complete or partial response/stable disease after four cycles of first-line treatment.

The goal of maintenance treatment is to maintain the clinical benefit achieved with first-line CTX. Maintenance treatment is continued until disease progression.

### Scope of the evidence review group report

Pemetrexed is licensed in Europe as monotherapy for the maintenance treatment of patients with NSCLC, other than predominantly squamous cell histology. First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.<sup>6</sup>

The ERG report presents the results of the evaluation of the manufacturer (Eli Lilly) evidence submission regarding the use of pemetrexed as a maintenance therapy in the patient group outlined above. The report includes an assessment of both the clinical effectiveness and cost-effectiveness evidence submitted by the manufacturer. The manufacturer submission (MS) described the use of pemetrexed + best supportive care (BSC) with BSC + placebo.

The primary clinical outcome measure was progression-free survival (PFS). Secondary outcomes included overall survival (OS), time to worsening of symptoms, objective tumour response rate, adverse events and changes in lung cancer symptom scale.

Cost-effectiveness was measured in terms of incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY).

Data for two populations were presented: patients with non-squamous NSCLC histology and patients with adenocarcinoma histology.

## 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 evaluated the quality of the manufacturer's clinical effectiveness review. Searches conducted by the manufacturer were assessed for completeness, and the single trial put forward as evidence of effectiveness was critically appraised using the manufacturer's responses to specific questions in the submission template. With regard to cost-effectiveness evidence, the ERG assessed the manufacturer's searches for completeness, critically appraised the submitted economic model using a standard assessment tool,<sup>7</sup> and conducted a detailed evaluation of the model. The ERG recalculated the base-case cost-effectiveness results, correcting a number of methodological errors and reanalysed the survival estimates. The ERG also undertook a basic probabilistic sensitivity analysis as this was not provided by the manufacturer.

## Results

### Summary of submitted clinical evidence

The evidence described in the MS is derived from a double-blind, placebo-controlled randomised controlled trial (RCT), the JMEN trial.<sup>8</sup> The trial compared the use of pemetrexed + BSC as maintenance therapy, with placebo + BSC in patients with NSCLC ( $n = 663$ ) who had received four cycles of platinum-based CTX and whose disease had not progressed. The MS focused on the clinical outcomes of the subgroup of patients with non-squamous histology ( $n = 481$ ), which is the population for which pemetrexed is licensed in this indication; the MS also focused on a subgroup of the licensed population, patients with adenocarcinoma.

The results for the licensed non-squamous population are summarised in *Table 1*. In the licensed population the trial demonstrated greater median PFS for patients treated with pemetrexed than for patients in the placebo arm [4.5 vs 2.6

TABLE 1 Key results of the JMEN trial (non-squamous population)

End point	Pemetrexed (n = 325)	Placebo (n = 156)	HR (95% CI)	p-value
<b>Primary</b>				
PFS (months) median	4.5	2.6	0.44 (0.36 to 0.55)	<0.00001
<b>Secondary</b>				
OS (months) median	15.5	10.3	0.70 (0.56 to 0.88)	0.002
Tumour response (%) (CR + PR)	7.4	1.9		0.018
Disease control rate (%) (CR+PR+SD)	57.7	32.7		<0.001
Survival rate at 1 year (%)	60	42		
Survival rate at 2 year (%)	28	22		

CI, confidence interval; CR, complete response; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

months; hazard ratio (HR) 0.44; 95% confidence interval (CI) 0.36 to 0.55,  $p < 0.00001$ ]. Median OS was also greater for the pemetrexed-treated patients (15.5 versus 10.3 months; HR 0.70; 95% CI 0.56 to 0.88,  $p = 0.002$ ). In addition, tumour response and disease control rates were statistically significantly greater for patients who received pemetrexed. Patient survival rates at 1 year and 2 years were higher in the pemetrexed arm. The health-related quality of life (HRQoL) data presented were limited owing to high levels of censoring/missing data. Safety data demonstrated that patients treated with pemetrexed had statistically significantly higher rates of grade 3 or 4 neutropenia, and experienced higher rates of transfusions and hospitalisation due to drug toxicity.

### Summary of submitted cost-effectiveness evidence

The manufacturer did not identify any published cost-effectiveness analyses of pemetrexed for the maintenance treatment of patients with NSCLC, and therefore developed a de novo economic model to support their economic case. The model compares pemetrexed + BSC with 'watch and wait' + BSC. The clinical data used in the economic model were primarily generated from the JMEN trial.<sup>8</sup> Although the model was trial-based, there was also a modelling component to allow the extrapolation of health effects beyond the 29 month trial period up to 6 years. The manufacturer's economic evaluation adopts a lifetime horizon (taken as 6 years) for the consideration of costs and benefits, and the

perspective is that of the UK NHS and Personal Social Services.

The ICERs estimated by the manufacturer's model are £33,732 per QALY for the licensed non-squamous population, and £39,364 per QALY for the adenocarcinoma subgroup. Both of these ICERs are above the standard NICE willingness-to-pay range (£20,000–£30,000 per QALY).

The manufacturer also presented a case for pemetrexed to be considered as an end-of-life treatment.

### Commentary on the robustness of submitted evidence

The manufacturer cited evidence from a well-designed trial (JMEN)<sup>8</sup> of the clinical benefit of pemetrexed + BSC as maintenance treatment compared with placebo + BSC. The trial recruited a substantial number of patients in a difficult disease area. It is noteworthy that patients and assessors in the JMEN<sup>8</sup> trial were blinded to treatment group allocation and that investigators' outcome assessments were independently verified.

The ERG noted that there was only one relevant RCT (JMEN)<sup>8</sup> that compared pemetrexed + BSC as maintenance treatment with placebo + BSC. Despite designing the trial to include a comprehensive analysis of HRQoL, very limited data was collected and reported in the MS. This means it was very difficult to determine how patients' HRQoL would be affected by pemetrexed in a maintenance setting.

**TABLE 2** Effect of corrections and amendments made by ERG to the manufacturer's model for the non-squamous population

Model amendment	Pemetrexed		Placebo		Incremental		ICER	Changes		
	Costs	QALYs	Costs	QALYs	Costs	QALYs	(£/QALY)	Costs	QALYs	ICER
Submitted base case	£17,455	0.9697	£8318	0.6988	£9137	0.2709	£33,732	–	–	–
All cycles of pemetrexed and revised CTX costs	£20,638	0.9841	£8323	0.6989	£12,315	0.2852	£43,179	+£3178	+0.0143	+£9447
Revised utility values	£17,455	0.9540	£8318	0.7057	£9137	0.2483	£36,798	–	–0.0226	+£3066
Continuity correction	£17,405	0.9467	£8288	0.6851	£9117	0.2615	£34,860	–£20	–0.0094	+£1128
Correct double discounting	£17,522	1.0006	£8352	0.7149	£9169	0.2857	£32,091	+£32	+0.0148	–£1641
Discounting assumptions	£17,421	0.9617	£8312	0.6909	£9109	0.2708	£33,640	–£60	–0.0001	–£88
Include monitoring costs	£17,838	0.9697	£8452	0.6988	£9386	0.2709	£34,651	+£249	–	+£919
Correct arithmetic	£17,398	0.9658	£8248	0.6953	£9149	0.2706	£33,817	+£12	–0.0003	+£85
Combined effect of above changes	£20,925	0.9539	£8370	0.6881	£12,555	0.2658	£47,239	+£3418	–0.0051	+£13,507
Combined effect of all changes including IPD survival analysis (excluding significant protocol violations)	£20,902	0.9851	£8382	0.7405	£12,520	0.2446	£51,192	+£3383	–0.0263	+£17,460

CTX, chemotherapy; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; QALYs, quality-adjusted life-years.

The primary end point of the key trial was changed by the manufacturer from OS to PFS during the course of the trial. No information was provided that fully justified the change of clinical end point.

The statistical analysis plan described by the manufacturer also included a test for treatment by histology interaction and corresponding subgroup analyses. The results for the subgroup of patients with non-squamous histology provided the clinical evidence in the MS. However, the trial randomisation process did not include stratification by histology status. Moreover, the restriction of the licensed population to only the non-squamous subgroup effectively reduced the statistical power of the trial, with consequences of increased uncertainty in the cost-effectiveness analysis.

The projection of survival from the end of the trial period, the costing of CTX treatment and the utility values used in the manufacturer's model were not ideal and underestimate the size of the ICER.

The manufacturer implemented a capping rule in its economic model to limit the maximum number of cycles of maintenance treatment that patients could receive. However, the cycle capping rule affected only costs; it did not take account of any reduction in outcomes caused by capping the maximum number of cycles at 17 rather than allowing the JMEN trial<sup>8</sup> maximum of 55. Again, this capping rule underestimated the size of the ICER.

Making all of the necessary ERG corrections/adjustments to the manufacturer's model, the ERG's base-case ICER for the non-squamous population was estimated at £51,192 per QALY (Table 2).

## Conclusions

The generalisability of the JMEN trial<sup>8</sup> to UK clinical practice is uncertain for a number of reasons:

- None of the patients in the trial were recruited from the UK. A sizeable proportion (35%) of patients were from Asian countries; these patients are documented in the literature as having a better prognosis for NSCLC than other ethnic groups, and the Asian patients in the trial appear to have improved survival

times compared with patients of other ethnicities.<sup>9</sup>

- Patients in the trial were able to receive unlimited cycles of maintenance therapy. This is unlikely to be the case in clinical practice in England and Wales and it is unclear how this difference would impact on survival in a clinical setting.
- Paclitaxel was used in the JMEN trial as a first-line treatment for a greater proportion of patients in the trial than might be the case in clinical practice in England and Wales. The impact of this when generalising the results is unknown.
- A number of patients in the trial received second-line therapies that are not available to patients in clinical practice in England and Wales, which may have affected the OS observed in the trial.
- Confirmed histological diagnosis of non-squamous NSCLC is required before patients can be offered maintenance treatment with pemetrexed. While histological testing is routinely carried out in many centres in England and Wales, this will not be available to all patients. Therefore, it is unclear if pemetrexed for maintenance therapy will be available in all centres in the UK, which may give rise to equity concerns.

### 'End-of-life' criteria

Analysis of the JMEN trial<sup>8</sup> individual patient data and revised projection modelling confirmed that the mean life extension from use of pemetrexed as maintenance therapy was likely to exceed 3 months. However, the number of patients who would be eligible to receive pemetrexed is uncertain. The manufacturer's estimates (used to present its end of life case) were based on amalgamation of information from different sources with differing definitions. The methods of calculation are not well reported and a number of assumptions were made which may not be valid.

Several factors serve to limit the generalisability of the trial to UK clinical practice, and the ERG could not be confident that the clinical results presented in the MS give a true reflection of the benefits that could be expected with pemetrexed for the maintenance treatment of patients with non-squamous NSCLC in UK clinical practice. Furthermore, in the economic analysis there were a number of problems identified with the model (in addition to the JMEN trial<sup>8</sup> data) which indicate

that the ICER (re-estimated as £51,192 per QALY gained) could well exceed NICE's willingness-to-pay thresholds.

## Summary of NICE guidance issued as a result of the STA

Following a revised economic analysis submitted by the manufacturer, the AC accepted that an ICER of £47,000 per QALY gained was most plausible. The AC also considered that maintenance treatment with pemetrexed fulfilled the end of life criteria. The guidance issued by NICE, on 20 June 2010, in TA190 as a result of the STA states that:

People who have received pemetrexed in combination with cisplatin as first-line chemotherapy cannot receive pemetrexed maintenance treatment.

1.1 Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.

## Key references

1. NICE. *Guide to the single technology (STA) process*. 2006. URL: [www.nice.org.uk/media/913/06/Guide\\_to\\_the\\_STA\\_proof\\_6-26-10-09.pdf](http://www.nice.org.uk/media/913/06/Guide_to_the_STA_proof_6-26-10-09.pdf)
2. Cancer Research UK. *Cancer stats*. 2009. URL: [www.cancerresearchuk.org/](http://www.cancerresearchuk.org/).
3. National lung cancer audit. *Key findings about the quality of care for people with lung cancer in England and Wales incorporating headline and completeness data from Scotland*. Report for the audit period 2006.
4. Gabrielson E. Worldwide trends in lung cancer pathology. *Respirology* 2006;**11**:533–8.
5. National lung cancer audit. *Key findings about the quality of care for people with lung cancer in England and Wales incorporating headline and completeness data from Scotland*. Report for the audit period 2007.
6. EMEA. *Committee for medicinal products for human use post authorisation summary of positive opinion for Alimta*. 2009. URL: [www.emea.europa.eu](http://www.emea.europa.eu).
7. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working. *BMJ* 1996;**313**:275–83.
8. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, *et al*. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;**374**:1432–40.
9. Ou S-H, Ziogas AP, Zell JA. Asian ethnicity is a favorable prognostic factor for overall survival in non-small cell lung cancer (NSCLC) and is independent of smoking status. *J Thorac Oncol* 2009;**4**:1083–93.





# Everolimus for the second-line treatment of advanced and/or metastatic renal cell cancer: a critique of the submission from Novartis

M Pitt, L Crathorne,\* T Moxham, M Bond and C Hyde

PenTAG, Peninsula Medical School, University of Exeter, Exeter, UK

\*Corresponding author

**Declared competing interests of authors:** none

## Abstract

This paper represents a summary of the evidence review group (ERG) report into the clinical efficacy, safety and cost-effectiveness of everolimus plus best supportive care (BSC) for the treatment of advanced renal cell carcinoma (RCC) which has progressed following or on vascular endothelial growth factor-targeted therapy (sunitinib, sorafenib, bevacizumab), compared to BSC alone. The submitting manufacturer's case for clinical effectiveness and cost-effectiveness was mainly based on a well-conducted randomised controlled trial (RCT), Renal Cell Cancer Treatment with Oral RAD001 Given Daily-1 (RECORD-1), comparing BSC plus everolimus with BSC plus placebo and a de novo economic model. The RCT indicated a marked statistically significant effect on progression-free survival. The base-case incremental cost-effectiveness ratio (ICER) estimate was £52,000 per quality-adjusted life-year (this included a reduction in drug cost associated with an approved patient access scheme). The ERG undertook a critical appraisal of the submission. The ERG was generally in agreement with the submitting manufacturer concerning its estimates of effectiveness; however, there was greater concern surrounding the estimates of cost-effectiveness. The ERG judged that if potential errors in the model were corrected, the ICERs offered by the submitting manufacturer would overstate the cost-effectiveness of everolimus for the second-line treatment of metastatic RCC (that this ICER would

## HTA 08/208/01

### Date of ERG submission:

30 November 2009

### TAR Centre(s):

Peninsula Technology Assessment Group (PenTAG)

### List of authors:

M Pitt, L Crathorne, T Moxham, M Bond and C Hyde

### Contact details:

Louise Crathorne, PenTAG, Peninsula Medical School, University of Exeter, Veysey Building, Salmon Pool Lane, Exeter EX2 4SG, UK

E-mail: [louise.crathorne@pcmd.ac.uk](mailto:louise.crathorne@pcmd.ac.uk)

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 08/208/01. The assessment report began editorial review in February 2010 and was accepted for publication in March 2010. See the HTA programme website for further project information ([www.hta.ac.uk](http://www.hta.ac.uk)). 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](http://www.hta.ac.uk/correspond)).

be a higher value). Concerning the estimates of cost-effectiveness in RCC, the observations in the ERG report provide strong further support for research collecting rigorous estimates of utilities associated with the main health states likely to be experienced by patients with renal cell cancer. At the time of writing, NICE was yet to issue the Appraisal Consultation Document for this appraisal.

## 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, where most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> 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 the Institute. This paper presents a summary of the ERG report for the STA entitled '*Everolimus for the second-line treatment of advanced and/or metastatic renal cell cancer*'.<sup>2</sup>

### Description of the underlying health problem

Renal cell carcinoma (RCC), also called renal adenocarcinoma or hypernephroma, is a cancer usually originating in the lining of the tubules of the kidney. The stage of RCC is usually reported using the tumour, node and metastasis (TNM) classification. This is based on the extent of the primary tumour (T), whether lymph nodes are affected (N) and whether metastases are present (M). Advanced and metastatic RCC falls within stages III and IV, stage III denotes disease that is locally advanced and/or has spread to regional lymph nodes and stage IV denotes that distant metastasis has occurred.

Early, small RCC tumours are usually asymptomatic; the diagnosis of early RCC is usually incidental after abdominal scans for other indications. The most common presenting symptoms of advanced RCC are blood in the urine (haematuria), a palpable mass in the flank or abdomen, and abdominal pain. Other non-specific symptoms include fever, night sweats, malaise and weight loss.

Kidney cancer accounts for around 2% of all cancers in the UK. In 2004, 6180 new kidney cancers were diagnosed in England and Wales, of which an estimated 85–90% were RCC. RCC is nearly twice as common in men as in women, and most commonly affects adults aged 50–80 years old. In 2005, there were 3134 registered deaths from kidney cancer in England and Wales.

Approximately 25% of RCC patients present with advanced and/or metastatic disease (stage III or IV). An estimated 50% of patients who have curative resection for earlier stages will develop recurrent and/or metastatic disease. Without treatment, these patients have a median survival rate of only 6–12 months and a 2-year survival rate of 10–20%.

Surgical resection to remove the entire kidney (radical nephrectomy) or part of the kidney (partial nephrectomy) is the only accepted curative treatment for patients with non-metastatic RCC (TNM stage I–III), and the success of surgery depends on the stage of disease. Current standard treatment of metastatic RCC (stage IV) is immunotherapy with interleukin-2 (sometimes called aldesleukin) or interferon-alpha (IFN- $\alpha$ ) which may lead to tumour shrinkage. Palliative surgery, arterial embolism or radiotherapy may also be considered in these patients. Bevacizumab plus IFN- $\alpha$ , sorafenib, sunitinib and temsirolimus all have UK marketing authorisations for use in the treatment of those with advanced and/or metastatic RCC who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group performance status of 0 or 1.

Everolimus (Afinitor, Novartis Pharmaceuticals, Camberley, Surrey, UK) is an oral, once-daily selective inhibitor of the mammalian target of rapamycin protein, that controls tumour cell division, growth and angiogenesis. It does not have a UK marketing authorisation for use in advanced/metastatic RCC. However, in May 2009, the European Medicines Agency adopted

a positive opinion, recommending everolimus for the treatment of patients with advanced RCC whose disease has progressed on, or after treatment with vascular endothelial growth factor targeted therapy.<sup>3</sup> Everolimus has a marketing authorisation for other indications in the European Union.

### Scope of the evidence review group report

The purpose of the ERG report was to comment on the validity of the manufacturer's submission on the technology of interest. The scope for this submission and hence the scope for the ERG report is shown in *Table 1*.

### 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.

Specific steps undertaken by the ERG included:

- discussion of the nature of the problem with a clinical expert
- rerunning searches indicated to have been performed to inform the manufacturer's submission
- extending searches
- formal critical appraisal of systematic review underpinning the manufacturer's submission, using the principles found in the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care<sup>4</sup>
- checking and appraising the economic model submitted
- rerunning the model to correct for potential problems as best as possible within the limited time available
- commenting on further analyses provided by the company immediately prior to the appraisal committee
- the work was carried out between 30 September 2009 and 30 November 2009.

Members of the ERG team attended and advised the meeting of the NICE appraisal committee where this guidance was discussed on 13 January 2010.

**TABLE 1** Submission scope

Appraisal objective	To appraise the clinical efficacy, safety and cost-effectiveness of everolimus plus BSC for the treatment of advanced RCC which has progressed after or during VEGF-targeted therapy (sunitinib, sorafenib, bevacizumab), compared to BSC alone
Intervention(s)	Everolimus plus BSC
Population(s)	Adults aged $\geq 18$ years with advanced RCC who had progressed on or within 6 months of stopping treatment with sunitinib, sorafenib or both drugs
Standard comparators	The standard comparator to be considered was placebo plus BSC
Outcomes	The outcome measures to be considered included: overall survival progression-free survival objective tumour response rate health-related quality of life adverse effects of treatment
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year The time horizon should be sufficiently long enough to reflect any differences in costs or outcomes between the technologies being compared Costs were considered from an NHS and Personal Social Services perspective
Other considerations	If the evidence allows, the following subgroups will be considered: resected vs unresected primary tumour; clear cell vs non-clear cell; prognostic risk group; and prior therapy Guidance will only be issued in accordance with the marketing authorisation
BSC, best supportive care; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.	

## Results

### Summary of submitted clinical evidence

The evidence for this submission is based on one randomised controlled trial (RCT), the RECORD-1 (Renal Cell Cancer Treatment with Oral RAD001 Given Daily-1) study.<sup>5</sup> This was a randomised, double-blind, placebo-controlled, phase III clinical trial of 416 participants. Eligible patients were adults aged  $\geq 18$  years with RCC whose disease had progressed on or within 6 months of stopping treatment with sunitinib, sorafenib or both drugs, a directly relevant population consistent with the scope of the appraisal. Of 416 patients, 277 were randomised to 10-mg everolimus once daily plus best supportive care (BSC), and 139 to an identical placebo tablet plus BSC. The blinded phase became open-label upon disease progression when patients were allowed to cross over from placebo to treatment group. Of 139 participants in the BSC plus placebo arm, 112 received everolimus following disease progression.

The primary outcome was progression-free survival (PFS). RECORD-1 (final analysis) showed an improvement in this outcome which was unlikely to have occurred by chance alone [hazard ratio (HR) 0.33; 95% confidence interval (CI) 0.25 to 0.43;  $p < 0.001$ ].<sup>5</sup> This equated to a mean PFS of 4.9 months in the BSC plus everolimus arm and 1.9 months for BSC plus placebo. No important variation in relative PFS estimates by subgroups were observed. In addition, a non-statistically significant treatment-related difference in overall survival (OS) was detected (HR 0.82; 95% CI 0.57 to 1.17;  $p = 0.137$ ).<sup>5</sup> This result was highly likely to have been influenced by the very high level of patients in the BSC plus placebo arm switching to everolimus treatment. Partial or stable tumour response was seen in 69% of patients with everolimus against 32% in the placebo arm, and stable quality of life (QoL)/patient-reported outcomes in the everolimus arm compared with placebo.

### Summary of submitted cost-effectiveness evidence

No published economic evaluations of everolimus in acute and/or metastatic RCC were identified and so the cost-effectiveness work focused on a new model and economic evaluation undertaken by the manufacturer.

A Markov state transition cost–utility model compared treatment with everolimus plus BSC

with BSC alone, mirroring the question addressed in the RECORD-1 RCT. The four states were: stable disease, stable disease with adverse events, progressive disease and death. Outputs were expressed as cost per quality-adjusted life-year (QALY). The base-case incremental cost-effectiveness ratio (ICER) was £61,330; this estimate was somewhat reduced when a patient access scheme (PAS) was applied. The base-case ICER when PAS was applied (leading to a reduction in the cost of the drug) was £51,613. PAS was formally approved by the Department of Health during the course of the appraisal, which led to cost-effectiveness estimates in the original submission no longer being commercially-in-confidence. The components of the base-case ICER (with PAS) were an incremental cost of £15,704, mostly attributable to the acquisition cost of everolimus, and 0.304 additional QALYs (a mean of 0.607 QALYs for BSC plus everolimus, compared to 0.302 QALYs for BSC plus placebo).

The Inverse Probability of Censoring Weight (IPCW) statistical approach was used to adjust for crossover bias in the trial data. This meant that the estimate of OS being used in the model was an HR of 0.55. In response to a request for clarification, the submitting manufacturer indicated that the ICER, using the unadjusted OS estimate from RECORD-1, was £91,000 (this incorporates the reduction in drug price consequent on the PAS).

In a supplementary analysis, the submitting manufacturer also used an alternative statistical approach, the Rank Preserving Structural Favouring Time (RPSFT) method, to adjust for crossover. This produced a very similar HR estimate to the IPCW of 0.52, and when incorporated into the economic model also produced an ICER of £53,128. However, on examination, the ERG found a significant error in the supplementary analysis which, when corrected, raised this ICER value considerably. This error was in addition to those uncovered in the original submission (as outlined below).

## Commentary on the robustness of submitted evidence

### Clinical effectiveness

The searches were appropriate and included all relevant studies. The main RCT, RECORD-1, was of high quality. No directly relevant ongoing trials were identified, but there did appear to be studies

in progress investigating the role of everolimus earlier in the management of advanced RCC.

### Cost-effectiveness

The overall approach taken to modelling was reasonable and the sources and justification of estimates were also generally reasonable.

### Weaknesses

The evidence was based on only one completed and published RCT, albeit a well-conducted and adequately powered study. The interpretation was reasonable, although the ERG would have more clearly presented the trial results on the higher frequency of adverse events, of a severity likely to have an impact on patient QoL, in the everolimus arm of the trial relative to the placebo arm. For example, 40.1% of participants experienced adverse events and serious adverse events in the BSC plus everolimus arm, compared to 22.6% in BSC plus placebo. Further data illustrating the same point were identified in the Clinical Study Report. The trial data available indicated that patient health-related QoL was identical in the early stage of the trial, despite there being a response to treatment in the everolimus arm.

Although the OS results from the RECORD-1 RCT are clear and uncontroversial, indicating a survival improvement that could have resulted from chance alone, the adjustment of the results for switching placebo patients to everolimus following disease progression is an area of genuine academic debate, particularly concerning the most appropriate analytical method. The ERG took expert statistical advice on this (but could not replicate the calculation of OS estimates correcting for crossover). There is an alternative, possibly slightly preferred, approach to the IPCW method used in the original submission, RPSFT. The submitting manufacturer provided an additional analysis offering an estimate of OS and ICER based on this method, which actually led to little change from its original submission (see Summary of submitted cost-effectiveness evidence, page 44).

More seriously, however, a number of potential errors were identified in the model:

1. Transition probabilities were not converted to rates before multiplying by the HRs in the model.
2. Introduction of a structural error in implementation of the mortality HR, with

the result that that the observed HR in the model in most cycles was substantially less than the HR intended, 0.55. This had the effect of seriously biasing the result in favour of everolimus.

3. Not introducing discounting into the model from the first cycle onwards (as opposed to introducing discounting from the first year onwards).

Of these potential errors, the second was the most serious. The ERG attempted to recalibrate the model to correct for the potential errors, and the result was an increase in the base-case model ICER to £65,231 (with PAS).

A further concern was that QoL data were not based on European Quality of Life-5 Dimensions sources. The resulting lack of confidence in the utility parameters in models dealing with advanced and metastatic RCC has been commented on in NICE appraisals before. A specific concern was that the small modelled difference in utility between stable disease and progressive disease (0.76 vs 0.68) does not seem consistent with the improvement in well-being likely to be present in practice.

### Conclusions

The ERG was generally in agreement with the submitting manufacturer concerning its estimates of effectiveness.

There was greater concern about the estimates of cost-effectiveness. The ERG judged that if the potential errors were corrected, the ICERs offered by the submitting manufacturer overstate the cost-effectiveness of everolimus for the second-line treatment of metastatic RCC (this ICER would be higher).

### Areas of uncertainty

The areas of uncertainty mirrored the areas of weakness indicated in the section Weaknesses (page 45).

### Key issues

The key issues were:

- The existence of errors in the model and the effects of correcting for them.

- The validity of adjusting for crossover bias in RCTs and the appropriate statistical technique required to adjust for it.
- The effect of concerns about utilities (as outlined above).

### Implications for research

Concerning the estimates of cost-effectiveness in RCC, the observations in the ERG report provide strong further support for research collecting rigorous estimates of utilities associated with the main health states likely to be experienced by patients with renal cell cancer. This specific appraisal highlights the possibility that the utility values associated with stable disease/progressive disease may vary depending on the number of additional potentially effective lines of further treatment available.

Switching in clinical trials for new cancer treatments as last line is a common and recurring problem in trial analysis. This STA considered a number of statistical approaches to adjustment. However, the issues highlighted have general applicability to other topics where switching from placebo to active treatment occurs when the primary end point has been reached, and this may be further enhanced by methodological research. Such research could, for example, focus on the appropriateness of alternative approaches in this context and towards the development of coherent guidelines for both the application of these statistical methods in health technology appraisals more generally as well as their integration in cost-effectiveness modelling.

Further investigation of the role of everolimus earlier in the management of RCC appears to be in progress and would not currently seem to be a priority for further research.

### Summary of NICE guidance issued as a result of the STA

At the time of writing, NICE was yet to issue the Appraisal Consultation Document for this appraisal.

### Key references

1. National Institute for Health and Clinical Excellence. *Guide to the single technology (STA) process*. URL: [www.nice.org.uk/nicemedia/pdf/STA\\_Process\\_Guide.pdf](http://www.nice.org.uk/nicemedia/pdf/STA_Process_Guide.pdf) (accessed 26 January 2010).
2. Pitt M, Crathorne L, Moxham T, Bond M, Hyde C. *Everolimus for the second-line treatment of advanced and/or metastatic renal cell cancer: a critique of the submission from Novartis*. London: NICE; 2010.
3. European Medicines Agency. *European Public Assessment Report (EPAR) Afinitor*. 2009.
4. NHS Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care. Report No. 4 update*. York: CRD University of York; 2009.
5. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, *et al*. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008;**372**:449-56.



# Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer

S Whyte,\* A Pandor, M Stevenson and A Rees

ScHARR Technology Assessment Group, The University of Sheffield, Sheffield, UK

\*Corresponding author

**Declared competing interests of authors:** none

## Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer based on the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Evidence was available in the form of one phase III, multicentre, multinational, randomised, open-label study (NO16966 trial). This two-arm study was originally designed to demonstrate the non-inferiority of oral capecitabine plus oxaliplatin (XELOX) compared with 5-fluorouracil plus folinic acid plus oxaliplatin (FOLFOX)-4 in adult patients with histologically confirmed metastatic colorectal cancer who had not previously been treated. Following randomisation of 634 patients, the open-label study was amended to include a 2×2 factorial randomised (partially blinded for bevacizumab) phase III trial with the coprimary objective of demonstrating superiority of bevacizumab in combination with chemotherapy compared with chemotherapy alone. Measured outcomes included overall survival, progression-free survival, response rate, adverse effects of treatment and health-related quality of life. The manufacturer's primary pooled analysis of superiority (using the intention-to-treat population) showed that after a median follow-up of 28 months, the addition of bevacizumab to chemotherapy significantly improved progression-free survival and overall survival compared

## HTA 08/211/01

### Date of ERG submission:

25 September 2009

### TAR Centre(s):

ScHARR Technology Assessment Group

### List of authors:

S Whyte, A Pandor, M Stevenson and A Rees

### Contact details:

Sophie Whyte, Research Associate, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK

E-mail: [sophie.whyte@shef.ac.uk](mailto:sophie.whyte@shef.ac.uk)

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 08/211/01. The assessment report began editorial review in November 2009 and was accepted for publication in March 2010. See the HTA programme website for further project information ([www.hta.ac.uk](http://www.hta.ac.uk)). 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](http://www.hta.ac.uk/correspond)).

with chemotherapy alone in adult patients with histologically confirmed metastatic colorectal cancer who were not previously treated [median progression-free survival 9.4 vs 7.7 months (absolute difference 1.7 months); hazard ratio (HR) 0.79, 97.5% confidence interval (CI) 0.72 to 0.87;  $p = 0.0001$ ; median overall survival 21.2 vs 18.9 months (absolute difference 2.3 months); HR 0.83, 97.5% CI 0.74 to 0.93;  $p = 0.0019$ ]. The NO16966 trial was of reasonable methodological quality and demonstrated a significant improvement in both progression-free survival and overall survival when bevacizumab was added to XELOX or FOLFOX. However, the size of the actual treatment effect of bevacizumab is uncertain. The ERG believed that the modelling structure employed was appropriate, but highlighted several key issues and areas of uncertainty. At the time of writing, NICE was yet to issue the guidance for this appraisal.

## 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, where most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> 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 the Institute. This paper presents a summary of the ERG report for the STA entitled '*Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer*'.

## Description of the underlying health problem

Colorectal cancer is the third most common cancer in the UK, with 36,766 new cases diagnosed in England and Wales in 2005.<sup>2</sup> Metastatic disease is,

in the majority of cases, incurable and treatment is palliative in nature. Although local radiotherapy and, less commonly, surgery both have a role, metastatic disease is essentially a systemic disease requiring systemic treatment. Traditionally this has meant cytotoxic chemotherapy although, in recent years, passive immunotherapy in the form of monoclonal antibody treatment has been added to chemotherapy regimens. Commonly used regimens include oral capecitabine monotherapy, oral capecitabine + intravenous (IV) oxaliplatin (XELOX), IV 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX), IV 5-fluorouracil + folinic acid + irinotecan (FOLFIRI), IV 5-fluorouracil ± folinic acid, and oral capecitabine + IV irinotecan (XELIRI). With current standard first-line chemotherapy, median survival is around 15–20 months.<sup>3–5</sup>

## Scope of the evidence review group report

The objective of the appraisal was to evaluate the clinical effectiveness and cost-effectiveness of bevacizumab, within its licensed indications, in combination with oxaliplatin and either 5-fluorouracil or capecitabine for the treatment of metastatic colorectal cancer. The comparator was oxaliplatin or irinotecan, including chemotherapy regimens without bevacizumab. Measured outcomes included overall survival, progression-free survival, response rate, adverse effects of treatment and health-related quality of life.

The licensed indication permits the use of bevacizumab in combination with fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic colorectal cancer but does not specify a line of treatment. The NICE scope included the use of bevacizumab in combination with oxaliplatin-based chemotherapy in individuals with histologically confirmed metastatic colorectal cancer as first-line therapy (for patients not previously treated for metastatic disease), and as second-line therapy. The manufacturer's submission (MS), however, focuses on first-line use only.

The main evidence presented in support of the clinical effectiveness of bevacizumab was based on one phase III, multicentre, multinational, randomised, open-label study (NO16966 trial).<sup>6</sup> This two-arm study was originally designed to demonstrate the non-inferiority of XELOX compared with FOLFOX-4 in adult patients with histologically confirmed metastatic colorectal

cancer who had not previously been treated. Following randomisation of 634 patients, the open-label study was amended (additional phase II and III studies that were published demonstrated the benefit of adding bevacizumab to irinotecan, 5-fluorouracil and folinic acid)<sup>7,8</sup> to include a 2×2 factorial randomised (partially blinded for bevacizumab) phase III trial ( $n = 1401$ ) with the coprimary objective of demonstrating superiority of bevacizumab in combination with chemotherapy (B-XELOX or B-FOLFOX-4) compared with chemotherapy alone (P-XELOX or P-FOLFOX-4). The dose of bevacizumab was 5 mg/kg every 2 weeks (B-FOLFOX-4) or 7.5 mg/kg every 3 weeks (B-XELOX).

The scope of the manufacturer's cost-effectiveness submission focused on a comparison with regimens containing oxaliplatin which was considered to be the most relevant comparator. A comparison with irinotecan-based chemotherapy was also included for completeness. The manufacturer submitted additional analyses in response to the ERG clarification questions. Further data and analyses were also submitted following the first committee meeting. These included further data on the patient access scheme's (PAS's) operating costs as well as pharmacy and preparation costs for bevacizumab.

## Methods

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

The manufacturer's literature searches were repeated and a narrative critique of the submitted evidence was undertaken. The economic model submitted by the manufacturer was considered structurally adequate to assess the decision problem, but not all of the model inputs were considered satisfactory. Additional work carried out by the ERG focused on conducting sensitivity analyses relating to areas of uncertainty.

## Results

### Summary of submitted clinical evidence

The manufacturer's main analysis pooled data from the initial two arms and the 2 × 2 factorial part of

the NO16966 trial and compared the addition of bevacizumab to chemotherapy with chemotherapy alone. The manufacturer's primary pooled analysis of superiority (using the intention-to-treat population) showed that after a median follow-up of 28 months, the addition of bevacizumab to chemotherapy (B-XELOX/B-FOLFOX-4 combined) significantly improved progression-free survival and overall survival compared with chemotherapy alone (P-XELOX/P-FOLFOX-4/XELOX/FOLFOX-4 combined) in adult patients with histologically confirmed metastatic colorectal cancer who were not previously treated [median progression-free survival 9.4 vs 7.7 months (absolute difference 1.7 months); hazard ratio (HR) 0.79, 97.5% confidence interval (CI) 0.72 to 0.87;  $p = 0.0001$ ; median overall survival 21.2 vs 18.9 months (absolute difference 2.3 months); HR 0.83, 97.5% CI 0.74 to 0.93;  $p = 0.0019$ ].

A secondary pooled analysis of superiority (requested by the ERG as it was believed to be more appropriate) restricted to patients in the second 2×2 factorial part of the NO16966 study as per the original statistical trial plan (B-XELOX/B-FOLFOX-4 combined vs P-XELOX/P-FOLFOX-4 combined) found similar results [median progression-free survival 9.4 vs 8.0 months (absolute difference 1.4 months); HR 0.83, 97.5% CI 0.72 to 0.95;  $p = 0.0023$ ; median overall survival 21.3 versus 19.9 months (absolute difference 1.4 months); HR 0.89, 97.5% CI 0.76 to 1.03;  $p = 0.0769$ ].

The manufacturer's pooled analysis of non-inferiority (using the eligible patient population and the intention-to-treat population) showed that the XELOX (XELOX/P-XELOX/B-XELOX combined) and FOLFOX-4 (FOLFOX-4/P-FOLFOX-4/B-FOLFOX-4 combined) based regimens were equivalent for both progression-free survival and overall survival ( $p$ -values were stated as not significant, but these values were not reported). No analysis was undertaken for the factorial design (P-XELOX/B-XELOX combined versus P-FOLFOX-4/B-FOLFOX-4 combined).

A pre-defined subgroup analysis on progression-free survival found that the statistical superiority of bevacizumab plus chemotherapy was evident in the XELOX subgroups (B-XELOX vs P-XELOX; HR 0.80, 97.5% CI 0.66 to 0.96;  $p$ -value not reported) but did not reach the significance level in the FOLFOX-4 subgroups (B-FOLFOX-4 vs P-FOLFOX-4; HR 0.89, 97.5% CI 0.74 to 1.06;  $p$ -value not reported). Additional post hoc

exploratory analyses, following the results from the Adjuvant Colon Cancer End Points (ACCENT) study,<sup>9</sup> found that there was a significant and direct correlation between time to recurrence after surgery and survival after recurrence in patients whose disease recurred after surgery and adjuvant treatment. Removing the subgroup of patients that may have slower tumour progression after adjuvant treatment (an imbalance between treatment groups with regard to an important prognostic factor that was not recognised at the start of the N016966 trial) significantly improved (i.e. lowered) the HRs for adding bevacizumab to chemotherapy compared with chemotherapy alone for both overall survival and progression-free survival. Depending on the analyses conducted (e.g. exclusion of patients with prior adjuvant chemotherapy from all four treatment arms of the factorial study, from FOLFOX groups only or from P-FOLFOX group only) the HRs for overall survival ranged from 0.83 to 0.85 ( $p < 0.03$ ) and the HRs for progression-free survival ranged from 0.74 to 0.77 ( $p < 0.0001$ ). Although this may be plausible, the ERG notes that caution should be exercised as this is a post hoc exploratory analysis.

The majority of adverse events were generally associated with cytotoxic chemotherapy. FOLFOX-4-based regimens were generally associated with increased neutropenia/granulocytopenia, and XELOX-based regimens were generally associated with increased diarrhoea and hand and foot syndrome. Adverse events that could be potentially related to bevacizumab included increased frequencies of high blood pressure, proteinuria, bleeding, gastrointestinal perforation, thromboembolic events and wound healing complications. Serious (grade 3) or life threatening (grade 4) adverse events that occurred more commonly in patients receiving bevacizumab plus chemotherapy (B-XELOX/B-FOLFOX-4 combined) than those receiving chemotherapy alone (P-XELOX/P-FOLFOX-4/XELOX/FOLFOX-4 combined) were thromboembolic events (7.8% vs 5.1%, respectively), hypertension (4.0% vs 0.8%, respectively), proteinuria (3.5% vs 0.9%, respectively) and bleeding problems (1.9% vs 1.5%, respectively). Grade 3 and 4 gastrointestinal perforations and wound healing complications were rare (< 1%). Similar results were observed when data were restricted to the factorial analyses.

The rates of discontinuation were higher in the bevacizumab containing groups (B-XELOX/B-FOLFOX-4 combined, 30.8%) than in the no bevacizumab containing groups (P-XELOX/P-

FOLFOX-4/XELOX/FOLFOX-4 combined, 25.3%). Corresponding data, restricted to the 2×2 factorial analyses, yielded similar results (B-XELOX/B-FOLFOX-4 combined, 30.8% vs P-XELOX/P-FOLFOX-4 combined, 20.8%). The statistical analysis comparing the rates of discontinuation between treatment groups was not reported in the MS or in the manufacturer's supplementary evidence.

### Summary of submitted cost-effectiveness evidence

Cost-effectiveness was estimated using a Microsoft EXCEL model with four states: pre-progression on treatment, pre-progression and post treatment, progressive disease and dead. An area under the curve approach was used to estimate the disease progression of metastatic colorectal cancer patients. The distribution of patients between health states was used to calculate total direct costs and quality-adjusted life-years (QALYs) for each intervention. Costs were considered from an NHS and Personal Social Services perspective. Cost-effectiveness was expressed in terms of incremental cost per QALY with a time horizon of 8 years, which is equivalent to a lifetime horizon in the population of interest. The analysis focused on the interventions B-XELOX and B-FOLFOX. The model was populated with efficacy data from the N016966 trial but as discussed in the clinical effectiveness section these trial data have been analysed in several different ways. Data on treatment duration and dose intensity were also based on the N016966 trial. Survival data were modelled using Kaplan–Meier data up to median survival of 28 months and a Weibull distribution after this point. The ERG requested several changes to the model inputs and modelling assumptions (including additional analyses).

A summary of the key incremental cost-effectiveness ratios (ICERs) included in the submission are presented in *Table 1*. Of the several analyses presented by the manufacturer, the ERG considered the analysis using the 2×2 part of the N016966 trial, with the XELOX and FOLFOX arms pooled, with patients with prior adjuvant treatment excluded to be the most appropriate. This analysis produced ICERs of £36,006 and £31,174 for B-XELOX versus XELOX and B-FOLFOX versus FOLFOX, respectively. The inclusion of patients with prior adjuvant chemotherapy resulted in higher ICERs. Unpooling the XELOX and FOLFOX arms affected the individual XELOX and

**TABLE 1** A summary of ICERs included in the manufacturer's submission (MS)

Scenario		ICERs (£ per QALY saved)	
		B-XELOX vs XELOX	B-FOLFOX vs FOLFOX
<b>MS original analysis</b>			
Without PAS	Analysis using data from all six arms of N016966, XELOX and FOLFOX-4 arms pooled	£82,098	£94,989
With PAS	Analysis using data from all six arms of N016966, XELOX and FOLFOX-4 arms pooled	£34,170	£41,388
<b>MS supplementary data, requested by ERG</b>			
With PAS	Analysis using data from all six arms of N016966, XELOX and FOLFOX-4 arms pooled	£35,912	£36,569
With PAS	Analysis using the 2×2 part of N016966, XELOX and FOLFOX-4 arms pooled	£48,111	£39,771
With PAS	Analysis using 2×2 part of N016966, XELOX and FOLFOX-4 arms unpooled	£35,662	£62,714
With PAS	Analysis using the 2×2 part of N016966, XELOX and FOLFOX-4 arms pooled, without prior adjuvant treatment	£36,006	£31,174
Without PAS	Analysis using data from all six arms of N016966, XELOX and FOLFOX-4 arms pooled, including bevacizumab wastage	£90,945	£98,436
Without PAS	Analysis using the 2×2 part of N016966, XELOX and FOLFOX-4 arms pooled, without prior adjuvant treatment	£92,698	£96,687
Without PAS	Analysis using 2×2 part of N016966, XELOX and FOLFOX-4 arms unpooled	£90,779	£240,324
Without PAS	Analysis using the 2×2 part of N016966, XELOX and FOLFOX-4 arms pooled	£129,911	£134,309
<b>MS additional submission (post first committee meeting)</b>			
With PAS	Analysis using the 2×2 part of N016966, XELOX and FOLFOX-4 arms pooled, without prior adjuvant treatment	£36,494	£31,122

ERG, evidence review group; B-FOLFOX-4, bevacizumab in combination with FOLFOX-4; B-XELOX, bevacizumab in combination with XELOX; FOLFOX-4, intravenous 5-fluorouracil plus folinic acid plus oxaliplatin; ICERs, incremental cost-effectiveness ratios; MS, manufacturer's submission; PAS, patient access scheme; QALY, quality-adjusted life-year; XELOX, oral capecitabine plus intravenous oxaliplatin.

FOLFOX ICERs in different directions. While no systematic review was undertaken with irinotecan as a comparator, a cost-effectiveness analysis was undertaken (data not presented here).

## Commentary on the robustness of submitted evidence

### Strengths

The N016966 trial was of reasonable methodological quality (with some limitations) and measured a range of outcomes that were as appropriate and clinically relevant as possible.

The ERG believed that the modelling structure employed was appropriate.

### Weaknesses

Despite no evidence to suggest that the statistical validity of the factorial approach was methodologically inappropriate, the validity of simply pooling data from essentially two different study designs (i.e. a two-arm design and a 2×2 factorial design) without accounting for between-study variability is inappropriate. Unweighted (for uncertainty) pooling of results from different studies is not advisable as there are almost certainly differences between trials that, if not accounted

for, are likely to lead to biased estimates of effect. The appropriateness of combining data from the two parts of the study was also questioned by the European Medicines Agency.<sup>10</sup> The resulting pooled data (manufacturer's primary pooled analysis of superiority and non-inferiority) should therefore be treated with caution. Additionally it is unclear whether patients with prior adjuvant chemotherapy should be excluded from the analysis.

The restriction to the trial data from the 2×2 part of the NO16966 study, the pooling of the XELOX and FOLFOX arms, and the restriction to the data of patients without prior adjuvant chemotherapy all had a large impact on the resulting ICERs.

The MS did not make use of the range of utility values identified from the literature review and did not explain why these values were not used. The sources of the utility values used in the MS were poorly referenced, resulting in the ERG being unable to verify them. The distributions used for the utility values in the probabilistic sensitivity analyses (PSA) reflected the uncertainty relating to the specific values used but underestimated the uncertainty relating to the selection of utility values. The ERG noted that using wider distributions for utility values would significantly increase the CIs around the mean ICERs from the PSA, and reducing the utility values by 20% markedly increased the ICERs.

Chemotherapy can be administered intermittently or continuously, but the difference in cost and effectiveness between intermittent and continuous treatment is unclear. Current care in England is often intermittent treatment with chemotherapy, but the trial and the model both represent continuous treatment chemotherapy. It is unclear how this difference may impact the ICERs but, as an example, if intermittent treatment was cheaper than continuous treatment whilst having a similar efficacy, then the ICER for continuous treatment with bevacizumab versus intermittent treatment would be greater than the ICER for continuous treatment with bevacizumab versus continuous treatment.

In clinical practice, treatment with non-oxaliplatin chemotherapy components may continue beyond oxaliplatin cessation although in the NO16966 trial this was rarely seen. Because of the structure of the PAS (in which oxaliplatin is received free of charge), the incremental cost of continuing bevacizumab after oxaliplatin cessation is almost

three times the incremental cost of adding bevacizumab to oxaliplatin. Hence the impact of continuing bevacizumab treatment on the ICERs could be considerable.

Under the PAS, bevacizumab has a fixed price per cycle, but for calculations without the PAS it is important that drug wastage should be included for both oxaliplatin and bevacizumab. The MS 'without PAS' ICERs did not include drug wastage within the base case although bevacizumab wastage was included within one analysis as stated in *Table 1*. The inclusion of drug wastage resulted in higher ICERs.

## Conclusions

The NO16966 trial was of reasonable methodological quality and demonstrated a significant improvement in both progression-free survival and overall survival when bevacizumab was added to XELOX or FOLFOX. However, the size of the actual treatment effect of bevacizumab is uncertain due to the following:

- trial design limitations (two-part study, open-label design)
- imbalance of known prognostic factor (time between primary treatment and recurrence)
- relatively short duration of chemotherapy treatment (approximately 6 months) despite the fact that the trial protocol allowed continuation of the study therapy until progressive disease or unacceptable toxicity
- interpretation of the statistical analyses (pooled analysis of all patients versus analysis by factorial design).

In addition, there was uncertainty around whether bevacizumab treatment should be continued until progression of the underlying disease.

The ERG believed that the modelling structure employed was appropriate, but highlighted several key issues and areas of uncertainty and included the following:

- It is unclear which approach to data analysis (pooling, excluding adjuvant therapy patients, etc.) is most appropriate and the choice of approach has a significant impact on the resulting ICERs.
- Unlike the NO16966 trial, in clinical practice chemotherapy may be administered intermittently rather than continuously.

This introduces considerable uncertainty as the differences in cost and efficacy between intermittent and continuous use are not known.

- At the time of writing the decision on whether the proposed PAS scheme would be accepted was unknown. The majority of the analysis presented by the manufacturer included the PAS. Running the model without the PAS resulted in much higher ICERs.
- The efficacy associated with the continuation of treatment with bevacizumab after cessation of oxaliplatin is unknown. However, with the PAS the incremental cost of continuing bevacizumab after oxaliplatin cessation is almost three times the incremental cost of adding bevacizumab to oxaliplatin. Hence bevacizumab treatment post oxaliplatin cessation has the potential to have a significant impact on the resulting ICERs.

## Research recommendations

The ERG makes three recommendations for areas requiring further research:

- research into the likely duration of bevacizumab treatment in clinical practice and the survival associated with longer treatment duration
- research into the cost-effectiveness of bevacizumab for patients currently receiving intermittent XELOX or FOLFOX
- finding ways to select patients who will benefit from bevacizumab.

## Summary of NICE guidance issued as a result of the STA

At the time of writing, NICE was yet to issue the guidance for this appraisal.

## Key references

1. National Institute for Health and Clinical Excellence. 2006. *Guide to the single technology appraisal (STA) process*. URL: [www.nice.org.uk/nicemedia/pdf/STA\\_Process\\_Guide.pdf](http://www.nice.org.uk/nicemedia/pdf/STA_Process_Guide.pdf).
2. Cancer Research UK. *Number of new cases of cancer diagnosed by site, UK, 2005*. URL: [http://publications.cancerresearchuk.org/WebRoot/crukstoredb/CRUK\\_PDFs/incidence/cs\\_inc\\_t8.3.pdf](http://publications.cancerresearchuk.org/WebRoot/crukstoredb/CRUK_PDFs/incidence/cs_inc_t8.3.pdf) (accessed 10 July 2009).
3. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000;**355**:1041–7.
4. de Gramont A, Figer A, Seymour MT, Homerin M, Hmissi A, Cassidy J, *et al.* Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;**18**:2938–47.
5. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;**22**:229–37.
6. Saltz LBC. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol* 2008;**26**:2013–19 (Erratum published in: *J Clin Oncol* 2008;**26**:3110; *J Clin Oncol* 2009;**27**:653).
7. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;**350**:2335–42.
8. Kabbinavar FFS. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: Results of a randomized phase II trial. *J Clin Oncol* 2005;**23**:3697–705.
9. O'Connell MJ, Campbell ME, Goldberg RM, Grothey A, Seitz JF, Benedetti JK, *et al.* Survival following recurrence in stage II and III colon cancer: findings from the ACCENT data set. *J Clin Oncol* 2008;**10**:2336–41.
10. European Medicines Agency. *Assessment Report for Avastin. Procedure Number: EMEA/H/C/000582/II/0014*. 2009. URL: [www.emea.europa.eu/humandocs/PDFs/EPAR/avastin/Avastin-H-582-II-14-AR.pdf](http://www.emea.europa.eu/humandocs/PDFs/EPAR/avastin/Avastin-H-582-II-14-AR.pdf) (accessed 6 September 2009).





## Dronedaronone for the treatment of atrial fibrillation and atrial flutter

E Maund,\* C McKenna, M Sarowar, D Fox, M Stevenson, C Pepper, S Palmer and N Woolacott

Centre for Reviews and Dissemination/Centre for Health Economics, University of York, York, UK

\*Corresponding author

**Declared competing interests of authors:** none

### Abstract

This paper presents a summary of the evidence review group (ERG) report on the clinical effectiveness and cost-effectiveness of dronedaronone for the treatment of atrial fibrillation (AF) or atrial flutter 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 process. The population considered in the submission were adult clinically stable patients with a recent history of or current non-permanent AF. Comparators were the current available anti-arrhythmic drugs: class Ic agents (flecainide and propafenone), sotalol and amiodarone. Outcomes were AF recurrence, all-cause mortality, stroke, treatment discontinuations (due to any cause or due to adverse events) and serious adverse events. The main evidence came from four phase III randomised controlled trials, direct and indirect meta-analyses from a systematic review, and a synthesis of the direct and indirect evidence using a mixed-treatment comparison. Overall, the results from the different synthesis approaches showed that the odds of AF recurrence appeared statistically significantly lower with dronedaronone and other anti-arrhythmic drugs than with non-active control, and that the odds of AF recurrence are statistically significantly higher for dronedaronone than for amiodarone. However, the results for outcomes of all-cause mortality, stroke and treatment discontinuations and serious adverse events were all uncertain. A discrete event simulation model was used to evaluate dronedaronone versus antiarrhythmic drugs

### HTA 08/214/01

**Date of ERG submission:**

28 October 2009

**TAR Centre(s):**

Centre for Reviews and Dissemination/Centre for Health Economics

**List of authors:**

E Maund, C McKenna, M Sarowar, D Fox, M Stevenson, C Pepper, S Palmer and N Woolacott

**Contact details:**

Emma Maund, Research Fellow, Centre for Reviews and Dissemination, University of York, Heslington, York YO10 5DD, UK

E-mail: em546@york.ac.uk

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 08/214/01. The assessment report began editorial review in January 2010 and was accepted for publication in March 2010. See the HTA programme website for further project information ([www.hta.ac.uk](http://www.hta.ac.uk)). 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](http://www.hta.ac.uk/correspond)).

and standard therapy alone. The incremental cost-effectiveness ratio of dronedarone was relatively robust and less than £20,000 per quality-adjusted life-year. Exploratory work undertaken by the ERG identified that the main drivers of cost-effectiveness were the benefits assigned to dronedarone for all-cause mortality and stroke. Dronedarone is not cost-effective relative to its comparators when the only effect of treatment is a reduction in AF recurrences. In conclusion, uncertainties remain in the clinical effectiveness and cost-effectiveness of dronedarone. In particular, the clinical evidence for the major drivers of cost-effectiveness (all-cause mortality and stroke), and consequently the additional benefits attributed in the economic model to dronedarone compared to other anti-arrhythmic drugs are highly uncertain. The final guidance, issued by NICE on 25 August 2010, states that: Dronedarone is recommended as an option for the treatment of non-permanent atrial fibrillation **only** in people: whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option, **and** who have at least one of the following cardiovascular risk factors: - hypertension requiring drugs of at least two different classes, diabetes mellitus, previous transient ischaemic attack, stroke or systemic embolism, left atrial diameter of 50 mm or greater, left ventricular ejection fraction less than 40% (noting that the summary of product characteristics [SPC] does not recommend dronedarone for people with left ventricular ejection fraction less than 35% because of limited experience of using it in this group) or age 70 years or older, **and** who do not have unstable New York Heart Association (NYHA) class III or IV heart failure. Furthermore, 'People who do not meet the criteria above who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop'.

## 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, where most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> 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 the Institute. This paper presents a summary of the ERG report for the STA.<sup>2</sup>

## Description of the underlying health problem

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence that increases with age. Symptoms of AF include difficulty breathing, palpitations, chest pain, dizziness and loss of consciousness. AF is also associated with an increased risk of thrombus formation and consequently a fivefold increased risk of stroke compared to people without AF.<sup>3</sup> AF and its symptoms can be treated using pharmacological or electrophysiological/surgical interventions to either control ventricular rate, which does not eliminate AF but improves AF symptoms, or restore normal sinus rhythm. There are three different types of AF: paroxysmal, which spontaneously terminates within 7 days; persistent, which requires treatment (cardioversion) to terminate; and permanent, in which normal heart rhythm can not be restored by treatment.

## Scope of the evidence review group report

Dronedarone, Multaq® (Sanofi–Aventis), is an antiarrhythmic drug (AAD) that has properties belonging to all four Vaughan–Williams' classes of AAD. It is indicated in adult clinically stable patients with history of, or current, non-permanent AF to prevent recurrence of AF or to lower ventricular rate. The recommended dose is 400 mg twice daily, with patients expected to remain indefinitely on dronedarone unless there is lack of efficacy, or intolerability.

The manufacturer (Sanofi Aventis Ltd) presented a submission to NICE on the use of dronedarone, (within the context of its licensed indication) for

the treatment of AF and atrial flutter (AFL), both as a first-line adjunctive treatment to standard baseline therapy (with or without beta-blockers and anticoagulation therapy) and as a second-line treatment compared to other AADs: (i) class 1c agents (flecainide and propafenone); (ii) sotalol; and (iii) amiodarone.

Evidence for the efficacy and safety of dronedarone and other AADs came from randomised controlled trials (RCTs), meta-analysis (presenting direct and indirect comparisons) and a synthesis of the direct and indirect evidence using a mixed-treatment comparison (MTC). A total of 39 studies, including four studies of dronedarone [EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) ADONIS (American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm), ATHENA (A placebo-controlled, double-blind parallel arm Trial to assess the efficacy of dronedarone 400mg bid for the prevention of cardiovascular Hospitalisation or death from any cause in patiENts with Atrial fibrillation/atrial flutter) and DIONYSOS (Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation)] conducted by the manufacturer, were considered eligible for inclusion in the direct and indirect meta-analyses and the MTC; however, the studies included in the direct meta-analysis and the MTC were subject to different inclusion criteria. Outcomes of interest were: AF recurrence, all-cause mortality, stroke, treatment discontinuation (due to any cause or adverse events) and serious adverse events of treatment (SAEs).

The manufacturer's submission included a discrete event simulation model which was used to estimate the cost-effectiveness of dronedarone with other licensed AADs and standard therapy alone for AF. The comparison with standard therapy alone was restricted to high-risk elderly AF patients with a CHADS<sub>2</sub> score  $\geq 4$  (CHADS<sub>2</sub> is a stroke risk stratification scheme which is based on specific risk factors including congestive heart failure, hypertension, age > 75 years, diabetes mellitus, and prior stroke or transient ischaemic attack). This model was used to evaluate the cost-effectiveness of five main patient groups according to their clinical AF type and baseline risk factors in line with UK guidelines: (i) paroxysmal AF with no structural heart disease (SHD); (ii) paroxysmal AF with coronary heart disease; (iii) paroxysmal AF

with left ventricular dysfunction; (iv) persistent AF with no SHD; and (v) persistent AF with SHD.

## 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 critiqued the search strategy, study selection, validity assessment, outcome selection and the statistical methods used in the manufacturer's submission of clinical effectiveness. It also explored the inconsistency of inclusion and exclusion of studies and use of continuity corrected data both within and between different types of statistical analyses. In addition, the ERG also checked the validity of the MTC analysis by running it using WINBUGS software. The ERG critiqued the methods used in the manufacturer's economic evaluation. It corrected the cost-effectiveness results presented by the manufacturer, undertook additional exploratory work to identify the main drivers of cost-effectiveness and key assumptions for the different comparisons, and explored the robustness of the cost-effectiveness to specific assumptions and additional uncertainties identified by itself.

## Results

### Summary of submitted clinical evidence

The EURIDIS/ADONIS trials (see *Table 1* for study details) demonstrated that dronedarone was statistically significantly more effective than placebo for maintenance of sinus rhythm [hazard ratio (HR) 0.75; 95% confidence interval (CI) 0.65 to 0.87,  $p < 0.001$ ] and in reducing the ventricular rate during recurrence of AF/AFL [ $103.4 \pm 25.9$  beats per minute (b.p.m) vs  $117.1 \pm 30.4$  b.p.m,  $p < 0.001$ ].<sup>4</sup>

The ATHENA study (see *Table 1*), which recruited only moderate- to high-risk elderly AF patients, 75% of whom were in sinus rhythm, showed that dronedarone resulted in a significant reduction in the primary composite end point of time to first cardiovascular hospitalisation or death from any cause (HR 0.76; 95% CI 0.69 to 0.84,  $p < 0.001$ ). The primary end point appeared to be mainly

**TABLE 1** Summary of dronedarone trials included in the manufacturer's submission

	<b>ADONIS/EURIDIS<sup>a</sup></b>	<b>ATHENA</b>	<b>DIONYSOS</b>
<b>Population characteristics</b>			
<i>n</i>	1237	4628	504
Dose	400mg BD	400mg BD	400mg BD
Age range	Dronedarone: mean 63.5 (10.7) years Placebo: mean 62.2 (11.1) years	Mean: 71.6 (SD 9.0) years <65 years: 18.9% 65 to <75 years: 39.5% ≥75 years: 41.6%	Mean 64 years Range 28–90 years <65 years: 52% >75 years: 19%
Type of AF	Paroxysmal and persistent AF	Paroxysmal and persistent AF At least one risk factor for cardiovascular hospitalisation	Persistent (cardioversion indicated); (although excluded, some were classed as having paroxysmal or permanent AF)
Anticoagulation used?	Majority of patients were receiving anticoagulants	44% receiving aspirin	Yes
Hypertension	Dronedarone: 60% Placebo: 50.1%	86.3%	67%
SHD	Dronedarone: 42.4% Placebo: 39.7%	59.6%	28%
CHF	Dronedarone: 17.3% Placebo: 17.87%	21.2%	22% (not III or IV at time of randomisation)
Treatment duration	12 months	Minimum 12 months	>6 months
<b>Outcome measure</b>			
Primary outcome measure	Recurrence of AF (measured by transtelephonic ECG when symptomatic)	First hospitalisation due to CV events or death	AF recurrence or premature discontinuation due to intolerance or lack of efficacy (AF recurrence measured by unscheduled ECG)
Secondary outcomes	Symptoms related to AF Mean ventricular rate during first recurrence of AF	Death from any cause Death from CV causes First hospitalisation due to CV event	Occurrence of major safety end point Occurrence of drug specific AEs
Post hoc analyses		AF recurrence (measured by scheduled ECGs, hospitalisation for AF/AFL, electrical cardioversion) Stroke	
AEs, adverse events; AF, atrial fibrillation; AFL, atrial flutter; BD, twice a day ; CHF, congestive heart failure; CV, cardiovascular; ECGs, electrocardiograms; SHD, structural heart disease; SD, standard deviation.			
a These two trials have identical protocols and are often considered as a single trial.			

driven by a reduction in time to first cardiovascular hospitalisation due to a significant reduction in hospitalisation for AF (HR 0.63; 95% CI 0.55 to 0.72,  $p < 0.001$ ). There was no statistically significant difference in all-cause mortality between patients receiving dronedarone and those receiving placebo (HR 0.84; 95% CI 0.66 to 1.08,  $p = 0.18$ ). A post hoc analysis showed that there was a statistically significant reduction in the risk of

stroke in patients receiving dronedarone compared to those receiving placebo (HR 0.66; 95% CI 0.46 to 0.96,  $p = 0.027$ ).<sup>5</sup>

The DIONYSOS trial (see *Table 1*), which directly compared dronedarone with amiodarone, showed that the incidence of recurrence of AF or premature study drug discontinuation was statistically significantly greater for dronedarone

**TABLE 2** Incremental cost per QALY results for the base-case analysis, a sensitivity analysis exploring the assumption that sotalol and amiodarone have the same effect on mortality as dronedarone; and a sensitivity analysis exploring the assumption of a treatment effect on AF recurrence alone

<b>Summary of incremental cost per QALY results for each of the base case populations</b>					
	<b>Paroxysmal AF</b>			<b>Persistent AF</b>	
	<b>No SHD</b>	<b>CAD</b>	<b>LVD</b>	<b>No SHD</b>	<b>SHD</b>
Dronedarone vs standard therapy	£3620	£4014	£3577	£3358	£3520
Dronedarone vs sotalol	£1692	£1,988	NA	£1848	NA
Dronedarone vs class Ic	£18,206	NA	NA	£18,955	NA
Dronedarone vs amiodarone	NA	NA	£1895	NA	£2349
<b>Incremental cost per QALY results for each base case population when amiodarone and sotalol are assumed to have the same effect on mortality as dronedarone</b>					
	<b>Paroxysmal AF</b>			<b>Persistent AF</b>	
	<b>No SHD</b>	<b>CAD</b>	<b>LVD</b>	<b>No SHD</b>	<b>SHD</b>
Dronedarone vs sotalol	£119,704	£102,668	NA	£92,009	NA
Dronedarone vs amiodarone	NA	NA	£55,063	NA	£71,306
<b>ERG's incremental cost per QALY results for each of the base case populations when the model assumes a treatment effect on AF recurrences alone</b>					
	<b>Paroxysmal AF</b>			<b>Persistent AF</b>	
	<b>No SHD</b>	<b>CAD</b>	<b>LVD</b>	<b>No SHD</b>	<b>SHD</b>
Dronedarone vs standard therapy	£7,486,908	£70,323,846	£1,355,984	£1,630,715	£2,254,522
Dronedarone vs sotalol	£5,232,678	D	NA	D	NA
Dronedarone vs class Ic	D	NA	NA	D	NA
Dronedarone vs amiodarone	NA	NA	£5,694,862	NA	D

AF, atrial fibrillation; CAD, coronary artery disease; D, dominated; LVD, left ventricular dysfunction; NA, not applicable; SHD, structural heart disease.

than for amiodarone (73.9% vs 55.3%,  $p$ -value < 0.0001).

Overall, the results from the direct and indirect meta-analyses and the MTC showed that the odds of AF recurrence appeared statistically significantly lower with all AADs than with non-active control, but that the odds of AF recurrence are statistically significantly higher for dronedarone than for other AADs.

There were no statistically significant differences between AADs for all-cause mortality based on the head-to-head RCT (DIONYSOS) or the results from the indirect comparison. However, in the MTC, dronedarone was reported to have a statistically significant reduction in the odds of all-cause mortality compared to both sotalol and amiodarone.

For stroke, results from the MTC analysis only were reported in the manufacturer's submission. Dronedarone was associated with a statistically

significant reduction in stroke compared to control. No significant difference was reported between dronedarone and either amiodarone or sotalol based on the results from the MTC.

With regard to treatment discontinuations, the results reported from the direct and indirect meta-analyses were inconsistent with the MTC, suggesting considerable uncertainty. Results from the different synthesis approaches showed that compared with other AADs, dronedarone had the lowest odds of SAEs. However, the omission of data from the EURIDIS/ADONIS trial for this outcome means that the results are unreliable.

### Summary of submitted cost-effectiveness evidence

No previous published cost-effectiveness studies of dronedarone in patients with AF/AFL were identified by the manufacturer. The results from the manufacturer's submission demonstrated that dronedarone appeared highly cost-effective in each

of the populations compared to using standard baseline therapy alone as first-line treatment, or compared to sotalol or amiodarone as a first-line antiarrhythmic (*Table 2*). The results for dronedarone, relative to class Ic agents, showed that dronedarone was borderline in terms of cost-effectiveness, with an incremental cost-effectiveness ratio (ICER) just above £20,000 per quality-adjusted life-year (QALY) and a 50% probability of being cost-effective at this threshold. The findings were reported to be robust across a wide range of alternative assumptions. The results appeared most sensitive to assumptions regarding the benefits from AADs on mortality.

The main driver of cost-effectiveness for the comparisons of dronedarone versus standard therapy as first-line treatment, and sotalol or amiodarone as first line antiarrhythmics, is the additional mortality benefit attributed to dronedarone. If sotalol and amiodarone are assumed to have the same effect on mortality as dronedarone, dronedarone is no longer considered to be cost-effective (see *Table 2*). Stroke benefits and differences in treatment-related adverse events have only a very limited impact on cost-effectiveness for these comparisons. In contrast, the main drivers of cost-effectiveness for the comparison of dronedarone versus class Ic agents are a combination of the benefits assumed from stroke and a reduction in adverse events. The ERG noted that if only the potential benefits of AF recurrence are included in the model then dronedarone does not appear cost-effective for any of the populations considered (see *Table 2*).

### Commentary on the robustness of submitted evidence

#### Strengths

The manufacturer conducted a comprehensive systematic review that identified not only all relevant trials of dronedarone but also additional RCTs for other relevant comparator AADs, including class Ic agents, sotalol and amiodarone. A range of alternative synthesis approaches was employed by the manufacturer in order to assess the relative effectiveness of dronedarone compared to other AADs that are currently used in the NHS. The results of these separate comparisons were reported for each of the main clinical outcomes.

In general, the ERG considered the economic submission to be of high quality, meeting the requirements of the NICE reference case. The

economic model structure was considered appropriate for the decision problem, and the detailed sensitivity analyses were thorough and informative in exploring the robustness of the results.

#### Weaknesses

Potential weaknesses that the ERG identified in relation to the clinical effectiveness evidence were:

1. The inclusion/exclusion criteria applied to studies to be included in the direct and indirect analyses were not explicitly stated.
2. Different inclusion/exclusion criteria were applied to studies for the direct meta-analysis and the MTC, with a substantial reduction in the number of studies entering the MTC compared to the direct meta-analysis.
3. Issues of clinical and statistical heterogeneity between the different studies were insufficiently reported or were not explored.
4. Neither the exchangeability of the ATHENA study with lower risk and younger AF populations nor the generalisability of the ATHENA population to the overall AF population managed in the NHS were considered.

The ERG identified a number of potential weaknesses related to the economic submission and electronic model which were considered to impact on the validity of the cost-effectiveness results. These included:

1. The treatment pathways evaluated by the manufacturer may not represent the full range of relevant strategies or sequences.
2. The use of baseline data from the ATHENA trial may not be generalisable to the UK AF population.
3. The use of a restricted set of studies to inform the relative effectiveness estimates applied in the model.
4. The assumptions used for class Ic agents, that for all-cause mortality there is no difference between dronedarone and class Ic agents, whilst for stroke, class Ic agents have no effect compared to standard care alone.
5. The estimates of the mortality effects of amiodarone and dronedarone.
6. Uncertainty surrounding the health-related quality of life (HRQoL) data used in the model.
7. Uncertainty in relation to the acquisition costs, initiation and monitoring costs of dronedarone.

The ERG explored the robustness to a number of these uncertainties. The ICER of dronedarone remained relatively robust throughout (< £20,000 per QALY) except for the following assumptions: (i) amiodarone and sotalol have the same effect on all-cause mortality as dronedarone; and (ii) class 1c has the same effect on stroke as dronedarone. In these situations, the ICER of dronedarone was well above £30,000 per QALY (see *Table 2*).

Finally, the submission does not explicitly consider the potential clinical effectiveness or cost-effectiveness of dronedarone for patients with AFL.

### Areas of uncertainty

The relative effectiveness and cost-effectiveness of dronedarone versus other AADs remains subject to a number of areas of uncertainty in terms of informing current NHS practice. These uncertainties include: (i) the generalisability of evidence from the ATHENA study to inform the management of a lower risk and younger AF population; (ii) the relative efficacy of dronedarone compared to other AADs; (iii) the validity of pooling the individual studies in the different synthesis approaches given the lack of consideration of clinical and statistical heterogeneity across the different studies; (iv) the clinical evidence for the major drivers of cost-effectiveness (e.g. all-cause mortality and stroke) and consequently, the additional benefits attributed in the economic model to dronedarone compared to other AADs; (v) the clinical evidence for the efficacy of dronedarone and other AADs to lower ventricular rate as rate control was not included as an outcome measure in the submission; and (vi) the presence and potential magnitude of any quality of life benefits attributed to dronedarone as HRQoL have not been directly assessed in any of the existing dronedarone RCTs.

There remains a number of additional sources of uncertainty related to the cost-effectiveness of dronedarone that the ERG has been unable to adequately address. This includes establishing the most appropriate source of data to inform the baseline event rates applied in the model; the position for dronedarone in the pathway of treatment sequences; HRQoL benefits of dronedarone; and the maintenance of benefits over the longer term.

## Conclusions

The effectiveness of dronedarone as an adjunctive treatment to standard care is highly uncertain, the key issue being the generalisability of the ATHENA study which reflects a moderate- to high-risk elderly AF population relative to the general AF population.

In terms of the broader comparison of dronedarone with AADs, the ERG considers that the clinical evidence is highly uncertain for the key drivers of the cost-effectiveness of dronedarone: all-cause mortality and stroke. The uncertainty arises because the potential clinical and statistical heterogeneity of the included RCTs has not been adequately considered, and the exchangeability of the ATHENA study with the other studies is questionable. Also, the additional restrictions imposed on the inclusion of RCTs in the MTC are likely to increase the overall decision uncertainty compared to a fuller use of this evidence. Furthermore, the question of how the reduction in all-cause mortality or stroke is mediated, given that dronedarone is the least effective AAD in terms of AF recurrence, remains to be elucidated.

Key issues specifically relevant to the economic evaluation include: establishing the most appropriate source of data to inform the baseline event rates applied in the model; the potential cost-effectiveness of dronedarone in a range of alternative and feasible treatment sequences; the potential HRQoL benefits of dronedarone and the maintenance of benefits over the longer term; and the absence of a final confirmed acquisition price at the time of the submission of the ERG report. Finally, the lower initiation and monitoring costs assumed for dronedarone are uncertain, although these do not appear to have a significant impact on the final ICER results.

### Implications for research

Further and longer term trials or the implementation of registries would be helpful to further establish the efficacy and safety of dronedarone relative to other AAD treatments that are regularly used in this indication within UK clinical practice. This is of particular importance in regard to outcomes of all-cause mortality and stroke, as these appear to be the key drivers of the cost-effectiveness results. Given the lack of existing HRQoL data, future RCTs of dronedarone and other AADs should also consider using a relevant

HRQoL measure. Additional evidence related to the effectiveness of AADs for patients with AFL would also be valuable.

## Summary of NICE guidance issued as a result of the STA

The final guidance, issued by NICE on 25 August 2010, states that:

Dronedarone is recommended as an option for the treatment of non-permanent atrial fibrillation only in people: whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option, and who have at least one of the following cardiovascular risk factors: - hypertension requiring drugs of at least two different classes, diabetes mellitus, previous transient ischaemic attack, stroke or systemic embolism, left atrial diameter of 50 mm or greater, left ventricular ejection fraction less than 40% (noting that the summary of product characteristics [SPC] does not recommend dronedarone for people with left ventricular ejection fraction less than 35% because of limited experience of using it in this group) or age 70 years or older, and who do not have unstable New York Heart Association (NYHA) class III or IV heart failure.

Furthermore, 'People who do not meet the criteria above who are currently receiving dronedarone

should have the option to continue treatment until they and their clinicians consider it appropriate to stop'.

## Key references

1. NICE. *Guide to the single technology appraisal (STA) process*. URL: [www.nice.org.uk/nicemedia/pdf/STA\\_Process\\_Guide.pdf](http://www.nice.org.uk/nicemedia/pdf/STA_Process_Guide.pdf).
2. McKenna C, Maund E, Sarowar M, Fox D, Stevenson M, Pepper C, *et al.* *Dronedarone for atrial fibrillation and atrial flutter. A single technology appraisal*. York: Centre for Reviews and Dissemination and Centre for Health Economics; 2009.
3. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;**82**:2N–9N.
4. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, *et al.* Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;**357**:987–99.
5. Connolly SJ, Crijns HJGM, Torp-Pedersen C, van Eickels M, Gaudin C, Page RL, *et al.* Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. *Circulation* 2009;**120**:1174–80.



# Imatinib as adjuvant treatment following resection of KIT-positive gastrointestinal stromal tumours

J Dretzke,<sup>1\*</sup> J Round,<sup>2</sup> M Connock,<sup>1</sup> S Tubeuf,<sup>2</sup> M Pennant,<sup>1</sup>  
A Fry-Smith,<sup>1</sup> C Hulme,<sup>2</sup> C McCabe<sup>2</sup> and C Meads<sup>1</sup>

<sup>1</sup>Unit of Public Health, Epidemiology & Biostatistics, University of Birmingham, Birmingham, UK

<sup>2</sup>Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, Leeds, UK

\*Corresponding author

**Declared competing interests of authors:** none

## Abstract

This is a summary of the evidence review group (ERG) report on the clinical effectiveness and cost-effectiveness of adjuvant imatinib post resection of KIT-positive gastrointestinal stromal tumours (GISTs) compared with resection only in patients at significant risk of relapse. The ERG report is based on the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The bulk of the clinical evidence submitted was in the form of one randomised controlled trial (RCT), the Z9001 trial, funded by the manufacturer, which compared resection + adjuvant imatinib for 1 year to resection only. Results were immature, with median recurrence-free survival (RFS) not yet having been reached at the time of analysis. The trial did provide evidence of a delay in disease recurrence [1-year RFS rate of 98% in the imatinib arm vs 83% in the placebo arm [hazard ratio (HR) 0.35, 95% confidence interval (CI) 0.22 to 0.53,  $p < 0.0001$ ]] but no evidence of an overall survival benefit. There was no long-term evidence around the rate of imatinib resistance over time with different treatment strategies ( $\pm$  adjuvant treatment). The relevant patient group for this appraisal is those at significant risk of relapse. These form a subgroup of the Z9001 trial, and all information regarding this group was designated 'Commercial-in-Confidence' (CIC).

## HTA 08/239/01

### Date of ERG submission:

1 November 2009

### TAR Centre(s):

West Midlands Health Technology Assessment Collaboration (WMHTAC)

### List of authors:

J Dretzke, J Round, M Connock, S Tubeuf, M Pennant, A Fry-Smith, C Hulme, C McCabe and C Meads

### Contact details:

Janine Dretzke, Unit of Public Health, Epidemiology & Biostatistics, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

E-mail: [j.dretzke@bham.ac.uk](mailto:j.dretzke@bham.ac.uk)

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 08/239/01. The assessment report began editorial review March 2010 and was accepted for publication in May 2010. See the HTA programme website for further project information ([www.hta.ac.uk](http://www.hta.ac.uk)). 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](http://www.hta.ac.uk/correspond)).

Median observation time for RFS was also CIC. The manufacturer constructed a Markov model comprising 10 health states designed to estimate costs and effects of treatment over a lifetime time horizon. The manufacturer's estimate of the base-case incremental cost-effectiveness ratio (ICER) was £22,937/quality-adjusted life-year (subsequently amended by the manufacturer to £23,601). While the structure of the model reasonably reflected the natural history of the disease, the ERG had numerous concerns regarding the selection of, and assumptions around, input parameters (utilities, monthly probabilities of recurrence and death). Furthermore, the model was set up in such a way that any delay in recurrence translated directly into a survival benefit, an assumption that has no evidence base. A further assumption not supported by evidence was that any treatment benefit gained in the first year is carried on for a further 2 years at the same rate. Appropriate probabilistic sensitivity analysis was undertaken on the base case only, but not on scenario analyses, or choice of model used to estimate long-term survival data. The model was not amenable to changes in input values, thus limiting any additional analyses by the ERG to test assumptions. Due to the large number of uncertainties and assumptions, the estimated ICERs should be regarded as highly uncertain. The guidance issued by NICE in June 2010 as a result of the STA does not recommend imatinib as adjuvant treatment after resection of gastrointestinal stromal tumours, although individuals currently receiving adjuvant imatinib should have the option to continue treatment until they and their clinician consider it appropriate to stop.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the UK 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<sup>1</sup> is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor (here, Novartis

Pharmaceuticals UK Ltd). Typically, it is used for new pharmaceutical products that are 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 the Institute. This paper presents a summary of the ERG report for the STA entitled '*Imatinib as adjuvant treatment following resection of KIT-positive gastrointestinal stromal tumours (GISTs)*'.<sup>2</sup>

## Description of the underlying health problem

Patients eligible for adjuvant imatinib according to the UK licence are those who have had a resection of KIT (CD117)-positive GIST and are deemed to be at significant risk of relapse. 'Significant' risk is not defined in the licence. In the industry submission it includes those patients in the moderate- and high-risk groups as defined by the Miettinen and Lasota criteria,<sup>3</sup> which take into account tumour size, location and mitotic count. Risk of relapse and choice of treatment also depend on the specific type of *KIT* exon gene mutations.

Based on the findings of studies in different countries, GIST has an annual incidence of between 6.8 and 14.5 per million; around two-thirds of patients with GIST are thought to be resectable. Of the resected patients, around one-half may have a significant risk of relapse.<sup>4</sup>

Survival after resection ranged from 48% to 80% at 5 years for low-risk GIST before the introduction of imatinib; the 5-year survival rate (approximately 95%) is similar to that of the general population, while for high-risk GISTs the 5-year survival rate ranged from 0% to 30% before the introduction of imatinib.<sup>5</sup> As imatinib is a relatively recent treatment for GIST, there are fewer long-term survival estimates. In a trial of imatinib for advanced GIST, with a reported follow-up of up to 71 months, median overall survival increased from 18 months to 60 months.<sup>6</sup>

Most patients eventually show resistance to imatinib due to secondary mutations in the *KIT* and/or *PDGFRA* (alpha-type platelet-derived growth factor receptor) kinase domains. One study found that secondary or acquired resistance develops after a median of about 2 years of treatment.<sup>7</sup>

Current guidelines state that imatinib increases recurrence-free survival (RFS) and suggest that it may be an effective treatment to prevent recurrence following primary surgery in those patients with a high risk of recurrence; these patients should be considered for inclusion in clinical trials of neoadjuvant and adjuvant therapy with imatinib.<sup>8</sup> Optimal treatment duration with adjuvant imatinib is not yet established, nor whether adjuvant treatment was a clinically effective or cost-effective option.

### Scope of the ERG report

The research question was the clinical effectiveness and cost-effectiveness of adjuvant imatinib following resection compared with resection only in patients with KIT-positive GISTs who are at significant risk of relapse. This is consistent with the licence indication.

The clinical effectiveness data was primarily based on one ongoing randomised controlled trial (RCT), the Z9001 trial<sup>4</sup> ( $n = 713$ ), which compared resection + adjuvant imatinib for 1 year with resection alone.

Data on those patients who were at significant risk of relapse and who formed a subgroup of the trial ( $n = 302$ ) were supplied as 'Commercial in Confidence' (CIC) data. Classification of patients according to risk was retrospective and was performed for only 78% of patients, making the results susceptible to bias. It is likely that patients in this trial are similar to patients in the UK who would be eligible for treatment with adjuvant imatinib, although there is a possibility of differing thresholds for what constitutes 'significant' risk.

Outcome measures in the Z9001 trial were RFS, overall survival (OS) and adverse events. Quality-of-life outcomes were not collected. Median follow-up time for OS was 19.7 months (data is CIC for RFS and for both RFS and OS in the significant-risk subgroup). It should be noted that on disease progression, all patients received treatment with imatinib or other treatment options (e.g. sunitinib) as appropriate, regardless of the treatment arm to which they were allocated; it is, in effect, different treatment strategies (one commencing with adjuvant imatinib) that are being compared long term.

The manufacturer submitted an economic model to assess the cost per quality-adjusted life-year

(QALY) of resection with 3 years' adjuvant imatinib (note: this differs from the trial where imatinib is given for 1 year) compared with resection only. Recurrence results were taken from the trial and extrapolated for longer time periods. Mortality results for patients in various health states were obtained from a variety of literature sources. Utility estimates were not available from the trial and were therefore taken from other literature sources or estimated by the manufacturer.

### Methods

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

Additional searches to confirm the completeness of published data on effectiveness and cost-effectiveness were undertaken. The ERG independently assessed the validity of the Z9001 trial and analysed CIC results for the significant-risk subgroup, which were provided separately by the manufacturer.

The model provided by the manufacturer was complex and not amenable to changes in parameter values, particularly with regard to running alternative probabilistic sensitivity analyses (PSAs). This limited the scope for the ERG to fully validate the model, and thus reduced the ERG's confidence in the results of the model. There was also a lack of information around uncertainty estimates for certain parameters, particularly utility values, again restricting any additional sensitivity analyses.

## Results

### Summary of submitted clinical evidence

All information relating to the relevant subgroup of patients (those at significant risk of relapse) was CIC and therefore cannot be reported here. The total trial population included patients at low risk of relapse, who would not be eligible for adjuvant treatment in the UK. For this total population, the estimated 1-year RFS rate was 98% in the imatinib arm and 83% in the placebo arm (HR 0.35, 95% CI 0.22 to 0.53,  $p < 0.0001$ ), therefore a delay in recurrence was evident (*Figure 1*). Median RFS had not yet been reached at the time of analysis and

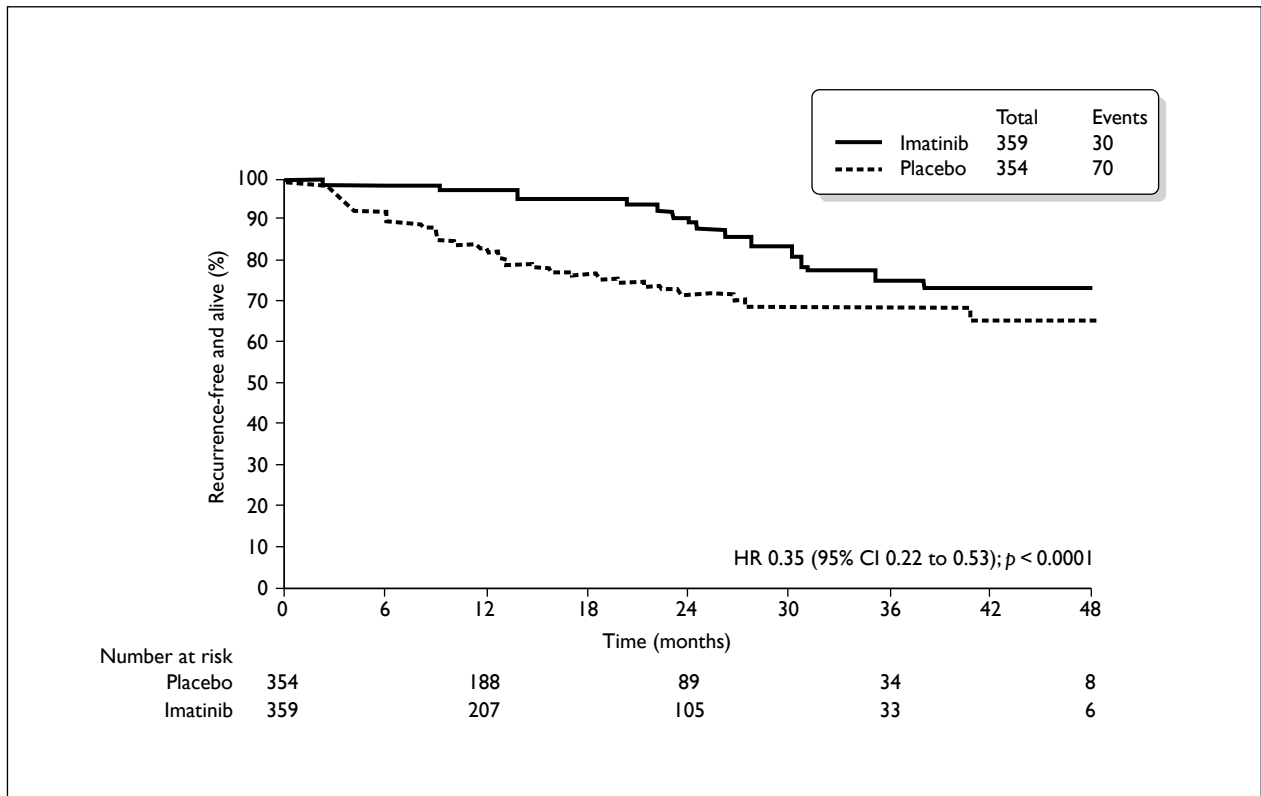


FIGURE 1 Recurrence-free survival in total population (from manufacturer's submission).

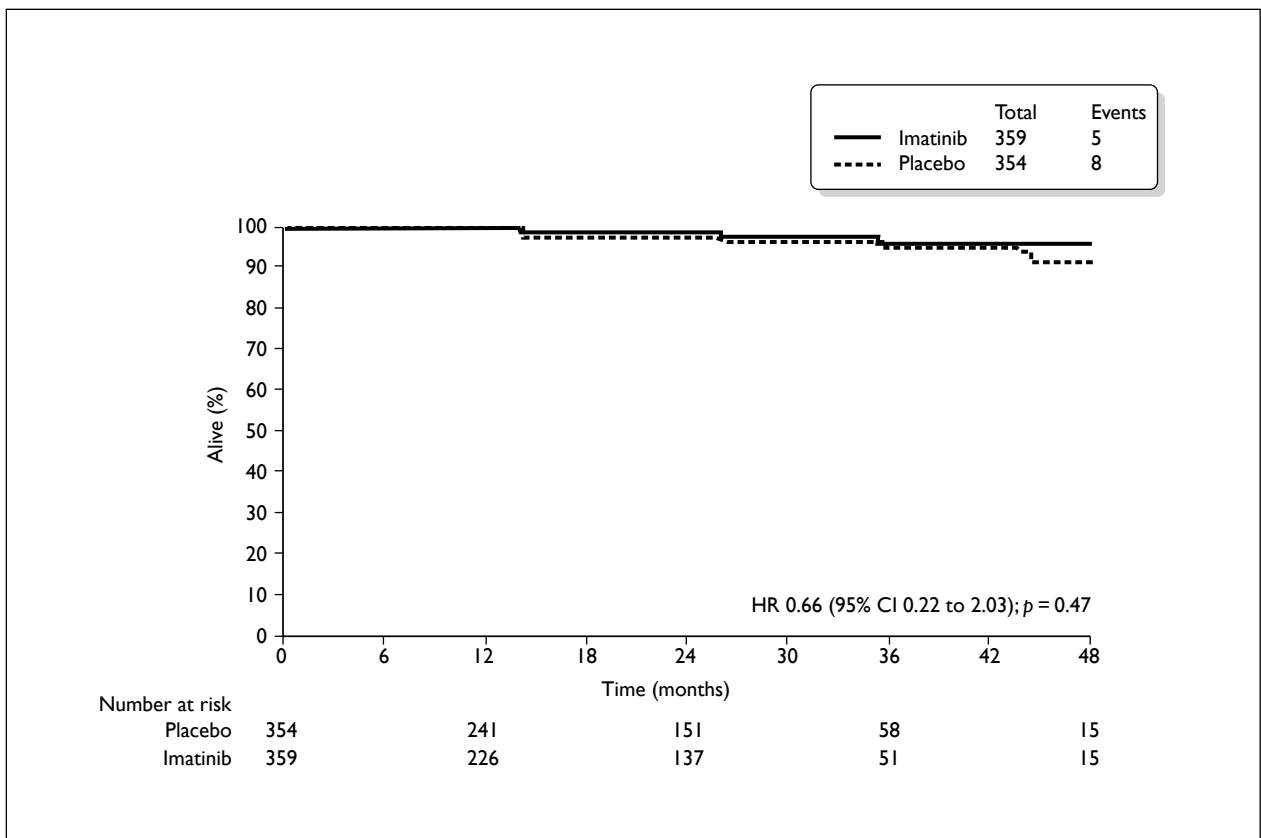


FIGURE 2 Overall survival in total population (from manufacturer's submission).

few patients were evaluable at later time points. The OS rates for the total population were similar and most patients were still alive at the time of data analysis (*Figure 2*). Results from the Z9001 trial on subsequent use of imatinib in patients who have previously had adjuvant imatinib were also CIC. The ERG identified no additional results on imatinib resistance rates with subsequent use in the long term.

### Summary of submitted cost-effectiveness evidence

The manufacturer's estimate of the base-case incremental cost-effectiveness ratio (ICER) was £22,937/QALY (subsequently amended by the manufacturer to £23,601). This estimate relies on patients receiving adjuvant imatinib for 3 years, for which there is no evidence from the Z9001 trial, which used 1 year of adjuvant treatment. The manufacturer's base-case analysis suggested that there was an approximately 60% chance that imatinib was cost-effective at willingness-to-pay thresholds of between £20,000 and £30,000 per QALY. Four additional analyses were submitted: (1) significant-risk patients, receiving imatinib for 1 year; (2) the overall at-risk population (no treatment time specified); (3) the high-risk only population, receiving 1 year of imatinib; and (4) the high-risk only population, receiving 3 years of imatinib. ICERs were £13,550, £32,981, £6109 and £19,813, respectively.

### Commentary on the robustness of submitted evidence

#### Clinical effectiveness

The population relevant to this appraisal was a subgroup of patients with significant risk of recurrence. Assignment of risk level was retrospective, and only 78% of patients were categorised according to risk. There is therefore a possibility of imbalances at baseline and risk of bias. Baseline characteristics of the significant risk population in the two trial arms are CIC.

There was some uncertainty around the handling of missing data and which definition of 'recurrence' was used for the analyses in the submission; the ERG was unable to gauge the potential impact on results. The results from the trial were immature, as follow-up times were short, and results at later time points were based on few patients at risk. There is no evidence to show that adjuvant imatinib given for 1 year prolongs overall survival. Median overall survival estimates were not reached in either

treatment arm (total trial population). There is no good long-term evidence on recurrence rates (resistance) when imatinib is given repeatedly. Quality of life was not measured as part of the Z9001 trial.

#### Cost-effectiveness

The model provided by the manufacturer contained no programming errors and the structure of the model reasonably reflected the natural history of the disease. However, the ERG was unable to conduct more than a limited range of alternative analyses to test assumptions made by the manufacturers, as the model was not amenable to changes in input values. Furthermore, the ERG had a number of concerns relating to the monthly probabilities of death in various health states and their application in the model. The manufacturer assumed that all monthly probabilities post health states A, B and D (*Figure 3*) were the same in both treatment arms, i.e. the probability of recurrence or death did not depend on whether a patient received adjuvant treatment or resection only. This seems implausible to the ERG. The result of this is that any differences in a delay in progression translate directly into a survival gain of the same length.

The manufacturer also provided no justification for the selection of studies from which the input parameters were derived, no details on how the death and recurrence rates were calculated, and there appeared to be some errors and inconsistencies. The impact on the ICER is unlikely to be large – because of the model structure, patients in both treatment arms received the same inputs post health states A, B and D – but this does not impart confidence in the modelling process.

The assumption of sustained benefit from treatment for 2 years beyond the evidence base is a generous one and systematically favours imatinib, resulting in a reduced ICER. Because of this way of extrapolating the treatment benefit, and because of the model structure, the logic of the model is that it is not sensible to stop adjuvant imatinib at any time point but to continue indefinitely. The ERG suggests that there is no proven benefit for this treatment strategy.

A further concern is that appropriate PSA was undertaken on the base case only, and not on the other scenario analyses. In particular, PSA was not undertaken on the subgroup analyses. One-way sensitivity analyses were conducted as part of the clarification process, but no scenario analyses were

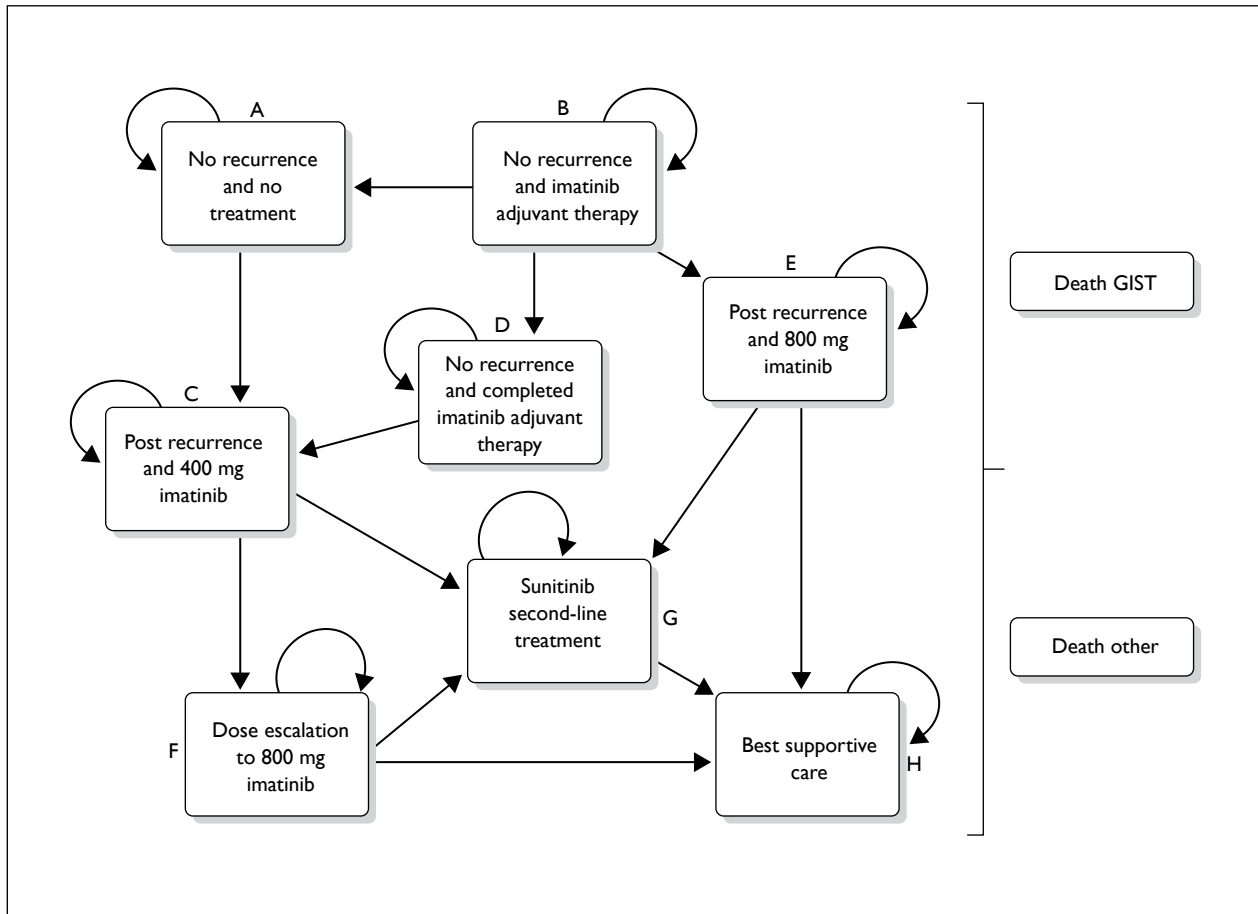


FIGURE 3 Transition pathways in manufacturer's model.

undertaken on choice of model used to estimate long-term survival data. The absence of PSA for the subgroup analyses provided further exacerbates the paucity of the evidence on the uncertainty around the cost-effectiveness estimates provided in the submission.

The utility values used relied heavily on one study (Chabot *et al.*<sup>9</sup>) based on treatment with sunitinib (after imatinib failure). The authors of this study advised caution in the interpretation of their results due to large uncertainty. The ERG also identified flaws in how health-state utilities were modelled, for example relating to age adjustment, and the use of a mean utility value only (rather than a range).

Table 1 shows ERG estimates of the likely impact on the ICER of a number of parameter assumptions/changes.

## Conclusions

A survival benefit with adjuvant imatinib has to date not been shown. There is a lack of good long-term evidence around the rate of imatinib resistance over time with different treatment strategies ( $\pm$  adjuvant imatinib, for 1 year or 3 years), and the effect on overall survival. There are serious concerns around the validity and application in the manufacturer's model of a number of input parameters, such as utilities and monthly probabilities of death. The model also makes a basic assumption that any benefit in delay of recurrence translates directly into an increase in survival over the long term; this assumption is not supported by any evidence and does not take into account the possibility of differing rates of imatinib resistance between the two treatment arms. Due to the large number of uncertainties and assumptions,

**TABLE 1** Effect of parameter changes on ICER (ERG estimates)

Parameter	Effect on ICER (↑ = increase, ↓ = decrease)
Decrease in utility value for RFS to 0.95 and 0.9 (manufacturer assumed a utility value of 1)	↑ (small)
No estimate of uncertainty associated with recurrence-free health state in model (benefit for patients likely to have been overestimated)	↑
No utilities <0 included (should have been included as within range of possible utilities)	↑
No disutility associated with adverse events of adjuvant treatment	↑
Gradual increase in recurrence rates after year 1 with adjuvant treatment (rather than sustained benefit over 3 years, which seems implausible)	↑
Correction of potential double-counting of utility loss (for health state and age)	↑
Error identified by manufacturer relating to recurrence rates	↑ (also wider 95% CI)
Increased resistance to imatinib over time (manufacturer's sensitivity analysis found a reduced ICER – this seems implausible to the ERG and no adequate explanation was given)	↑
Reduction in survival benefit with adjuvant treatment (manufacturer's sensitivity analysis found a reduced ICER – this seems implausible as this means a net benefit from patients dying earlier)	↑
Reduction in length of time of imatinib use (1 year only)	↓
Use of adjuvant imatinib in high-risk population only	↓

CI, confidence interval; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; RFS, recurrence-free survival.

the estimated ICERs should be regarded as highly uncertain. It is possible that results from ongoing trials will inform this issue. The EORTEC 62024 trial<sup>10</sup> in particular has as an end point time to imatinib resistance, which may be a more useful proxy for overall survival. Should adjuvant imatinib treatment be shown to be beneficial in the future, further research would also be required into the type of patient most likely to benefit from adjuvant treatment based on mutational analysis.

### Summary of NICE guidance issued as a result of the STA

NICE guidance issued in June 2010 does not recommend imatinib as adjuvant treatment after resection of gastrointestinal stromal tumours, although individuals currently receiving adjuvant imatinib should have the option to continue treatment until they and their clinician consider it appropriate to stop.

### Key references

1. National Institute for Health and Clinical Excellence (NICE). *Guide to single technology (STA) process*. URL: [www.nice.org.uk/media/42D/B3/STAGuideLrFinal.pdf](http://www.nice.org.uk/media/42D/B3/STAGuideLrFinal.pdf) (accessed 24 September 2010).
2. Dretzke J, Round J, Connock M, Tubeuf S, Pennant M, Fry-Smith A, *et al.* *Imatinib as adjuvant treatment following resection of KIT-positive gastrointestinal stromal tumours*; 2009. 25 March 2010. URL: <http://www.nice.org.uk/nicemedia/live/12178/48128/48128.pdf>.
3. Miettinen M, Lasota J. Gastrointestinal stromal tumours: pathology and prognosis at different sites. *Semin Diagn Pathol* 2006;**23**:70–83.
4. DeMatteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PWT, Demetri GD, *et al.* Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised,

- double-blind, placebo-controlled trial. *Lancet* 2009;**373**:1097–104.
5. Park CK, Lee EJ, Kim M, Lim HY, Choi DI, Noh JH, *et al.* Prognostic stratification of high-risk gastrointestinal tumours in the era of targeted therapy. *Ann Surg* 2008;**247**:1011–18.
  6. Blanke CD, Demetri GD, von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA, *et al.* Long-term results from a randomised phase II trial of standard versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumours expressing KIT. *J Clin Oncol* 2008;**26**:620–5.
  7. Demetri GD, van Oosterom AT, Garrett CR. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006;**368**:1329–38.
  8. Reid R, Bulusu R, Buckels JEA. *Guidelines for the management of gastrointestinal stromal tumours (GISTs)*; 2009. URL: [www.mccn.nhs.uk/userfiles/documents/04%20GIST\\_Mngmnt\\_Gdlns.pdf](http://www.mccn.nhs.uk/userfiles/documents/04%20GIST_Mngmnt_Gdlns.pdf).
  9. Chabot I, LeLorier J, Blackstein ME. The challenge of conducting pharmacoeconomic evaluations in oncology using crossover trials: the example of sunitinib for gastrointestinal stromal tumours. *Eur J Cancer* 2008;**44**:972–7.
  10. US National Institutes of Health. *Imatinib mesylate or observation only in treating patients who have undergone surgery for localised gastrointestinal stromal tumor*; 2010. URL: [www.clinicaltrials.gov/ct2/show/NCT00103168?term=62024&rank=1](http://www.clinicaltrials.gov/ct2/show/NCT00103168?term=62024&rank=1).



# Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer

T Brown,\* A Boland, A Bagust, J Oyee, J Hockenhull,  
Y Dundar, R Dickson, VS Ramani and C Proudlove

Liverpool Reviews and Implementation Group, University of Liverpool, Liverpool, UK

\*Corresponding author

**Declared competing interests of authors:** none

## Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in accordance with the licensed indication, based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The submitted clinical evidence consisted of the IRESSA Pan-Asian Study (IPASS); a phase III open-label randomised controlled trial conducted in 87 centres in East Asia which compared the use of gefitinib with paclitaxel/carboplatin in 1217 chemotherapy (CTX)-naive patients with stage IIIB/IV pulmonary adenocarcinoma. The manufacturer's submission focused on a subgroup of patients in IPASS who were epidermal growth factor receptor (EGFR) gene mutation-positive (M+) ( $n = 261$ ; 21% of the total IPASS population). The primary clinical outcome was progression-free survival (PFS). Secondary outcomes included overall survival, clinically relevant improvement in quality of life and adverse events (AEs). Cost-effectiveness was measured in terms of incremental cost per quality-adjusted life-year (QALY). In the overall population, PFS was significantly longer in patients treated with gefitinib than in those treated with paclitaxel/carboplatin (hazard ratio 0.74, 95% confidence interval 0.65 to 0.85;  $p < 0.0001$ ). The manufacturer reported an incremental cost-effectiveness ratio (ICER) of £20,744 per QALY gained for the target population. The probabilistic sensitivity analysis illustrated that for patients who are EGFR M+, gefitinib compared with

## HTA 09/59/01

### Date of ERG submission:

16 February 2010

### TAR Centre(s):

Liverpool

### List of authors:

T Brown, A Boland, A Bagust, J Oyee, J Hockenhull,  
Y Dundar, R Dickson, VS Ramani and C Proudlove

### Contact details:

Tamara Brown, Research Fellow (Clinical Reviews),  
Liverpool Reviews and Implementation Group, University  
of Liverpool, Room 2.07, Whelan Building, The Quadrangle,  
Brownlow Hill, Liverpool L69 3GB, UK

E-mail: [tamara.brown@liverpool.ac.uk](mailto:tamara.brown@liverpool.ac.uk)

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 09/59/01. The assessment report began editorial review in June 2010 and was accepted for publication in July 2010. See the HTA programme website for further project information ([www.hta.ac.uk](http://www.hta.ac.uk)). 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](http://www.hta.ac.uk/correspond)).

doublet CTX was not likely to be cost-effective at what would usually be considered standard levels of willingness to pay for an additional QALY; the mean ICER for gefitinib EGFR M+ versus doublet CTX EGFR M+ was reported as £35,700 per QALY. Additional analysis by the ERG included amendments to the base-case analysis, including an alternative approach to projecting survival, inclusion of two important additional comparators, sensitivity to EGFR M+ prevalence, and AE costs and disutilities. The manufacturer's submission provides clinical evidence to support the use of gefitinib in EGFR M+ patients with adenocarcinoma histology only. Before patients can be offered first-line treatment with gefitinib they must undergo EGFR mutation status testing which is currently not routinely available in the NHS. At the time of writing, the guidance document issued by NICE on 28 July 2010 states that 'Gefitinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation and the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme'.

## 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, where most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> 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 the Institute. This paper presents a summary of the ERG report for the STA entitled '*Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)*'.

## Description of the underlying health problem

Lung cancer is the leading cause of cancer death worldwide and is responsible for over 33,000 deaths a year in England and Wales.<sup>2</sup> NSCLC is the most common subtype, accounting for 80% of all lung cancer cases. Despite advances in early detection, most patients still present with late-stage disease.

Survival rates for lung cancer are very poor. In England, for patients diagnosed between 1993 and 1995 and followed up to 2000, 21.4% of men and 21.8% of women with lung cancer were alive 1 year after diagnosis and less than 1% of advanced NSCLC lung cancer patients were alive after 5 years.<sup>3,4</sup>

The majority of patients with lung cancer are diagnosed, or relapse, with incurable disease and receive palliative treatment only. For otherwise fit patients with stage III/IV NSCLC, first-line treatment consists of platinum-based combination chemotherapy (CTX) followed by docetaxel CTX or erlotinib, as currently recommended in NICE clinical guidelines.<sup>3</sup>

## Scope of the evidence review group report

Gefitinib is an orally active, selective epidermal growth factor receptor (EGFR) gene tyrosine kinase inhibitor which helps to slow the growth and spread of the cancer.

Gefitinib is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with activating mutations of EGFR;<sup>5</sup> the scope issued by NICE is for first-line treatment only.

Before patients can be offered first-line treatment with gefitinib they must undergo EGFR mutation status testing which is currently not routinely available in the NHS.

The ERG report includes an assessment of both the clinical effectiveness and cost-effectiveness evidence submitted by the manufacturer (AstraZeneca) for the use of gefitinib compared with doublet CTX for the treatment of CTX-naïve patients with stage III/IV pulmonary adenocarcinoma who tested positive (M+) for the EGFR mutation. Data were presented for all patients and a subgroup of patients who were EGFR M+.

The primary clinical outcome was progression-free survival (PFS). Secondary outcomes included overall survival (OS), clinically relevant improvement in quality of life (QoL) and adverse events (AEs). Cost-effectiveness was measured in terms of incremental cost per quality-adjusted life-year (QALY).

## Methods

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

The ERG evaluated the quality of the manufacturer's clinical effectiveness review which comprised of a systematic review, meta-analysis and mixed-treatment comparison (MTC). Searches conducted by the manufacturer were assessed for completeness and the single trial put forward as evidence of effectiveness was critically appraised using the manufacturer's responses to specific questions in the submission template.

Cost-effectiveness evidence submitted by the manufacturer consisted of a systematic review and a de novo economic evaluation. The ERG assessed the manufacturer's searches for completeness, critically appraised the submitted economic model using the NICE reference case checklist<sup>6</sup> and the Drummond 10-point checklist,<sup>7</sup> and conducted a detailed evaluation of the model and the validity of the MTC results for economic analysis of non-trial comparators.

Additional analysis by the ERG included amendments to the base-case analysis, including an alternative approach to projecting survival, inclusion of two important additional comparators, sensitivity to EGFR M+ prevalence, and AE costs and disutilities.

## Results

### Summary of submitted clinical evidence

Only one relevant randomised controlled trial (RCT) was identified by the manufacturer; the IRESSA Pan-Asian Study (IPASS).<sup>8</sup> IPASS<sup>8</sup> is a phase III open-label RCT conducted in 87 centres in East Asia which compared the use

of gefitinib with paclitaxel/carboplatin in 1217 CTX-naive patients with stage IIIB/IV pulmonary adenocarcinoma.<sup>8</sup> The manufacturer's submission focused on a subgroup of patients in IPASS<sup>8</sup> who were EGFR M+ ( $n = 261$ ; 21% of the total IPASS population).

In the overall population, PFS was significantly longer in patients treated with gefitinib than in those treated with paclitaxel/carboplatin [hazard ratio (HR) 0.74, 95% confidence interval (CI) 0.65 to 0.85;  $p < 0.0001$ ]. In a subgroup analysis of 261 patients who were EGFR M+, PFS was significantly longer among those who received gefitinib than among those who received paclitaxel/carboplatin (HR 0.48, 95% CI 0.36 to 0.64;  $p < 0.0001$ ). In the subgroup of patients who were EGFR mutation-negative (M-) ( $n = 176$ ), PFS was significantly longer among those who received paclitaxel/carboplatin (HR with gefitinib 2.85, 95% CI 2.05 to 3.98;  $p < 0.001$ ).

Overall survival estimates were based on an interim analysis (37% maturity) and were similar for gefitinib and paclitaxel/carboplatin patients in the overall trial population [18.6 months for gefitinib vs 17.3 months for paclitaxel/carboplatin (HR 0.91, 95% CI 0.76 to 1.10)]. There was no significant difference in OS between gefitinib and paclitaxel/carboplatin in EGFR M+ patients groups (HR 0.78, 95% CI 0.50 to 1.20). Median OS was 12.1 months in the gefitinib EGFR M- subgroup and was 12.6 months in the paclitaxel/carboplatin EGFR M- subgroup.

Significantly more patients in the gefitinib group than in the paclitaxel/carboplatin group had a clinically relevant improvement in QoL, as assessed by scores on the Functional Assessment of Cancer Therapy – Lung questionnaire,<sup>9</sup> [odds ratio (OR) 1.34, 95% CI 1.06 to 1.69;  $p = 0.01$ ] and by scores on the Trial Outcome Index (OR 1.78, 95% CI 1.40 to 2.26;  $p < 0.001$ ). Gefitinib was associated with fewer grade 3 or 4 AEs.

After late identification of interim analysis data from an ongoing RCT, the manufacturer performed a meta-analysis using data from IPASS<sup>8</sup> and the North East Japan Gefitinib Study Group (NEJGSG).<sup>10</sup> Meta-analysis demonstrated significant improvement in PFS for EGFR M+ patients in the gefitinib arm compared with EGFR M+ patients in the paclitaxel/carboplatin arm (HR 0.43, 95% CI 0.34 to 0.53;  $p < 0.00001$ ).

The manufacturer conducted an MTC comparing doublet CTX in CTX-naïve patients with NSCLC, using paclitaxel/carboplatin evidence from IPASS<sup>8</sup> as a baseline and including 29 RCTS. The MTC did not identify any individual doublet CTX as offering both significant clinical benefit and significantly improved tolerability over the other doublet CTX regimens.

### Summary of submitted cost-effectiveness evidence

The manufacturer conducted a de novo economic evaluation. A Markov model was developed to evaluate the cost-effectiveness of gefitinib compared to four different doublet CTX regimens. The clinical data used in the economic evaluation were generated from a variety of sources. The HR for PFS for gefitinib EGFR M+ patients was derived from a meta-analysis conducted by the manufacturer and the HR for OS for gefitinib EGFR M+ patients was extrapolated from IPASS.<sup>8</sup> Estimates of the HRs for PFS and OS for the doublet CTX regimens were sourced indirectly from the MTC. Although the economic evaluation is primarily trial-based, there is a modelling component with regard to the extrapolation of health effects because IPASS<sup>8</sup> is ongoing. The economic evaluation adopts a lifetime horizon for consideration of costs and benefits and the perspective is that of the UK NHS and Personal Social Services.

The manufacturer reported an incremental cost-effectiveness ratio (ICER) of £20,744 per QALY gained for the target population. In addition to the main cost-effectiveness results, ICERs for selected subgroups were presented. Univariate sensitivity analysis, scenario analyses and probabilistic sensitivity analysis (PSA) were undertaken by the manufacturer.

The PSA illustrated that for patients who are EGFR M+, gefitinib compared with doublet CTX was not likely to be cost-effective at what would usually be considered standard levels of willingness to pay for an additional QALY; the mean ICER for gefitinib EGFR M+ versus doublet CTX EGFR M+ was reported as £35,700 per QALY.

### Commentary on the robustness of submitted evidence

#### Clinical evidence

Before patients can be offered first-line treatment with gefitinib they must undergo EGFR mutation

status testing. Currently, EGFR mutation testing is not routinely available in the NHS. It is uncertain how future testing of newly diagnosed patients with NSCLC will be orchestrated within the NHS in England and Wales. In addition, patients with adenocarcinoma histology would need to be identified prior to EGFR mutation testing. This diagnostic service is not routinely available to patients in the NHS.

The ERG highlighted that the clinical validity characteristics of EGFR tests could impact on treatment outcomes with gefitinib. In particular, a positive result for EGFR mutation status does not guarantee a good outcome, as a proportion (clinical false-positives) of such patients receiving gefitinib will not experience any benefit (shorter PFS) compared with current treatment with doublet CTX and may in fact be worse off by not receiving doublet CTX (*Figure 1*). The implications of using EGFR mutation tests must be carefully considered for both EGFR M+ and EGFR M- patients.

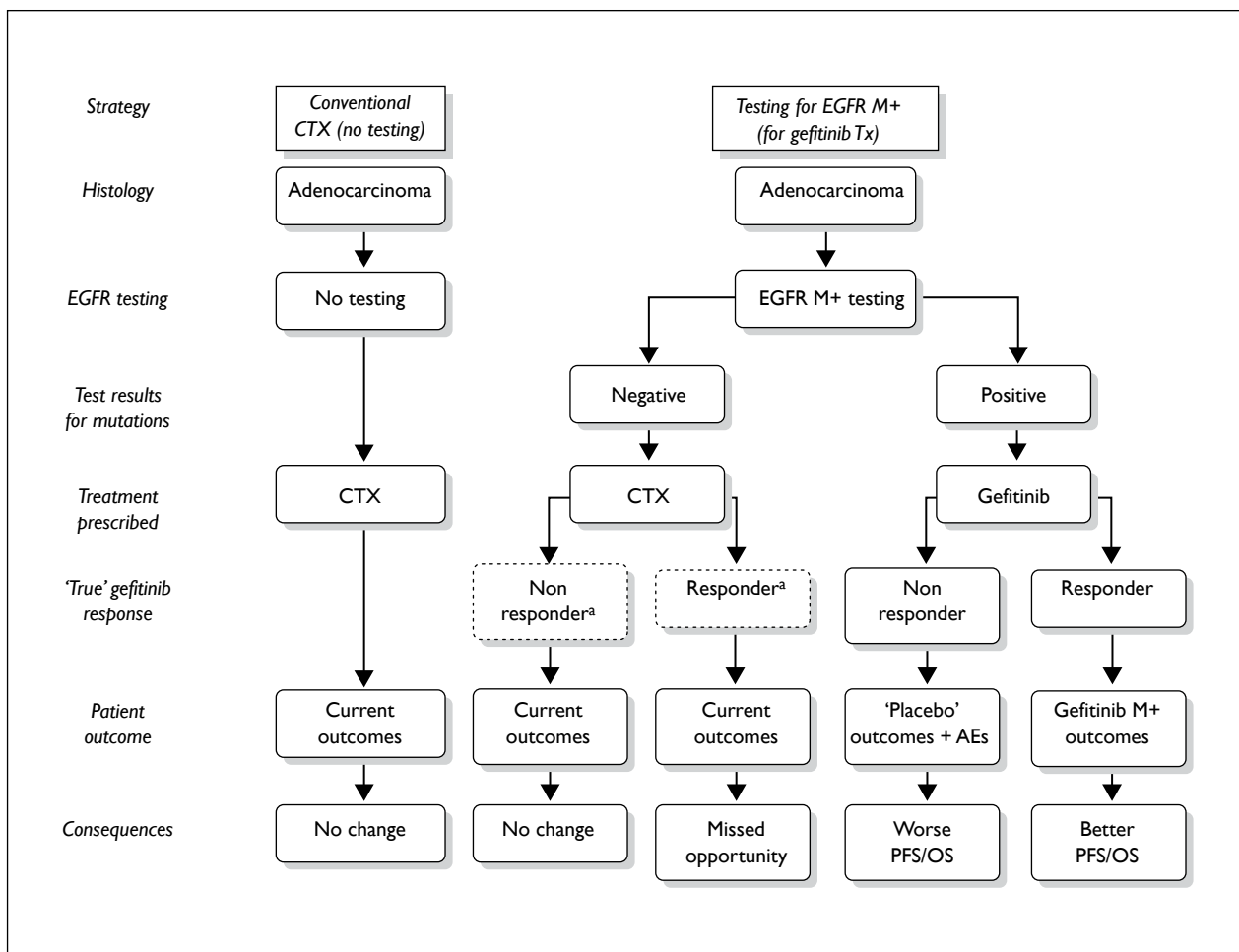
The number of patients requiring first-line treatment for NSCLC who are EGFR M+ in England and Wales is currently uncertain. A recent publication has estimated this figure to be between 5% and 10% in the Western population.<sup>11</sup>

The clinical evidence was derived from a high quality trial in patients with NSCLC; convincing efficacy and QoL evidence were presented by the manufacturer for a specific group of patients.

The main evidence cited by the manufacturer was derived from the IPASS<sup>8</sup> trial; this study has reached only 37% maturity for the determination of OS. The final OS estimates for patients in IPASS<sup>8</sup> will be available in 2010. However, it may be difficult for the investigators to interpret the final OS data from IPASS<sup>8</sup> owing to the substantial number of patients in both groups who went on to receive a variety of second-line CTX regimens.

Clinical data from two other smaller trials [the NEJGSG<sup>10</sup> trial and the First-SIGNAL (First-line Single agent Iressa versus Gemcitabine and cisplatin trial in Never-smokers with Adenocarcinoma of the Lung)<sup>12</sup> trial] comparing gefitinib with doublet CTX are also available.

The main focus of the manufacturer's submission was on patients who were EGFR M+; this subgroup of patients cannot be considered to have been truly randomised in the trial as the randomisation process did not include stratification by biomarker



**FIGURE 1** Effects of diagnostic test on treatment pathways and patient outcome. AEs, adverse events; CTX, chemotherapy; EGFR, epidermal growth factor receptor gene; M+, mutation-positive; PFS, progression-free survival; OS, overall survival; Tx, treatment.

type. In addition, the trial was not powered to perform this subgroup analysis.

The generalisability of the IPASS<sup>8</sup> study to patients in England and Wales is limited. None of the IPASS<sup>8</sup> centres were based in the UK; all of the patients were from East Asia. All of the IPASS<sup>8</sup> patients had adenocarcinoma histology; in the UK patients with adenocarcinoma are estimated to make up approximately 25% of the population with NSCLC.<sup>13</sup> IPASS<sup>8</sup> includes patients with performance status (PS) 2; in England and Wales, CTX is not recommended by NICE for patients with metastatic disease with PS 2 unless as part of a clinical trial.<sup>3</sup> The demographic characteristics of patients in IPASS<sup>8</sup> do not match those of the relevant population in England and Wales; IPASS<sup>8</sup> patients are predominantly female and never smokers.

In the UK, the most common first-line CTX regimen for patients with NSCLC is gemcitabine with either carboplatin or cisplatin. In IPASS,<sup>8</sup> gefitinib is compared with paclitaxel/carboplatin; it has been estimated by the manufacturer that approximately only 5% of patients receive paclitaxel/carboplatin as a first-line treatment for NSCLC in England and Wales.

The MTC methods used by the manufacturer to compare paclitaxel/carboplatin with a range of doublet CTX regimens in unselected populations are appropriate. However, the ERG considered that the MTC was weak as it was reliant on the assumption that EGFR mutation status does not affect treatment outcomes if patients are receiving doublet CTX. The ERG believes this assumption is too strong as it is wholly reliant on the results of a subgroup analysis from a single RCT of patients with adenocarcinoma histology. The evidence base

for the studies used in the comparison of gefitinib with doublet CTX may not be generalisable to the EGFR M+ population.

### Economic evidence

The manufacturer's economic evaluation did not compare gefitinib with docetaxel or pemetrexed; both of these CTX regimens are listed as relevant comparators in the final NICE scope. In response to the ERG's clarification letter, the manufacturer provided an updated version of the MTC and included pemetrexed. The ERG considered that not including pemetrexed or docetaxel as comparators in the economic evaluation was a major weakness of the manufacturer's submission.

The ERG identified key areas where corrections and/or adjustments to the economic model are required: CTX costs, cycles, and exposure; OS and PFS modelling; and use of discounting and continuity correction methods. Taken together, the ERG's corrections and/or adjustments to the submitted model increased the size of the ICER for the base-case population from £20,010 to over £70,000 per QALY (Tables 1 and 2). This suggests that the cost-effectiveness of gefitinib compared to doublet CTX for CTX-naive EGFR M+ patients may be less favourable than presented by the manufacturer in the manufacturer's submission.

The ERG highlighted that the results of the manufacturer's economic evaluation were predicated on the use of the EGFR mutation test (or similar) described in IPASS.<sup>8</sup> This means that if a different EGFR mutation test is used and/or does not demonstrate similar analytic validity, the manufacturer's cost-effectiveness results may no longer be valid. This assessment does not relate solely to use of gefitinib, but to the specific combination of mutation testing and gefitinib treatment studied in IPASS.<sup>8</sup>

Finally, during the clarification process the manufacturer was asked to provide individual patient data (IPD) from IPASS<sup>8</sup> that would allow the ERG to explore a number of weaknesses identified in the economic model. The manufacturer replied that it could not share IPD, but would be willing to conduct specific analyses on behalf of the ERG. A request was made to the manufacturer to conduct

these analyses. The manufacturer responded that it would not be able to provide the results of the requested analyses within the timeframe of the STA process.

### Conclusions

The manufacturer's submission provides clinical evidence to support the use of gefitinib in EGFR M+ patients with adenocarcinoma histology only. Before patients can be offered first-line treatment with gefitinib they must undergo EGFR mutation status testing which is currently not routinely available in the NHS.

Major weaknesses in the clinical section of the manufacturer's submission identified by the ERG include: (i) the clinical results of IPASS<sup>8</sup> are not generalisable to the majority of patients with NSCLC in clinical practice in England and Wales; and (ii) to date, there are no direct clinical trial data to demonstrate that use of gefitinib as a first-line treatment by EGFR M+ patients leads to improved OS compared with the use of paclitaxel/carboplatin.

The ERG's corrections and/or adjustments to the submitted economic model have increased the size of the ICER for the base-case population; the cost-effectiveness of gefitinib compared to doublet CTX for CTX-naive EGFR M+ patients may be less favourable than presented by the manufacturer in the manufacturer's submission.

### Summary of NICE guidance issued as a result of the STA

The guidance document issued by NICE on 28 July 2010 states that:

Gefitinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if:

they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation and

the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.

**TABLE 1** Effect of corrections and amendments made by ERG to the manufacturer's model for the base-case analysis (other modelled comparators) over 6 years

Model amendment	Gemcitabine/carboplatin			Vinorelbine/cisplatin			Gemcitabine/cisplatin		
	Inc. Costs	Inc. QALYs	ICER (£/QALY)	Inc. Costs	Inc. QALYs	ICER (£/QALY)	Inc. Costs	Inc. QALYs	ICER (£/QALY)
Submitted model	£3666	0.1767	£20,744	£8024	0.2229	£35,992	£4138	0.1445	£28,633
Base case with 6-year horizon	£3761	0.1767	£21,284	£8151	0.2229	£36,562	£4222	0.1445	£29,217
Revised MTC	£3858	0.1824	£21,151	£8149	0.2229	£36,557	£4218	0.1445	£29,181
Amend first-line CTX costs	£4057	0.1767	£22,956	£8447	0.2229	£37,890	£4077	0.1445	£28,215
Reduced cycles of CTX	£5599	0.1735	£32,278	£9547	0.2194	£43,512	£6244	0.1409	£44,308
Revise OS models	£1985	0.1174	£16,907	£7175	0.1893	£37,905	£2245	0.0788	£28,509
Revise PFS models	£5019	0.1630	£30,788	£9299	0.2097	£44,356	£5409	0.1313	£41,209
IPASS PFS HR (not MA)	£4450	0.1678	£26,520	£8840	0.2140	£41,304	£4911	0.1356	£36,219
Revise discounting method	£3674	0.1796	£20,453	£8123	0.2266	£35,839	£4146	0.1469	£28,229
Omit GCSF prophylaxis	£4039	0.1767	£22,855	£8429	0.2229	£37,809	£4500	0.1445	£31,141
Continuity correction	£3362	0.1767	£19,024	£7891	0.2229	£35,398	£3895	0.1445	£26,956
Correct misaligned cycles	£3762	0.1767	£21,290	£8152	0.2229	£36,567	£4223	0.1445	£29,223
Correct second-line CTX costs	£4380	0.1767	£24,785	£8085	0.2229	£36,264	£4657	0.1445	£32,228
Common CTX outcomes	£5114	0.1892	£27,028	£7043	0.1896	£37,148	£5149	0.1880	£27,394
CTX treatment exposure	£4543	0.1767	£25,706	£8737	0.2229	£39,189	£5067	0.1445	£35,062
Combined effect of all changes	£7554	0.1253	£60,273	£8842	0.1256	£70,390	£7322	0.1241	£59,016

CTX, chemotherapy; GCSF, granulocyte colony stimulating factor; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPASS, IRESSA Pan-Asian Study; MA, meta-analysis; MTC, mixed-treatment comparison; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

**TABLE 2** Effect of corrections and amendments made by ERG to the manufacturer's model for the base-case analysis (other modelled comparators) over 6 years (continuation of Table 1)

Model amendment	Docetaxel/cisplatin			Pemetrexed/cisplatin		
	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. costs	Inc. QALYs	ICER (£/QALY)
Submitted model <sup>a</sup>	—	—	—	—	—	—
With revised MTC	£4434	0.1627	£27,252	-£134	0.0601	-£2223
Reduced cycles of CTX <sup>b</sup>	£6254	0.1593	£39,263	£2484	0.0565	£43,984
Revise OS models	£2591	0.1013	£25,590	-£3115	-0.0379	£82,125
Revise PFS models	£5636	0.1494	£37,735	£1091	0.0469	£23,271
IPASS PFS HR (not MA)	£5123	0.1538	£33,311	£555	0.0512	£10,838
Revise discounting method	£4356	0.1654	£26,340	-£264	0.0610	-£4323
Omit GCSF prophylaxis	£4712	0.1627	£28,961	£144	0.0601	£2402
Continuity correction	£4024	0.1627	£24,728	-£600	0.0601	-£9984
Correct misaligned cycles	£4435	0.1627	£27,257	-£134	0.0601	-£2223
Correct second-line CTX costs	£4944	0.1627	£30,385	£842	0.0601	£14,004
CTX treatment exposure	£5200	0.1627	£31,961	£958	0.0601	£15,931
Combined effect of all changes	£6285	0.0862	£72,908	£1574	-0.0560	-£28,080 (gefitinib dominated)

CTX, chemotherapy; GCSF, granulocyte colony stimulating factor; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPASS, IRESSA Pan-Asian Study; MA, meta-analysis; MTC, mixed-treatment comparison; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

a Submitted model did not include these comparators.  
b Submitted model did not include costs for these comparators.

## Key references

- National Institute for Health and Clinical Excellence. *Guide to the single technology (STA) process*. 19 September 2006. URL: [www.nice.org.uk/page.aspx?o=STAprcessguide](http://www.nice.org.uk/page.aspx?o=STAprcessguide).
- Cancer Research UK. *Lung cancer incidence statistics*. 2007. URL: <http://info.cancerresearchuk.org/cancerstats/types/lung/index.htm>.
- National Institute for Health and Clinical Excellence, National Collaborating Centre for Acute Care. *Clinical Guideline 24, Lung cancer: the diagnosis and treatment of lung cancer*. London: National Institute for Health and Clinical Excellence; 2009.
- National Institute for Health and Clinical Excellence. *Lung cancer: the diagnosis and treatment of lung cancer*. National Cost Impact Report. 2005.
- European Medicines Agency, Evaluation of Medicines for Human Use. *Assessment report for Iressa*. 2009. URL: [www.emea.europa.eu/humandocs/PDFs/EPAR/iressa/H-1016-en6.pdf](http://www.emea.europa.eu/humandocs/PDFs/EPAR/iressa/H-1016-en6.pdf).
- National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal*. 2008. URL: [www.nice.org.uk/pdf/TAP\\_Methods.pdf](http://www.nice.org.uk/pdf/TAP_Methods.pdf).
- Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working. *BMJ* 1996;**313**:275.
- Mok TS, Wu YL, Thongsprasert S, Yang CH, Chu DT, Saijo N, *et al*. Gefitinib or Carboplatin-Paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;**361**:947.
- Cella DF, Bonomi AE, Lloyd SR, Tulskey DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy – Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995;**12**:199–220.
- Kobayashi K, Inoue A, Maemondo M, Sugawara S, Oizumi S, Saji Y, *et al*. First-line gefitinib versus first-line chemotherapy by carboplatin (CBDCA) plus paclitaxel (TXL) in non-small cell lung cancer (NSCLC) patients with EGFR mutations: a phase

- III study (002) by North East Japan (NEJ) Gefitinib Study Group. *J Clin Oncol* 2009;**27**:8016.
11. Mitsudomi T, Yatabe Y. Mutations of the epidermal growth factor receptor gene and related genes as determinants of epidermal growth factor receptor tyrosine kinase inhibitors sensitivity in lung cancer. *Cancer Sci* 2007;**98**:1817.
  12. Lee J, Park K, Kim S, Lee D, H K. *A randomized phase III study of gefitinib (IRESSA) versus standard chemotherapy (gemcitabine plus cisplatin) as a first-line treatment for never smokers with advanced or metastatic adenocarcinoma of the lung*. 13th Biennial World Conference on Lung Cancer of the International Association of the Study of Lung Cancer (IASLC), San Francisco, CA, 2009.
  13. The Information Centre for Health and Social Care. *National Lung Audit: Key findings about the quality of care for people with lung cancer in England and Wales. Report for the audit period 2006*. Leeds: The Information Centre for Health and Social Care; 2007.



# Health Technology Assessment reports published to date

## Volume 1, 1997

### No. 1

Home parenteral nutrition: a systematic review.

By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

### No. 2

Diagnosis, management and screening of early localised prostate cancer.

A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

### No. 3

The diagnosis, management, treatment and costs of prostate cancer in England and Wales.

A review by Chamberlain J, Melia J, Moss S, Brown J.

### No. 4

Screening for fragile X syndrome.

A review by Murray J, Cuckle H, Taylor G, Hewison J.

### No. 5

A review of near patient testing in primary care.

By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al.*

### No. 6

Systematic review of outpatient services for chronic pain control.

By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

### 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 Koukounne 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 Peticrew 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, Towler 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, Kluiters 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, Freemantle 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, Riemsma 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, Hohenstein 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, Sakaravitch 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- $\beta$  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 LD, 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  $\alpha$ -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, Griebisch 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, Castelnovo 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, Brauholtz 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, Sakarovich 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, Coglán 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, Griebisch 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 Castelnovo 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, Tumor 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, Tumor 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 Fayer 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, Rafferty 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, Dünder 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, Snowden 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, Thalany 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, Tumor 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, Oyeboode 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<sub>2</sub> 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<sub>2</sub> 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, Tumor 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-effectiveness 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.

**No. 18**

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.*

**No. 19**

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.*

**No. 20**

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.*

**No. 21**

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.

**Suppl. 1**

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

By Ward S, Pilgrim H, Hind D.

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

By Chilcott J, Lloyd Jones M, Wilkinson A.

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

By Griffin S, Dunn G, Palmer S, Macfarlane K, Brent S, Dyker A, *et al.*

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

By Dundar Y, Bagust A, Hounsome J, McLeod C, Boland A, Davis H, *et al.*

Bortezomib for the treatment of multiple myeloma patients.

By Green C, Bryant J, Takeda A, Cooper K, Clegg A, Smith A, *et al.*

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

By Walker S, Palmer S, Erhorn S, Brent S, Dyker A, Ferrie L, *et al.*

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

By McLeod C, Bagust A, Boland A, Hockenhull J, Dundar Y, Proudlove C, *et al.*

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

By Griffin S, Walker S, Sculpher M, White S, Erhorn S, Brent S, *et al.*

Infliximab for the treatment of adults with psoriasis.

By Loveman E, Turner D, Hartwell D, Cooper K, Clegg A.

**No. 30**

Psychological interventions for postnatal depression: cluster randomised trial and economic evaluation. The PoNDER trial.

By Morrell CJ, Warner R, Slade P, Dixon S, Walters S, Paley G, *et al.*

**No. 31**

The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis.

By Rogowski R, Burch J, Palmer S, Craigs C, Golder S, Woolcott N.

**No. 32**

Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care.

By Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, *et al.*

**No. 33**

A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial.

By Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, *et al.*, on behalf of the 3CPO study investigators.

**No. 34**

Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation.

By Ara R, Pandor A, Stevens J, Rees A, Rafia R.

**No. 35**

Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation.

By Jones J, Shepherd J, Baxter L, Gospodarevskaya E, Hartwell D, Harris P, *et al.*

**No. 36**

Methods to identify postnatal depression in primary care: an integrated evidence synthesis and value of information analysis.

By Hewitt CE, Gilbody SM, Brealey S, Paulden M, Palmer S, Mann R, *et al.*

**No. 37**

A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with persistent bilateral otitis media with effusion in primary care.

By Williamson I, Bengt S, Barton S, Petrou S, Letley L, Fasey N, *et al.*

**No. 38**

The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model.

By Bond M, Pitt M, Akoh J, Moxham T, Hoyle M, Anderson R.

**No. 39**

Rehabilitation of older patients: day hospital compared with rehabilitation at home. A randomised controlled trial.

By Parker SG, Oliver P, Pennington M, Bond J, Jagger C, Enderby PM, *et al.*

**No. 40**

Breastfeeding promotion for infants in neonatal units: a systematic review and economic analysis.

By Renfrew MJ, Craig D, Dyson L, McCormick F, Rice S, King SE, *et al.*

**No. 41**

The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation.

By Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, *et al.*

**No. 42**

Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness.

By Daniels J, Gray J, Pattison H, Roberts T, Edwards E, Milner P, *et al.*

**No. 43**

Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling.

By Honest H, Forbes CA, Durée KH, Norman G, Duffy SB, Tsourapas A, *et al.*

**No. 44**

The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model.

By Bond M, Mealing S, Anderson R, Elston J, Weiner G, Taylor RS, *et al.*

**Suppl. 2**

Gemcitabine for the treatment of metastatic breast cancer.

By Jones J, Takeda A, Tan SC, Cooper K, Loveman E, Clegg A.

Varenicline in the management of smoking cessation: a single technology appraisal.

By Hind D, Tappenden P, Peters J, Kenjegalieva K.

Alteplase for the treatment of acute ischaemic stroke: a single technology appraisal.

By Lloyd Jones M, Holmes M.

Rituximab for the treatment of rheumatoid arthritis.

By Bagust A, Boland A, Hockenhull J, Fleeman N, Greenhalgh J, Dundar Y, *et al.*

Omalizumab for the treatment of severe persistent allergic asthma.

By Jones J, Shepherd J, Hartwell D, Harris P, Cooper K, Takeda A, *et al.*

Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma.

By Boland A, Bagust A, Hockenhull J, Davis H, Chu P, Dickson R.

Adalimumab for the treatment of psoriasis.

By Turner D, Picot J, Cooper K, Loveman E.

Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: a single technology appraisal.

By Holmes M, Carroll C, Papaioannou D.

Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura: a single technology appraisal.

By Mowatt G, Boachie C, Crowther M, Fraser C, Hernández R, Jia X, *et al.*

Sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer.

By Bond M, Hoyle M, Moxham T, Napier M, Anderson R.

**No. 45**

Vitamin K to prevent fractures in older women: systematic review and economic evaluation.

By Stevenson M, Lloyd-Jones M, Papaioannou D.

**No. 46**

The effects of biofeedback for the treatment of essential hypertension: a systematic review.

By Greenhalgh J, Dickson R, Dundar Y.

**No. 47**

A randomised controlled trial of the use of aciclovir and/or prednisolone for the early treatment of Bell's palsy: the BELLS study.

By Sullivan FM, Swan IRC, Donnan PT, Morrison JM, Smith BH, McKinstry B, *et al.*

**Suppl. 3**

Lapatinib for the treatment of HER2-overexpressing breast cancer.

By Jones J, Takeda A, Picot J, von Keyserlingk C, Clegg A.

Infliximab for the treatment of ulcerative colitis.

By Hyde C, Bryan S, Juarez-Garcia A, Andronis L, Fry-Smith A.

Rimonabant for the treatment of overweight and obese people.

By Burch J, McKenna C, Palmer S, Norman G, Glanville J, Sculpher M, *et al.*

Telbivudine for the treatment of chronic hepatitis B infection.

By Hartwell D, Jones J, Harris P, Cooper K.

Entecavir for the treatment of chronic hepatitis B infection.

By Shepherd J, Gospodarevskaya E, Frampton G, Cooper K.

Febuxostat for the treatment of hyperuricaemia in people with gout: a single technology appraisal.

By Stevenson M, Pandor A.

Rivaroxaban for the prevention of venous thromboembolism: a single technology appraisal.

By Stevenson M, Scope A, Holmes M, Rees A, Kaltenthaler E.

Cetuximab for the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck.

By Greenhalgh J, Bagust A, Boland A, Fleeman N, McLeod C, Dundar Y, *et al.*

Mifamurtide for the treatment of osteosarcoma: a single technology appraisal.

By Pandor A, Fitzgerald P, Stevenson M, Papaioannou D.

Ustekinumab for the treatment of moderate to severe psoriasis.

By Gospodarevskaya E, Picot J, Cooper K, Loveman E, Takeda A.

#### No. 48

Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model.

By Chambers D, Epstein D, Walker S, Fayter D, Paton F, Wright K, *et al.*

#### No. 49

Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation.

By Chen Y-F, Jowett S, Barton P, Malottki K, Hyde C, Gibbs JSR, *et al.*

#### No. 50

Cessation of attention deficit hyperactivity disorder drugs in the young (CADDY) – a pharmacoepidemiological and qualitative study.

By Wong ICK, Asherson P, Bilbow A, Clifford S, Coghill D, DeSoysa R, *et al.*

#### No. 51

ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening.

By Kitchener HC, Almonte M, Gilham C, Dowie R, Stoykova B, Sargent A, *et al.*

#### No. 52

The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation.

By Black C, Clar C, Henderson R, MacEachern C, McNamee P, Quayyum Z, *et al.*

#### No. 53

Randomised preference trial of medical versus surgical termination of pregnancy less than 14 weeks' gestation (TOPS).

By Robson SC, Kelly T, Howel D, Deverill M, Hewison J, Lie MLS, *et al.*

#### No. 54

Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes.

By Jeffcoate WJ, Price PE, Phillips CJ, Game FL, Mudge E, Davies S, *et al.*

#### No. 55

VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers.

By Dumville JC, Worthy G, Soares MO, Bland JM, Cullum N, Dowson C, *et al.*

#### No. 56

A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: the VULCAN trial.

By Michaels JA, Campbell WB, King BM, MacIntyre J, Palfreyman SJ, Shackley P, *et al.*

#### No. 57

Communication of carrier status information following universal newborn screening for sickle cell disorders and cystic fibrosis: qualitative study of experience and practice.

By Kai J, Ulph F, Cullinan T, Qureshi N.

#### No. 58

Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation.

By Burch J, Paulden M, Conti S, Stock C, Corbett M, Welton NJ, *et al.*

#### No. 59

Development of a toolkit and glossary to aid in the adaptation of health technology assessment (HTA) reports for use in different contexts.

By Chase D, Rosten C, Turner S, Hicks N, Milne R.

#### No. 60

Colour vision testing for diabetic retinopathy: a systematic review of diagnostic accuracy and economic evaluation.

By Rodgers M, Hodges R, Hawkins J, Hollingworth W, Duffy S, McKibbin M, *et al.*

#### No. 61

Systematic review of the effectiveness and cost-effectiveness of weight management schemes for the under fives: a short report.

By Bond M, Wyatt K, Lloyd J, Welch K, Taylor R.

#### No. 62

Are adverse effects incorporated in economic models? An initial review of current practice.

By Craig D, McDaid C, Fonseca T, Stock C, Duffy S, Woolacott N.

### Volume 14, 2010

#### No. 1

Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE).

By Turnbull LW, Brown SR, Olivier C, Harvey I, Brown J, Drew P, *et al.*

#### No. 2

Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation.

By Thompson Coon J, Hoyle M, Green C, Liu Z, Welch K, Moxham T, *et al.*

#### No. 3

The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation.

By Fleeman N, McLeod C, Bagust A, Beale S, Boland A, Dundar Y, *et al.*

#### No. 4

Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer.

By Mowatt G, Zhu S, Kilonzo M, Boachie C, Fraser C, Griffiths TRL, *et al.*

#### No. 5

Effectiveness and cost-effectiveness of arthroscopic lavage in the treatment of osteoarthritis of the knee: a mixed methods study of the feasibility of conducting a surgical placebo-controlled trial (the KORAL study).

By Campbell MK, Skea ZC, Sutherland AG, Cuthbertson BH, Entwistle VA, McDonald AM, *et al.*

#### No. 6

A randomised 2 × 2 trial of community versus hospital pulmonary rehabilitation for chronic obstructive pulmonary disease followed by telephone or conventional follow-up.

By Waterhouse JC, Walters SJ, Oluboyede Y, Lawson RA.

#### No. 7

The effectiveness and cost-effectiveness of behavioural interventions for the prevention of sexually transmitted infections in young people aged 13–19: a systematic review and economic evaluation.

By Shepherd J, Kavanagh J, Picot J, Cooper K, Harden A, Barnett-Page E, *et al.*

**No. 8**

Dissemination and publication of research findings: an updated review of related biases.

By Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, *et al.*

**No. 9**

The effectiveness and cost-effectiveness of biomarkers for the prioritisation of patients awaiting coronary revascularisation: a systematic review and decision model.

By Hemingway H, Henriksson M, Chen R, Damant J, Fitzpatrick N, Abrams K, *et al.*

**No. 10**

Comparison of case note review methods for evaluating quality and safety in health care.

By Hutchinson A, Coster JE, Cooper KL, McIntosh A, Walters SJ, Bath PA, *et al.*

**No. 11**

Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation.

By Cummins E, Royle P, Snaith A, Greene A, Robertson L, McIntyre L, *et al.*

**No. 12**

Self-monitoring of blood glucose in type 2 diabetes: systematic review.

By Clar C, Barnard K, Cummins E, Royle P, Waugh N.

**No. 13**

North of England and Scotland Study of Tonsillectomy and Adeno-tonsillectomy in Children (NESSTAC): a pragmatic randomised controlled trial with a parallel non-randomised preference study.

By Lock C, Wilson J, Steen N, Eccles M, Mason H, Carrie S, *et al.*

**No. 14**

Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial.

By Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FGR, Gillespie I, *et al.*

**No. 15**

A randomised controlled multicentre trial of treatments for adolescent anorexia nervosa including assessment of cost-effectiveness and patient acceptability – the TOuCAN trial.

By Gowers SG, Clark AF, Roberts C, Byford S, Barrett B, Griffiths A, *et al.*

**No. 16**

Randomised controlled trials for policy interventions: a review of reviews and meta-regression.

By Oliver S, Bagnall AM, Thomas J, Shepherd J, Sowden A, White I, *et al.*

**No. 17**

Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review.

By McDaid C, Maund E, Rice S, Wright K, Jenkins B, Woolcott N.

**No. 18**

A systematic review of outcome measures used in forensic mental health research with consensus panel opinion.

By Fitzpatrick R, Chambers J, Burns T, Doll H, Fazel S, Jenkinson C, *et al.*

**No. 19**

The clinical effectiveness and cost-effectiveness of topotecan for small cell lung cancer: a systematic review and economic evaluation.

By Loveman E, Jones J, Hartwell D, Bird A, Harris P, Welch K, *et al.*

**No. 20**

Antenatal screening for haemoglobinopathies in primary care: a cohort study and cluster randomised trial to inform a simulation model. The Screening for Haemoglobinopathies in First Trimester (SHIFT) trial.

By Dormandy E, Bryan S, Gulliford MC, Roberts T, Ades T, Calnan M, *et al.*

**No. 21**

Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis.

By Black C, Sharma P, Scotland G, McCullough K, McGurn D, Robertson L, *et al.*

**No. 22**

A randomised controlled trial of cognitive behaviour therapy and motivational interviewing for people with Type 1 diabetes mellitus with persistent sub-optimal glycaemic control: A Diabetes and Psychological Therapies (ADAPT) study.

By Ismail K, Maissi E, Thomas S, Chalder T, Schmidt U, Bartlett J, *et al.*

**No. 23**

A randomised controlled equivalence trial to determine the effectiveness and cost-utility of manual chest physiotherapy techniques in the management of exacerbations of chronic obstructive pulmonary disease (MATREX).

By Cross J, Elender F, Barton G, Clark A, Shephstone L, Blyth A, *et al.*

**No. 24**

A systematic review and economic evaluation of the clinical effectiveness and cost-effectiveness of aldosterone antagonists for postmyocardial infarction heart failure.

By McKenna C, Burch J, Suekarran S, Walker S, Bakhai A, Witte K, *et al.*

**No. 25**

Avoiding and identifying errors in health technology assessment models: qualitative study and methodological review.

By Chilcott JB, Tappenden P, Rawdin A, Johnson M, Kaltenthaler E, Paisley S, *et al.*

**No. 26**

BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A.

By Shaw L, Rodgers H, Price C, van Wijck F, Shackley P, Steen N, *et al.*, on behalf of the BoTULS investigators.

**No. 27**

Weighting and valuing quality-adjusted life-years using stated preference methods: preliminary results from the Social Value of a QALY Project.

By Baker R, Bateman I, Donaldson C, Jones-Lee M, Lancsar E, Loomes G, *et al.*

**Suppl. 1**

Cetuximab for the first-line treatment of metastatic colorectal cancer.

By Meads C, Round J, Tubeuf S, Moore D, Pennant M, Bayliss S.

Infliximab for the treatment of acute exacerbations of ulcerative colitis.

By Bryan S, Andronis L, Hyde C, Connock M, Fry-Smith A, Wang D.

Sorafenib for the treatment of advanced hepatocellular carcinoma.

By Connock M, Round J, Bayliss S, Tubeuf S, Greenheld W, Moore D.

Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B infection.

By Jones J, Colquitt J, Shepherd J, Harris P, Cooper K.

Prasugrel for the treatment of acute coronary artery syndromes with percutaneous coronary intervention.

By Greenhalgh J, Bagust A, Boland A, Saborido CM, Fleeman N, McLeod C, *et al.*

Alitretinoin for the treatment of severe chronic hand eczema.

By Paulden M, Rodgers M, Griffin S, Slack R, Duffy S, Ingram JR, *et al.*

Pemetrexed for the first-line treatment of locally advanced or metastatic non-small cell lung cancer.

By Fleeman N, Bagust A, McLeod C, Greenhalgh J, Boland A, Dundar Y, *et al.*

Topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix.

By Paton F, Paulden M, Saramago P, Manca A, Misso K, Palmer S, *et al.*

Trabectedin for the treatment of advanced metastatic soft tissue sarcoma.

By Simpson EL, Rafia R, Stevenson MD, Papaioannou D.

Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia.

By Edlin R, Connock M, Tubeuf S, Round J, Fry-Smith A, Hyde C, *et al.*

#### No. 28

The safety and effectiveness of different methods of earwax removal: a systematic review and economic evaluation.

By Clegg AJ, Loveman E, Gospodarevskaya E, Harris P, Bird A, Bryant J, *et al.*

#### No. 29

Systematic review of the clinical effectiveness and cost-effectiveness of rapid point-of-care tests for the detection of genital chlamydia infection in women and men.

By Hislop J, Quayyum Z, Flett G, Boachie C, Fraser C, Mowatt G.

#### No. 30

School-linked sexual health services for young people (SSHYP): a survey and systematic review concerning current models, effectiveness, cost-effectiveness and research opportunities.

By Owen J, Carroll C, Cooke J, Formby E, Hayter M, Hirst J, *et al.*

#### No. 31

Systematic review and cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared to episodic in-hospital treatment or continuous antiarrhythmic drug therapy.

By Martin Saborido C, Hockenhull J, Bagust A, Boland A, Dickson R, Todd D.

#### No. 32

Chemoprevention of colorectal cancer: systematic review and economic evaluation.

By Cooper K, Squires H, Carroll C, Papaioannou D, Booth A, Logan RF, *et al.*

#### No. 33

Cross-trimester repeated measures testing for Down's syndrome screening: an assessment.

By Wright D, Bradbury I, Malone F, D'Alton M, Summers A, Huang T, *et al.*

#### No. 34

Exploring the needs, concerns and behaviours of people with existing respiratory conditions in relation to the H1N1 'swine influenza' pandemic: a multicentre survey and qualitative study.

By Caress A-L, Duxbury P, Woodcock A, Luker KA, Ward D, Campbell M, *et al.*

Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant.

By Yates L, Pierce M, Stephens S, Mill AC, Spark P, Kurinczuk JJ, *et al.*

The impact of communications about swine flu (influenza A H1N1v) on public responses to the outbreak: results from 36 national telephone surveys in the UK.

By Rubin GJ, Potts HWW, Michie S.

The impact of illness and the impact of school closure on social contact patterns.

By Eames KTD, Tilston NL, White PJ, Adams E, Edmunds WJ.

Vaccine effectiveness in pandemic influenza – primary care reporting (VIPER): an observational study to assess the effectiveness of the pandemic influenza A (H1N1)v vaccine.

By Simpson CR, Ritchie LD, Robertson C, Sheikh A, McMenamin J.

Physical interventions to interrupt or reduce the spread of respiratory viruses: a Cochrane review.

By Jefferson T, Del Mar C, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, *et al.*

#### No. 35

Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR).

By Peek GJ, Elbourne D, Mugford M, Tiruvoipati R, Wilson A, Allen E, *et al.*

#### No. 36

Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation.

By Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, *et al.*

#### No. 37

Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin.

By Fayer D, Corbett M, Heirs M, Fox D, Eastwood A.

#### No. 38

Towards single embryo transfer? Modelling clinical outcomes of potential treatment choices using multiple data sources: predictive models and patient perspectives.

By Roberts SA, McGowan L, Hirst WM, Brison DR, Vail A, Lieberman BA.

#### No. 39

Sugammadex for the reversal of muscle relaxation in general anaesthesia: a systematic review and economic assessment.

By Chambers D, Paulden M, Paton F, Heirs M, Duffy S, Craig D, *et al.*

#### No. 40

Systematic review and economic modelling of the effectiveness and cost-effectiveness of non-surgical treatments for women with stress urinary incontinence.

By Imamura M, Abrams P, Bain C, Buckley B, Cardozo L, Cody J, *et al.*

#### No. 41

A multicentred randomised controlled trial of a primary care-based cognitive behavioural programme for low back pain. The Back Skills Training (BeST) trial.

By Lamb SE, Lall R, Hansen Z, Castelnuovo E, Withers EJ, Nichols V, *et al.*

#### No. 42

Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation.

By Takeda A, Cooper K, Bird A, Baxter L, Frampton GK, Gospodarevskaya E, *et al.*

#### No. 43

A pragmatic randomised controlled trial to compare antidepressants with a community-based psychosocial intervention for the treatment of women with postnatal depression: the RESPOND trial.

By Sharp DJ, Chew-Graham C, Tylee A, Lewis G, Howard L, Anderson I, *et al.*

#### No. 44

Group cognitive behavioural therapy for postnatal depression: a systematic review of clinical effectiveness, cost-effectiveness and value of information analyses.

By Stevenson MD, Scope A, Sutcliffe PA, Booth A, Slade P, Parry G, *et al.*

#### No. 45

Screening for hyperglycaemia in pregnancy: a rapid update for the National Screening Committee.

By Waugh N, Royle P, Clar C, Henderson R, Cummins E, Hadden D, *et al.*

**No. 46**

Open-label, randomised, parallel-group, multicentre study to evaluate the safety, tolerability and immunogenicity of an AS03B/oil-in-water emulsion-adjuvanted (AS03B) split-virion versus non-adjuvanted wholevirion H1N1 influenza vaccine in UK children 6 months to 12 years of age.

By Waddington CS, Andrews N, Hoschler K, Walker WT, Oeser C, Reiner A, *et al.*

Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections.

By Simonds AK, Hanak A, Chatwin M, Morrell MJ, Hall A, Parker KH, *et al.*

Evaluation of triage methods used to select patients with suspected pandemic influenza for hospital admission: cohort study.

By Goodacre S, Challen, K, Wilson R, Campbell M.

Virus shedding and environmental deposition of novel A (H1N1) pandemic influenza virus: interim findings.

By Killingley B, Greatorex J, Cauchemez S, Enstone JE, Curran M, Read R, *et al.*

Neuraminidase inhibitors for preventing and treating influenza in healthy adults: a Cochrane review.

By Jefferson T, Jones M, Doshi P, Del Mar C, Dooley L, Foxlee R.

**No. 47**

Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation.

By Hummel S, Simpson EL, Hemingway P, Stevenson MD, Rees A.

**No. 48**

Computerised decision support systems in order communication for diagnostic, screening or monitoring test ordering: systematic reviews of the effects and cost-effectiveness of systems.

By Main C, Moxham T, Wyatt JC, Kay J, Anderson R, Stein K.

**No. 49**

Relapse prevention in UK Stop Smoking Services: current practice, systematic reviews of effectiveness and cost-effectiveness analysis.

By Coleman T, Agboola S, Leonardi-Bee J, Taylor M, McEwen A, McNeill A.

**No. 50**

A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence.

By Pennant M, Takwoingi Y, Pennant L, Davenport C, Fry-Smith A, Eisinga A, *et al.*





# Health Technology Assessment programme

**Director,**  
**Professor Tom Walley,**  
Director, NIHR HTA  
programme, Professor of  
Clinical Pharmacology,  
University of Liverpool

**Deputy Director,**  
**Professor Jon Nicholl,**  
Director, Medical Care Research  
Unit, University of Sheffield

## Prioritisation Strategy Group

### Members

**Chair,**  
**Professor Tom Walley,**  
Director, NIHR HTA  
programme, Professor of  
Clinical Pharmacology,  
University of Liverpool

**Deputy Chair,**  
**Professor Jon Nicholl,**  
Director, Medical Care Research  
Unit, University of Sheffield

Dr Bob Coates,  
Consultant Advisor, NETSCC,  
HTA

Dr Andrew Cook,  
Consultant Advisor, NETSCC,  
HTA

Dr Peter Davidson,  
Director of NETSCC, Health  
Technology Assessment

Professor Robin E Ferner,  
Consultant Physician and  
Director, West Midlands Centre  
for Adverse Drug Reactions,  
City Hospital NHS Trust,  
Birmingham

Professor Paul Glasziou,  
Professor of Evidence-Based  
Medicine, University of Oxford

Dr Nick Hicks,  
Consultant Adviser, NETSCC,  
HTA

Dr Edmund Jessop,  
Medical Adviser, National  
Specialist, National  
Commissioning Group (NCG),  
Department of Health, London

Ms Lynn Kerridge,  
Chief Executive Officer,  
NETSCC and NETSCC, HTA

Professor Ruairidh Milne,  
Director of NETSCC External  
Relations

Ms Kay Pattison,  
Senior NIHR Programme  
Manager, Department of  
Health

Ms Pamela Young,  
Specialist Programme Manager,  
NETSCC, HTA

## HTA Commissioning Board

### Members

**Programme Director,**  
**Professor Tom Walley,**  
Director, NIHR HTA  
programme, Professor of  
Clinical Pharmacology,  
University of Liverpool

**Chairs,**  
**Professor Sallie Lamb,**  
Director, Warwick Clinical Trials  
Unit

**Professor Hywel Williams,**  
Director, Nottingham Clinical  
Trials Unit

**Deputy Chair,**  
**Dr Andrew Farmer,**  
Senior Lecturer in General  
Practice, Department of  
Primary Health Care,  
University of Oxford

Professor Ann Ashburn,  
Professor of Rehabilitation  
and Head of Research,  
Southampton General Hospital

Professor Deborah Ashby,  
Professor of Medical Statistics,  
Queen Mary, University of  
London

Professor John Cairns,  
Professor of Health Economics,  
London School of Hygiene and  
Tropical Medicine

Professor Peter Croft,  
Director of Primary Care  
Sciences Research Centre, Keele  
University

Professor Nicky Cullum,  
Director of Centre for Evidence-  
Based Nursing, University of  
York

Professor Jenny Donovan,  
Professor of Social Medicine,  
University of Bristol

Professor Steve Halligan,  
Professor of Gastrointestinal  
Radiology, University College  
Hospital, London

Professor Freddie Hamdy,  
Professor of Urology,  
University of Sheffield

Professor Allan House,  
Professor of Liaison Psychiatry,  
University of Leeds

Dr Martin J Landray,  
Reader in Epidemiology,  
Honorary Consultant Physician,  
Clinical Trial Service Unit,  
University of Oxford

Professor Stuart Logan,  
Director of Health & Social  
Care Research, The Peninsula  
Medical School, Universities of  
Exeter and Plymouth

Dr Rafael Perera,  
Lecturer in Medical Statistics,  
Department of Primary Health  
Care, University of Oxford

Professor Ian Roberts,  
Professor of Epidemiology &  
Public Health, London School  
of Hygiene and Tropical  
Medicine

Professor Mark Sculpher,  
Professor of Health Economics,  
University of York

Professor Helen Smith,  
Professor of Primary Care,  
University of Brighton

Professor Kate Thomas,  
Professor of Complementary &  
Alternative Medicine Research,  
University of Leeds

Professor David John  
Torgerson,  
Director of York Trials Unit,  
University of York

### Observers

Ms Kay Pattison,  
Section Head, NHS R&D  
Programme, Department of  
Health

Dr Morven Roberts,  
Clinical Trials Manager,  
Medical Research Council

## Diagnostic Technologies and Screening Panel

### Members

**Chair,**  
**Professor Paul Glasziou,**  
Professor of Evidence-Based  
Medicine, University of Oxford

**Deputy Chair,**  
**Dr David Elliman,**  
Consultant Paediatrician and  
Honorary Senior Lecturer,  
Great Ormond Street Hospital,  
London

Professor Judith E Adams,  
Consultant Radiologist,  
Manchester Royal Infirmary,  
Central Manchester &  
Manchester Children's  
University Hospitals NHS  
Trust, and Professor of  
Diagnostic Radiology, Imaging  
Science and Biomedical  
Engineering, Cancer &  
Imaging Sciences, University of  
Manchester

Mr A S Arunkalaivanan,  
Honorary Senior Lecturer,  
University of Birmingham and  
Consultant Urogynaecologist  
and Obstetrician, City Hospital

Dr Dianne Baralle,  
Consultant & Senior Lecturer  
in Clinical Genetics, Human  
Genetics Division & Wessex  
Clinical Genetics Service,  
Southampton, University of  
Southampton

Dr Stephanie Dancer,  
Consultant Microbiologist,  
Hairmyres Hospital, East  
Kilbride

Dr Ron Gray,  
Consultant, National Perinatal  
Epidemiology Unit, Institute of  
Health Sciences, University of  
Oxford

Professor Paul D Griffiths,  
Professor of Radiology,  
Academic Unit of Radiology,  
University of Sheffield

Mr Martin Hooper,  
Service User Representative

Professor Anthony Robert  
Kendrick,  
Professor of Primary  
Medical Care, University of  
Southampton

Dr Susanne M Ludgate,  
Director, Medical Devices  
Agency, London

Dr Anne Mackie,  
Director of Programmes, UK  
National Screening Committee

Dr David Mathew  
Service User Representative

Dr Michael Millar, Lead  
Consultant in Microbiology,  
Department of Pathology &  
Microbiology, Barts and The  
London NHS Trust, Royal  
London Hospital

Mr Stephen Pilling,  
Director, Centre for Outcomes,  
Research & Effectiveness,  
University College London

Mrs Una Rennard,  
Service User Representative

Ms Jane Smith,  
Consultant Ultrasound  
Practitioner, Ultrasound  
Department, Leeds Teaching  
Hospital NHS Trust, Leeds

Dr W Stuart A Smellie,  
Consultant, Bishop Auckland  
General Hospital

Professor Lindsay Wilson  
Turnbull,  
Scientific Director of the  
Centre for Magnetic Resonance  
Investigations and YCR  
Professor of Radiology, Hull  
Royal Infirmary

Dr Alan J Williams,  
Consultant in General  
Medicine, Department of  
Thoracic Medicine, The Royal  
Bournemouth Hospital

### Observers

Dr Tim Elliott,  
Team Leader, Cancer  
Screening, Department of  
Health

Dr Catherine Moody,  
Programme Manager,  
Neuroscience and Mental  
Health Board

Dr Ursula Wells,  
Principal Research Officer,  
Department of Health

## Disease Prevention Panel

### Members

**Chair,**  
**Dr Edmund Jessop,**  
Medical Adviser, National  
Specialist Commissioning  
Advisory Group (NSCAG),  
Department of Health

**Deputy Chair,**  
**Professor Margaret  
Thorogood,**  
Professor of Epidemiology,  
University of Warwick Medical  
School, Coventry

Dr Robert Cook  
Clinical Programmes Director,  
Bazian Ltd, London

Dr Elizabeth Fellow-Smith,  
Medical Director, West London  
Mental Health Trust, Middlesex

Dr Colin Greaves  
Senior Research Fellow,  
Peninsular Medical School  
(Primary Care)

Dr John Jackson,  
General Practitioner, Parkway  
Medical Centre, Newcastle  
upon Tyne

Dr Russell Jago,  
Senior Lecturer in Exercise,  
Nutrition and Health, Centre  
for Sport, Exercise and Health,  
University of Bristol

Dr Chris McCall,  
General Practitioner, The  
Hadleigh Practice, Corfe  
Mullen, Dorset

Miss Nicky Mullany,  
Service User Representative

Dr Julie Mytton,  
Locum Consultant in Public  
Health Medicine, Bristol  
Primary Care Trust

Professor Irwin Nazareth,  
Professor of Primary Care  
and Director, Department of  
Primary Care and Population  
Sciences, University College  
London

Professor Ian Roberts,  
Professor of Epidemiology and  
Public Health, London School  
of Hygiene & Tropical Medicine

Professor Carol Tannahill,  
Glasgow Centre for Population  
Health

Mrs Jean Thurston,  
Service User Representative

Professor David Weller,  
Head, School of Clinical  
Science and Community  
Health, University of  
Edinburgh

### Observers

Ms Christine McGuire,  
Research & Development,  
Department of Health

Ms Kay Pattison  
Senior NIHR Programme  
Manager, Department of  
Health

Dr Caroline Stone,  
Programme Manager, Medical  
Research Council

## External Devices and Physical Therapies Panel

### Members

<b>Chair,</b> <b>Dr John Pounsford,</b> Consultant Physician North Bristol NHS Trust, Bristol	Dr Dawn Carnes, Senior Research Fellow, Barts and the London School of Medicine and Dentistry, London	Dr Peter Martin, Consultant Neurologist, Addenbrooke's Hospital, Cambridge	Dr Pippa Tyrrell, Stroke Medicine, Senior Lecturer/Consultant Stroke Physician, Salford Royal Foundation Hospitals' Trust, Salford
<b>Deputy Chair,</b> <b>Professor E Andrea Nelson,</b> Reader in Wound Healing and Director of Research, University of Leeds, Leeds	Dr Emma Clark, Clinician Scientist Fellow & Cons. Rheumatologist, University of Bristol, Bristol	Dr Lorraine Pinnigton, Associate Professor in Rehabilitation, University of Nottingham, Nottingham	Dr Sarah Tyson, Senior Research Fellow & Associate Head of School, University of Salford, Salford
Professor Bipin Bhakta Charterhouse Professor in Rehabilitation Medicine, University of Leeds, Leeds	Mrs Anthea De Barton-Watson, Service User Representative	Dr Kate Radford, Division of Rehabilitation and Ageing, School of Community Health Sciences. University of Nottingham, Nottingham	Dr Nefyn Williams, Clinical Senior Lecturer, Cardiff University, Cardiff
Mrs Penny Calder Service User Representative	Professor Christopher Griffiths, Professor of Primary Care, Barts and the London School of Medicine and Dentistry, London	Mr Jim Reece, Service User Representative	
Professor Paul Carding, Professor of Voice Pathology, Newcastle Hospital NHS Trust, Newcastle	Dr Shaheen Hamdy, Clinical Senior Lecturer and Consultant Physician, University of Manchester, Manchester	Professor Maria Stokes, Professor of Neuromusculoskeletal Rehabilitation, University of Southampton, Southampton	

### Observers

Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health, London	Ms Kay Pattison Senior NIHR Programme Manager, Department of Health	Dr Morven Roberts, Clinical Trials Manager, MRC, London	Dr Ursula Wells PRP, DH, London
---	--	---	------------------------------------

## Interventional Procedures Panel

### Members

<b>Chair,</b> <b>Professor Jonathan Michaels,</b> Consultant Surgeon & Honorary Clinical Lecturer, University of Sheffield	Mr Seamus Eckford, Consultant in Obstetrics & Gynaecology, North Devon District Hospital	Dr Nadim Malik, Consultant Cardiologist/ Honorary Lecturer, University of Manchester	Dr Ashish Paul, Medical Director, Bedfordshire PCT
Mr David P Britt, Service User Representative, Cheshire	Professor David Taggart, Consultant Cardiothoracic Surgeon, John Radcliffe Hospital	Mr Hisham Mehanna, Consultant & Honorary Associate Professor, University Hospitals Coventry & Warwickshire NHS Trust	Dr Sarah Purdy, Consultant Senior Lecturer, University of Bristol
Mr Sankaran ChandraSekharan, Consultant Surgeon, Colchester Hospital University NHS Foundation Trust	Dr Matthew Hatton, Consultant in Clinical Oncology, Sheffield Teaching Hospital Foundation Trust	Dr Jane Montgomery, Consultant in Anaesthetics and Critical Care, South Devon Healthcare NHS Foundation Trust	Mr Michael Thomas, Consultant Colorectal Surgeon, Bristol Royal Infirmary
Professor Nicholas Clarke, Consultant Orthopaedic Surgeon, Southampton University Hospitals NHS Trust	Dr John Holden, General Practitioner, Garswood Surgery, Wigan	Dr Simon Padley, Consultant Radiologist, Chelsea & Westminster Hospital	Professor Yit Chiun Yang, Consultant Ophthalmologist, Royal Wolverhampton Hospitals NHS Trust
			Mrs Isabel Boyer, Service User Representative, London

## Pharmaceuticals Panel

### Members

#### Chair,

**Professor Imti Choonara**,  
Professor in Child Health,  
University of Nottingham

#### Deputy Chair,

**Dr Lesley Wise**,  
Unit Manager,  
Pharmacoepidemiology  
Research Unit, VRMM,  
Medicines & Healthcare  
Products Regulatory Agency

Mrs Nicola Carey,  
Senior Research Fellow,  
School of Health and Social  
Care, The University of  
Reading

Mr John Chapman,  
Service User Representative

Dr Peter Elton,  
Director of Public Health,  
Bury Primary Care Trust

Professor Robin Ferner,  
Consultant Physician and  
Director, West Midlands Centre  
for Adverse Drug Reactions,  
City Hospital NHS Trust,  
Birmingham

Dr Ben Goldacre,  
Research Fellow, Division of  
Psychological Medicine and  
Psychiatry, King's College  
London

Dr Bill Gutteridge,  
Medical Adviser, London  
Strategic Health Authority

Dr Dyfrig Hughes,  
Reader in Pharmacoeconomics  
and Deputy Director, Centre  
for Economics and Policy in  
Health, IMSCaR, Bangor  
University

Dr Yoon K Loke,  
Senior Lecturer in Clinical  
Pharmacology, University of  
East Anglia

Professor Femi Oyeboode,  
Consultant Psychiatrist  
and Head of Department,  
University of Birmingham

Dr Andrew Prentice,  
Senior Lecturer and Consultant  
Obstetrician and Gynaecologist,  
The Rosie Hospital, University  
of Cambridge

Dr Martin Shelly,  
General Practitioner, Leeds,  
and Associate Director, NHS  
Clinical Governance Support  
Team, Leicester

Dr Gillian Shepherd,  
Director, Health and Clinical  
Excellence, Merck Serono Ltd

Mrs Katrina Simister,  
Assistant Director New  
Medicines, National Prescribing  
Centre, Liverpool

Mr David Symes,  
Service User Representative

### Observers

Ms Kay Pattison  
Senior NIHR Programme  
Manager, Department of  
Health

Mr Simon Reeve,  
Head of Clinical and Cost-  
Effectiveness, Medicines,  
Pharmacy and Industry Group,  
Department of Health

Dr Heike Weber,  
Programme Manager,  
Medical Research Council

Dr Ursula Wells,  
Principal Research Officer,  
Department of Health

## Psychological and Community Therapies Panel

### Members

#### Chair,

**Professor Scott Weich**,  
Professor of Psychiatry,  
University of Warwick

Professor Jane Barlow,  
Professor of Public Health in  
the Early Years, Health Sciences  
Research Institute, Warwick  
Medical School

Dr Sabyasachi Bhaumik,  
Consultant Psychiatrist,  
Leicestershire Partnership NHS  
Trust

Mrs Val Carlill,  
Service User Representative,  
Gloucestershire

Dr Steve Cunningham,  
Consultant Respiratory  
Paediatrician, Lothian Health  
Board

Dr Anne Hesketh,  
Senior Clinical Lecturer in  
Speech and Language Therapy,  
University of Manchester

Dr Yann Lefevre,  
GP Partner, Burrage Road  
Surgery, London

Dr Jeremy J Murphy,  
Consultant Physician &  
Cardiologist, County Durham &  
Darlington Foundation Trust

Mr John Needham,  
Service User, Buckinghamshire

Ms Mary Nettle,  
Mental Health User Consultant,  
Gloucestershire

Professor John Potter,  
Professor of Ageing and Stroke  
Medicine, University of East  
Anglia

Dr Greta Rait,  
Senior Clinical Lecturer and  
General Practitioner, University  
College London

Dr Paul Ramchandani,  
Senior Research Fellow/Cons.  
Child Psychiatrist, University of  
Oxford

Dr Howard Ring,  
Consultant & University  
Lecturer in Psychiatry,  
University of Cambridge

Dr Karen Roberts,  
Nurse/Consultant, Dunston Hill  
Hospital, Tyne and Wear

Dr Karim Saad,  
Consultant in Old Age  
Psychiatry, Coventry &  
Warwickshire Partnership Trust

Dr Alastair Sutcliffe,  
Senior Lecturer, University  
College London

Dr Simon Wright,  
GP Partner, Walkden Medical  
Centre, Manchester

### Observers

Ms Kay Pattison  
Senior NIHR Programme  
Manager, Department of  
Health

Dr Morven Roberts,  
Clinical Trials Manager, MRC,  
London

Professor Tom Walley,  
HTA Programme Director,  
Liverpool

Dr Ursula Wells,  
Policy Research Programme,  
DH, London

## Expert Advisory Network

### Members

Professor Douglas Altman,  
Professor of Statistics in  
Medicine, Centre for Statistics  
in Medicine, University of  
Oxford

Professor John Bond,  
Professor of Social Gerontology  
& Health Services Research,  
University of Newcastle upon  
Tyne

Professor Andrew Bradbury,  
Professor of Vascular Surgery,  
Solihull Hospital, Birmingham

Mr Shaun Brogan,  
Chief Executive, Ridgeway  
Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,  
Chief Executive, Regulation  
and Improvement Authority,  
Belfast

Ms Tracy Bury,  
Project Manager, World  
Confederation for Physical  
Therapy, London

Professor Iain T Cameron,  
Professor of Obstetrics and  
Gynaecology and Head of the  
School of Medicine, University  
of Southampton

Dr Christine Clark,  
Medical Writer and Consultant  
Pharmacist, Rossendale

Professor Collette Clifford,  
Professor of Nursing and  
Head of Research, The  
Medical School, University of  
Birmingham

Professor Barry Cookson,  
Director, Laboratory of Hospital  
Infection, Public Health  
Laboratory Service, London

Dr Carl Counsel, Clinical Senior Lecturer in  
Neurology, University of  
Aberdeen

Professor Howard Cuckle,  
Professor of Reproductive  
Epidemiology, Department  
of Paediatrics, Obstetrics &  
Gynaecology, University of  
Leeds

Dr Katherine Darton,  
Information Unit, MIND – The  
Mental Health Charity, London

Professor Carol Dezateux,  
Professor of Paediatric  
Epidemiology, Institute of Child  
Health, London

Mr John Dunning,  
Consultant Cardiothoracic  
Surgeon, Papworth Hospital  
NHS Trust, Cambridge

Mr Jonothan Earnshaw,  
Consultant Vascular Surgeon,  
Gloucestershire Royal Hospital,  
Gloucester

Professor Martin Eccles,  
Professor of Clinical  
Effectiveness, Centre for Health  
Services Research, University of  
Newcastle upon Tyne

Professor Pam Enderby,  
Dean of Faculty of Medicine,  
Institute of General Practice  
and Primary Care, University of  
Sheffield

Professor Gene Feder,  
Professor of Primary Care  
Research & Development,  
Centre for Health Sciences,  
Barts and The London School  
of Medicine and Dentistry

Mr Leonard R Fenwick,  
Chief Executive, Freeman  
Hospital, Newcastle upon Tyne

Mrs Gillian Fletcher,  
Antenatal Teacher and Tutor  
and President, National  
Childbirth Trust, Henfield

Professor Jayne Franklyn,  
Professor of Medicine,  
University of Birmingham

Mr Tam Fry,  
Honorary Chairman, Child  
Growth Foundation, London

Professor Fiona Gilbert,  
Consultant Radiologist and  
NCRN Member, University of  
Aberdeen

Professor Paul Gregg,  
Professor of Orthopaedic  
Surgical Science, South Tees  
Hospital NHS Trust

Bec Hanley,  
Co-director, TwoCan Associates,  
West Sussex

Dr Maryann L Hardy,  
Senior Lecturer, University of  
Bradford

Mrs Sharon Hart,  
Healthcare Management  
Consultant, Reading

Professor Robert E Hawkins,  
CRC Professor and Director  
of Medical Oncology, Christie  
CRC Research Centre,  
Christie Hospital NHS Trust,  
Manchester

Professor Richard Hobbs,  
Head of Department of Primary  
Care & General Practice,  
University of Birmingham

Professor Alan Horwich,  
Dean and Section Chairman,  
The Institute of Cancer  
Research, London

Professor Allen Hutchinson,  
Director of Public Health and  
Deputy Dean of ScHARR,  
University of Sheffield

Professor Peter Jones,  
Professor of Psychiatry,  
University of Cambridge,  
Cambridge

Professor Stan Kaye,  
Cancer Research UK Professor  
of Medical Oncology, Royal  
Marsden Hospital and Institute  
of Cancer Research, Surrey

Dr Duncan Keeley,  
General Practitioner (Dr Burch  
& Pttrs), The Health Centre,  
Thame

Dr Donna Lamping,  
Research Degrees Programme  
Director and Reader in  
Psychology, Health Services  
Research Unit, London School  
of Hygiene and Tropical  
Medicine, London

Mr George Levy,  
Chief Executive, Motor  
Neurone Disease Association,  
Northampton

Professor James Lindesay,  
Professor of Psychiatry for the  
Elderly, University of Leicester

Professor Julian Little,  
Professor of Human Genome  
Epidemiology, University of  
Ottawa

Professor Alistaire McGuire,  
Professor of Health Economics,  
London School of Economics

Professor Rajan Madhok,  
Medical Director and Director  
of Public Health, Directorate  
of Clinical Strategy & Public  
Health, North & East Yorkshire  
& Northern Lincolnshire  
Health Authority, York

Professor Alexander Markham,  
Director, Molecular Medicine  
Unit, St James's University  
Hospital, Leeds

Dr Peter Moore,  
Freelance Science Writer,  
Ashted

Dr Andrew Mortimore,  
Public Health Director,  
Southampton City Primary  
Care Trust

Dr Sue Moss,  
Associate Director, Cancer  
Screening Evaluation Unit,  
Institute of Cancer Research,  
Sutton

Professor Miranda Mugford,  
Professor of Health Economics  
and Group Co-ordinator,  
University of East Anglia

Professor Jim Neilson,  
Head of School of Reproductive  
& Developmental Medicine  
and Professor of Obstetrics  
and Gynaecology, University of  
Liverpool

Mrs Julietta Patnick,  
National Co-ordinator, NHS  
Cancer Screening Programmes,  
Sheffield

Professor Robert Peveler,  
Professor of Liaison Psychiatry,  
Royal South Hants Hospital,  
Southampton

Professor Chris Price,  
Director of Clinical Research,  
Bayer Diagnostics Europe,  
Stoke Poges

Professor William Rosenberg,  
Professor of Hepatology  
and Consultant Physician,  
University of Southampton

Professor Peter Sandercock,  
Professor of Medical Neurology,  
Department of Clinical  
Neurosciences, University of  
Edinburgh

Dr Susan Schonfield,  
Consultant in Public Health,  
Hillingdon Primary Care Trust,  
Middlesex

Dr Eamonn Sheridan,  
Consultant in Clinical Genetics,  
St James's University Hospital,  
Leeds

Dr Margaret Somerville,  
Director of Public Health  
Learning, Peninsula Medical  
School, University of Plymouth

Professor Sarah Stewart-Brown,  
Professor of Public Health,  
Division of Health in the  
Community, University of  
Warwick, Coventry

Professor Ala Szczepura,  
Professor of Health Service  
Research, Centre for Health  
Services Studies, University of  
Warwick, Coventry

Mrs Joan Webster,  
Consumer Member, Southern  
Derbyshire Community Health  
Council

Professor Martin Whittle,  
Clinical Co-director, National  
Co-ordinating Centre for  
Women's and Children's  
Health, Lymington





### **Feedback**

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website ([www.hta.ac.uk](http://www.hta.ac.uk)) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

***We look forward to hearing from you.***