Health Technology Assessment 2009; Vol. 13: No. 35

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

J Jones, J Shepherd, L Baxter,
E Gospodarevskaya, D Hartwell,
P Harris, A Price

July 2009
DOI: 10.3310/hta13350

Health Technology Assessment
NIHR HTA programme
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). 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
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). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

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

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

J Jones,[1] J Shepherd,[1*] L Baxter,[1]
E Gospodarevskaya,[1] D Hartwell,[1]
P Harris,[1] A Price[2]

[1]Southampton Health Technology Assessments Centre (SHTAC), UK
[2]NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), Southampton, UK

*Corresponding author

Declared competing interests of authors: none

Published July 2009
DOI: 10.3310/hta13350

This report should be referenced as follows:

Jones J, Shepherd J, Baxter L, Gospodarevskaya E, Hartwell D, Harris P, *et al*. Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation. *Health Technol Assess* 2009;**13**(35).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

NIHR Health Technology Assessment programme

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

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

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

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

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

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

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.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series 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 journal was commissioned and funded by the HTA programme on behalf of NICE as project number 07/15/01. The protocol was agreed in December 2007. The assessment report began editorial review in July 2008 and was accepted for publication in October 2008. 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.

ISSN 1366-5278

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

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

Abstract

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

J Jones,[1] J Shepherd,[1]* L Baxter,[1] E Gospodarevskaya,[1] D Hartwell,[1] P Harris,[1] A Price[2]

[1]Southampton Health Technology Assessments Centre (SHTAC), UK
[2]NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), Southampton, UK

*Corresponding author

Objective: To update and extend a 2006 report on the clinical effectiveness and cost-effectiveness of adefovir dipivoxil (ADV) and pegylated interferon alpha (PEG-α) for the treatment of chronic hepatitis B (CHB).
Data sources: Thirteen bibliographic databases were searched including MEDLINE, EMBASE and the Cochrane Library. Searches were run from the beginning of 2005 to September 2007.
Review methods: For the clinical effectiveness review, randomised controlled trials (RCTs) comparing ADV, PEG-α-2a and PEG-α-2b with currently licensed treatments for CHB, including non-pegylated interferon alpha (IFN-α) and lamivudine (LAM), were included. Outcomes included biochemical, histological and virological response to treatment, drug resistance and adverse effects. A systematic review of economic evaluations of antiviral treatments for CHB was conducted. The economic Markov model used in the 2006 report was updated in terms of utility values, discount rates and costs.
Results: Of the 82 papers retrieved for detailed screening, eight RCTs were included. Three evaluated ADV, four evaluated PEG-α-2b and one (from the original literature search) compared PEG-α-2b plus LAM with PEG-α-2b monotherapy. No RCTs of PEG-α-2a were identified. One ADV trial showed a statistically significant difference between ADV and placebo in terms of ALT response and HBV DNA levels, favouring ADV. Following withdrawal of ADV, levels were similar to those in placebo patients. In the ADV versus ADV plus LAM trial, there was a statistically significant difference in favour of the combination treatment. In the PEG-α trials, there were statistically significant differences favouring PEG-α-2b plus LAM compared with either one of the drugs given as monotherapy. For the comparison between PEG-α-2b and IFN-α and the comparison between different staggered regimens of the commencement of PEG-α-2b and LAM, there were no statistically significant differences between groups. Four full economic evaluations were identified, in addition to one identified in the original report. Two assessed PEG-α-2a; the remainder assessed ADV. PEG-α-2a was associated with increased treatment costs and gains in quality-adjusted life expectancy. In a UK study, the incremental cost-effectiveness ratio (ICER) for PEG-α-2a was £10,444 per QALY gained compared with LAM. Evaluations of ADV found that LAM monotherapy was dominated; the ICER for ADV monotherapy compared with 'doing nothing' was $19,731. The results of the updated analysis were generally robust to changes in deterministic sensitivity analysis. In a probabilistic sensitivity analysis, the same sequence of treatments was identified as optimal. In a probabilistic sensitivity analysis, PEG-α-2b had a probability of being cost-effective of 79% at a willingness-to-pay threshold of £20,000 per QALY, and 86% at a willingness-to-pay threshold of £30,000 per QALY.
Conclusions: Both ADV and PEG-α are beneficial for patients with CHB in terms of suppressing viral load, reducing liver damage-associated biochemical activity, inducing HBeAg seroconversion, and reducing liver fibrosis and necroinflammation. The effects of long-term treatment with ADV are generally durable, with relatively low rates of resistance. In most cases, cost-effectiveness estimates were within acceptable ranges. Further research should assess the clinical effectiveness and cost-effectiveness of newer antiviral agents in relation to existing drugs, including the role of initiating treatment with combination therapy.

Contents

List of abbreviations

AAA	adefovir–adefovir–adefovir
AAP	adefovir–adefovir–placebo
ADV	adefovir dipivoxil
ALT	alanine aminotransferase
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CHB	chronic hepatitis B
CRD	Centre for Reviews and Dissemination
CUA	cost–utility analysis
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBV DNA	hepatitis B deoxyribonucleic acid
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IFN-α	interferon alpha
ITT	intention to treat
LAM	lamivudine
MIU	million international units
NICE	National Institute for Health and Clinical Excellence
NS	not statistically significant
NTD	new Taiwan dollars
PAA	placebo–adefovir–adefovir
pg	picogram
PCR	polymerase chain reaction
PEG-α-2a	pegylated interferon alpha-2a
PEG-α-2b	pegylated interferon alpha-2b
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SHTAC	Southampton Health Technology Assessments Centre (SHTAC)
SVR	sustained virological response
TAR	technology assessment report
ULN	upper limit of the normal range
YMDD	tyrosine-methionine-aspartate-aspartate

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

This short report is an update and extension of a technology assessment report published in 2006 on the clinical effectiveness and cost-effectiveness of adefovir dipivoxil (ADV) and pegylated interferon alpha (PEG-α) for the treatment of chronic hepatitis B (CHB).

Hepatitis B is an infectious disease caused by the hepatitis B virus (HBV). If not successfully treated, it can lead to progressive liver damage, including cirrhosis, hepatocellular carcinoma and death. Patients with CHB may be HBeAg positive or HBeAg negative, depending on the presence or absence of the 'e' antigen. It is estimated that around 180,000 people (0.3%) in the UK are chronically infected, with around 7000 new cases each year, primarily from immigrants, most of whom are asymptomatic.

Methods

Assessment of clinical effectiveness

We searched for studies of the clinical effectiveness of adefovir dipivoxil, pegylated interferon alpha-2a (PEG-α-2a) and pegylated interferon alpha-2b (PEG-α-2b) (note that the latter was not included in the original report). Searches were run from the beginning of 2005 to September 2007. Thirteen bibliographic databases were searched, including MEDLINE, EMBASE and the Cochrane Library.

All studies were screened against a set of pre-specified inclusion criteria. For the clinical effectiveness review, we included randomised controlled trials (RCTs) which compared ADV, PEG-α-2a, and PEG-α-2b with currently licensed treatments for CHB, including the immunomodulatory drug non-pegylated interferon alpha (IFN-α) and the nucleoside analogue lamivudine (LAM).

Outcomes included biochemical (alanine aminotransferase, ALT), histological (liver fibrosis and necroinflammation) and virological [HBV deoxyribonucleic acid (DNA)] response to treatment, drug resistance and adverse effects. The trials were reviewed in a narrative synthesis but meta-analysis was not undertaken because of heterogeneity in the interventions and comparators evaluated.

Assessment of cost-effectiveness

A systematic review of economic evaluations of antiviral treatments for CHB was conducted. In addition, the economic model devised for our previous report was updated using utility values based on a recent study eliciting health-state valuations from CHB-infected patients. The model was also updated to account for changes in methodological guidance on discount rates for costs and outcomes. Health-state and treatment costs were inflated to 2006–7 prices. Evidence for the clinical effectiveness of PEG-α-2b was used in the model to estimate the cost-effectiveness of PEG-α-2b compared with IFN-α.

Results

Clinical effectiveness

Literature searches yielded a total of 735 articles. Of these, 653 were excluded on the basis of title and, where available, abstract. Eighty-two papers were retrieved for detailed screening and eight randomised controlled trials (RCTs) were included in the systematic review:

- Three evaluated ADV, one of which was a long-term follow-up of a trial included in our original assessment report. In two trials ADV was compared with placebo, and in a third ADV was compared with ADV added to LAM in patients with LAM resistance.
- Four evaluated PEG-α-2b. In two of these PEG-α-2b was combined with LAM and compared with either PEG-α-2b monotherapy or LAM monotherapy. Another compared three staggered regimens of PEG-α-2b combined with LAM. The fourth trial compared PEG-α-2b monotherapy with IFN-α.
- A further PEG-α-2b RCT was included from our original literature search database (but not included in the original assessment report as it

was not in the scope of the review at that time). This RCT compared PEG-α-2b combined with LAM with PEG-α-2b monotherapy.
- No RCTs of PEG-α-2a were identified.

The trials varied in terms of aims, size and design characteristics. Five included only HBeAg-positive patients, with the remaining three including only HBeAg-negative patients.

Methodological quality also varied. Some trials reported adequate blinding, allocation concealment and randomisation methods, while other trials either failed to report such details or were judged inadequate.

ADV trials

In one trial there was a statistically significant difference between ADV and placebo in terms of ALT response and HBV DNA levels after 12 weeks, favouring ADV. Following withdrawal of ADV after 40 weeks, the proportion of patients exhibiting HBV DNA and ALT responses declined to levels similar to those experienced by patients who had received placebo. There was no viral resistance to ADV. The rate of adverse events and dose discontinuations was low and generally similar between study groups.

In the trial that compared switching to ADV versus adding ADV to LAM in patients with LAM resistance there was a statistically significant difference in favour of the combination treatment in terms of zero resistance to ADV. For the other outcomes there were no statistically significant differences between groups.

A follow-up publication of an RCT included in our original assessment report, comparing ADV with placebo in HBeAg-negative patients, reported generally sustained HBV DNA and ALT response rates among those treated with ADV for 5 years. Cumulative probabilities of resistance to ADV in the cohort varied from 11% to 29% depending on how resistance was defined.

PEG-α trials

Where statistical testing was reported, there were statistically significant differences favouring PEG-α-2b in combination with LAM compared with either one of the drugs given as monotherapy. This was the case for HBV DNA and ALT responses in two trials. However, another trial reported no significant differences between groups for these measures. There was a significant difference for HBeAg seroconversion, favouring combination therapy in one trial. For liver histology either there was no significant difference between groups or no statistical tests were performed.

For the comparison between PEG-α-2b and IFN-α and the comparison between different staggered regimens of the commencement of PEG-α-2b and LAM, there were no statistically significant differences between groups across the outcome measures where tests were reported.

Cost-effectiveness

The systematic review of cost-effectiveness studies identified four relevant full economic evaluations, in addition to one full economic evaluation identified and partially reviewed in our original assessment report. Two of the evaluations assessed PEG-α-2a; the remainder assessed ADV. Four of the five economic evaluations used Markov models, with lifetime horizons, while the other study used a decision tree with a 4-year time horizon. State-transition diagrams in the evaluations were similar, identifying the treatment aim as inducing HBeAg seroconversion for patients with HBeAg-positive CHB and viral suppression for patients with either HBeAg-positive or HBeAg-negative CHB.

Economic evaluations of PEG-α-2a found that it was associated with increased treatment costs but also gains in quality-adjusted life expectancy. In a UK study, the incremental cost-effectiveness ratio (ICER) for PEG-α-2a was £10,444 per QALY gained compared with LAM. Evaluations of ADV found that LAM monotherapy was dominated, while the ICER for ADV monotherapy compared with 'doing nothing' was $19,731($14,342–$24,224) at 2005 prices.

A review of health-state utility values used in economic evaluations of antiviral treatments for CHB showed that widely varying values were used, many of which were not specific to CHB patients. A recently published study reporting health-state utilities for patients with CHB infection and for non-infected general population samples, derived using the standard gamble technique, was identified and reviewed.

The ICERs generated by the update of our economic model were generally less favourable than those reported in the original assessment report. However, it appears that much of the difference arises from recent changes to

methodological guidance (i.e. discounting costs and outcomes at 3.5% rather than 6% and 1.5% respectively) rather than from changes in costs or health-state utilities.

The sequential treatment strategies identified as optimal in our original report remained optimal in the updated model, i.e. interferon (pegylated or non-pegylated) followed by LAM, with ADV as salvage for patients who develop LAM resistance.

The results of the updated analysis were generally robust to changes in deterministic sensitivity analysis. The most notable changes were in the ICER for the strategy including ADV as salvage therapy for patients who develop resistance to LAM, in some cases increasing the ICER beyond the threshold conventionally used to indicate cost-effectiveness in the context of NHS decision making.

- The most influential structural assumption was excluding the possibility of HBeAg seroconversion (in HBeAg-positive CHB) in patients with compensated cirrhosis, which increased the ICER to £40,833 per QALY gained.
- In terms of the baseline characteristics of the treated cohort, decreasing the proportion with HBeAg-positive CHB and increasing age were associated with less favourable ICERs.
- The most influential parameter values related to the gain in utility associated with HBeAg seroconversion and loss of the surface antigen (HBsAg). This affected the ICERs for all strategies, but was most notable for the strategy including ADV as salvage for patients who develop resistance to LAM. If there is no utility gain for HBeAg seroconversion or loss of HBsAg, the ICER increases to £31,114.

In a probabilistic sensitivity analysis the same sequence of treatments was identified as optimal. However, the strategy including ADV as salvage becomes optimal only above a willingness-to-pay threshold of £27,000 per QALY. This is at the upper limit of the range of ICERs regarded as cost-effective from an NHS decision-making perspective. Interferon (conventional or pegylated) followed by LAM is optimal for a willingness to pay of £9000–£26,000, compared with a range of £5000–£11,500 in our previous report. As discussed, much of this difference arises from changes in the practice of discounting rather than changes to input values in the model.

The ICER for PEG-α-2b, compared with IFN-α-2b, in patients with HBeAg-positive CHB was £9169, based on the results of a clinical trial of 24 weeks of interferon treatment. The trial did not include a placebo arm, so no ICER for PEG-α-2b compared with best supportive care was estimated. Results were generally robust to changes in deterministic sensitivity analysis.

- Increasing age of the cohort and lower utility gains from HBeAg seroconversion or loss of HBsAg were associated with less favourable ICERs.
- Alternative discount rates (6% for costs and 1.5% for outcomes, as in our previous report, or 0% for both costs and outcomes) and a reduction in cost for PEG-α-2b were associated with more favourable ICERs.
- All ICERs in the one-way sensitivity analyses were below the threshold conventionally deemed as cost-effective.

In a probabilistic sensitivity analysis, PEG-α-2b had a probability of being cost-effective (compared with IFN-α-2b) of 79% at a willingness-to-pay threshold of £20,000 per QALY, and 86% at a willingness-to-pay threshold of £30,000 per QALY.

Conclusions

Overall, the evidence from RCTs suggests that the effects of long-term treatment with ADV are generally durable, with relatively low rates of resistance. It is also apparent that beneficial effects are lost once ADV is withdrawn. Furthermore, in LAM-resistant HBeAg-negative patients there were no significant differences between adding ADV to ongoing LAM or switching from LAM to ADV, except for viral resistance where the combination was more favourable.

PEG-α-2a was associated with some benefit in terms of virological and biochemical response, HBeAg seroconversion and liver histology, relative to comparators. However, not all differences were statistically significant, and often significance tests were not reported at all. Consequently, there are uncertainties regarding the clinical effectiveness of this drug across different outcomes relevant to the control of CHB.

In terms of cost-effectiveness, optimum treatment strategies include IFN-α or PEG-α followed by LAM, with ADV used in patients who become

resistant to LAM. In most cases, cost-effectiveness estimates were within acceptable ranges.

Further high-quality RCTs are required to assess the durability of long-term antiviral treatment, optimum treatment of patients with LAM resistance, and the clinical effectiveness and cost-effectiveness of initiating treatment with nucleoside combination therapy, including newer antiviral agents.

Chapter 1
Background

Description of underlying health problem

Hepatitis B is an infectious disease caused by the hepatitis B virus (HBV), and was first identified in 1965. Key routes of transmission include sexual contact (via exposure to blood, saliva and other body fluids), injecting drug use, and from mother to child (particularly in South-east Asia). In health-care workers, needlestick injuries are also a relatively rare source of transmission. Some patients with haemophilia in the UK have been infected via contaminated blood products [as well as being infected with the hepatitis C virus (HCV)].

The virus infects cells in the liver (hepatocytes) and the immune system will at some point mount a response to try to remove the infection (in some cases after several years). If untreated, HBV can result in long-term complications such as cirrhosis and liver cancer (hepatocellular carcinoma, HCC). Carriers of the virus can remain asymptomatic for many years before presenting with symptoms of chronic liver disease.

In acute infection, the majority of cases are self-limiting within 6 months, with patients developing lasting immunity to reinfection as the virus (surface antigen) is cleared from the blood and liver, although viral DNA can be detected in many cases.

There may be no or few symptoms (about 70% of patients are asymptomatic), and treatment is generally not indicated.

Chronic hepatitis B (CHB) results from an inadequate immune response to the primary infection, where viral replication continues and there is continuing presence of the surface antigen (HBsAg). It can follow acute hepatitis or be transmitted vertically from mother to baby (in the latter case there may be no acute infection). The hepatitis B surface antigen is present in all forms of the disease.

HBeAg-positive chronic hepatitis B

HBeAg-positive CHB (also referred to as 'wild type' CHB) is, for many, the first stage of chronic disease. This form of the disease prevails in Europe and North America. The first stage is the 'immunotolerant' phase, during which the immune system does not actively fight the virus, and this may last for a number of years.[1] Those who acquire the disease as neonates or in early childhood will undergo this phase, but adults and those infected during adolescence generally will not. During the immunotolerant phase, HBV deoxyribonucleic acid (DNA) levels are increased but aminotransferase levels remain normal. Treatment is not indicated in this phase.[2]

Progression to the 'immunoactive' phase (also referred to as the 'immune clearance phase') of chronic HBeAg-positive disease, whereby the immune system is actively fighting the virus, is characterised by HBV DNA replication and an increase in alanine aminotransferase (ALT) levels (ALT being an enzyme that indicates inflammation of the liver). Symptoms may appear during this phase, and 'flares' (short-lived rises in ALT levels) of aminotransferases may occur before seroconversion from HBeAg to anti-HBe in some patients.[3] Treatment, the goal of which is to induce HBeAg seroconversion in the first instance, is indicated in this phase.[2]

HBeAg seroconversion results in the disease progressing either to an inactive carrier state (also referred to as the 'low-' or 'non-replicative state' or 'immune control phase') or to the HBeAg-negative form of the disease. Between 50% and 70% of patients with elevated aminotransferases spontaneously seroconvert within 5–10 years of diagnosis, with a mean annual rate of 8–15% in Western countries.[3] HBeAg seroconversion is more likely to occur in older people, females and those with high aminotransferase levels. A proportion of seroconverted patients will also reacquire the e antigen (i.e. become HBeAg positive again), effectively reactivating the disease. Although, for most patients, HBeAg seroconversion results in transition to the inactive carrier state, between 1% and 5% of patients progress to the 'immune escape phase' whereby a pre-core viral mutation emerges.[2] This is characterised by undetectable HBeAg and detectable anti-HBe levels, high serum HBV DNA levels and elevated aminotransferase levels (see below).[3]

The low- or non-replicative state is characterised by low HBV DNA levels and normal ALT. Unless cirrhosis is present, this stage usually has a benign prognosis, but around 3% of patients per annum may undergo reactivation and develop progressive liver disease.[3]

HBeAg-negative chronic hepatitis B

HBeAg-negative CHB (also known as 'pre-core mutant' or 'variant' hepatitis B) was identified relatively recently. It is a variant HBV strain carrying a mutation within the pre-core region of the HBV genome that permits viral replication but prevents production of HBeAg (or a mutation within the core region of the genome that diminishes HBeAg expression).[4] Although some patients acquire HBeAg-negative infection on or following HBeAg seroconversion (as mentioned above), many develop the variant at an earlier stage or from the outset.

HBeAg-negative infection, common in Mediterranean areas and South-east Asia, is considered to be the most severe form of the disease. It is characterised by raised (but fluctuating) ALT and detectable HBV DNA levels.[2] There are three main patterns of ALT activity: recurrent flares with normalisation in between; recurrent flares with persistently abnormal serum aminotransferase levels in between; and persistently abnormal ALT without flares.[3]

HBsAg seroconversion

Around 0.5–2% of people with CHB (0.05–0.08% in Asia) each year lose the surface antigen (HBsAg) and develop antibodies (anti-HBs), thereby undergoing HBsAg seroconversion. This is most common in the year following HBeAg seroconversion (although patients can also seroconvert from the immunotolerant phase) and signifies resolution of chronic infection. Although HBsAg seroconversion is believed to be a relatively rare occurrence, it has been recommended that future clinical trials use it as an outcome measure as it represents the ultimate goal of therapy.[2]

Long-term complications

People with CHB, in common with chronic hepatitis C, are at increased risk of progressing to long-term complications, including cirrhosis (scarring) of the liver, decompensated liver disease and/or HCC. The risk of progression varies with geographical location and mode of transmission. Evidence suggests that 2–5.5% of HBeAg-positive people and 8–10% of those who are negative progress to cirrhosis annually.[3] Decompensated liver disease occurs when the liver can no longer compensate for scarred tissue. It is characterised by ascites (fluid in the peritoneal cavity), variceal bleeding and hepatic encephalopathy, and is associated with irreversible liver failure, requiring liver transplantation. Death from liver disease and HCC is common in CHB. It is estimated that there are more than 1200 new cases of HCC in the UK each year, of which 430 are caused by viral hepatitis.

The 5-year mortality rate for CHB without cirrhosis is 0–2%, but this increases to 14–20% for those with compensated cirrhosis and 70–80% after the occurrence of decompensation.[3]

Incidence and prevalence

Approximately 400 million people worldwide are infected with chronic HBV, although levels vary geographically.[5] In North-western Europe, North America and Australia there is a low level of endemic HBV, and the virus is usually transmitted by needle sharing among intravenous drug users (IDUs) and by sexual transmission. High levels of infection are found in Africa and Asia, where the virus is usually transmitted perinatally or during early childhood. The UK is considered to be a low prevalence country, with around 156,000 people in England and Wales infected with CHB[6] (180,000/0.3% in the UK) and around 7000 estimated new chronic cases every year (mostly from immigration of established HBV carriers, many of whom are thought to be HBeAg negative and in the immunotolerant phase, and thus not currently symptomatic). The Hepatitis B Foundation recently estimated that the prevalence of CHB in the UK may have increased to 325,000 and is thought likely to increase further as a consequence of increasing rates of immigration of people from countries with a high CHB prevalence.[7]

Vaccination

A safe and effective vaccine for hepatitis B has been available since 1982 and many countries operate a universal vaccination programme for newborns or adolescents. However, the UK has not introduced such a policy, instead offering selective vaccination to key risk groups (e.g. men who have sex with men, injecting drug users and health-care workers).

Morbidity and quality of life

The impact of CHB on quality of life in the early stages of disease is not thought to be great. Many people do not know that they are infected and consequently may not present to health services for many years until symptoms of liver disease become evident.

However, quality of life becomes significantly impaired as the disease progresses to cirrhosis, decompensated liver disease and HCC.[8] Patients who seroconvert into the low- or non-replicative state are thought to have a relatively good quality of life. There is evidence to suggest that quality of life impairment in CHB is not as great as it is with chronic HCV.[9,10]

Antiviral treatment

There are two modes of antiviral treatment for CHB:

1. Short-term or finite, circumscribed therapy with interferon alpha (IFN-α). The goal is to achieve an immune response in terms of HBeAg seroconversion (for patients who are HBeAg positive), suppression of HBV DNA and, where possible, HBsAg seroconversion. This mode of treatment is a first-line attempt to 'switch' the immune system into clearing the infection or into remission. Although IFN-α appears to be commonly used in this scenario, some clinicians may use a nucleotide/nucleoside analogue.
2. Long-term maintenance treatment for patients who have failed IFN-α or for whom disease has advanced such that IFN-α is contraindicated. This would usually involve lamivudine (LAM), a nucleoside analogue. This mode of treatment may be particularly suitable for those HBeAg-negative patients with high levels of HBV DNA and ALT. In these patients, long-term suppression of HBV replication with either nucleoside or nucleotide analogues will be necessary until the infected cells have been eliminated. The half-life of these cells may be 10 years or more.[11] Reducing levels to 'normal' will likely limit disease progression.

IFN-α was used as first-line treatment of CHB for a number of years. Versions available include IFN-α-2a (Roferon-A®; Hoffman–La Roche) and IFN-α-2b (IntronA®, Viraferon®; Schering–Plough). In 1998, LAM (Epivir, Zeffix; GlaxoSmithKline), an oral nucleoside reverse transcriptase inhibitor, was licensed for the treatment of CHB. In the last 5 years, newer agents have been licensed, such as adefovir dipivoxil (ADV) and the pegylated form of IFN-α (PEG-α).

Adefovir dipivoxil (Hepsera®; Gilead Sciences), a prodrug of adefovir, was the first licensed nucleotide analogue for the treatment of CHB. It is currently licensed in the UK for CHB infection with either compensated liver disease with evidence of active viral replication, persistently elevated serum ALT levels and histological evidence of active liver inflammation and fibrosis, or decompensated liver disease. The recommended dose is 10 mg per day, taken orally.

A newer 'pegylated' derivative of IFN-α has become available recently. Pegylation involves the attachment of an inert polyethylene glycol polymer to the IFN-α molecule to produce a larger molecule with a prolonged half-life. Pegylation prolongs the biological effect and thus fewer injections are necessary.

Two versions are available: (1) 40 kD PEG-α-2a (Pegasys®; Hoffman–La Roche) and (2) 12 kD PEG-α-2b (PegIntron®, ViraferonPeg®; Schering–Plough). Only the former is currently licensed in the UK.

Recently licensed drugs for CHB include nucleoside analogues entecavir (Baraclude®; Bristol–Myers Squibb) and telbivudine (Sebivo®; Novartis). These are not within the scope of the current report, but have undergone appraisal by the National Institute for Health and Clinical Excellence (NICE).

Current service provision

In 2006 NICE issued guidance to the health service in England and Wales on the use of PEG-α-2a and ADV, based on an independent technology assessment report (TAR).[12] The guidance recommends:

- PEG-α-2a as an option for the initial treatment of adults with CHB, within its licensed indications.
- ADV as an option for the treatment of adults with CHB within its licensed indications if:
  - treatment with IFN-α or PEG-α-2a has been unsuccessful, or
  - a relapse occurs after successful initial treatment, or
  - treatment with IFN-α or PEG-α-2a is

poorly tolerated or contraindicated.

The guidance also states that ADV should not normally be given before treatment with LAM. It may be used either alone or in combination with LAM when:

- treatment with LAM has resulted in viral resistance, or
- LAM resistance is likely to occur rapidly (e.g. in the presence of highly replicative hepatitis B disease) and development of LAM resistance is likely to have an adverse outcome (e.g. if a flare of the infection is likely to precipitate decompensated liver disease).

Our previous assessment report, which underpinned this guidance, was produced in early 2005.[12] The current report is an update of the assessment for the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (and is not intended to inform any NICE appraisal). The aim of the report is to update the systematic review of clinical effectiveness and the economic evaluation conducted in the original report. It also expands on the original report by including PEG-α-2b, which was not included in NICE's appraisal because of its unlicensed status.

Chapter 2
Methods

The methods used in this update are similar to those reported in the original assessment[12] (which can be downloaded free of charge from www.hta.ac.uk). A protocol outlining the scope and methods was published prior to the start of the project. This report was commissioned by the HTA programme as a 'short technology assessment report'. Consequently the time and resources allocated to it were less than those allocated to the original report, which was commissioned as a 'full technology assessment report'.

Search strategy

A sensitive search strategy was developed, tested and refined by an information scientist. Specific searches were conducted to identify studies of clinical effectiveness and cost-effectiveness. The strategies were the same as those used in our previous assessment report;[12] please refer to that report for further detail.

The strategies were applied to the following electronic databases:

- Cochrane Systematic Reviews Database
- Cochrane Central Register of Controlled Trials
- NHS Centre for Reviews and Dissemination (CRD) (University of York) databases:
  - DARE (Database of Abstracts of Reviews of Effects)
  - Health Technology Assessment (HTA) database
  - NHS EED (Economic Evaluations Database)
- MEDLINE (Ovid)
- PREMEDLINE
- EMBASE (Ovid)
- EconLit (Silver Platter)
- National Research Register
- ISI Web of Science – Science Citation Index
- ISI Proceedings
- ISI BIOSIS
- Clinical trials.gov
- Current Controlled Trials.

In our original report, searches were carried out for the period 1995/1996 to April 2005. In this update they were run from the beginning of 2005 to September 2007. All searches were limited to the English language.

We rescreened our original bibliographic database to identify any relevant trials of PEG-α-2b. Although not included in our original report, our search strategies were designed to identify studies of PEG-α-2a as well as PEG-α-2b.

Inclusion and exclusion criteria

Studies identified by the search strategy were assessed for inclusion in two stages. Firstly, the titles and abstracts of all identified studies were screened for possible inclusion by one reviewer, and a random sample of 10% of these were checked by a second reviewer. Any differences in opinion between reviewers were discussed and a final decision was reached. Secondly, full-text versions of relevant papers were retrieved, and an inclusion worksheet was applied independently by two reviewers. Any differences in judgement at either stage were resolved through discussion. The level of agreement between reviewers on selection decisions was not assessed.

The inclusion criteria, as specified in the study protocol, were as follows. (Note that the inclusion criteria for this update are the same as for the original assessment report with one key difference, i.e. studies of PEG-α-2b were eligible.)

Interventions

- Interventions (alone and in combination with other treatment options):
  - PEG-α-2a†
  - PEG-α-2b†
  - ADV
- Comparators (alone and in combination with other treatment options):
  - PEG-α-2a*
  - PEG-α-2b*
  - ADV*
  - IFN-α-2a
  - IFN-α-2b

  - LAM
  - best supportive care.

Note that † = not indicated for patients with decompensated liver disease; * = intervention was not compared with itself.

Patients

- Adults with CHB infection, including HBeAg-positive and HBeAg-negative patients, with compensated or decompensated liver disease.

Types of studies

- Randomised controlled trials (RCTs) comparing the different drugs with placebo or each other or best supportive care. (Note that observational follow-up studies of RCTs included in our original report, where fully published, were eligible.)
- Unpublished material, including studies published as abstracts or conference presentations were not included.
- Full economic evaluations of the specified interventions in patients with CHB were included in the review of cost-effectiveness.

Outcomes

- The following outcome measures were included, where available:
  - survival
  - health-related quality of life
  - drug resistance
  - time to treatment failure
  - histological response (e.g. inflammation/fibrosis – on biopsy)
  - biochemical response (e.g. liver function – aminotransferase)
  - virological response (e.g. seroconversion rate and viral replication – HBV DNA)
  - seroconversion (e.g. HBeAg loss/anti-HBe; HBsAg loss/anti-HBs)
  - adverse effects of treatment.

Data extraction strategy

Data were extracted from the included clinical effectiveness studies using a standardised template. Data extraction was undertaken by one reviewer and checked by a second, with any disagreements resolved through discussion. The level of agreement between reviewers was not assessed. The full data extraction forms of all the included studies can be seen in Appendix 1.

Quality assessment strategy

The methodological quality of RCTs was assessed using the CRD (University of York) criteria[13] (Appendix 1). Quality criteria were applied by one reviewer and checked by a second, with any disagreements resolved through discussion.

Methods of analysis/synthesis

A narrative synthesis was undertaken with the main results of the included clinical effectiveness and cost-effectiveness studies described qualitatively and in tabular form. A meta-analysis was not possible because of heterogeneity in the interventions and comparators evaluated by the included clinical trials.

Chapter 3
Clinical effectiveness

Results

Quantity and quality of research available

Appendix 2 illustrates the inclusion and exclusion of studies over the various stages of screening, adapted from the QUOROM flowchart. The literature searches yielded a total of 735 articles. Of these, 653 were excluded on the basis of title and, where available, abstract. In many cases, studies were excluded on the basis of inappropriate study design (i.e. they were not RCTs). The remaining 82 papers were retrieved for detailed screening. Of these, 65 were excluded, again primarily because of inappropriate study design. The remaining 17 papers were included, and of these:

- Four were follow-up publications relating to RCTs included in our original report.[14–17] These publications explored different aspects of the RCTs, such as predictors of treatment effect and subgroup analyses (e.g. based on genotype). As they do not report any updated findings on the main outcomes of the RCTs (e.g. long-term follow-up of HBV DNA, ALT, HBeAg seroconversion) they are not discussed further in the current report.
- Thirteen papers described a total of seven studies which met the inclusion criteria for the review. Of these seven studies:
  - three were RCTs of ADV, one of which was a long-term follow-up of an RCT included in our original assessment report
  - four were RCTs of PEG-α-2b (no RCTs of PEG-α-2a were identified in the update search).
- An additional RCT of PEG-α-2b from our original bibliographic database was also included in the review, to make a total of eight included RCTs.

In summary, a total of eight RCTs met the inclusion criteria as described by 13 publications. These are the focus of this report.

Characteristics of included studies from the update search

For details of the RCTs included in our original report see Appendix 3.

The key characteristics of the eight included studies, in terms of interventions, patients, methods and methodological quality, are described in the following sections.

Characteristics of ADV studies

Three fully published RCTs which evaluated treatment with ADV in CHB patients were identified and included.[18–20] One trial, by Rapti and colleagues,[18] recruited patients from a long-term open-label study of LAM monotherapy and evaluated the efficacy of switching to ADV monotherapy or adding ADV to LAM.[18] Results at 12 and 24 months are reported but the study is ongoing. The second trial, by Zeng and colleagues,[19] had three arms, with participants receiving either ADV or placebo for 12 weeks, ADV for 28 weeks and ADV or placebo for a further 12 weeks (52 weeks' total treatment duration):

- placebo–ADV–ADV
- ADV–ADV–ADV
- ADV–ADV–placebo.

The rationale of both these studies was based upon the need for well-tolerated efficacious drugs that have a high barrier to the development of resistance, given that many CHB patients develop resistance to first-line LAM therapy. In the Rapti and colleagues study,[18] this was investigated by evaluating long-term therapy for LAM-resistant patients by adding ADV to LAM, compared with switching to ADV. The trial by Zeng and colleagues[19] tested the long-term antiviral efficacy and safety of ADV monotherapy, and also investigated the impact of cessation of therapy (placebo phases).

The third trial, by Hadziyannis and colleagues,[20] was a long-term follow-up of Study 438,[21,22] an RCT that was included in our original assessment report.[12] The trial compared ADV with placebo for 48 weeks, at which point patients who had received ADV were re-randomised to ADV for a further 48 weeks ($n = 80$, the ADV–ADV group) or to placebo ($n = 40$, the ADV–placebo group). Patients originally randomised to placebo switched to ADV ($n = 60$, the placebo–ADV group). At week 97, the ADV–placebo group discontinued treatment and all remaining patients ($n = 125$) entered an open-label

long-term safety and efficacy study until week 240. In the ADV–ADV group, 70 patients were analysed, while in the placebo–ADV group 55 patients were analysed. (Note that a 2005 publication reported interim results at week 144 for the ADV–ADV group, and results at week 96 for the ADV–placebo and placebo–ADV groups; these results are reported in our original assessment report,[12] and can also be found in Appendix 1 of the current report). In all studies, the dose of ADV was 10 mg once daily.

The key characteristics of the trials and the participants involved are shown in *Table 1*. The Rapti and colleagues trial[18] was a relatively small, single-centre, open-label study carried out in Greece. The source of funding was not reported by the authors but the ADV capsules used in the study were supplied on a 'compassionate basis' by Gilead Sciences. In contrast, the trial by Zeng and colleagues[19] was a larger, multicentre study incorporating both double-blind and open-label phases, and was carried out across seven cities in China. The trial was supported by GlaxoSmithKline. The study by Hadziyannis and colleagues[20] was supported by Gilead Sciences.

The primary outcome measure in the Zeng and colleagues trial[19] was the reduction in serum HBV DNA after 12 weeks' treatment. The main secondary efficacy end point was the proportion of patients with ALT normalisation in week 12. Other secondary outcome measures included HBV DNA change from baseline at end of treatment, the proportion of subjects with HBV DNA $< 10^5$ copies/ml and with undetectable HBV DNA, ALT normalisation at end of treatment, HBeAg loss and seroconversion, and health-related quality of life. Rapti and colleagues[18] did not specify which of their outcomes were primary and secondary measures, but reported median HBV DNA levels and non-detectability of HBV DNA at 6, 12 and 24 months. Biochemical measures reported included ALT change from baseline and ALT normalisation. Both studies reported adverse effects. The outcomes reported by Hadziyannis and colleagues[20] were HBV DNA, ALT, histological response, HBsAg seroconversion and resistance to ADV.

Both trials included only adult patients, although the median age reported varied between trials [median 56 years (range 39–76)[18] versus median 30 years (range 17–61)[19]]. Participants were predominantly male in both trials, with the proportion ranging from 83% to 93%. Patients in the Rapti and colleagues trial[18] were HBeAg negative while those in the Zeng and colleagues trial[19] were HBeAg positive. In terms of ethnicity, one trial included 100% white Europeans,[18] in another all patients were Chinese,[19] and in the third around two-thirds were described as white, with the remaining patients being Asian or black.[20]

The majority of patients across the two trials had received previous antiviral therapy for CHB. All patients in the Rapti and colleagues trial[18] had previously received LAM [for a median duration of 32 months (range 12–84)] and exhibited genotypical LAM resistance with virological and clinical breakthroughs. Prior to enrolment in the long-term LAM study, none had received any other antiviral drug other than IFN-α.

In the Zeng and colleagues trial,[19] approximately one-third of patients had previously received treatment with LAM, one-third had previously received treatment with traditional Chinese medicines and one-third were treatment naïve. All patients in the included trials had compensated liver disease. In the Zeng and colleagues trial,[19] no patients had cirrhosis, while in the Rapti and colleagues trial[18] about one-third of patients had histological evidence of cirrhosis. None of the patients had co-infection with hepatitis C, hepatitis D or HIV, or any co-morbidities.

Table 2 provides an overview of the methodological quality of two of the ADV RCTs. The third, the open-label follow-up study, is discussed below.

The two RCTs varied in terms of methodological quality. The trial by Zeng and colleagues[19] generally appeared to be of better quality than the trial by Rapti and colleagues[18]. It provided an adequate description of the method of randomisation; baseline characteristics were similar across the trial arms; the reporting of the primary outcome was adequate; and the study comprised both blinded and open-label phases (hence judged 'partial'). However, concealment of allocation was only partially met. The level of reporting in the trial by Rapti and colleagues was poor, and prohibited a full assessment of its methodological quality. Importantly, the methods of randomisation and concealment are unknown, although there were no reported statistically significant differences between study groups at baseline, suggesting that selection bias was unlikely.

The third study, the long-term open-label study by Hadziyannis and colleagues,[20] became an observational study beyond the initial 48

TABLE 1 *Study characteristics – ADV studies*

Study and methods	HBeAg status	No. of participants (*n*), duration of trial (T_d), additional follow-up (F_d) and total duration (total)	Patient characteristics	Group A	Group B	Group C	Outcomes
Zeng *et al.*, 2006[19] *Design:* Multicentre, double-blind/open-label RCT[d] *Number of centres:* 7 *Sponsor:* GlaxoSmithKline *Country:* China	Positive	$n = 480$ $T_d = 52$ weeks F_d = ongoing[e] Total = ongoing[e]	Detectable HBsAg and HBeAg Serum HBV DNA $\geq 10^6$ copies/ml Serum ALT level > 1×ULN (and > 2×ULN sometime within the previous 6 months) Compensated liver disease Chinese population Average age: ≈ 32 years Sex: 83% male No LAM therapy within 3 months prior to screening, or ADV (or other anti-HBV therapy) in previous 6 months ≈ one-third treatment naive No cirrhosis No co-infection with hepatitis C or HIV	PAA Placebo (12 weeks) ADV 10 mg/day (28 weeks) ADV 10 mg/day (12 weeks) (*Total ADV duration: 40 weeks*) (*n* = 120)	AAA ADV 10 mg/day (12 weeks) ADV 10 mg/day (28 weeks) ADV 10mg/day (12 weeks) (*Total ADV duration: 52 weeks*) (*n* = 240)	AAP ADV 10 mg/day (12 weeks) ADV 10 mg/day (28 weeks) Placebo (12 weeks) (*Total ADV duration: 40 weeks*) (*n* = 120)	*Primary outcomes:* Change from baseline[f] of serum HBV DNA at week 12 *Secondary outcomes:* Virological response: HBV DNA change from baseline[f] at weeks 40 and 52 HBV DNA < 10^5 copies/ml Undetectable HBV DNA (< 300 copies/ml) Biochemical response: ALT normalisation at weeks 12, 40 and 52 ALT flares Serological response: HBeAg loss HBeAg seroconversion *Other measures:* Quality of life ADV resistance

continued

TABLE 1 *Study characteristics – ADV studies (continued)*

Study and methods	HBeAg status	No. of participants (*n*), duration of trial (T_d), additional follow-up (F_d) and total duration (total)	Patient characteristics	Group A	Group B	Group C	Outcomes
Rapti *et al.*, 2007[18] *Design:* Open-label RCT *Number of centres:* 1 *Sponsor:* Not specified (drugs supplied by Gilead Sciences) *Country:* Greece	Negative	*n* = 42 T_d = 37.5 months[a] F_d = ongoing[b] Total = ongoing	HBsAg +ve or HbeAg –ve/anti-HBe +ve for ≥ 6 months Elevated ALT on 3 separate monthly occasions HBV DNA > 10^5 copies/ml within last month before starting LAM therapy Compensated liver disease Greek population Average age: ≈ 56 years Sex: 93% male Previous LAM monotherapy (all LAM-resistant) No co-infection with HIV or hepatitis C	ADV 10 mg daily (*n* = 14)	ADV 10 mg daily + LAM (dose not specified)[c] (*n* = 28)	–	*Primary outcomes:* Virological response: non-detectability of HBV DNA levels Biochemical response; ALT change from baseline and ALT normalisation *Secondary outcomes:* Adverse effects *Other measures:* ADV resistance
Hadziyannis *et al.*, 2006[20] *Design:* Open-label 5-year long-term study based on RCT (Study 438)[g] *Number of centres:* 32 *Sponsor:* Gilead Sciences *Country:* International	Negative	*n* = 125 T_d = 240 weeks (192 weeks for PAA group)	HBeAg negative Detection of HBsAg ≥ 6 months Compensated liver disease Serum HBV DNA ≥ 10^5 copies/ml Serum ALT level between > 1.5 and 15× ULN Average age: ≈ 46 years Sex: ≈ 83% male No co-infection with hepatitis C or HIV No prior nucleoside/nucleotide therapy for more than 3 months	AA ADV 10 mg/day (48 weeks) ADV 10 mg/day (48 weeks) ADV 10 mg/day (144 weeks) (*Total ADV duration: 240 weeks*) (*n* = 70)	PA Placebo (48 weeks) ADV 10 mg/day (48 weeks) ADV 10 mg/day (144 weeks) (*Total ADV duration: 192 weeks*) (*n* = 55)	–	Virological response: % pts with undetectable serum HBV DNA ≤ 1000 copies per ml Biochemical response: Normalisation of ALT levels Serological response: HBsAg seroconversion Histological response: Change in Knodell necroinflammation and Ishak fibrosis scores

Study and methods	HBeAg status	No. of participants (*n*), duration of trial (T_d), additional follow-up (F_d) and total duration (total)	Patient characteristics	Group A	Group B	Group C	Outcomes
							Histological response: Assessments of improvement, no change or worsening of necroinflammation and fibrosis *Other measures:* ADV resistance

ALT, alanine aminotransferase; ULN, upper limit of the normal range.

AAA = ADV–ADV–ADV; PAA = placebo–ADV–ADV.

a Median duration of treatment for all participants.

b Results are presented at 6, 12 and 24 months; study is ongoing.

c Patients were taken from a previous long-term study of LAM monotherapy and either switched to ADV or added ADV; details of LAM dosage not reported in this publication.

d Study design was 12 weeks double-blind and randomised to ADV or placebo, then 28 weeks open-label ADV; the original ADV group was then re-randomised to ADV or placebo for 12 weeks and the original placebo group remained on open-label ADV for 12 weeks.

e 52-week results are presented; the study is ongoing for an additional 4 years.

f Log_{10} reduction from baseline.

g Patients were originally randomised to ADV (*n* = 123) or placebo (*n* = 62). The cohort reported in this observational study includes 70 patients who received ADV in double-blind phase one (for 48 weeks), double-blind phase two (from week 49 to week 96) and the observational phase (from week 97 to week 240) (the AAA group); and 55 patients who received placebo in double-blind phase one (for 48 weeks) then switched to ADV at double-blind phase two (from week 49 to week 96) and continued ADV in the observational phase (from week 97 to week 240).

TABLE 2 *Quality assessment – ADV randomised controlled trials*

	Zeng et *al*., 2006[19]	**Rapti et *al*., 2007[18]**
Randomisation	Adequate	Unknown
Concealment of allocation	Partial	Unknown
Baseline characteristics similar	Adequate	Reported
Blinding of assessors	Partial	Unknown
Care provider blinding	Partial	Unknown
Patient blinding	Partial	Unknown
Reporting outcomes	Adequate	Partial
Intention-to-treat analysis	Inadequate	Adequate
Withdrawals explained	Partial	Adequate

weeks' randomised double-blind treatment (the assessment of methodological quality of the original RCT is available in our earlier assessment report[12]). Results for most of the outcomes are presented for all 125 patients in the observational cohort, regardless of study group. The authors report two types of intention-to-treat (ITT) analysis for the analysis of HBV DNA and ALT. In the 'ITT missing equals failure' analysis (ITT; M = F), all patients who discontinued were considered to have failed treatment. In the 'ITT missing equals failure for resistance or HCC' analysis (ITT; M = F R/HCC), patients were considered failures if they (1) harboured HBV with an ADV-resistance mutation and either terminated the study or had LAM added (if a patient had HBV with a resistance mutation and remained in the study on ADV monotherapy, his or her serum HBV DNA and ALT values were included in analyses rather than being deemed failures), or (2) were diagnosed with HCC. Missing values from patients who left the study for other reasons were excluded. The ITT; M = F R/HCC analysis was considered to provide a more realistic view of efficacy as drop-outs unrelated to efficacy are expected in a 5-year trial.

Characteristics of PEG-α-2b studies

Five published RCTs evaluating PEG-α-2b were included, all using similar inclusion and exclusion criteria. Four RCTs evaluated combined treatment of PEG-α-2b plus LAM,[23–26] while one compared PEG-α-2b with IFN-α-2b.[27] The studies had varied regimens and differing aims, as follows:

- Chan and colleagues (2007)[23] included three treatment arms of combined PEG-α-2b, with arms differing in the commencement of LAM. One group received PEG-α-2b for 32 weeks and LAM for 104 weeks concurrently. A second group received PEG-α-2b for 32 weeks, beginning 8 weeks before commencing LAM for 96 weeks. The third group received PEG-α-2b for 32 weeks, beginning 8 weeks after commencing LAM, which they received for 104 weeks. The rationale for this pilot study was to establish if staggered commencement would have a more potent HBV DNA suppression than simultaneous commencement of PEG-α-2b plus LAM, with an extended LAM treatment of up to 2 years.
- Chan and colleagues (2005)[24] compared combined treatment with LAM alone. A separate publication reported long-term sustained virological response outcomes.[28] The rationale was to ascertain if combination therapy increased HBeAg seroconversion rates and improved antiviral efficacy more than did LAM monotherapy.
- Kaymakoglu and colleagues[25] compared PEG-α-2b and LAM with PEG-α-2b alone. The rationale of this trial was to discover if combination therapy could lead to an increased rate of sustained response.
- Janssen and colleagues[26] evaluated combined PEG-α-2b and LAM with PEG-α-2b plus placebo. Separate publications report long-term histology,[29] safety results,[30] and subgroup analyses (e.g. advanced fibrosis versus no advanced fibrosis;[31] genotypes,[32] early responders[33]). The aim was to assess whether combination therapy was associated with

increased rates of sustained response in CHB compared with PEG-α-2b monotherapy.
- Zhao and colleagues[27] compared PEG-α-2b with IFN-α-2b. The authors aimed to establish factors predicting sustained combined response and adverse effects for a lower dose in patients with different genotypes (B versus C), in order to determine the most cost-effective treatment for developing countries with high HBV infection rates.

The key characteristics of the trials are shown in *Table 3*. Two trials were single-centre RCTs[23,24] and three were multicentre studies,[25–27] of which only one trial appeared to take place in more than one country.[26] Two of the RCTs received funding (the Research Fund for the Control of Infections Diseases, Health, Welfare and Food Bureau;[23] the Rotterdam Foundation for Liver Research[26]). Schering–Plough supplied PEG-α-2b to three studies and the same studies also received LAM from GlaxoSmithKline.[23,24,26]

Outcome measures employed by the RCTs were similar, with differences in relation to participants' HBeAg status, such as HBeAg seroconversion rates. Primary outcomes were changes from baseline in rate of serum HBV DNA,[27] HBeAg seroconversion,[24] loss of HBeAg at end of treatment,[26] reduction of HBV DNA[23] and levels of HBV DNA.[25] Secondary outcome measures included ALT normalisation, development of genotypic LAM resistance, histological improvement (necroinflammatory and fibrosis score) using the Knodell score, adverse events and LAM-resistant mutations, as well as assessment of HBsAg and HBV genotypes.

All trials defined CHB by the presence of detectable HBsAg for a minimum of 6 months prior to enrolment. Serum HBV DNA levels were at least 10^5 copies/ml (10^6 in one study[27]) and ALT levels ranged between 1.3 and 10 times the upper limit of the normal range (ULN), although not all of the RCTs stated higher ALT limits.[25,26] Three of the PEG-α-2b studies required participants to be HBeAg positive,[23,24,27] one included both HBeAg-positive and HBeAg-negative patients,[27] and one included HBeAg-negative patients only.[25] The trials generally excluded patients with decompensated/advanced liver disease. A small proportion of participants with cirrhosis were included in two of the studies (4%;[25] 8%[26]). Comorbidities and co-infections were specifically excluded by three RCTs[23,24,26] and were not remarked upon by the others.[25,27]

Trial size varied considerably, ranging from 30 participants[23] to 307.[26] Duration of treatment also varied from 24 to 104 weeks, with an average 24-week follow-up. All trials were carried out on adult patients. While Chan and colleagues[23,24] recruited only treatment-naive participants, two studies included participants with a mixture of prior and no prior treatment.[26,27] Kaymakoglu and colleagues failed to mention prior treatment history.[25] Previous IFN therapy was recorded for 13%[27] and about 20%[26]of participants, while 33% of participants had previous LAM therapy.[26] However, no LAM resistance was reported.

Details of ethnicity were sparse. Chan and colleagues included Chinese participants,[23] while the Kaymakoglu and colleagues trial primarily included white participants (74%) along with 20% Asian and 6% mixed.[25] The mean age of study participants was between 30 and 43 years, and entailed a higher proportion of male participants (range 63–82%).

The methodological quality of the five PEG-α-2b trials was assessed using CRD criteria,[13] and is shown in *Table 4*. Four of the five trials adequately reported the method of randomisation,[23,24,26,27] and three of these adequately reported the concealment of allocation to treatment groups.[23,24,26] The allocation process was unclear in the remaining two studies. All of the included RCTs reported patients' baseline characteristics. Four of these reported that study groups were similar at baseline, with only Zhao and colleagues reporting a difference in previous treatment with interferon therapy between study groups, which was statistically significant ($p < 0.05$).[27]

Only one of the studies adequately described all aspects of blinding,[26] stating, for example, that the placebo was similar in appearance to the study drug and that HBV markers were assessed at a central laboratory, with staff unaware of treatment allocation. Each of the remaining trials was open label. Two of these[23,24] did report some blinding of outcome assessors. For example, in one of the studies, histological specimens were assessed by a single histopathologist who was unaware of the treatment assignments or the times at which the specimens were obtained.[23]

Reporting of primary outcomes was variable across the five studies, with only two adequately reporting point estimates and measures of variability.[25,26] Three studies adequately described an ITT method of data analysis. The other two studies

TABLE 3 *Study characteristics – PEG-α-2b studies*

Study and methods	HBeAg status	No. of participants, duration of trial (T_d), additional follow-up (F_d) and total duration (total)	Patients' characteristics	Group A	Group B	Group C	Outcomes
Chan et *al.*, 2007[23] *Design:* Open-label RCT (pilot study) *Number of centres:* 1 *Country:* China	Positive	*n* = 30 T_d = 104 weeks[a] F_d = 24 weeks Total = 128 weeks	No co-infection with HIV or hepatitis C Chinese Average age: ≈ 32 years Sex: 73% male No previous use of IFN-α or antiviral agents	PEG-α-2b[a] 1.5 μg/kg/week body weight < 65 kg or 100 μg/kg/week body weight > 65 kg + LAM 100 mg daily (*n* = 10)	PEG-α-2b[a] 1.5 μg/kg/week body weight < 65 kg or 100 μg/kg/week body weight > 65 kg + LAM 100 mg daily (*n* = 10)	PEG-α-2b[a] 1.5 μg/kg/week body weight < 65 kg or 100 μg/kg/week body weight > 65 kg + LAM 100 mg daily (*n* = 10)	*Primary outcomes:* Reduction of serum HBV DNA at week 52> *Secondary outcomes:* HBV DNA reduction HBV DNA undetectable by PCR ALT normalisation Development of genotypic LAM resistance up to week 104
Chan et *al.*, 2005[24] *Design:* Phase III, open-label RCT *Number of centres:* 1 *Country:* China	Positive	*n* = 100 (96) T_d = 52 weeks F_d = Arm 1: 60 weeks; Arm 2: 52 weeks Total = Arm 1: 112 weeks (117 ± 34 weeks); Arm 2: 104 weeks (124 ± 29 weeks)	No co-infection with hepatitis C, D or HIV No information provided on ethnic groups Average age: ≈ 33 years Sex: 67% male Treatment-naive patients	PEG-α-2b[b] (subcutaneous injection) 1.5 μg/kg body weight per week; maximum 100 μg for patients over 65 kg + LAM[c] Dose: 100 mg daily (*n* = 50)	LAM (orally) 100 mg daily (*n* = 50)		*Primary outcomes:* Sustained virological response: HBeAg seroconversion and HBV DNA level < 500,000 copies/ml at 24 weeks after cessation of treatment *Secondary outcomes:* End-of-treatment virological and sustained biochemical response Reduction in HBV DNA levels and normalisation of ALT level Histological improvement Knodell scoring system (0–18) and liver fibrosis using the Ishak scoring system (0 –6) Adverse events Sustained HBeAg loss and HBV DNA < 100,000 copies/ml from treatment cessation to end of follow-up

DOI: 10.3310/hta13350

Study and methods	HBeAg status	No. of participants, duration of trial (T_d), additional follow-up (F_d) and total duration (total)	Patients' characteristics	Group A	Group B	Group C	Outcomes
							Other measures: LAM-resistant mutant (serum sample at end of treatment) Liver biopsy (4 weeks prior to and at end of treatment)
Janssen *et al.*, 2005[26] *Design:* Double-blind, RCT *Number of centres:* 42 *Country:* 15 (including Europe, Israel, Canada and Asia)	Positive	$n = 266$ $T_d = 52$ weeks $F_d = 26$ weeks Total = 78 weeks	No co-infection with hepatitis C, D or HIV 74% white; 20% Asian; 6% other/mixed Sex: 77% male 21% had previously used PEG-α < 15% had previously used LAM	PEG-α-2b[d] Dose 1: 100 μg/week Duration: 32 weeks Dose 2: 50 μg/week Duration: 20 weeks (weeks 32–52) + LAM 100 mg/day	PEG-α-2b[d] Dose 1: 100 μg/week Duration: 32 weeks Dose 2: 50 μg/week Duration: 20 weeks (weeks 32–52) + Placebo		*Primary outcomes:* Loss of HBeAg *Secondary outcomes:* Concentration of HBV DNA below 200,000 copies/ml Concentrations of HBV DNA below level of detection Return to normal of ALT concentrations Presence of mutations in YMDD motif of HBV polymerase HBsAg and HBV genotype were also assessed Baseline liver histology (within a year of starting therapy) and optional biopsy sample at end of treatment Histological activity index Necroinflammatory and fibrosis score Adverse events

continued

TABLE 3 *Study characteristics – PEG-α-2b studies (continued)*

Study and methods	HBeAg status	No. of participants, duration of trial (T_d), additional follow-up (F_d) and total duration (total)	Patients' characteristics	Group A	Group B	Group C	Outcomes
Kaymakoglu *et al.*, 2007[25] *Design:* Open-label, RCT *Number of centres:* 8 *Country:* Turkey	Negative	*n* = 48 T_d = 48 weeks F_d = 24 weeks Total = 72 weeks	No information given on co-infection Patients with any other cause of liver disease excluded No information provided on ethnic groups Average age ≈ 43 years Sex: 69% male	PEG-α-2b 1.5 μg/kg body weight/week (*n* = 19)	PEG-α-2b 1.5 μg/kg body weight/week + LAM 100 mg daily (*n* = 29)		*Outcomes:* HBV DNA level ALT level normalisation – both at week 48 and week 72
Zhao *et al.*, 200727 *Design:* RCT *Number of centres:* 6 *Country:* China	Positive	*n* = 230 T_d = 24 weeks F_d = 24 weeks Total = 48 weeks	No information given on co-infection No information provided on ethnic groups Average age ≈ 31 years (median) Sex: 82% male < 20% had previously used IFN-α	PEG-α-2b 1.0 μg/kg/week subcutaneously (*n* = 115)	IFN-α-2b 3 MIU three times/week subcutaneously (*n* = 115)		*Primary outcomes:* Rate of serum HBV DNA < 10^5 copies/ml and < 10^3 copies/ml Mean reduction of serum HBV DNA level (from baseline) Serological response (rate of HBeAg loss and seroconversion, rate of HBsAg seroconversion) Sustained combined response (HBeAg –ve, HBV DNA < 5 $\log_{10}$ copies/ml and normal ALT level at week 48) Normalisation of ALT *Secondary outcomes:* Adverse events

ALT, alanine aminotransferase; MIU, million international units; PCR, polymerase chain reaction; YMDD, tyrosine-methionine-aspartate-aspartate.

a Group A received PEG-α-2b for 32 weeks and LAM for 104 weeks concurrently; Group B received PEG-α-2b for 32 weeks, starting 8 weeks prior to LAM commencement, and LAM for 96 weeks; Group C received PEG-α-2b for 32 weeks, starting 8 weeks after LAM commenced, and LAM for 104 weeks. At week 104, HBeAg-positive patients could continue LAM for a further 28 weeks or discontinue therapy; HBeAg-negative patients at week 104 had treatment stopped.

b Group A received 8 weeks' PEG-α-2b and 24 weeks' PEG-α-2b + LAM, followed by 28 weeks' LAM only. Group A received therapy for 8 weeks longer than Group B

c Open-label LAM given to patients with severe post-treatment relapse of CHB (defined as ALT level > 10 times the ULN and HBV DNA level > 500,000 copies/ml). No patients assigned to Group B received PEG during the study.

d Patients of ≤ 55 kg body weight received weight-adjusted dose of PEG: 1.50 μg/kg/week for first 32 weeks and 0.75 μg/kg/week from week 32 to week 52).

TABLE 4 *Quality assessment – PEG-α-2b randomised controlled trials*

	Chan et *al.*, 2007[23]	**Chan et *al.*, 2005[24]**	**Janssen et *al.*, 2005[26]**	**Kaymakoglu et *al.*, 2007[25]**	**Zhao et *al.*, 2007[27]**
Randomisation	Adequate	Adequate	Adequate	Unknown	Adequate
Concealment of allocation	Adequate	Adequate	Adequate	Unknown	Unknown
Baseline characteristics similar	Adequate	Adequate	Adequate	Adequate	Partial
Blinding of assessors	Partial	Partial	Adequate	Inadequate	Inadequate
Care provider blinding	Unknown	Unknown	Adequate	Inadequate	Inadequate
Patient blinding	Inadequate	Inadequate	Adequate	Inadequate	Inadequate
Reporting outcomes	Inadequate	Partial	Adequate	Adequate	Partial
Intention-to-treat analysis	Inadequate	Adequate	Inadequate	Adequate	Adequate
Withdrawals explained	Adequate	Adequate	Partial	Inadequate	Partial

reported a 'modified' ITT analysis. For example, in Janssen and colleagues' study, 41 (13%) of the 307 randomised patients were excluded from the modified ITT. Of these, 24 patients from one study centre (12 from each arm) were excluded because of 'misconduct'; 10 lost HBeAg before the start of the study; and seven did not receive any study medication. It is unclear whether all of those excluded received at least one dose of the study medication, therefore it is recorded as 'inadequate' in the table.[26]

Withdrawals were fully described in two of the five studies. One study reported early withdrawals, with no other details given. Studies are described in *Table 4* as partially explaining withdrawals where early attrition or withdrawals due to adverse events were reported, but where later losses to follow-up are not fully explained.[26,34]

Assessment of effectiveness

Virological response

Proportion of patients achieving an HBV DNA response – ADV studies

Table 5 presents the proportion of patients achieving a defined threshold of HBV DNA response in the two trials. In the trial by Zeng and colleagues,[19] the proportion of patients whose HBV DNA level dropped below 10^5 copies/ml reached 67% by week 52 in patients treated continuously with ADV [the adefovir–adefovir–adefovir (AAA) group]. For the group who commenced open-label ADV after 12 weeks of placebo [the placebo–adefovir–adefovir (PAA) group], the proportion reached 70% at week 52. For the group who initially received ADV and were then re-randomised to placebo at week 40 [the adefovir–adefovir–placebo (AAP) group], the proportion fell to 11% at week 52, having previously reached 59%. Zeng and colleagues[19] also reported the proportion of patients whose HBV DNA was undetectable, defined as HBV DNA < 300 copies/ml. At week 52, the proportions were similar in the AAA and the PAA groups (28% and 30% respectively). In the AAP group, the proportion fell from 59% at week 40 to 11% by week 52, following the withdrawal of ADV. No statistical tests were reported for any of these comparisons.

In the trial by Rapti and colleagues,[18] the proportion of patients with HBV DNA ≤ 1000 copies/ml after 24 months of therapy was higher in the group treated with ADV and LAM than in the group treated with ADV monotherapy (82.6% versus 75% respectively). However, this difference did not reach statistical significance.

TABLE 5 *Proportion of patients achieving an HBV DNA response – ADV studies*

Study, patient type, outcome	Treatment group			*p*-value
Zeng *et al.*, 2006[19]	**PAA**	**AAA**	**AAP**	
HBeAg +ve				
HBV DNA < 10^5 copies/ml, week 12, *n/N* (%)	4/115 (3)	113/227 (50)	55/116 (47)	NR
HBV DNA < 10^5 copies/ml, week 40, *n/N* (%)	75/115 (65)	147/231 (64)	68/115 (59)	NR
HBV DNA < 10^5 copies/ml, week 52, *n/N* (%)	81/115 (70)	155/231 (67)	13/115 (11)	NR
HBV DNA undetectable, week 12, *n/N* (%)[a]	0/119 (0)	11/232 (5)	7/120 (6)	NR
HBV DNA undetectable, week 40, *n/N* (%)[a]	23/119 (19)	42/236 (18)	23/119 (19)	NR
HBV DNA undetectable, week 52, *n/N* (%)[a]	36/119 (30)	67/236 (28)	1/119 (1)	NR
Rapti *et al.*, 2007[18]	**ADV**	**ADV + LAM**		
HBeAg –ve				
HBV DNA ≤ 1000 copies/ml at 6 months, %	45.5	57.1		0.723
HBV DNA ≤ 1000 copies/ml at 12 months, %	78.6	68		0.713
HBV DNA ≤ 1000 copies/ml at 24 months, %	75	82.6		0.670

a HBV DNA < 300 copies/ml.
PAA = placebo–ADV–ADV; AAA = ADV–ADV–ADV; AAP = ADV–ADV–placebo.

Table 6 presents HBV DNA response rates for all 125 patients in the long-term open-label study.[20] (Note that results after 240 weeks apply only to the ADV–ADV group as the placebo–ADV group commenced ADV only after week 48.)

In the 'ITT missing data = failure for resistance or HCC' analysis (i.e. missing values from patients who left the study for other reasons were excluded), the proportion of patients whose HBV DNA levels were < 1000 copies/ml peaked after 96 weeks, after which they gradually fell to 67%. In the 'ITT missing data = failure' analysis, the proportion peaked after 144 weeks, and fell to 53% after 240 weeks.

In summary, a greater proportion of ADV-treated patients experienced an HBV DNA response relative to comparators, although this was not confirmed statistically. The proportion of responders was generally maintained during long-term treatment.

Proportion of patients achieving an HBV DNA response – PEG-α-2b studies

Table 7 shows the proportion of patients achieving an HBV DNA response as reported in four of the five studies. Response was measured by reductions in HBV DNA levels to a given threshold. Each of the studies of PEG-α-2b used differing thresholds of HBV DNA response. These proportions also vary across the studies.

Chan and colleagues[23] report HBV DNA response for three groups of patients, receiving staggered regimens of PEG-α-2b and LAM. At week 52, Group A had a higher proportion of patients (44%) with negative HBV DNA than either Group B (22%) or Group C (10%). Neither of these differences was statistically significant ($p = 0.62$ and $p = 0.24$). At end of treatment (week 104) Group B had the highest proportion of patients (56%) with negative HBV DNA, compared with Group A (33%) and Group C (40%). Baseline HBV DNA had been significantly lower in this group. At end of follow-

TABLE 6 *Proportion of patients achieving an HBV DNA response – long-term ADV follow-up study*

	Weeks of ADV treatment				
Study, patient type, outcome	**48**	**96**	**144**	**192**	**240[a]**
Hadziyannis *et al.*, 2006[20]					
HBeAg –ve					
HBV DNA < 1000 copies/ml, % of enrolled patients[b]	72	80	77	73	67
HBV DNA < 1000 copies/ml, % of enrolled patients[c]	71	71	73	62	53

HCC, hepatocellular carcinoma; ITT, intention to treat.
a Includes only patients in the ADV–ADV group.
b ITT missing data = failure for resistance or HCC.
c ITT missing data = failure.

TABLE 7 *Proportion of patients achieving an HBV DNA 'response' – PEG-α-2b studies*

Study, patient type, outcome	**Treatment group**			***p*-value**
Chan *et al.*, 2007[23]	**Group A PEG-α-2b +LAM**	**Group B PEG-α-2b + LAM**	**Group C PEG-α-2b +LAM**	
HBeAg +ve				
Negative HBV DNA at week 52, *n/N* (%)	4/9 (44)	2/9 (22)	1/10 (10)	Group B vs Group A: 0.62 Group C vs Group A: 0.24
Negative HBV DNA at week 104, *n/N* (%)	3/9 (33)	5/9 (56)	4/10 (40)	NR
Undetectable HBV DNA at follow-up (week 128), *n/N* (%)	2/9 (22)	1/9 (11)	2/10 (20)	NR
Janssen *et al.*, 2005[26]	**Group A PEG-α-2b + LAM**	**Group B PEG- α-2b + placebo**		
HBeAg +ve				
HBV DNA < 200,000 copies/ml, EOT (week 52), *n/N* (%)	96/130 (74)	40/136 (29)		< 0.0001
HBV DNA < 200,000 copies/ml (week 78), *n/N* (%)	41/130 (32)	37/136 (27)		0.44
HBV DNA < 400 copies/ml (week 52), *n/N* (%)	43/130 (33)	13/136 (10)		< 0.0001
HBV DNA < 400 copies/ml (week 78), *n/N* (%)	12/130 (9)	9/136 (7)		0.43
Kaymakoglu *et al.*, 2007[25]	**Group A PEG-α-2b**	**Group B PEG-α-2b +LAM**		
HBeAg –ve				
HBV DNA < 4 pg/ml, EOT (week 48), *n/N* (%)	12/19 (63)	23/29 (79)		> 0.05
HBV DNA < 4 pg/ml, EOF-U (week 72), *n/N* (%)	7/19(37)	10/29 (34)		> 0.05
HBV DNA < 400 copies/ml, EOF-U (week 72), *n/N* (%)	5/19 (26)	7/29 (24)		>0.05

continued

TABLE 7 *Proportion of patients achieving an HBV DNA 'response' – PEG-α-2b studies (continued)*

Study, patient type, outcome	Treatment group		*p*-value
	Group A	**Group B**	
Zhao et *al*., 2007[27]	**PEG-α-2b**	**IFN**	
HBeAg +ve			
HBV DNA level < 5 $\log_{10}$ copies/ml, EOF-U (week 48), *n/N* (%)	34/115 (29.6)	22/115 (19.1)	0.06
HBV DNA level < 3 $\log_{10}$ copies/ml, EOF-U (week 48), *n/N* (%)	14/115 (12.2)	14/115 (12.2)	1.00

EOF-U, end of follow-up; EOT, end of treatment; NR, not reported; pg, picograms.

up (week 128), Group A had a slightly higher proportion of patients reaching 'undetectable' HBV DNA of 22%, compared with Group B at 11% and Group C at 20%. Statistical significance was not given for these results. Definitions of 'negative' and 'undetectable' are not reported, and so it is unclear how these differ.

The trial by Janssen and colleagues[26] compares a group receiving PEG-α-2b and LAM (Group A), and a group receiving PEG-α-2b and placebo (Group B). At end of treatment (week 52) the proportion of patients in Group A reaching < 200,000 copies/ml was 74%, compared with 29% in Group B ($p < 0.0001$). At end of follow-up this had fallen in Group A to 32% and in Group B to 27% ($p = 0.44$). Thirty-three per cent of patients in Group A at end of treatment reached < 400 copies/ml, compared with 10% in Group B ($p < 0.0001$). This, again, fell by end of follow-up to 9% in Group A and 7% in Group B ($p = 0.43$).

In the trial by Kaymakoglu and colleagues,[25] a higher proportion of patients receiving PEG-α-2b and LAM achieved HBV DNA < 4 pg/ml (picograms per millilitre; in this paper defined as the 'lower limit of detection') at end of treatment (week 48) than of those receiving PEG-α-2b alone: 79% versus 63% respectively. At end of follow-up, the proportions reaching 400 copies/ml were similar for both groups: 24% versus 26%. However, none of these differences was statistically significant.

Zhao and colleagues[27] compared patients receiving PEG-α-2b (Group A) with those taking IFN-α (Group B). A higher proportion of patients in Group A (29.6%) reached < 5 $\log_{10}$ copies/ml at end of follow-up (week 48), compared with 19.1% in Group B ($p = 0.06$). In both groups, 12.2% reached < 3 $\log_{10}$ copies/ml ($p = 1.00$).

In summary, the results of these studies show that there was no significant difference between concurrent and staggered commencement of PEG-α-2b and LAM; and no consistent statistically significant differences between the combination of PEG-α-2b and LAM versus PEG-α-2b monotherapy, or between PEG-α-2b and IFN-α.

Changes in HBV DNA levels – ADV studies

Table 8 reports the median changes in HBV DNA from baseline in the trial by Zeng and colleagues.[27]

At week 12 there was a statistically significant difference between the patients randomised to ADV (the AAA group) and those randomised to placebo (the PAA group) ($p < 0.001$). At week 40, median reductions in HBV DNA appeared to be similar for all three groups (all three had been receiving open-label ADV since week 12). At week 52, median HBV DNA reductions appeared to be similar for the patients who had received ADV continuously (the AAA group) and those who had switched to ADV from placebo after week 12 (the PAA group) (–4.5 and –5.0 $\log_{10}$ copies/ml respectively). However, those who had received ADV until week 40 and were then re-randomised to placebo had a smaller reduction (–0.2 $\log_{10}$ copies/ml).

Changes in HBV DNA levels – PEG-α-2b studies

Changes in HBV DNA levels are shown in *Table 9*.

Chan and colleagues (2007)[23] report the median log HBV DNA reduction from baseline at weeks 4, 8, 52 and 104. The median difference between Group A and Group B was 3.59 (95% CI 1.49–5.65, $p < 0.0001$) at week 4 (at this stage, because of the staggered regimen, Group A was receiving PEG-α-2b and LAM, Group B was receiving PEG-α-2b monotherapy and Group C received LAM

TABLE 8 *Changes in HBV DNA levels – ADV studies*

Study, patient type, outcome	Treatment group			*p*-value
Zeng *et al.*, 2006[19]	**PAA**	**AAA**	**AAP**	
HBeAg +ve				
HBV DNA change (log_{10} copies/ml) from baseline to week 12, median range [25%, 75% (interquartile values)]	–0.1, –5.2 to 3.1 (–0.7 to 0.3)	–3.4, –7.7 to 0.5 (–4.6 to –2.6)	–3.3, –6.8 to –1.0 (–4.3 to –2.7)	< 0.001[a]
HBV DNA change (log_{10} copies/ml) from baseline to week 40, median range [25%, 75% (interquartile values)]	–4.6, –7.7 to 2.0 (–5.6 to –3.1)	–4.2, –8.0 to 0.5 (–5.5 to –3.0)	–4.0, –8.6 to 0.7 (–5.3 to –3.0)	NR
HBV DNA change (log_{10} copies/ml) from baseline to week 52, median range [25%, 75% (interquartile values)]	–5.0, –8.0 to 2.1 (–6.0 to –3.3)	–4.5, –8.0 to 0.7 (–5.8 to –3.1)	–0.2, –6.1 to 2.1(–1.6 to 0.3)	NR

NR, not reported.
a For AAA vs PAA.
PAA = placebo–ADV–ADV; AAA = ADV–ADV–ADV; AAP = ADV–ADV–placebo.

monotherapy). At week 52, the point at which the primary outcome was measured, the difference between Groups A and B was significant (6.38 versus 3.43, $p = 0.030$), but the difference between Groups A and C was not ($p = 0.06$). By end of treatment, week 104, there were no significant differences in median log HBV DNA reduction between any of the groups.

In the trial by Chan and colleagues (2005),[24] there were greater reductions in HBV DNA for combination treatment than for monotherapy. The median difference between groups at end of treatment was reported as 1.24 copies/ml (95% CI 0.78–1.66); however, no statistical tests were reported for this outcome.

The HBV DNA change from baseline in Janssen and colleagues[26] was estimated by the reviewers from a figure in the paper, and showed a similar reduction in mean log HBV DNA copies/ml of 2.3 for Group A and 2.2 for Group B at end of follow-up.

Zhao and colleagues[27] reported the HBV DNA mean reduction from baseline, log_{10} copies/ml at end of treatment and end of follow-up. The difference was significant at week 24 (end of treatment) (Group A 2.22 versus Group B 1.66, $p = 0.03$), but again was not statistically significant by end of follow-up ($p = 0.34$). At end of follow-up, the 'mean reduction' in Group A was -1.4 ± 2.2, and in Group B it was -1.1 ± 2.1, indicating that overall there had been an increase in the HBV DNA level in both groups from baseline.

In summary, the results of the trials show that PEG-α-2b is generally associated with greater reductions in HBV DNA levels than are comparators. This was the case when PEG-α-2b was added to LAM, or vice versa, and for PEG-α-2b versus IFN. However, there were no consistent statistically significant differences between treatments. The results suggested a greater reduction in HBV DNA for those who received concurrent commencement of PEG-α-2b and LAM, but by the end of treatment there were no statistically significant differences between this and the staggered regimens.

Biochemical response (ALT)

ALT normalisation – ADV studies

Table 10 reports the proportion of patients with normal ALT levels in two of the studies.

Four of the trials reported changes in HBV DNA. In the trial by Zeng and colleagues,[19] the proportion of patients with normal ALT appeared similar at week 12 in the groups randomised to receive ADV (42% and 44% in the AAA and AAP groups respectively). There was a statistically significant difference between the AAA and AAP groups combined compared with the group randomised to placebo (the PAA group). The proportion of responders in the AAA and AAP groups remained similar to each other at week 40 after 28 weeks of open-label ADV (73% and 74% respectively). At week 40, in the group randomised to placebo in the first 12 weeks and who had subsequently received open-label ADV for 28 weeks (the PAA group), the proportion of ALT responders was slightly lower than in the other two groups

TABLE 9 *Changes in HBV DNA levels – PEG-α-2b studies*

Study, patient type, outcome	Treatment group			*p*-value
Chan *et al*., 2007[23]	**Group A PEG-α-2b +LAM**	**Group B PEG-α-2b +LAM**	**Group C PEG-α-2b + LAM**	
HBeAg +ve				
Median log HBV DNA reduction, week 4[a,b]	4.21	1.39	2.95	< 0.0001 (Groups A and B) 0.027 (Groups A and C)
Median log HBV DNA reduction, week 8[b,c]	5.46	1.55	3.14	< 0.0001 (Groups A and B) 0.004 (Groups A and C)
Median log HBV DNA reduction, week 52[d]	6.38	3.43	4.44	0.030 (Groups A and B) 0.060 (Groups A and C)
Median log HBV DNA reduction, EOT, week 104[e]	6.13	5.24	5.15	0.20 (Groups A and B) 0.46 (Groups A and C)
Chan *et al*., 2005[24]	**Group A PEG-α-2b + LAM**		**Group B LAM**	
HBeAg +ve				
HBV DNA median $\log_{10}$ reduction, copies/ml (range), EOT[f]	3.89 (1.59–6.35)		2.74 (–0.10 to 5.68)	NR
HBV DNA median $\log_{10}$ reduction, copies/ml (range), week 48[g]	4.65 (–0.84 to 7.83)		3.62 (1.32–7.33)	NR
Janssen *et al*., 2005[26] HBeAg +ve	**Group A PEG-α-2b + LAM**		**Group B PEG-α-2b + placebo**	
HBV DNA change from baseline: mean log HBV DNA, copies/ml (estimated from paper), EOF-U	2.3[h]		2.2[h]	NR
Zhao *et al*., 2007[27]	**Group A PEG-α-2b**		**Group B IFN**	
HBeAg +ve				
Mean reduction of HBV DNA level from baseline, $\log_{10}$ copies/ml week 24 (EOT)	2.22		1.66	0.03
Mean reduction of HBV DNA level from baseline, $\log_{10}$ copies/ml, week 48 (EOF-U) ± SD	–1.4 ± 2.2		–1.1 ± 2.1	0.34

EOF-U, end of follow-up; EOT, end of treatment; NR, not reported.
a Median difference between Groups A and B was 3.59 (95% CI 1.49–5.65) and between Groups A and C was 1.45 (95% CI 0.11–2.78).
b Due to staggered regimes, at weeks 4 and 8, Group A was PEG + LAM, Group B was PEG monotherapy and Group C was LAM monotherapy.
c Median difference between Groups A and B was 3.91 (95% CI 2.06–6.34) and between Groups A and C was 1.95 (95% CI 0.79–3.09).
d Median difference between Groups A and B was 2.07 (95 CI 0.31–3.96) and between Groups A and C was 1.61 (95 CI –0.07–2.08).
e Median difference between Groups A and B was 0.90 (95% CI –1.05 to 2.63) and between Groups A and C was 0.56 (95% CI –0.97 to 2.07).
f Median difference 1.24 (95% CI 0.78–1.66).
g Median difference 1.10 (95% CI 0.55–1.65).
h These results are estimated from a figure in the paper.

TABLE 10 *Proportion of patients with normal ALT – ADV studies*

Study, patient type, outcome	Treatment group			*p*-value
Zeng *et al.*, 2006[19]	**PAA**	**AAA**	**AAP**	
HBeAg +ve[a,b]				
ALT normalisation at week 12, *n/N* (%)	15/108 (14)	92/220 (42)	48/110 (44)	0.001[c]
ALT normalisation at week 40, *n/N* (%)	69/106 (65)	163/223 (73)	81/109 (74)	NR
ALT normalisation at week 52, *n/N* (%)	74/107 (69)	176/224 (79)	23/109 (21)	NR
Rapti *et al.*, 2007[18]	**ADV**	**ADV + LAM**		
HBeAg –ve				
% of patients with ALT ≤ 49 IU/l (ULN) at 24 months	72.7	91		0.304

ALT, alanine aminotransferase; IU/l = international units per litre; NR, not reported; ULN, upper limit of normal.
a ULN was 49 IU/l.
b Subjects with elevated serum ALT at baseline.
c For the AAA and AAP groups combined compared with the PAA group.
PAA, placebo–ADV–ADV; AAA = ADV–ADV–ADV; AAP = ADV–ADV–placebo.

(65%). At week 52, the proportion of responders in the PAA group had increased to 69%, while the proportion of responders of those who had received ADV continuously (the AAA group) had increased to 79%. The proportion of responders fell to 21% in the group re-randomised at week 40 to placebo (the AAP group). No statistical tests were reported for these comparisons.

In the trial by Rapti and colleagues, there was a higher proportion of responders in the group who received ADV and LAM compared with the group that received ADV monotherapy (91% versus 72.7% respectively). However, the difference was not statistically significant.

Table 11 presents HBV DNA response rates for all 125 patients in the long-term open-label study.[20] (Note that results after 240 weeks apply only to the ADV–ADV group as the placebo–ADV group commenced ADV only after week 48.)

The proportion of patients with normal ALT values declined from 75% after 48 weeks to 69% and 59% at week 240 for the 'ITT missing data = failure for resistance or HCC' and 'ITT missing data = failure' analyses respectively.

In summary, a greater proportion of ADV-treated patients experienced ALT normalisation relative to comparators, although this was not always

TABLE 11 *Proportion of patients achieving an HBV DNA response – long-term ADV follow-up study*

	Weeks of ADV treatment				
Study, patient type, outcome	**48**	**96**	**144**	**192**	**240[a]**
Hadziyannis *et al.*, 2006[20]					
HBeAg –ve					
ALT normalisation, % of enrolled patients[b]	75	74	71	73	69
ALT normalisation, % of enrolled patients[c]	75	65	68	63	59

ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; ITT, intention to treat.
a Includes only patients in the ADV–ADV group.
b ITT, missing data = failure for resistance or HCC.
c ITT, missing data = failure.

statistically significant. The proportion of ALT responders was generally maintained during long-term treatment.

ALT normalisation – PEG-α-2b studies
Table 12 reports the proportions of patients with ALT normalisation in the PEG-α-2b studies.

All five of the PEG-α-2b trials reported results of the proportion of patients with ALT normalisation.[23–27] All reported ALT normalisation at end of follow-up, and four also reported results at end of treatment.[23–26] None stated the 'normalisation' threshold used.

In the trial by Chan and colleagues (2007),[23] three groups of patients on staggered regimens of PEG-α-2b and LAM had similar rates of ALT normalisation at end of treatment [Group A 9 (100%), Group B 9 (100%), Group C 9 (90%)]. At end of follow-up these numbers had decreased to Group A 4/9 (44%), Group B 5/9 (56%) and Group C 4/9 (40%). There were no statistical tests reported.

In the study by Chan and colleagues (2005),[24] a slightly higher proportion (90%) of Group A (PEG-α-2b and LAM), had normal ALT levels compared with 78% of Group B (LAM alone) at end of treatment. This was similar at follow-up (Group A 50% versus Group B 30%). No statistical tests were reported for these differences.

The trial by Janssen and colleagues[26] found a significant difference between Group A (PEG-α-2b and LAM) and Group B (PEG-α-2b and placebo) in ALT normalisation at end of treatment (51% and 34% respectively, $p = 0.005$). By end of follow-up, the difference between groups was no longer significant (35% and 32% respectively, $p = 0.60$).

There were no significant differences in the proportions of patients reaching normal ALT levels at end of treatment or end of follow-up in the trial by Kaymakoglu and colleagues.[25] The proportions of patients with normal ALT at these points were slightly higher in Group B (PEG-α-2b and LAM) ($p > 0.05$). Again, these proportions had decreased between end of treatment and end of follow-up, e.g. 53% of patients in Group A (PEG-α-2b) at end of treatment and 42% at end of follow-up.

The proportion of patients reaching ALT normalisation in the trial by Zhao and colleagues[27] was very similar at end of follow-up for the two study groups (33.9% in Group A receiving PEG-α-2b versus 34.8% in Group B receiving IFN-α; $p = 0.93$).

In summary, the proportion of patients with normalised ALT tended to be greater for the combination of PEG-α-2b and LAM compared with either as monotherapy. The proportions were generally similar when comparing different commencement regimens of PEG and LAM, or PEG-α-2b with IFN-α. Rates of normalisation usually fell between end of treatment and follow-up. Few statistically significant differences between treatments were reported.

Changes in ALT levels – ADV studies
Table 13 presents median ALT levels in the two ADV trials which reported this outcome.

In the trial by Zeng and colleagues,[19] median ALT was similar at week 12 in the groups randomised to receive ADV (1.1 × ULN, in both the AAA and AAP groups). Median ALT remained similar in the AAA and AAP groups at week 40, after 28 weeks of open-label ADV (0.7 and 0.9 × ULN respectively). At week 40, in the group randomised to placebo in the first 12 weeks and who had subsequently received open-label ADV for 28 weeks (the PAA group), median ALT was similar to the other two groups (0.9 × ULN). At week 52, median ALT levels remained similar in the PAA and AAA groups, but increased to 3.0 × ULN in the group who were re-randomised to placebo at week 40 (the AAP group). No statistical tests were reported for these comparisons.

In the trial by Rapti and colleagues,[18] median ALT fell to around 24 IU/l in both treatment groups at 24 months of treatment, with no statistically significant difference between groups.

Changes in ALT levels – PEG-α-2b studies
Only one of the PEG-α-2b studies reported this outcome (*Table 14*). In the trial by Chan and colleagues,[24] medial ALT fell to around 60–70 IU/l at 24 weeks' post-treatment follow-up.

HBeAg loss/seroconversion
HBeAg loss/seroconversion – ADV studies
Table 15 presents rates of HBeAg loss and seroconversion for the Zeng and colleagues trial.[19] (This outcome was not reported in the study by Rapti and colleagues,[18] and was not applicable to the study of HBeAg-negative patients in the study by Hadziyannis and colleagues.[20])

TABLE 12 *ALT normalisation – PEG-α-2b studies*

Study, patient type, outcome	Treatment group			*p*-value
Chan *et al.*, 2007[23]	**Group A PEG-α-2b + LAM**	**Group B PEG-α-2b + LAM**	**Group C PEG-α-2b + LAM**	
HBeAg +ve				
Normal ALT levels, EOT (week 104),[a] *n/N* (%)	9/9 (100)	9/9 (100)	9/10 (90)	NR
Normal ALT levels at follow-up (week 128),[a] *n/N* (%)	4/9 (44)	59 (56)	4/10 (40)	NR
Chan *et al.*, 2005[24]	**Group A PEG-α-2b + LAM**	**Group B LAM**		
HBeAg +ve				
Normalisation of ALT levels, EOT, *n/N* (%)[b]	45/50 (90)	39/50 (78)		NR
Normalisation of ALT levels at follow-up (24 weeks after treatment), *n/N* (%)[c]	25/50 (50)	15/50 (30)		NR
Janssen *et al.*, 2005[26]	**Group A PEG-α-2b + LAM**	**Group B PEG-α-2b + placebo**		
HBeAg +ve				
ALT returned to normal, EOT (week 52), *n/N* (%)	66/130 (51)	46/136 (34)		0.005
ALT returned to normal, EOF-U (week 78), *n/N* (%)	46/130 (35)	44/136 (32)		0.60
Kaymakoglu *et al.*, 2007[25]	**Group A PEG-α-2b**	**Group B PEG-α-2b + LAM**		
HBeAg –ve				
ALT normalisation EOT, *n/N* (%)	10/19 (53)	19/29 (66)		> 0.05
ALT normalisation EOF-U, *n/N* (%)	8/19 (42)	14/29 (48)		> 0.05
Zhao *et al.*, 2007[27]	**Group A PEG-α-2b**	**Group B IFN**		
HBeAg +ve				
ALT level normalisation, week 48 *n/N* (%)	39/115 (33.9)	40/115 (34.8)		0.93

ALT, alanine aminotransferase; EOF-U, end of follow-up; EOT, end of treatment; NR, not reported.
a Two patients in Group B and two in Group C had post-treatment ALT reactivation to > 5 times ULN (range 465–1980 IU/l) between weeks 120 and 128.
b Absolute difference 12% points (95% CI –2 to 26).
c Absolute difference 20% points (95% CI 1–39).

At week 52, rates of HBeAg loss and seroconversion were highest for patients randomised to placebo in the first 12 weeks and who then received open-label ADV until week 52 (the PAA group). The authors attribute this to the six cases of HBeAg loss in this group within the first 12 weeks (actual date not recorded) which, it is suggested, represent spontaneous cases. At week 40, 16 of the 114 patients (14%) in the AAP group lost HBeAg. Following re-randomisation to placebo at week 40, nine of them regained HBeAg between week 40 and week 52. The higher rate of seroconversion in the PAA group at week 52 compared with the AAA group is again attributed by the study authors to the six patients who spontaneously seroconverted on placebo in the first 12 weeks. The authors also acknowledged that the seroconversion rate in the AAA group was lower than achieved in other trials. In summary, the results of this study suggest that HBeAg seroconversion rates are generally maintained with continued ADV treatment, and are reduced when treatment is withdrawn.

TABLE 13 *Median ALT – ADV studies*

Study, patient type, outcome	Treatment group			*p*-value
Zeng *et al.*, 2006[19]	**PAA**	**AAA**	**AAP**	
HBeAg +ve				
Median (range) ALT (× ULN), week 12	2.4 (0.1–14.4)	1.1 (0.3–9.1)	1.1 (0.2–5.9)	NR
Median (range) ALT (× ULN), week 40	0.8 (0.2–4.1)	0.7 (0.1–4.4)	0.9 (0.3–30)	
Median (range) ALT (× ULN), week 52	0.7 (0.2–4.0)	0.6 (0.2–5.1)	3.0 (0.2–36.4)	
Rapti *et al.*, 2007[18]	**ADV**	**ADV + LAM**		
HBeAg –ve				
Median ALT at baseline, IU/l (range)	135 (74–608)	108 (52–1004)		0.088
Median ALT at 24 months, IU/l (range)	24 (15–55)	24.5 (12–69)		0.863

ALT, alanine aminotransferase; IU/l = international units per litre; NR, not reported; ULN = upper limit of normal.
PAA, placebo–ADV–ADV; AAA = ADV–ADV–ADV; AAP = ADV–ADV–placebo.

HBeAg loss/seroconversion – PEG-α-2b studies

Table 16 reports the results for HBeAg loss and seroconversion in four of the PEG-α-2b studies. This outcome was not applicable in the trial of HBeAg-negative patients by Kaymakoglu and colleagues.[25] All four trials reports HBeAg seroconversion at end of follow-up; three of these report rates at end of treatment.

Chan and colleagues (2007)[23] compared three groups who received staggered regimens of PEG-α-2b and LAM as described above. At end of treatment (week 104) 56% of patients in Group A, 33% of patients in Group B and 60% of patients in Group C had seroconverted. At week 128, these figures remained the same in Groups A and B and had fallen in Group C to 40%. None of the between-group differences were statistically significant.

Chan and colleagues (2005)[24] report the rate of seroconversion at end of treatment in Group A receiving PEG-α-2b and LAM (8 weeks of PEG-α-2b only, followed by 24 weeks of combination and then 28 weeks of LAM only) compared with Group B receiving LAM alone. In Group A, 60% of patients had seroconverted during the last 28 weeks of LAM therapy; in Group B this figure was 28%. No statistical tests were reported for these results.

Janssen and colleagues[26] reported HBeAg loss and HBeAg seroconversion at end of treatment (week 52) and end of follow-up (week 78). At week 52, 44% of patients in Group A (PEG-α-2b and LAM) lost HBeAg compared with 29% in Group B (PEG-α-2b and placebo) ($p = 0.01$). Also at this time, 25% of patients in Group A and 22% of patients in Group B had seroconverted ($p = 0.52$). At week 78, 35% of patients in Group A and 36% of patients in Group B had lost HBeAg ($p = 0.91$). At this time,

TABLE 14 *Changes in ALT levels – PEG-α-2b studies*

Study, patient type, outcome	Group A PEG-α-2b + LAM	Group B LAM	*p*-value
Chan *et al.*, 2005[24]			
HBeAg +ve			
Median ALT at baseline, IU/l (range)	144 (48–1179)	119 (36–461)	NR
Median ALT at 24 weeks' follow-up, IU/l (range)[a]	60	70	NR

IU/l, international units per litre; NR, not reported.
a Estimated by the reviewers from a graph in the study publication.

TABLE 15 *HBeAg loss and seroconversion – ADV studies*

Study, patient type, outcome	Treatment group		
Zeng *et al.*, 2006[19]	**PAA**	**AAA**	**AAP**
HBeAg +ve			
HBeAg loss at week 12, *n/N* (%)	6/119 (5)	14/239 (6)	6/115 (5)
HBeAg loss at week 40, *n/N* (%)	22/118 (18)	25/233 (11)	16/114 (14)
HBeAg loss at week 52, *n/N* (%)	24/118 (20)	30/233 (13)	10/114 (9)
HBeAg seroconversion at week 12, *n/N* (%)	6/119 (5)	14/229 (6)	6/115 (5)
HBeAg seroconversion at week 40, *n/N* (%)	22/118 (18)	23/233 (10)	13/114 (11)
HBeAg seroconversion at week 52, *n/N* (%)	21/118 (18)	19/233 (8)	8/114 (7)

PAA = placebo–ADV–ADV; AAA = ADV–ADV–ADV; AAP = ADV–ADV–placebo.

38 patients (29%) in Group A and 29 patients (29%) in Group B had seroconverted ($p = 0.92$).

Zhao and colleagues[27] reported that the difference between groups in the rate of HBeAg loss at end of treatment (week 24) was not significant: Group A (PEG-α-2b monotherapy) 22.6% versus Group B (IFN-α monotherapy) 17.4% (actual p-value not reported). At end of follow-up (week 48) this number had decreased in Group B (i.e. some of the patients re-acquired HBeAg; Group A 24.4% versus Group B 13.9%) and the difference was statistically significant ($p = 0.04$). HBeAg seroconversion rates at end of follow-up were 21.7% in Group A and 13.9% in Group B ($p = 0.92$).

In summary, the results for HBeAg seroconversion and loss were mixed. In one trial, higher rates of HBeAg seroconversion were reported for the combination of PEG-α-2b and LAM compared with LAM monotherapy, although these were not confirmed statistically. In another trial, HBeAg seroconversion rates were similar for PEG-α-2b and LAM compared with PEG-α-2b monotherapy. There were higher rates of seroconversion for PEG-α-2b compared with IFN-α, but the difference was not statistically significant. There was also no significant difference between staggered commencement regimens of PEG-α-2b and LAM.

HBsAg loss/seroconversion

HBsAg loss/seroconversion – ADV studies

This outcome was reported in only one of the three ADV studies, the long-term open-label follow-up study by Hadziyannis and colleagues.[20]

Six patients (5%) had HBsAg loss after a median of 196 weeks (range 20–260) of ADV. Five of these patients developed antibody to hepatitis B surface antigen (anti-HBs) at their last measurement.

HBsAg loss/seroconversion – PEG-α-2b studies

Table 17 reports HBsAg loss or seroconversion as reported in three of the PEG-α-2b studies.[24,26,27]

Chan and colleagues[24] reported that five patients in Group A (staggered regimen of PEG-α-2b and LAM) and seven in Group B (LAM alone) underwent HBsAg clearance. No statistical test was reported.

Janssen and colleagues[26] reported results for HBsAg loss and seroconversion at both end of treatment (week 52) and end of follow-up (week 78). The results show very similar, small proportions of patients from each group undergoing HBsAg loss or seroconversion. For example, HBsAg loss at end of treatment had occurred in nine patients (7%) in Group A and in seven (5%) in Group B ($p = 0.54$). By end of follow-up this was nine (7%) in both groups ($p = 0.92$).

In the trial by Zhao and colleagues,[27] none of the patients in Group A (receiving PEG-α-2b alone) had experienced HBsAg seroconversion, compared with two (1.7%) in Group B (receiving IFN therapy alone). This difference was not statistically significant ($p = 0.50$).

In summary, rates of HBsAg loss/seroconversion were comparatively low (< 15%) and there were no consistent statistically significant differences between treatment groups. However, statistical differences are less likely to be reported for a relatively rare outcome.

TABLE 16 *HBeAg loss and seroconversion – PEG-α-2b studies*

Study, patient type, outcome	Treatment group			*p*-value
Chan *et al*., 2007[23]	**Group A PEG-α-2b + LAM**	**Group B PEG-α-2b + LAM**	**Group C PEG-α-2b + LAM**	
HBeAg +ve				
Rate of HBeAg seroconversion, week 52, *n*/*N* (%)	6/9 (67)	3/9 (33)	1/10 (10)	0.35 (Groups A and B) 0.037 (Groups A and C)
Rate of HBeAg seroconversion, EOT (week 104), *n*/*N* (%)	5/9 (56)	3/9 (33)	6/10 (60)	0.64 (Groups A and B) 1.00 (Groups A and C)
Rate of HBeAg seroconversion at follow-up (week 128), *n*/*N* (%)	5/9 (56)	3/9 (33)	4/10 (40)	0.64 (Groups A and B) 0.83 (Groups A and C)
Chan *et al*., 2005[24]	**Group A PEG-α-2b + LAM**	**Group B LAM**		
HBeAg +ve				
Rate of HBeAg seroconversion, week 8 (before commencement of LAM in Group A), *n*/*N* (%)	9/50 (18)	0/50		NR
Rate of HBeAg seroconversion, week 32 (after 24 weeks of LAM in both groups), *n*/*N* (%)	20/50 (40)	11/50 (22)		NR
Rate of HBeAg seroconversion, last 28 weeks of extended LAM, *n*/*N* (%)	30/50 (60)	14/50 (28)		NR
Janssen *et al*., 2005[26]	**Group A PEG-α-2b + LAM**	**Group B PEG-α-2b + placebo**		
HBeAg +ve				
HBeAg loss, EOT (week 52), *n*/*N* (%)	57/130 (44)	40/136 (29)		0.01
HBeAg loss, EOF-U (week 78), *n*/*N* (%)	46/130 (35)	49/136 (36)		0.91
HBeAg seroconversion, EOT (week 52), *n*/*N* (%)	33/130 (25)	30/136 (22)		0.52
HBeAg seroconversion, EOF-U (week 78), *n*/*N* (%)	38/130 (29)	39/136 (29)		0.92
Zhao *et al*., 2007[27]	**Group A PEG-α-2b**	**Group B IFN**		
HBeAg +ve				
HBeAg loss, EOT (week 24), *n*/*N* (%)	26/115 (22.6)	20/115 (17.4)		NS
HBeAg loss, EOF-U (week 48), *n*/*N* (%)	28/115 (24.4)	16/115 (13.9)		0.04
HBeAg seroconversion, EOF-U (week 48), *n*/*N* (%)	25/115 (21.7)	16/115 (13.9)		0.12

EOF-U, end of follow-up; EOT, end of treatment; NR, not reported; NS, not significant.

Liver histological response

Of the three ADV trials, only the long-term open-label ADV study[20] reported this outcome. *Table 18* presents histological results for a subset of 45 patients who had a liver biopsy at the end of the study. (Note that there is a discrepancy in the journal publication for this study, such that the total number of patients is reported as being 45 as well as 44.)

Compared with pre-treatment biopsy, there were improvements in necroinflammation in the range of 83–86% of patients, and in improvements in fibrosis in the range of 73–75% of patients. There were similar reductions in median Knodell necroinflammation scores (in the range –5.0 to –4.5 points) and in median Ishak fibrosis scores.

Liver histological response – PEG-α-2b studies

Liver histological response, as reported in three of the PEG-α-2b studies,[23,24,26] is shown in *Table 19*. One of these trials reported using both the Ishak and the Knodell classification systems,[24] another used the Ishak system[26] and the third trial did not state which system was used.[23]

Chan and colleagues (2007)[23] reported no significant differences across their three groups receiving staggered regimens of PEG-α-2b and LAM (described above), although group B had a slightly lower proportion of patients for each change: six (75%) for both necroinflammation improvement and fibrosis change, compared with eight (89%) in Group A for both results, and eight (89%) and nine (100%) in Group C for necroinflammation and fibrosis change respectively.

In the trial by Chan and colleagues (2005),[24] the results across groups were again broadly similar, for both improvements and worsening in the necroinflammatory score; e.g. four (10%) in Group A (PEG-α-2b) versus four (9%) in Group B (LAM) for a ≥ 2-point decrease in this score. For both improvement and worsening in fibrosis scores, Group A had the highest proportion of patients: six (15%) versus four (9%) for a ≥ 2-point decrease, for example. No *p*-values are reported for these results.

Janssen and colleagues[26] reported improvement, no change and deterioration for both fibrosis and inflammation. A higher proportion in Group A (PEG-α-2b and LAM) improved their fibrosis scores: 33% versus 22% in Group B (PEG-α-2b and placebo). A higher proportion in Group B experienced no change, and the proportions were equal for deterioration (38% in each group). There was no statistically significant difference between groups for improvement or no change versus worsening ($p = 0.22$).

This pattern was reversed for the inflammation results, with Group B having a higher proportion of patients with improvement. The groups were again equal for the proportion that deteriorated. Again, the differences between groups for improvement and no change versus worsening were not statistically significant. The authors of this study advise caution with these results as post-treatment biopsies were optional and selection bias may have occurred.[26]

A follow-up paper to this study[29] reported the improvements in necroinflammatory and fibrosis scores (mean ± SD, range) and these are presented in *Table 19*. Results show that Group B had a smaller reduction in necroinflammatory score than Group A (–1.5 and –1.7 respectively). While the improvements in these scores within groups were significant, no *p*-value is given for the difference between groups. This is repeated for the changes in fibrosis score, where again improvements within the groups were significant, but the difference between groups in improvements was not ($p = 0.59$).

In summary, there were mixed results for liver histology. In some instances, differences between treatments in necroinflammation and fibrosis favoured PEG-α-2b and LAM combination therapy, while in other instances, PEG-α-2b or LAM monotherapy appeared more favourable. Where statistical tests were reported there were no significant differences between treatments.

Combined outcomes

Combined outcomes – ADV studies

None of the ADV studies reported combined outcome measures.

Combined outcomes – PEG-α-2b studies

Table 20 reports results for the two PEG-α-2b trials that reported combined outcome measures. In the trial by Chan and colleagues,[24] a virological response was defined as HBeAg seroconversion, detection of antibody to HBeAg and HBV DNA level < 500,000 copies/ml and normalisation of ALT. In a follow-up study,[28] sustained virological response (SVR) was defined as persistent HBeAg

TABLE 17 *HBsAg loss and seroconversion – PEG-α-2b studies*

Study, patient type, outcome	Treatment group		*p*-value
	Group A	***Group B***	
Chan et al., 2005[24]	***PEG-α-2b + LAM***	***LAM***	
HBeAg +ve			
HBsAg clearance, *n/N*	5/50	7/50	NR
	Group A	**Group B**	
Janssen et *al*., 2005[26]	**PEG-α-2b + LAM**	**PEG- α-2b + placebo**	
HBeAg +ve			
HBsAg loss, EOT (week 52), *n/N* (%)	9/130 (7)	7/136 (5)	0.54
HBsAg loss, EOF-U (week 78), *n/N* (%)	9/130 (7)	9/136 (7)	0.92
HBsAg seroconversion, EOT (week 52), *n/N* (%)	8/130 (6)	6/136 (4)	0.53
HBsAg seroconversion, EOF-U (week 78), *n/N* (%)	9/130 (7)	7/136 (5)	0.54
	Group A	**Group B**	
Zhao et *al*., 2007[27]	**PEG-α-2b**	**IFN**	
HBeAg +ve			
HBsAg seroconversion, *n/N* (%)	0/115 (0)	2/115 (1.7)	0.50

EOF-U, end of follow-up; EOT, end of treatment; NR, not reported.

TABLE 18 *Histological results – long-term ADV follow-up study*

	Study group	
Study, patient type, outcome	**240 weeks, ADV–ADV (*n* = 24)**	**192 weeks, placebo–ADV (*n* = 22)**
Hadziyannis et *al*., 2006[20]		
HBeAg –ve		
Ranked assessment		
Improved necroinflammation, %	83	86
Improved fibrosis, %	75	73
Median change in Knodell necroinflammation score from baseline	–5.0 points	–4.5 points
Median change in Ishak fibrosis score	–1.0 points	–1.0 points
% improvement in Ishak fibrosis score[a]	71	55

a Proportion of patients with at least a 1-point improvement in Ishak fibrosis score.

TABLE 19 *Liver histological response – PEG-α-2b studies*

Study, patient type, outcome	Treatment group			*p*-value
Chan *et al.*, 2007[23]	**Group A PEG-α-2b + LAM**	**Group B PEG-α-2b + LAM**	**Group C PEG-α-2b + LAM**	
HBeAg +ve				
Necroinflammatory score, ≥ 2-point improvement, week 104, *n*/*N* (%)	8/9 (89)	6/8 (75)	8/9 (89)	Group A vs Group B: 0.91 Group A vs Group C: 1.00
Fibrosis score, ≤ 1-point change, week 104, *n*/*N* (%)	8/9 (89)	6/8 (75)	9/9 (100)	Group A vs Group B: 0.91 Group A vs Group C: 1.00
Chan *et al.*, 2005[24]	**Group A PEG-α-2b + LAM**	**Group B LAM**		
HBeAg +ve				
≥ 2-point increase in necroinflammatory score, EOT, *n*/*N* (%)[a]	24/40 (60)	26/44 (59)		NR
≥ 2-point decrease in necroinflammatory score, EOT, *n*/*N* (%)	4/40 (10)	4/44 (9)		NR
≥ 2-point increase in fibrosis scores, EOT, *n*/*N* (%)[b]	6/40 (15)	4/44 (9)		NR
≥ 2-point decrease in fibrosis scores, EOT, *n*/*N* (%)[c]	4/40 (10)	2/44 (5)		NR
Janssen *et al.*, 2005[26]	**Group A PEG-α-2b + LAM**	**Group B PEG-α-2b + placebo**		
HBeAg +ve				
Fibrosis[f]				
Improvement, EOT (week 52), *n*/*N* (%)	17/52 (33)	13/58 (22)		0.22 for improvement or no change vs worsening
No change, EOT (week 52), *n*/*N* (%)	15/52 (29)	23/58 (40)		
Deteriorated, EOT (week 52), *n*/*N* (%)	20/52 (38)	22/58 (38)		
Inflammation[d]				
Improvement, EOT (week 52), *n*/*N* (%)	25/52 (48)	31/58 (53)		0.57 for improvement or no change vs worsening
No change, EOT (week 52), *n*/*N* (%)	22/52 (42)	21/58 (36)		
Deteriorated, EOT (week 52), *n*/*N* (%)	5/52 (10)	6/58 (10)		
Necroinflammatory score, EOT (week 52)[e]				
Pre-treatment, mean ± SD (range)	5.4 ± 2.0 (2–9)	5.6 ± 2.2 (1–10)		<0.001 for pre-treatment vs post-treatment
Post-treatment, mean ± SD (range)	3.7 ± 2.0 (1–8)	4.1 ± 1.8 (1–9)		
Change, mean ± SD (range)	–1.7 ± 2.6 (–7 to 3)	–1.5 ± 2.3 (–7 to 4)		

continued

TABLE 19 *Liver histological response – PEG-α-2b studies (continued)*

Study, patient type, outcome	Treatment group		*p*-value
Fibrosis score, EOT (week 52)[f]			
Pre-treatment, mean ± SD (range)	2.6 ± 1.5 (0–6)	2.3 ± 1.6 (0–6)	Group A: 0.23 for pre-treatment vs post-treatment
Post-treatment, mean ± SD (range)	2.8 ± 1.8 (0–6)	2.7 ± 1.6 (0–6)	Group B: 0.07 for pre-treatment vs post-treatment
Change, mean ± SD (range)	0.2 ± 1.4 (–3 to 3)	0.4 ± 1.5 (–2 to 5)	

EOF-U, end of follow-up; EOT, end of treatment; NR, not reported.
a Absolute difference 1% point (95% CI –20 to 22).
b Absolute difference 6% points (95% CI –8 to 20).
c Absolute difference 5% points (95% CI –6 to 17).
d Improvement in histology was defined as a decrease of ≥ 2 points for the necroinflammatory score (range 0–18) and 1 point for the fibrosis score (range 0–6); worsening was defined as an increase of ≥ 2 points for the necroinflammatory score and 1 point for the fibrosis score.
e Overall mean necroinflammatory score improved by 1.6 points, a significant improvement in both groups ($p < 0.001$). Largest improvements were in focal inflammation (mean 0.7 points) and interface hepatitis (mean 0.6 points). Necroinflammation score improved in 51% of patients (decrease ≥ 2 points) and only 10% showed worsening (increase ≥ 2 points). Inflammation improved in 48% of patients in Group A and 53% of patients in Group B ($p = 0.57$).
f Overall mean fibrosis score increased by 0.3 points ($p = 0.03$). Fibrosis score improved in 27% of patients (decrease ≥ 2 points). Improvement in fibrosis was found in 33% of patients in Group A and 22% of patients in Group B ($p = 0.23$), while mean fibrosis score increased by 0.2 points in Group A and by 0.4 points in Group B ($p = 0.59$).

loss and HBV DNA < 100,000 copies/ml from treatment cessation until the end of follow-up (up to 124 weeks). In the Zhao and colleagues trial,[27] a 'sustained combined response' was defined as serum HBV DNA level < 10^5 copies/ml, HBeAg loss and normal ALT levels.

In the study by Chan and colleagues,[24] 60% of patients taking the combination of PEG-α-2b and LAM (Group A) achieved the virological response at week 52, compared with 28% in the LAM group (Group B) ($p = 0.001$). Results are also given for SVR at both follow-up and long-term follow-up. A higher proportion of patients in Group A (18/50, 36%) achieved an SVR at 24 weeks' follow-up than of those in Group B (7/50, 14%) ($p = 0.011$). At end of long-term follow-up, these numbers decreased in Groups A and B (29% and 8% respectively). No statistical test is reported for this difference.

In the trial by Zhao and colleagues,[27] a slightly higher proportion of patients receiving PEG-α-2b (17.4%) achieved the sustained combined response than of those receiving IFN-α (10.4%). This difference was not statistically significant.

Viral resistance

Viral resistance – ADV studies

Table 21 presents rates of viral resistance in two of the ADV studies.

No participants in the trial by Zeng and colleagues[19] developed a resistance to ADV during the course of the study. Those included in analysis for resistance were patients with an increase in serum HBV DNA of at least 1 $\log_{10}$ copies/ml while on ADV from their lowest point during treatment and therefore had isolates analysed for the presence of ADV associated-mutations at week 52. These totalled 45 in the study, and are distributed among treatment groups as shown *Table 21*.

In the trial by Rapti and colleagues,[18] a higher proportion of patients (21%) developed resistance in the group receiving ADV alone, compared with 0% of patients in the groups receiving ADV and LAM combination therapy. This difference was statistically significant ($p = 0.0182$).

Table 22 presents HBV DNA response rates for all 125 patients in the long-term open-label study.[20] (Note that results after 240 weeks apply only to the ADV–ADV group as the placebo–ADV group only commenced ADV after week 48.)

The incidence of three definitions of resistance was measured: (1) ADV resistance mutations (N236T or A181V); (2) ADV-resistant mutations with HBV DNA increased from nadir by at least 1 $\log_{10}$ copies/ml (confirmed or last measurement) or never suppressed to less than 3 $\log_{10}$ copies/ml

('virological resistance'); and (3) ADV resistance mutations with virological resistance and ALT elevations (ALT greater than ULN after normalising ALT; 'clinical resistance'). At 240 weeks of ADV treatment, the cumulative probabilities of ADV resistance were 29%, 20% and 11% for the three definitions of resistance respectively.

In summary, rates of ADV reported in these studies were relatively low and tended to remain so over long-term treatment.

Viral resistance – PEG-α-2b studies

Table 23 presents rates of LAM resistance rates in three of the four PEG-α-2b trials that included LAM.[23–26]

Chan and colleagues (2007)[23] reported low rates of LAM resistance. In Group C there were two patients with LAM resistance, compared with one patient in each of Groups A and B at week 104 (end of treatment).

In the trial by Chan and colleagues (2005),[24] a higher proportion of patients exhibited LAM resistance in the group receiving LAM monotherapy than in the group receiving PEG-α-2b and LAM (40% versus 21%). No statistical test was reported for these results.

In the trial by Janssen and colleagues,[26] 14 patients (11%) in Group A (PEG-α-2b and LAM) exhibited LAM resistance at the end of treatment. The comparison group in this trial did not receive LAM. Seven of the 14 had previously been treated with LAM and had a mutant from the start of therapy.

In summary, the addition of LAM to PEG-α-2b was associated with lower rates of LAM resistance, although this was not confirmed statistically.

Adverse events

Adverse events – ADV studies

Table 24 reports dose discontinuations, reductions and incidence of serious adverse events in the ADV studies.

Zeng and colleagues[19] reported that two patients in the AAA group and one patient in the AAP group discontinued the study drug because of adverse events. The authors state that adverse events were similar in nature and severity between treatment groups. No patients died during the trial. The authors stated that adverse events rarely occurred at a frequency of 5% or greater in any treatment group. The incidence of CHB-related adverse events was reported, with 9% in the AAP group, compared with < 1% in the AAA and PAA groups.

TABLE 20 *Combined outcomes – PEG-α-2b studies*

Study, patient type, outcome	Treatment group		*p*-value
	Group A	**Group B**	
Chan *et al.*, 2005[24]	**PEG-α-2b + LAM**	**LAM**	
HBeAg +ve			
HBV DNA virological response, EOT (week 52), *n*/*N* (%)	30/50 (60)	14/50 (28)	0.001
HBV DNA virological response, week 48, *n*/*N* (%)	25/50 (50)	14/50 (28)	NR
SVR at follow-up (24 weeks after treatment), *n*/*N* (%)	18/50 (36)	7/50 (14)	0.011
SVR at long-term follow-up, *n*/*N* (%)	14/48 (29)	4/47 (8)	NR
	Group A	**Group B**	
Zhao *et al.*, 2007[27]	**PEG-α-2b**	**IFN**	
HBeAg +ve			
Sustained combined response at week 48 *n*/*N* (%)	20/115 (17.4)	12/115 (10.4)	0.13

EOT, end of treatment; NR, not reported; SVR, sustained virological response.

TABLE 21 *Viral resistance – ADV studies*

Study, patient type, outcome	Treatment group			*p*-value
Zeng *et al.*, 2006[19]	**PAA**	**AAA**	**AAP**	
HBeAg +ve[a]				
Viral resistance at week 52, N236T or A181V mutation, *n/N*	0/11	0/28	0/6	
Rapti *et al.*, 2007[18]	**ADV**	**ADV + LAM**		
HBeAg –ve				
Genotypic ADV resistance, %	21	0		0.0182

PAA = placebo–ADV–ADV; AAA = ADV–ADV–ADV; AAP = ADV–ADV–placebo.
a A total of 45 subjects (28 from AAA, 11 from PAA and 6 from AAP) had an increase in serum HBV DNA of at least 1 $\log_{10}$ copies per ml while on ADV from their lowest point during treatment and therefore had isolates analysed for the presence of ADV-associated mutations at week 52.

The authors report that these events all occurred after patients in the AAP group were randomised to placebo at week 40.

There were no dose discontinuations in the trial by Rapti and colleagues,[18] but two patients in the group receiving ADV and LAM had their ADV dose reduced, compared with zero reductions in the ADV monotherapy group. Three patients experienced HCC during the course of the trial, all in the ADV and LAM group. There was no statistically significant difference between groups ($p = 0.545$). Only serious adverse events were reported.

In summary, the incidence of adverse events was low and generally similar between treatment groups.

Adverse events – PEG-α-2b studies

Table 25 reports dose discontinuations, reductions and incidence of serious adverse events in the PEG-α-2b studies.

Chan and colleagues (2007)[23] compared three groups receiving staggered regimens of PEG-α-2b and LAM as described above. Two patients in both Group A and Group C had their dose of PEG-α-2b halved owing to neutropenia ($0.7–0.9 \times 10^9$/ml) at doses 6–19. While no patients in Group B had a dose reduction, one experienced a serious adverse event (hysterectomy for menorraghia). The authors state that this was unrelated to the study drug, and the study medication was uninterrupted. No patients in this study died. Each of the groups in this trial experienced generally similar numbers of adverse events; however, Group B (receiving PEG-α-2b for 8 weeks prior to commencing LAM) experienced the fewest adverse events. The largest apparent difference was in upper respiratory tract symptoms, where one incident occurred in Group B, compared with five (50%) in Group A and seven (70%) in Group C (not shown in *Table 25*; for more information refer to Appendix 1).

In the trial by Chan and colleagues (2005),[24] Group A (PEG-α-2b and LAM) had a larger proportion

TABLE 22 *Drug resistance – long-term open-label ADV study*

	Weeks of ADV treatment				
Study, patient type, outcome	**48**	**96**	**144**	**192**	**240**
Hadziyannis *et al.*, 2006[20]					
HBeAg –ve					
Mutation, % of enrolled patients	0	3	11	18	29
Mutation with virological resistance, % of enrolled patients	0	3	8	14	20
Mutation with virological resistance and ALT elevation (clinical resistance), % of enrolled patients	0	2	6	10	11

TABLE 23 *Viral resistance – PEG-α-2b studies*

Study, patient type, outcome	Treatment group			*p*-value
	Group A	**Group B**	**Group C**	
Chan *et al*., 2007[23]	**PEG-α-2b +LAM**	**PEG-α-2b +LAM**	**PEG-α-2b +LAM**	
HBeAg +ve				
Resistance to LAM at week 104, rtM204V, *n/N*	1/9	1/8	1/9	NR
Resistance to LAM at week 104, rtL108M and rtM205I, *n/N*	0	0	1/9	NR
	Group A	**Group B**		
Chan *et al*., 2005[24]	**PEG-α-2b + LAM**	**LAM**		
HBeAg +ve				
LAM-resistant mutants, EOT, *n/N* (%)[a]	10/48 (21)	19/48 (40)		NR
	Group A	**Group B**		
Janssen *et al*., 2005[26]	**PEG-α-2b + LAM**	**PEG-α-2b + placebo**		
HBeAg +ve				
YMDD mutation (resistance to LAM), EOT, *n/N* (%)	14/130 (11)	Not applicable		

EOT, end of treatment; NR, not reported; YMDD, tyrosine-methionine-aspartate-aspartate.
a Absolute difference 19% points (CI 8–37).

TABLE 24 *Adverse events – ADV studies*

Study, patient type, outcome	Treatment group			*p*-value
Zeng *et al*., 2006[19]	**PAA**	**AAA**	**AAP**	
HBeAg +ve				
Dose discontinuation for any adverse event, *n/N*		2/240	1/120	NR
Incidence of hepatitis B-related adverse events, %	< 1	< 1	9[a]	NR
Rapti *et al*., 2007[18]	**ADV**	**ADV + LAM**		
HBeAg –ve				
Dose discontinuation for any adverse event, *n/N*	0/14	0/28		NR
Dose reduction for any adverse event, *n/N*	0/14	2/28[b]		NR

a All events occurred after re-randomisation to placebo at week 40.
b ADV dose reduced to 10 mg every other day.
PAA = placebo–ADV–ADV; AAA = ADV–ADV–ADV; AAP = ADV–ADV–placebo.

than Group B (LAM monotherapy) of patients discontinuing the study drug (4 versus 0), dose reduction (5 versus 0) and serious adverse events (4 versus 0). The authors report that most adverse events were transient and related to the use of PEG-α-2b. No patient died or required liver transplantation. Reduction of the PEG-α-2b dose to 50 µg/week (if body weight > 65 kg) or 1.0 µg/kg/week if < 65kg) was due to anaemia ($n = 1$), neutropenia ($n = 3$) and/or thrombocytopenia ($n = 4$). PEG-α-2b was discontinued in all four cases of serious adverse events, which were: bipolar disorder, pulmonary tuberculosis, thyrotoxicosis and severe local reaction at injection sites. Three patients continued with LAM through to week 60, while the fourth patient withdrew from the study and was considered a treatment failure.

The most common adverse events in Groups A and B were upper respiratory tract symptoms, which

TABLE 25 *Adverse events – PEG-α-2b studies*

Study, patient type, outcome	Treatment group			*p*-value
Chan et *al*., 2007[23]	**Group A PEG-α-2b + LAM**	**Group B PEG-α-2b + LAM**	**Group C PEG-α-2b + LAM**	
HBeAg +ve				
Dose reduction for any adverse event, *n*/*N*	2/9	0/8	2/9	NR
Serious adverse event, *n*/*N*	0/9	1/8	0/9	NR
Total number of adverse events, *n*	42	34	45	
Chan et *al*., 2005[24]	**Group A PEG-α-2b + LAM**	**Group B LAM**		
HBeAg +ve				
Dose discontinuation (PEG-α-2b) for any adverse event, *n*/*N* (%)	4/40 (8)	0/44		NR
Dose reduction (PEG-α-2b) for any adverse event, *n*/*N* (%)	5/40 (10)	0/44		NR
Serious adverse events, *n*/*N* (%)	4/40 (8)	0/44		NR
Total number of adverse events, *n*	429	55		NR
Janssen et *al*., 2005[26]	**Group A PEG-α-2b + LAM**	**Group B PEG-α-2b + placebo**		
HBeAg +ve				
Dose reduction (PEG-α-2b) for any adverse event, *n*/*N* (%)	37/148 (54)	32/152 (47)		NS
Blinded drug reduction	–	0		
Blinded drug discontinuation	–	24		
Incidents of common adverse events, *n*	557	539		
Kaymakoglu et *al*., 2007[25]	**Group A PEG-α-2**	**Group B PEG-α-2b + LAM**		
HBeAg –ve				
Dose discontinuation for any adverse event, *n*/*N*	0/19	0/29		
Dose reduction for any adverse event, *n*/*N*	0/19	0/29		
Zhao et *al*., 2007[27]	**Group A PEG-α-2b**	**Group B IFN**		
HBeAg +ve				
Dose discontinuation for any adverse event, *n*/*N*	0/115	4/115		NR
Dose reduction for any adverse event, *n*/*N* (%)	0/115	0/115		
Adverse events experienced (%)	75	75		

NR, not reported; NS, not significant.

included cough, running nose and sore throat. Group A had a higher proportion of patients experiencing adverse events across all types, and all of these differences between the two groups were statistically significant, apart from vomiting and diarrhoea, weight loss > 10% and abdominal discomfort (not shown in *Table 25*, for more information refer to Appendix 1).

A follow-up publication[30] of the trial by Janssen and colleagues[26] reported that a slightly higher percentage of patients in Group A (PEG-α-2b and LAM) than Group B (PEG-α-2b and placebo) had the dose of PEG-α-2b reduced for any adverse event: 37 (54%) and 32 (47%) respectively. There was no significant difference between treatment groups, for these and for all side effects. The authors of this study reported discontinuations of PEG-α-2b across the two groups of patients (28, 9%) but not how these were distributed between groups. Neutropenia was the most common reason for dose reduction in this trial ($n = 36$, 52%). The most common reason for early discontinuation was local reaction ($n = 10$, 36%). There were no dose reductions of LAM or placebo. Fifty per cent of the dose reductions occurred within the first 10 weeks, with numbers of dose reductions decreasing thereafter and only two reported after week 32, when the scheduled dose reduction took place. Discontinuation of therapy was reported more frequently before the scheduled dose reduction of PEG-α-2b at week 32.

There were 33 serious adverse events in the trial by Janssen and colleagues;[26] the authors state that 17 (53%) were probably related to therapy, and that all were reversible after treatment had stopped. The frequency of all side effects is reported as not being statistically significant between groups.

Kaymakoglu and colleagues[25] reported that no patients from either treatment group had their dose reduced or discontinued for any adverse event. Of the adverse events experienced, 71% were of flu-like symptoms. The authors do not comment on severity or likelihood of relation to the study drug.

The study drug was discontinued in four patients in the group receiving IFN-α, and in no patients in the group receiving PEG-α-2b in the trial by Zhao and colleagues.[27] There were no dose reductions in either group. The authors report that 75% of patients in each group experienced 'various forms' of drug-related adverse events, the most common of which, again, were flu-like symptoms and fever.

In summary, there were mixed findings for adverse events. In some trials, the incidence of events and dose discontinuations was generally similar between treatments. In at least one trial, there was a higher incidence of events and discontinuations for PEG-α-2b and LAM compared with LAM. Common adverse events included flu-like symptoms and upper respiratory tract infections.

Chapter 4
Economic analysis

Methods for economic analysis

The aim of this section is to provide an update of the cost-effectiveness assessment of PEG-α and ADV in our original report.[12] The economic analysis comprises:

- a systematic review of the 2005–7 publications on the cost-effectiveness of PEG-α and ADV
- an update of our previously published economic model.[12]

Systematic review of economic evaluations

Search strategy

This review was guided by the general principles for conducting a systematic review outlined in the CRD Report 4.[13] Details on the literature search methods to identify published economic evaluations are described in Chapter 2.

Titles and abstracts of studies identified by the search strategy were independently assessed for potential eligibility by two health economists. Full economic evaluations were eligible for inclusion if they reported on the cost-effectiveness of PEG-α (2a and 2b) and/or ADV versus the specified comparators (IFN-α and LAM or best supportive care) in adults with CHB. Studies reporting the economic evaluation of comparator treatments were also identified. In addition, recently published studies on health-related quality of life in patients with CHB were considered for potential use in the update of our economic model (see below). Health-related quality of life literature searches were run in MEDLINE, PREMEDLINE, EMBASE and PsycINFO Ovid databases. The searches were limited to 2005 to September 2007 and to English language only.

Data extraction strategy

Data were extracted from the included cost-effectiveness studies using a standardised template. Data extraction was undertaken by one reviewer and checked by a second, with any disagreements resolved through discussion. Full data extraction forms of all the included studies can be found in Appendix 4.

Quality assessment strategy

Economic evaluations were assessed using the critical appraisal checklist for economic evaluations. The checklist was consistent with methodology proposed by Drummond and colleagues[36] and Philips and colleagues[37] for assessing good practice in decision-analytic modelling in published economic evaluations. See Appendix 4 for details.

Results of the systematic review: cost-effectiveness

Our previously published assessment report[12] included:

- one fully published economic evaluation of treatments for CHB, including ADV as monotherapy and as a salvage strategy for LAM-resistant patients[38]
- six fully published economic evaluations of antiviral treatments for CHB (IFN-α and LAM)[8,39–43]
- two unpublished drug manufacturers' submissions to NICE – the Roche submission evaluating PEG-α-2a versus IFN-α, LAM, ADV and best supportive care; and the Gilead Sciences submission evaluating ADV as first- and second-line treatment versus LAM as first- or second-line treatment.

The characteristics and results of these studies are not presented in the current report. However, where appropriate, two of these evaluations, Kanwal and colleagues[38] and the Roche submission, are discussed. For clarity of presentation, the outcomes reported by Kanwal and colleagues[38] are presented separately for HBeAg-positive and HBeAg-negative patients. The original model used in the Roche submission remains unpublished and is not reviewed here. A description is available in our previous report.[12]

A total of 67 publications of the cost-effectiveness of PEG-α and/or ADV in CHB were identified through our updated searches. Four fully published economic evaluations met the inclusion criteria and were included.[44–47] In addition, one systematic review of economic evidence of cost-effectiveness of antiviral therapies in CHB patients (Sun and colleagues[48]) was included.

The studies by Veenstra and colleagues[44] and Sullivan and colleagues[45] estimated cost-effectiveness of PEG-α-2a compared with LAM in HBeAg-positive patients. The same model was used in both studies; however, the perspective in Veenstra and colleagues[44] was that of the UK NHS, while in Sullivan and colleagues[45] the perspective was of the Taiwan Bureau of National Health Insurance. The newly identified study by Kanwal and colleagues (2006)[46] used the model first presented in Kanwal and colleagues (2005)[38] to estimate cost-effectiveness of alternative treatments for CHB in the subgroup of patients with cirrhosis (both compensated and decompensated). Buti and colleagues[47] conducted an economic evaluation comparing ADV with LAM in HBeAg-negative patients.

A systematic review of cost-effectiveness of antiviral therapies (Sun and colleagues[48]) described studies published from 2000 to 2007, including three studies described here (Kanwal and colleagues[38], Buti and colleagues[47] and Sullivan and colleagues[45]) and some of the studies identified in our previous review.[12] Sun and colleagues[48] also reviewed other cost studies based on randomised, non-randomised and retrospective cohort data that did not meet the inclusion criteria of the present or previous reviews and were generally assessed by Sun and colleagues[48] as being of moderate or poor quality. These studies are therefore not discussed any further in the present review.

Description of the published economic evaluations

Table 26 provides a summary of characteristics of the identified economic evaluations reporting the cost-effectiveness of antiviral treatments for CHB.

Four of the five economic evaluations presented in *Table 26* employed a Markov state-transition model; Buti and colleagues [47] used a decision tree analysis. All modelled economic evaluations incorporate health states that correspond to the natural history of the disease. The model presented in Buti and colleagues[47] has a 4-year time horizon; other models have a lifetime horizon as appropriate for the chronic nature of the disease.

The state-transition diagrams presented in each of these evaluations are broadly similar. Typically, patients enter the model in the 'chronic HBV' health state and receive the evaluated intervention, one of the comparator treatments or best supporting care. In accordance with the natural history of the disease, patients may then remain in this state, achieve treatment-induced response (HBeAg seroconversion in HBeAg-positive patients or viral suppression that can be achieved by both HBeAg-positive and -negative patients) or experience treatment relapse (return to CHB). Patients could also develop resistance to the active treatment (a virological breakthrough). Patients who do not achieve a response can also enter more progressive stages of liver disease (such as compensated or decompensated cirrhosis or hepatocellular carcinoma). Patients in the study by Kanwal and colleagues[46] enter the model at the cirrhotic stage, which can be either compensated or decompensated. The best outcome in this subgroup of CHB patients is to remain in the compensated cirrhosis stage or revert from decompensated to compensated cirrhosis either as a result of treatment or spontaneously.

With the exception of the model reported by Buti and colleagues,[47] the models presented here allow

TABLE 26 *Model structure and assumptions of economic evaluations for antiviral treatment of hepatitis B*

	Veenstra *et al.*, 2007[44]	**Sullivan *et al.*, 2007[45]**	**Buti *et al.*, 2006[47]**	**Kanwal *et al.*, 2005[38]**	**Kanwal *et al.*, 2006[46]**
Type of model	Adapted from Crowley[42] and Crowley *et al.*[43] and Pwu and Chan.[49] Two additional health states – 'liver transplantation' and 'post-liver transplant' – were added	Adapted from Crowley[42] and Crowley *et al.*[43] and Pwu and Chan[49]. Two additional health states – 'liver transplantation' and 'post-liver transplant' – were added	A new decision-analytic model	A new hybrid model[a] consisting of two submodels	Adapted from Kanwal *et al.*[38] for the subgroup of patients with cirrhosis

TABLE 26 *Model structure and assumptions of economic evaluations for antiviral treatment of hepatitis B*

	Veenstra et *al.*, 2007[44]	**Sullivan et *al.*, 2007**[45]	**Buti et *al.*, 2006**[47]	**Kanwal et *al.*, 2005**[38]	**Kanwal et *al.*, 2006**[46]
Health states/ stages of treatment pathway	Seroconversion Chronic hepatitis B Compensated cirrhosis Decompensated cirrhosis Hepatocellular carcinoma Liver transplantation Post-liver transplant Death	Seroconversion Chronic hepatitis B Compensated cirrhosis Decompensated cirrhosis Hepatocellular carcinoma Liver transplantation Post-liver transplant Death	Over 4 years patients may progress though the following stages: Receiving initial active treatment with response Continuing initial active treatment with response Developing resistance to initial active treatment Receiving ADV treatment and continuing with response (applies to LAM-refractory patients) Developing resistance and no response to ADV salvage therapy No active treatment after developing resistance[b]	Chronic HBV infection Virological response (either spontaneously or due to treatment) Virological relapse Developing viral resistance Compensated cirrhosis Decompensated cirrhosis Liver transplant Hepatocellular carcinoma Death	Compensated cirrhosis Decompensated cirrhosis Successful liver transplant Hepatocellular carcinoma Death
Characteristics of baseline cohort	32 years old 78% male 87% Asian 17% with compensated cirrhosis or transition to cirrhosis	32 years of age 78% male 87% Asian 17% with compensated cirrhosis or transition to cirrhosis	Mean age of patients varied from 45 to 49 years Proportion of males varied from 74% to 83% Proportion of patients with cirrhosis, wherever reported, varied from 23% to 54% across four studies that were used to obtain estimates of outcome	40 years of age Elevated ALT, no evidence of cirrhosis and no previous CHB treatment 55% of the cohort were HBeAg –ve	50 years of age 50% with compensated cirrhosis and 50% with decompensated cirrhosis
Cycle length	1 year	1 year	1 year	1 year	1 year
Time horizon	Lifetime	Not reported, appears to be lifetime	4 years	Lifetime	Lifetime

a Patient progression through pre-cirrhotic health states is analysed with decision-analytic model. Progression through cirrhotic health states is analysed by means of a Markov model.
b Although not clearly identified, 'progressing to decompensated liver disease' is used as an implicit outcome that only applies to patients who received no treatment as a result of developing resistance to LAM and/or ADV. This outcome is not associated with a defined health state but is associated with additional costs.

TABLE 27 *Characteristics of economic evaluations of antiviral treatment of CHB*

				Kanwal et *al.*, 2005[38]		**Kanwal et *al.*, 2006[46]**
	Veenstra et *al.*, 2007[44]	**Sullivan et *al.*, 2007[45]**	**Buti et *al.*, 2006[47]**	**HBeAg +ve cohort[a]**	**HBeAg –ve cohort[a]**	**CHB patients with cirrhosis**
Perspective	UK National Health Service	Taiwan Bureau of National Health Insurance	Spanish Public Health System	US third-party payers	US third-party payers	US third-party payers
Study type	CEA and CUA	CEA and CUA	CEA (incremental cost per additional patient with response)	CUA	CUA	CUA
HBeAg status	+ve	+ve	–ve	+ve	–ve	Not differentiated
Intervention(s)/ strategies	PEG-α-2a 180 mg daily for 48 weeks vs LAM 100 mg daily for up to a maximum of 4 years	PEG-α-2a 180 mg daily for 48 weeks vs LAM 100 mg daily for 48 weeks	LAM monotherapy 100 mg daily followed by ADV monotherapy 10 mg daily as a salvage therapy for patients developing resistance to LAM treatment vs ADV monotherapy 10 mg daily	*Strategy 1:* no pharmacological treatment *Strategy 2:* IFN monotherapy 10 MIU three times weekly for 4 months *Strategy 3:* LAM monotherapy 100 mg once daily for lifetime unless responded to treatment *Strategy 4:* ADV monotherapy 10 mg once daily for lifetime unless responded to treatment *Strategy 5:* LAM with crossover to ADV on development of resistance ('ADV salvage' strategy)	*Strategy 1:* no pharmacological treatment *Strategy 2:* IFN monotherapy 10 MIU three times weekly for 12 months *Strategy 3:* LAM monotherapy 100 mg once daily for lifetime unless responded to treatment *Strategy 4:* ADV monotherapy 10 mg once daily for lifetime unless responded to treatment *Strategy 5:* LAM with crossover to ADV on development of resistance ('ADV salvage' strategy)	*Strategy 1:* no pharmacological treatment of chronic HBV *Strategy 2:* LAM monotherapy 100 mg once daily for an indefinite period *Strategy 3:* ADV monotherapy 10 mg once daily for an indefinite period *Strategy 4:* LAM with crossover to ADV on development of resistance ('ADV salvage' strategy) *Strategy 5:* entecavir monotherapy 0.5 mg once daily for an indefinite period *Strategy 6:* LAM with crossover to entecavir on development of resistance ('entecavir salvage' strategy)

	Veenstra *et al.*, 2007[44]	Sullivan *et al.*, 2007[45]	Buti *et al.*, 2006[47]	Kanwal *et al.*, 2005[38] HBeAg +ve cohort[a]	Kanwal *et al.*, 2005[38] HBeAg –ve cohort[a]	Kanwal *et al.*, 2006[46] CHB patients with cirrhosis
Treatment effect(s) modelled	HBeAg seroconversion (32% PEG-α-2a vs 19% LAM; Lau *et al.*, 2005[50])	HBeAg seroconversion (32% PEG-α-2a vs 19% LAM; Lau *et al.*, 2005[50])	'Response to treatment' is defined as a 'decrease in serum HBV DNA to undetectable levels by polymerase chain reaction assay; 'resistance to treatment is defined as 'reappearance of HBV DNA in serum due to the emergence of drug resistant HBV mutants'	Virological response is defined as HBeAg seroconversion. In addition the following outcomes are used in the model: developing resistance to active treatment; relapsing from virological response; progression to compensated cirrhosis; progression from compensated to decompensated cirrhosis; regression from decompensated to compensated cirrhosis; progression to hepatocellular carcinoma The end points were estimated by collecting data across 149 studies and clinical trials. A weighted mean across relevant outcomes was calculated using a sample size as the weight	Virological response is defined as 'fully suppressed HBV replication while maintaining normal ALT'. In addition the following outcomes are used in the model: developing resistance to active treatment; relapsing from virological response; progression to compensated cirrhosis; progression from compensated to decompensated cirrhosis; regression from decompensated to compensated cirrhosis; progression to hepatocellular carcinoma; The end points were estimated by collecting data across 149 studies and clinical trials. A weighted mean across relevant outcomes was calculated using a sample size as the weight	The following clinical outcomes were included in the model: progression from compensated to decompensated cirrhosis; regression from decompensated to compensated cirrhosis; progression from cirrhosis to hepatocellular carcinoma; developing resistance to initial pharmacotherapy; progression to liver transplantation; progression to cirrhosis following liver transplantation. The end points were estimated by collecting data across 83 studies and clinical trials. A weighted mean across relevant outcomes was calculated using a sample size as the weight

continued

TABLE 27 *Characteristics of economic evaluations of antiviral treatment of CHB (continued)*

				Kanwal *et al.*, 2005[38]		Kanwal *et al.*, 2006[46]
	Veenstra *et al.*, 2007[44]	**Sullivan *et al.*, 2007[45]**	**Buti *et al.*, 2006[47]**	**HBeAg +ve cohort[a]**	**HBeAg –ve cohort[a]**	**CHB patients with cirrhosis**
Currency base	2005 UK£	2004 NTD	2004 €	2004 US$	2004 US$	2005 US$
Base-case results	A 32-year-old with HBeAg +ve CHB gains 0.39 life-years and 0.30 QALYs (both discounted at 1.5%) with incremental lifetime cost of £3100 (discounted at 6%) for PEG-α-2a treatment compared with LAM treatment	A 32-year-old with HBeAg +ve CHB gains 0.33 life-years and 0.41 QALYs (both discounted at 3%) with incremental lifetime cost of NTD 156,000 (discounted at 3%) for PEG-α-2a treatment compared with LAM treatment	An incremental cost (discounted at 3%) of an additional HBeAg –ve patient with response is about €280,000	ADV salvage is a dominant strategy Both costs and QALYs were discounted at 3%	ICER of IFN monotherapy vs 'doing nothing' is $2280 ICER of ADV monotherapy vs IFN monotherapy is $16,693 ICER of ADV monotherapy vs ADV salvage is $90,983 LAM monotherapy was dominated Both costs and QALYs were discounted at 3%	ICER of ADV monotherapy vs 'doing nothing' is $19,731($14,342– $24,224) ICER of ADV monotherapy vs entecavir monotherapy is $25,626 ($19,637 –$31,184) ADV salvage, entecavir salvage and LAM monotherapy are all dominated Both costs and QALYs were discounted at 3%

ALT, alanine aminotransferase; CEA, cost-effectiveness analysis; CHB, chronic hepatitis B; CUA, cost–utility analysis; ICER, incremental cost-effectiveness ratio; MIU, million international units; QALY, quality-adjusted life-year.

a For clarity of presentation, the outcomes of economic evaluations reported in Kanwal *et al.*[38] are presented separately for HBeAg +ve and HBeAg –ve subgroups of patients. In the base-case analysis, ICER of IFN monotherapy vs 'doing nothing' is $6337; ICER of ADV monotherapy vs interferon monotherapy is $8446. Both ADV monotherapy and LAM monotherapy were dominated. The restricted use of ADV as salvage therapy was more cost-effective than both LAM and ADV monotherapies.

the possibility of patients with progressive liver disease to undergo liver transplantation. Kanwal and colleagues (2006)[46] specified that patients in decompensated cirrhosis health states (ascites, variceal haemorrhage and hepatic encephalopathy) and HCC could undergo liver transplantation. According to the assumptions of the model reported in Veenstra and colleagues[44] and Sullivan and colleagues,[45] patients with HCC do not receive a liver transplant. *Table 27* presents further details of the included economic evaluations including base-case results.

Details of economic evaluations based on the Roche model

As noted earlier, two economic evaluations (Veenstra and colleagues[44] and Sullivan and colleagues[45]) use the same model to evaluate PEG-α-2a versus LAM in HBeAg-positive patients. This model uses the structure and some of the transition probabilities presented in 2005 in the Roche submission to NICE for their appraisal of PEG-α-2a. The model evaluated a 48-week course of PEG-α-2a versus comparators IFN-α, LAM, ADV and best supportive care. (For a fuller description see our previous report.[12]) However, unlike the Roche model, economic evaluations reported in Veenstra and colleagues[44] and Sullivan and colleagues[45] apply exclusively to an HBeAg-positive population.

The 48-week outcomes of the RCT of PEG-α-2a versus LAM reported by Lau and colleagues[50] provided short-term clinical effectiveness data for the base-case analysis in all three of these models. Long-term clinical effectiveness data (rates of seroconversion, relapse and LAM resistance) were taken from previously published studies (Liaw and colleagues,[51] Leung and colleagues [52] and Lok and colleagues[53]). The Roche model estimated cost-effectiveness of a 48-week course of PEG-α-2a versus two LAM treatment alternatives: treatment for 48 weeks and for 4 years. Veenstra and colleagues[44] estimated cost-effectiveness of a 48-week course of PEG-α-2a versus up to 4 years of LAM treatment (i.e. patients who do not achieve a sustained seroconversion after 48 weeks continue LAM treatment for up to 4 years or until they achieve seroconversion). Sullivan and colleagues[45] assumed that a 48-week course duration is applied to both PEG-α-2a and the comparator, LAM.

Demographic and clinical characteristics of the hypothetical cohort of patients in Veenstra and colleagues[44] and Sullivan and colleagues[45] mirrored the baseline characteristics of patients enrolled in the RCT reported by Lau and colleagues.[50] Of note, 87% of patients in the modelled cohort of CHB patients were Asian. This population may not be representative of the general population in England and Wales, which may limit generalisability of the outcomes of the cost-effectiveness analysis.

All three studies use a Markov model consisting of the following health states (CHB, HBeAg seroconversion, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplantation, post-liver transplantation and death). A health state not included in these studies is HBsAg seroconversion, a state which has been included in other economic evaluations (e.g. Crowley[42] and Crowley and colleagues[43]). The outcomes are expressed as incremental cost per quality-adjusted life-year (QALY) in these studies. Sensitivity analysis is performed in all three studies.

As in the model presented in the Roche submission to NICE, Veenstra and colleagues[44] and Sullivan and colleagues[45] did not include the short-term effect of antiviral therapy on progression to compensated cirrhosis, such as that estimated in recent economic evaluations of LAM (Orlewska,[41] Crowley[42] and Crowley and colleagues[43] The base-case analyses in Veenstra and colleagues[44] and Sullivan and colleagues[45] did not include the effect of LAM resistance. Drug resistance was explored in the scenario analysis reported in Veenstra and colleagues[44] but not in Sullivan and colleagues[45] In the base-case analysis of these models, it was assumed that by taking HBeAg seroconversion rates from long-term follow-up (which show reducing denominators over time), some of the effects of drug resistance, as indicated by reduced seroconversion rates, will have been captured.

Drug acquisition costs were taken from the most recent (at the time of writing) *British National Formulary* in Veenstra and colleagues[44] and in the Roche model, and from the 2004 Taiwan Fee Schedule for Medical Service in Sullivan and colleagues[45]

As stated in our previous review,[12] in the Roche model the health-state costs were developed by means of a combination of methods, including assumption, bottom-up costing using protocols based on expert opinion and extrapolation from costs developed for previous submissions. These costs were not adjusted for the differences in the intensity of medical management between the treatment groups. We previously[12] also noted that the assumption that the HBeAg seroconverted

health state has zero costs and does not correspond with current clinical guidelines that suggest that seroconverted patients should be reviewed every 6–12 months, during which time their serological status/HBV DNA should be assessed and a screen for HCC should be undertaken.

In the recent publication by Veenstra and colleagues,[44] estimates of the costs of management of patients in different health states were taken directly from the economic evaluation in our previous report.[12] Health-state costs used in our previous economic evaluation were estimated specifically for the assessment. The costs were a combination of values from published cost estimates for the progressive stages of liver disease and estimates based on treatment protocols developed with expert advisors to the project. Unit costs for health-care resources were obtained from the finance department at Southampton University Hospitals Trust.

Sullivan and colleagues[45] obtained cost estimates for the disease states of CHB and compensated and decompensated cirrhosis by applying the 2004 Taiwan Fee Schedule for Medical Service unit costs to the resource use reported by treating clinicians (no further details are provided). Cost estimates for HCC were taken from the published literature (Wang and Kowdley[54]). Liver transplantation and post-transplantation costs were obtained from the Chang Gung Memorial Hospital in 2004.

Veenstra and colleagues[44] and the Roche submission used the same approach to estimating utility values. This was based principally on values reported by Wong and colleagues.[8] Sullivan and colleagues[45] used higher estimates of utility in four health states (seroconversion, CHB, compensated cirrhosis and HCC), based on Pwu and Chan[49] and Bennett and colleagues[55] (see *Table 28* below).

Sullivan and colleagues[45] concluded that treatment with PEG-α-2a compared with LAM results in higher total cost but longer quality-adjusted life expectancy, yielding an ICER of NTD381,000 or US$12,000 at 2004 prices). As in the Roche submission, Veenstra and colleagues[44] confirmed that PEG-α-2a is associated with higher discounted total health-care cost but also with additional discounted QALYs compared with long-term (up to 4 years) LAM treatment. The estimated ICER of £10,444 is almost twice as high as the ICER of £5948 reported in the Roche original submission. The difference most likely relates to the different method of cost estimation and the difference in the population cohort.

Details of economic evaluations based on the Kanwal and colleagues[38] model

The original model was published in 2005 (Kanwal and colleagues[38]) and assessed in our earlier report.[12] Kanwal and colleagues concluded that in the base-case analysis (with 55% of patients being HBeAg negative at baseline), neither LAM nor ADV monotherapy is cost-effective in chronic HBV infection. However, depending on financial restrictions, either IFN or a hybrid strategy that reserves ADV as a salvage therapy only for LAM-resistant patients may be cost-effective. The objective of the more recent publication of Kanwal and colleagues[46] was to estimate cost-effectiveness of alternative therapies in the subgroup of the CHB population with cirrhosis, and, in particular, to test whether the newer and more expensive agents such as ADV and entecavir become cost-effective in this subgroup. The structure and transition probabilities in the model reported by Kanwal and colleagues[38] were adjusted for the subgroup of CHB patients with cirrhosis.

At baseline, 50% of patients in the cohort have compensated cirrhosis and 50% have decompensated cirrhosis, and in each treatment arm separate transition probabilities are assigned to patients in the compensated and decompensated cirrhosis groups as they progress through the stages of the disease. The baseline ratio of patients with compensated versus decompensated cirrhosis was tested in the sensitivity analysis.

As noted earlier, in the study by Kanwal and colleagues,[46] the best outcome in the subgroup of cirrhotic patients is either to remain in the compensated cirrhosis stage or to revert from decompensated to compensated cirrhosis as a result of treatment or spontaneously. Patients reverting to compensated cirrhosis were eligible to decompensate a second time. The rate of subsequent decompensation was higher than the initial rate. Hepatocellular carcinoma could develop at any stage and all patients with decompensated cirrhosis or HCC were eligible for a liver transplant.

The study evaluated cost-effectiveness of six strategies in treatment of cirrhosis in CHB patients:

- strategy 1: no pharmacological treatment of chronic HBV ('do nothing' strategy)

- strategy 2: LAM monotherapy 100 mg once daily for an indefinite period
- strategy 3: ADV monotherapy 10 mg once daily for an indefinite period
- strategy 4: LAM with crossover to ADV on development of resistance ('ADV salvage' strategy)
- strategy 5: entecavir monotherapy 0.5 mg once daily for an indefinite period
- strategy 6: LAM with crossover to entecavir on development of resistance ('entecavir salvage' strategy).

The first four strategies are relevant to the scope of this report.

Unlike the 2005 study by Kanwal and colleagues,[38] the 2006 study[46] did not include a treatment strategy based on IFN-α, as this is not approved for patients with decompensated cirrhosis. In both studies, the perspective is of a US third-party payer.

In both studies[38,46] estimates of costs of health-care resources were obtained by (1) calculating direct cost estimates by multiplying unit prices for the drugs and medical services by the estimated use of these resources in natural units, and (2) combining these costs with other cost estimates (e.g. costs of complications) obtained from the literature. In particular, in Kanwal and colleagues,[46] costs of physician services and procedures were obtained from the 2005 American Medical Association *Current Procedural Terminology* codebook and the 2005 *Medicare Fee Schedule*. Pharmaceutical costs were obtained from the average wholesale prices (AWPs) listed in the 2006 *Red Book*. Cost estimates for cirrhosis and related health states were obtained from a published study of detailed, itemised inpatient and outpatient direct costs incurred by patients with cirrhosis (Bennett and colleagues[55]). While the model first presented in the Roche submission has only one health state corresponding to decompensated cirrhosis, the structure of the model in Kanwal and colleagues[38,46] differentiates between different types of decompensation (i.e. variceal haemorrhage, ascites and encephalopathy), which allowed for a more precise estimation of the associated costs in the first and subsequent years.

In both studies,[38,46] transition probabilities were obtained from a systematic review of the literature. Appendix 5 compares transition probabilities used in studies assessed in our previous report[12] and those in the present report (the study by Buti and colleagues[47] is not included in this appendix, as explained below).

The model reported in Kanwal and colleagues[38,46] used utility values obtained from the literature that reported utilities for chronic liver disease associated with hepatitis C. Kanwal and colleagues argue that both hepatitis C and hepatitis B lead to cirrhosis and related complications and there is no a priori reason to believe that the quality of life decrements assigned to the corresponding health states would depend on the underlying aetiology. (The same approach was used in the economic evaluation conducted in our previous report.[12] *Table 28* compares utility values used in studies assessed in our previous report[12] and in the present report, with the exception of the study by Buti and colleagues[47]).

The result of economic modelling in Kanwal and colleagues (2006)[46] indicated that:

- LAM monotherapy is dominated.
- The ICER of ADV monotherapy versus 'doing nothing' is $19,731($14,342–$24,224) at 2005 prices.
- The ICER of ADV monotherapy versus entecavir monotherapy is $25,626 ($19,637–$31,184) at 2005 prices.
- ADV salvage strategy is dominated.
- Entecavir salvage strategy is dominated.

The sensitivity analysis showed that the model outcomes were sensitive to the cost of ADV and entecavir; the annual rate of progression from compensated to decompensated cirrhosis with LAM resistance; the annual rate of progression from compensated to decompensated cirrhosis with entecavir (no resistance); the annual rate of progression from compensated to decompensated cirrhosis with ADV (no resistance); and the annual rate of progression from compensated to decompensated cirrhosis with ADV resistance. For example, if the incidence of progression from compensated to decompensated cirrhosis in LAM-resistant patients is less than the threshold of 3.5% (8% in the base-case analysis), than LAM becomes cost-effective. The results were robust with respect to the baseline ratio of patients with compensated versus decompensated cirrhosis.

Details of economic evaluation reported by Buti and colleagues[47]

Buti and colleagues[47] estimate cost-effectiveness of a 4-year LAM with ADV as a salvage therapy strategy for LAM-resistant patients compared with ADV monotherapy.

In the decision tree model, different health states in two treatment groups are assigned to describe patient progression:

- In the LAM arm, these are: receiving LAM treatment with response; continuing LAM treatment with response; developing resistance to LAM, followed by receiving ADV as a salvage therapy; receiving ADV treatment with response; and developing resistance and no response to ADV treatment, in which case no other active treatment is received.
- In the ADV arm, these are: receiving ADV treatment with response; continuing ADV treatment with response; and developing resistance to ADV, in which case no other active treatment is received.

Other health states that characterise disease progression (e.g. compensated and decompensated cirrhosis, HCC, liver transplant) are not explicitly included in the model. Nevertheless, a certain proportion of patients who do not receive treatment are assumed to develop a 'decompensated CHB', which includes cirrhosis, hepatic encephalopathy, varicose haemorrhage, ascites and hepatocarcinoma, and is associated with the aggregated 'cost of decompensation' of €172.50. Buti and colleagues[47] do not provide a clear explanation of either the proportion of patients with decompensation or the monetary value of health-care resources associated with treatment of decompensated CHB. In particular, it is not clear what proportion of patients (if any) start at the compensated cirrhosis state from which decompensated cirrhosis is later developed. It does not appear that a systematic review of the clinical evidence used in the model was undertaken. The probability of response, non-response and resistance seem to have been derived from averaging the response rate across a few selected studies, including non-randomised observational studies (see Appendix 4 for details). It assumed that patients receiving an active treatment, including those with compensated cirrhosis at baseline, do not develop decompensated CHB. This assumption is not consistent with assumptions used in other economic evaluations.[12,38,44–46]

Although the systematic review by Sun and colleagues[48] assessed the economic evaluation reported in Buti and colleagues[47] as being of high quality in comparison with the other models discussed above, it is characterised by a number of shortcomings, in addition to the issues outlined earlier. It has a short time horizon of just 4 years rather than a lifetime horizon, as is appropriate in a chronic disease. A discounting factor is applied only to costs and not to the outcomes. The outcome of cost-effectiveness analysis is expressed in terms of additional cost per patient with response [defined as decrease of serum HBV DNA to undetectable levels by polymerase chain reaction (PCR) assay] instead of the conventional incremental cost per incremental QALY. Another methodological shortcoming is that clinical effectiveness data used in the two treatment groups come from different clinical trials and may therefore involve patient populations with different baseline characteristics. These shortcomings may potentially introduce a bias to the cost-effectiveness estimates, which may compromise the outcomes of the cost-effectiveness analysis.

Buti and colleagues[47] estimated an incremental cost of ADV per additional patient with response at €27,872 at 2003 prices. Notwithstanding the shortcomings listed above, the results expressed in units other than QALYs renders the study outcomes of limited use for decision making in the area of allocating the limited health-care resources across the treatment alternatives.

Health-related quality of life in patients with chronic hepatitis B

The models reported in Kanwal and colleagues,[38,46] Veenstra and colleagues[44] and Sullivan and colleagues[45] assume that health states corresponding to the stages of natural disease progression (CHB, response, resistance, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation) determine the patients' quality of life. This is consistent with approaches used in previous published economic evaluations of CHB treatments (Wong and colleagues[8], Shepherd and colleagues[12]). The study by Buti and colleagues[47] does not include outcomes assessed in terms of QALYs.

A recent study by Levy and colleagues[56] was identified during the literature search. In this study, standard gamble utilities were elicited using an interviewer-administered survey from populations in six countries, with a total of 534 HBV-infected patients and a total of 600 uninfected respondents. The study aimed to recruit 100 HBV-infected and 100 uninfected respondents from each country. Chronic hepatitis B was not differentiated with respect to its variants (i.e. HBeAg positive or negative). Utility values were obtained in relation to six CHB states: CHB, compensated cirrhosis,

decompensated cirrhosis, liver transplantation, post-liver transplantation and HCC. Utility values for other health states that are typically included in the models (e.g. response to treatment or resistance to treatment) were not elicited.

Although the study by Levy and colleagues[56] included a representative sample of the population from six countries, it is uncertain whether the UK sample consisting of 100 HBV-infected patients and 100 uninfected respondents is representative of the UK population. Levy and colleagues[56] observed that uninfected respondents had higher mean utility values than infected respondents for most of the health states.

Table 28 presents the age- and sex-adjusted utility values elicited from 100 HBV-infected patients and 100 uninfected respondents in the UK study by Levy and colleagues,[56] alongside the baseline values used in the economic evaluation presented in our original report.[12]

The utility weights, reported by Levy and colleagues,[56] elicited from the compensated cirrhosis state, liver transplant and post-liver transplant health states are markedly higher than the utility weights used in our previous economic evaluation.[12] Another observation is that, according to Levy and colleagues,[56] there is a substantial decrease in utility in patients in transition from compensated to decompensated cirrhosis. In our economic model,[12] the largest decrease in utility occurs in patients in transition from CHB to compensated cirrhosis. The effect of these differences on the cost-effectiveness analysis of alternative treatments for CHB is explored in the update of our economic model, below.

Comparison of estimates of health-related quality of life

Table 29 compares health-state utilities used in different economic evaluations of antiviral treatment for patients with CHB. For completeness, the methodologically robust studies that used utility weights and were assessed in our previous report[12] are included, along with the economic evaluations identified in our update search.

Economic evaluations by Wong and colleagues,[8] Crowley,[42] Crowley and colleagues[43] and Dusheiko and Roberts[39] applied health-state utility estimates derived from clinicians' opinion rather than from patients' preferences. These estimates are characterised by a large variation. Some of these estimates were subsequently reused in our previous model,[12] and in models by Kanwal and colleagues[38,46] Veenstra and colleagues[44] and Sullivan and colleagues,[45] along with utility weights elicited from patients with hepatitis C (see Appendix 4 for details). The utility values elicited by Levy and colleagues[56] from the HBV population generally fall within this broad range of estimates used in different economic evaluations.

Summary

We identified four recently published economic evaluations in our update search. The studies assessed the cost-effectiveness of PEG-α-2a, LAM, ADV, entecavir and best supportive care. None of the studies featured PEG-α-2b.

The economic evaluation reported in Kanwal and colleagues (2006),[46] based on the evaluation by Kanwal and colleagues (2005),[38] was strongest methodologically. They conducted comprehensive economic evaluations across the broad range

TABLE 28 *Utility values assigned to CHB patients in different health states as reported in Levy* et al.[56] *and Shepherd* et al.[12]

Health state	Values elicited from uninfected/infected UK respondents[56]	Values at baseline in HBeAg +ve model[12]	Values at baseline in HBeAg –ve model[12]
CHB	0.88/0.69	0.89	0.87
Compensated cirrhosis	0.87/0.68	0.49	0.47
Decompensated cirrhosis	0.36/0.35	0.39	0.37
Hepatocellular carcinoma	0.42/0.42	0.39	0.37
Liver transplant	0.69/0.57	0.38	0.36
Post-liver transplant	0.82/0.66	0.61	0.59

CHB, chronic hepatitis B.

TABLE 29 *Health-state utilities used in economic evaluations of antiviral treatment for patients with CHB*

Health state	[a]Wong *et al.*, 1995[8]	[a]Crowley, 2000,[42] and Crowley *et al.*, 2002[43]	[a]Dusheiko and Roberts, 1995[39]	[d]Shepherd *et al.*, 2006[12]	[e]Veenstra *et al.*, 2007[44]	Sullivan *et al.*, 2007[45]	[h]Kanwal *et al.*, [38,46]	Levy *et al.*, 2007[56] (uninfected/ infected respondents)
'Cured' state (HBsAg –ve)	Not used in model	Not used in model	Not used in model	UK age-specific population-based utility (Kind *et al.*, 1999[57])	Not used in model	Not used in model	Not used in model	Not estimated
Seroconversion (HBeAg –ve, HBsAg +ve)	0.93	0.78	0.90	UK age-specific population-based utility (Kind *et al.*, 1999[57])	UK age-specific population-based utility (Kind *et al.*, 1999[57])	1.0 (Pwu and Chan, 2002[49])	1.0[h] (Wong *et al.*,1995[8])	Not estimated
Chronic hepatitis B	0.89[b]	0.69[c]	0.80	0.91 – 0.04 = 0.87 (Wong *et al.*,1995[8])	0.87[f] (Wong *et al.*,1995[8])	0.95 (Pwu and Chan, 2002[49])	0.99[i] (Wong *et al.*,1995[8])	0.88/0.69
Compensated cirrhosis	0.87	0.56	0.50	0.91 – 0.44 = 0.47 (Wright *et al.*, 2005[58])	0.84 (Wong *et al.*,1995[8])	0.9 (Pwu and Chan, 2002[49])	0.8 (Chong *et al.*, 2003[59])	0.87/0.69
Decompensated cirrhosis	0.54	0.15	0.20	0.91 – 0.54 = 0.37 (Wright *et al.*, 2005[58])	0.46 (Wong *et al.*,1995[8])[8]	0.54[g] (Wong *et al.*,1995[8])	0.6 (Chong *et al.*, 2003[59])	0.36/0.35
Hepatocellular carcinoma	0.49	0.12	0.20	0.91 – 0.54 = 0.37 (Wright *et al.*, 2005[58])	0.41 (Wong *et al.*,1995[8])	0.5[g] (Bennett *et al.*, 1997[55])	0.73 (Chong *et al.*, 2003[59])	0.42/0.42
First liver transplant	Not used in model	Not used in model	Not used in model	0.91 – 0.55 = 0.36 (Ratcliffe *et al.*, 2002[60])	0.42 (Bennett *et al.*, 1997[55])	0.5[g] (Bennett *et al.*, 1997[55])	Not used in model	0.69/0.57
Post-liver transplantation	Not used in model	Not used in model	Not used in model	0.91 – 0.32 = 0.59 (Ratcliffe *et al.*, 2002[60])	0.62 (Bennett *et al.*, 1997[55])	0.7[g] (Bennett *et al.*, 1997[55])	0.86 (Chong *et al.*, 2003[59])	0.82/0.66

a Derived utilities based on clinical opinion.
b An absolute decrease in utility of 0.13 applied to IFN arm compared with no treatment arm for the duration of IFN treatment (16 weeks).
c An absolute decrease in utility of 0.23 applied to IFN arm compared with no treatment arm for the duration of IFN treatment (16 weeks). An absolute decrease in utility of 0.08 applied to LAM arm compared with no treatment arm.
d Decrements in utility values are applied to the cohort of 40-year-old patients entering the first cycle of the model.
e Utility values reported in Veenstra *et al.*[44] are applied to the cohort of 40-year-old patients entering the first cycle of the model.
f An absolute decrease in utility of 0.05 applied to PEG-α-2a arm compared with LAM arm (Wong *et al.*[8]).
g In contrast to the utility values reported in Veenstra *et al.*[44], those reported in Sullivan *et al.*[45] are not adjusted for age-specific population-based utilities.
h Kanwal *et al.*[46] applied the utility value of 1.0 to the health state described as 'durable virological response'. In Wong *et al.*,[8] the utility value of 1.0 is assigned to HBsAg +ve and HBeAg –ve patients.
i Utility value for chronic hepatitis reported in Wong *et al.*[8] is 0.94. Utility values for other health states were obtained from HCV study.

of HBV therapies using a population that was representative of the patient mix observed in practice. In contrast, Veenstra and colleagues,[44] Sullivan and colleagues[45] and Buti and colleagues[47] undertook only a pairwise comparison of treatment alternatives in a particular subgroup of patients.

However, the results reported by Kanwal and colleagues[38,46] are not likely to be fully generalisable to the NHS. This is because they were conducted from the perspective of the US health-care system which differs in prices, structure of resource use and economic incentives. The same disadvantage applies to the results reported in Sullivan and colleagues[45] and Buti and colleagues,[47] which were conducted from the Taiwanese and Spanish health system perspectives respectively. The study by Buti and colleagues[47] is also characterised by the number of methodological shortcomings.

The study by Veenstra and colleagues,[44], the only one conducted from the UK perspective, reported that PEG-α-2a is associated with higher discounted total health-care cost but also with additional discounted QALYs compared with long-term (up to 4 years) of LAM treatment in HBeAg-positive patients. The estimated ICER was £10,444. Our original report[12] estimated the ICER of PEG-α-2a versus IFN-α in line with the scope of the assessment.

The estimates of utility values reported in Levy and colleagues[56] were obtained in relation to six CHB states: CHB, compensated cirrhosis, decompensated cirrhosis, liver transplantation, post-liver transplantation and HCC. Although utility values for the health states 'response to treatment' or 'resistance to treatment' were not assessed, the important contribution of the study by Levy and colleagues[56] lies in eliciting utility estimates directly from patients. Previous models, in contrast, derived utility estimates from either clinician opinion or patients with hepatitis C.[12,38,44–46]

Update of the Southampton Health Technology Assessments Centre (SHTAC) economic model

Summary of methods and results of economic modelling in the assessment report

Our previous report[12] presented estimates of the cost-effectiveness of PEG-α-2a and ADV using a state-transition model. Development of the model was informed by systematic review of the literature on natural history, epidemiology and quality of life for patients with CHB and on the clinical and cost-effectiveness of antiviral treatment. It has not been possible to repeat all of the methodological detail of the model here. Readers are therefore encouraged to consult the original report which is freely available to download from the internet (www.hta.ac.uk).

The model included eight health states (CHB, HBeAg seroconversion/remission, HBsAg seroconversion, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplantation and death) and used 'tunnel states' to account for previous treatment history (such as switching drugs owing to the development of resistance). The model was used to extrapolate long-term outcomes (in terms of life expectancy and quality-adjusted life expectancy) and lifetime costs (including costs of managing progressive liver disease as well as costs of antiviral treatment) based on short-term outcomes included in the clinical effectiveness review (HBeAg seroconversion for HBeAg-positive patients and ALT normalisation for HBeAg-negative patients).

Published, age-specific quality of life weights for healthy populations were used to estimate utility values for patients who achieved HBsAg or HBeAg seroconversion. Utility values for other health states were estimated relative to these values, based on the published literature (not all of which were specific to patients with CHB).

The model had a lifetime horizon and the analysis adopted the perspective of the NHS and Personal Social Services, in accordance with NICE methodological guidance. The base-case results reported were for a mixed cohort of patients, with 70% having HBeAg-positive and the remainder HBeAg-negative CHB. The mean age at start of treatment was assumed to be 32 years for patients with HBeAg-positive CHB and 40 years for those with HBeAg-negative CHB. The majority of patients in both groups were male. Incremental cost-effectiveness ratios were calculated for each intervention compared with its closest comparator (for PEG-α-2a this was IFN-α-2a and for ADV it was LAM). The ICERs for individual antiviral agents were within the range considered to represent good value for money by NHS decision-makers:

- £5994 per QALY gained for IFN-α compared with best supportive care and £6119 per QALY gained for PEG-α-2a compared with IFN-α-2a.

- £3685 per QALY gained for LAM compared with best supportive care and £16,569 per QALY gained for ADV compared with LAM.

In addition, a number of sequential treatment scenarios (IFN-α-2a or PEG α-2a as first-line treatment followed by LAM or ADV until resistance develops) were modelled (*Table 30*). A similar logic to that adopted for individual antiviral agents (identifying the closest comparator, for calculating ICERs) was applied to the cost-effectiveness analysis of sequential treatment strategies:

- Strategies using IFN-α as first-line treatment followed by LAM or ADV were compared with IFN-α alone.
- The strategy using IFN-α as first-line treatment followed by LAM, with ADV for patients developing LAM resistance was compared with IFN-α followed by LAM.
- Strategies using PEG-α-2a as first-line treatment followed by nucleoside/nucleotide analogue were compared with the equivalent strategy using conventional IFN as first-line treatment.

ICERs derived for these comparisons are reported in *Table 30*.

To simplify the analysis, *Figure 1* shows an optimal treatment sequence consisting of IFN-α or PEG-α-2a followed by LAM, with ADV reserved as a salvage strategy for patients who develop LAM resistance. The dashed line in *Figure 1* indicates the cost-effectiveness frontier, joining the optimal treatment strategies (those which provide a given output at minimum cost). Other sequences were excluded using the principle of extended dominance, i.e. points above the cost-effectiveness frontier are non-optimal and can be eliminated, as the same output can theoretically be provided at lower cost by a combination of strategies that are found on the frontier.

Incremental cost-effectiveness ratios estimated using the optimal strategies are: IFN followed by LAM (ICER = £4772 per QALY gained relative to best supportive care); PEG-α-2a followed by LAM (ICER = £6765 relative to IFN-α followed by LAM); and PEG-α-2a followed by LAM followed by ADV (ICER = £11,460 relative to PEG-α-2a followed by LAM).

Deterministic sensitivity analyses showed that the results were robust to assumptions about the baseline cohort, but were sensitive to assumptions regarding:

TABLE 30 *Cost-effectiveness results for sequential treatment strategies (previous report[12])*

Strategy	Cost (£)	Discounted life expectancy	Discounted QALYs	ICER
Best supportive care	8555	22.29	17.07	
IFN-α	12,609	22.98	17.75	5994
IFN-α followed by LAM	15,159	23.76	18.45	3604[a]
IFN-α followed by ADV	27,442	24.81	19.40	8987[b]
IFN-α followed by LAM followed by ADV	27,740	25.00	19.56	11,402[c]
PEG-α-2a	15,745	23.51	18.26	6119
PEG-α-2a followed by LAM	18,053	24.20	18.88	6766[d]
PEG-α-2a followed by ADV	28,907	25.13	19.71	4649[e]
PEG-α-2a followed by LAM followed by ADV	28,976	25.28	19.83	4452[f]

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
a Comparing IFN-α-2a followed by LAM with IFN-α-2a alone.
b Comparing IFN-α-2a followed by ADV with IFN-α-2a alone.
c Comparing IFN-α-2a followed by LAM followed by ADV salvage with IFN-α-2a followed by LAM.
d Comparing PEG-α-2a followed by LAM with IFN-α-2a followed by LAM.
e Comparing PEG-α-2a followed by ADV with IFN-α-2a followed by ADV.
f Comparing PEG-α-2a followed by LAM followed by ADV salvage with IFN-α-2a followed by LAM followed by ADV salvage.

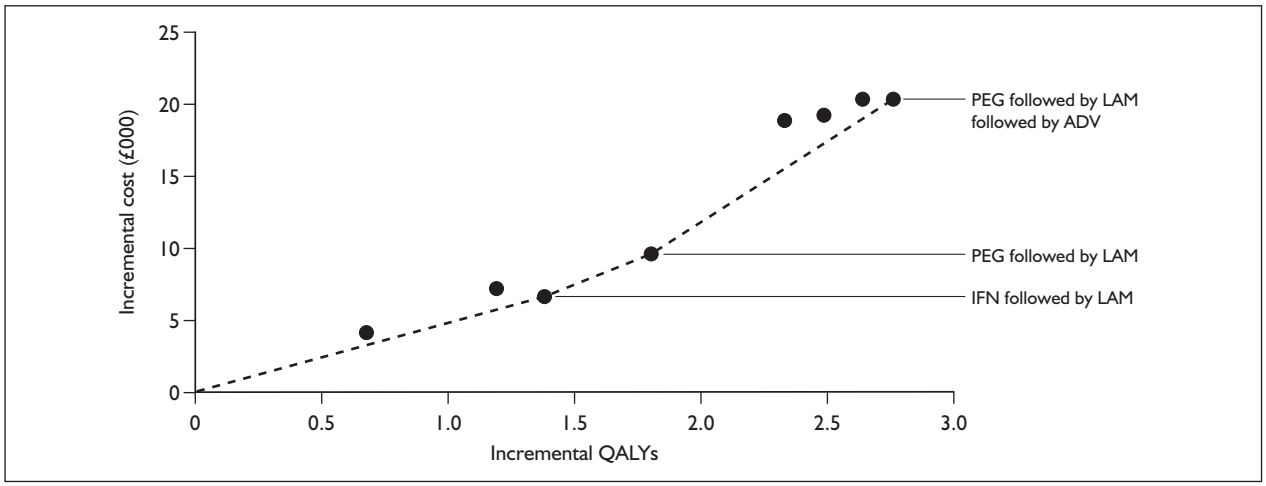

FIGURE 1 *Incremental cost-effectiveness and cost-effectiveness frontier results (previous report[12]).*

- efficacy of long-term treatment with ADV (whether or not treatment effects observed in clinical trials were extrapolated beyond the time horizon of the trials)
- relapse of HBeAg-negative patients following treatment with PEG-α-2a
- HBeAg seroconversion probability of patients with compensated cirrhosis receiving antiviral treatment, particularly for strategies including ADV.

Summary of findings of current review and implications for economic model

This update has identified:

- a recently published study of health-related quality of life in patients with CHB which estimated relevant state-specific utility weights using a preference-based method[56] suitable for updating our model (see earlier in this chapter)
- RCT evidence on the clinical effectiveness of PEG-α-2b, compared with IFN-α-2b (see Chapter 3, HBeAg loss/seroconversion), which can be used in our model to estimate the cost-effectiveness of PEG α-2b.

Costs and outcomes in our previous report were discounted at different rates (6% for costs and 1.5% for outcomes) in accordance with NICE methodological guidance applicable at the time the review was conducted. Since then it has become accepted practice (including in updated NICE methodological guidance) to discount both costs and outcomes at 3.5%. These rates were applied in this update.

In addition, while the cost of all drug treatments have not changed since our previous report was completed, we have updated monitoring and health-state costs used in the original report to 2006–7 prices. This enables an assessment of the robustness of the original report's findings to changes in costs as well as to assumptions over quality of life for treated patients.

The update identified no requirement to change assumptions regarding disease progression in the model.

Estimation of cost-effectiveness

Specification of changed inputs

Health-state utilities applied in the updated model are reported in *Table 31*. The first set of values adopted is based on the age- and sex-adjusted valuations for UK infected patients reported by Levy and colleagues.[56] As discussed earlier, Levy and colleagues[56] did not elicit health-state valuations for treatment response or seroconversion states. We have assumed, in this first set of valuations, that there is a 0.1-point increase in health-state utility for patients who HBeAg seroconvert or who lose the surface antigen (see *Table 31*, set 1). This was based on the difference between the average utility estimated for uninfected respondents' current health (mean = 0.87 and median = 0.95) and the average utility estimated for CHB in the same group (mean = 0.76 and median = 0.85). This utility gain is more than double the value of 0.04 applied in our original model, based on values estimated by Wong and colleagues.[8] We assessed the robustness of our results to this assumption using two further sets of weights in a sensitivity analysis. These utility

weights were identical to those in set 1 with the following exceptions:

- In the first sensitivity analysis, no utility gain was applied for HBeAg seroconversion or losing the surface antigen (i.e. the health-state utility value of 0.69, for chronic hepatitis B, was also applied to HBeAg-seroconverted and HBsAg-seroconverted health states).
- In a second sensitivity analysis, no utility gain was applied for HBeAg seroconversion, but it was assumed that patients who lose the surface antigen have the same utility as the uninfected population (i.e. the 0.10 utility gain was applied only to the HBsAg-seroconverted health state).
- In a third sensitivity analysis, the smaller gain of 0.04 was applied for both HBeAg- and HBsAg-seroconverted health states.

The utility weights in set 1 were not related to age, in contrast to the approach adopted in the model developed for our previous report. To examine the robustness of the results to this assumption, we derived a further set of health-state utility weights, based on the valuations reported by Levy and colleagues,[56] but estimated as state-specific utility decrements (see *Table 31*, set 2). These utility decrements were applied to age-specific utility values, as in the previous report. As before, we assumed a 0.1-point increase in utility for patients who HBeAg seroconvert or who lose the surface antigen (compared with patients in the chronic hepatitis B health state). The robustness of our results to this assumption was tested in sensitivity analyses:

- In the first sensitivity analysis, no utility gain was applied for HBeAg seroconversion or losing the surface antigen (i.e. the –0.10 utility decrement for chronic hepatitis B was also applied to the age-specific utility values for patients in the HBeAg-seroconverted and HBsAg-seroconverted health states).
- In a second sensitivity analysis, no utility gain was applied for HBeAg seroconversion, but it was assumed that patients who lose the surface antigen experience have the same utility as the general populations (i.e. the –0.10 utility decrement for chronic hepatitis B was also applied to the age-specific utility values only for patients in the HBeAg-seroconverted health state).
- In a third sensitivity analysis, the smaller gain of 0.04 adopted in our previous report was applied.

TABLE 31 *Health-state utilities applied in updated model (based on Levy* et al.*[56])*

	Health-state utility	
Health state	**Set 1**	**Set 2[a]**
HBsAg seroconverted	0.79	0.00
HBeAg seroconverted	0.79	0.00
Chronic hepatitis B	0.69	–0.10
Compensated cirrhosis	0.68	–0.11
Decompensated cirrhosis	0.35	–0.44
Hepatocellular carcinoma	0.42	–0.37
Liver transplantation		
Year of transplantation	0.57	–0.22
Years following year of transplantation	0.66	–0.13

a State-specific utility decrements.

TABLE 32 *Updated treatment monitoring costs adopted in model (2006–7 prices)*

Health state	Cost (£)
Evaluation of a new patient	376
Tests prior to initiation of treatment	1024
Monitoring/management for 24 weeks of conventional IFN	464
Monitoring/management for 48 weeks of PEG-α	890
Monitoring/management for each year of LAM or ADV treatment	524

TABLE 33 *Updated health-state costs adopted in model (2006–7 prices)*

Health state	Cost (£)
HBsAg seroconverted	0
HBeAg seroconverted	290
Chronic hepatitis B	584
Compensated cirrhosis	1341
Decompensated cirrhosis	10,750
Hepatocellular carcinoma	9580
Liver transplantation	
Cost of transplant	32,215
First year following transplant	11,149
Subsequent years following transplant	1633

TABLE 34 *Response to treatment with PEG-α-2b*

	PEG-α-2b	IFN-α
HBeAg seroconversion (24 weeks' treatment, follow-up at 48 weeks),[27] *n/N* (%)	25/115 (21.7)	16/115 (13.9)

Tables 32 and *33* report the inflated costs applied in the model. Costs derived for the previous report were inflated to 2006–7 prices using the Hospital and Community Health Services (HCHS) Pay and Prices Index.[61]

Table 34 reports treatment responses to PEG-α-2b included in the model, based on the results of the RCT by Zhao and colleagues[27] as reported in Chapter 3, HBeAg loss/seroconversion.

The frequency and intensity of monitoring of patients being treated with IFN-α-2b or PEG-α-2b were based on protocols developed for 24 weeks of treatment with IFN-α, described in our previous report.[12] Updated costs for monitoring patients receiving 24 weeks of IFN-α are reported in *Table 32*. In this costing we assumed that patients would be seen 10 times, during a 24-week treatment period, corresponding to weekly visits for the first month of treatment, then fortnightly for the second month and then monthly visits. The protocol stated that full blood counts, liver function tests, urea and electrolytes and blood clotting tests would be assessed at each consultation, with a more detailed assessment undertaken every 3 months (during which HBeAg and HBsAg serology, HBV DNA and thyroid function were assessed). The detailed assessments also included screening for hepatocellular carcinoma using abdominal ultrasound and α-fetoprotein tests. Standard consultations were assumed to take 30 minutes, whereas the detailed assessments were assumed to require 1 hour of clinical time. All assessments for treated patients were assumed to be performed by specialist nurses.

Drug costs for IFN-α-2b were calculated for a dosage of 3 million units of IntronA® (Schering–Plough), self-administered by patients three times per week, as used in the trial reported by Zhao and colleagues.[27] Unit costs of £77.76 for a 1.5-ml multidose cartridge (at a concentration of 15 million units/ml, which delivers six doses of 0.2 ml) were taken from the *British National Formulary*.[62] This corresponds to a cost per 3-million-unit injection of £12.96, a weekly cost of £38.88 and a total drug cost of £933.12 for a 24-week course of treatment.

Drug costs for PEG-α-2b were calculated for a dosage of 1.0 mg/kg of PegIntron® (Schering–Plough), self-administered by patients once per week. Assuming an average body weight of 79 kg, this would require one 80 µg vial per week. The unit cost, from the *British National Formulary*, is £108.00, which includes injection equipment and water for injections. This corresponds to a total drug cost of £2592 for a 24-week course of treatment.

Results from updated model

Applying alternative utility sets – base case

Table 35 reports total cost, discounted life expectancy and discounted QALYs for the overall cohort of patients with HBeAg-positive and HBeAg-negative CHB modelled in our previous report, using updated assumptions on health-state utility (utility set 1), updated costs and applying a discount rate of 3.5% for both costs and benefits. Incremental cost-effectiveness ratios are substantially higher than for the base case reported in our previous report (see *Table 30*). Total costs are between 23% and 45% higher, while discounted QALYs are 27–28% lower. However, much of this difference arises from the change in discount rates, rather than from changes in utility weights or inflating costs to current prices. For example, for IFN-α the same analysis, but using discount rates of 6% for costs and 1.5% for QALYs, yields total costs of £13,768, total QALYs of 16.96 and an ICER of £6981 relative to best supportive care, which is broadly comparable to the ICER of £5994 from our previous report.

The cost-effectiveness frontier in *Figure 2* shows that allowable interventions (in cost-effectiveness terms) are the same as for the analysis based on our previous report (shown in *Figure 1*). These are: IFN-α followed by LAM (ICER = £8552 per QALY gained relative to best supportive care), PEG-α-2a followed by LAM (ICER = £12,801 relative to IFN-α followed by LAM) and PEG-α-2a followed by LAM followed by ADV (ICER = £26,379 relative to PEG-α-2a followed by LAM).

Again, much of the difference with the results based on our previous model (reported earlier in this chapter) is due to changes in discount rate. As an example, ICERs for these strategies, discounted at 6% for costs and 1.5% for outcomes are: IFN-α

TABLE 35 *Cost-effectiveness results applying updated utility set 1 (derived from Levy* et al.[56]*)*

Strategy	Cost (£)	Discounted life expectancy	Discounted QALYs	ICER
Best supportive care	12,433	16.42	11.97	
IFN-α	16,482	16.86	12.35	10,492
IFN-α followed by LAM	19,376	17.35	12.78	6794[a]
IFN-α followed by ADV	34,268	17.97	13.31	18,615[b]
IFN-α followed by LAM followed by ADV	35,494	18.08	13.39	26,271[c]
PEG-α-2a	19,564	17.18	12.62	11,459
PEG-α-2a followed by LAM	22,228	17.62	13.00	12,800[d]
PEG-α-2a followed by ADV	35,557	18.16	13.47	7833[e]
PEG-α-2a followed by LAM followed by ADV	36,398	18.25	13.54	6173[f]

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
a Comparing IFN-α-2a followed by LAM with IFN-α-2a alone.
b Comparing IFN-α-2a followed by ADV with IFN-α-2a alone.
c Comparing IFN-α-2a followed by LAM followed by ADV salvage with IFN-α-2a followed by LAM.
d Comparing PEG-α-2a followed by LAM with IFN-α-2a followed by LAM.
e Comparing PEG-α-2a followed by ADV with IFN-α-2a followed by ADV.
f Comparing PEG-α-2a followed by LAM followed by ADV salvage with IFN-α-2a followed by LAM followed by ADV salvage.

followed by LAM (ICER = £5367 per QALY gained relative to best supportive care), PEG-α-2a followed by LAM (ICER = £8192 relative to IFN-α followed by LAM) and PEG-α-2a followed by LAM followed by ADV (ICER = £12,171 relative to PEG-α-2a followed by LAM).

Results for separate cohorts of HBeAg-positive and HBeAg-negative patients are reported in Appendix 7.

Applying alternative utility sets – deterministic sensitivity analysis

A series of one-way sensitivity analyses was conducted using the updated model, based on the range of values and sources of uncertainty reported in sensitivity analyses in our previous review.[12] These are reported in *Table 36*. To simplify the presentation and interpretation of the cost-effectiveness estimates in the sensitivity analyses,

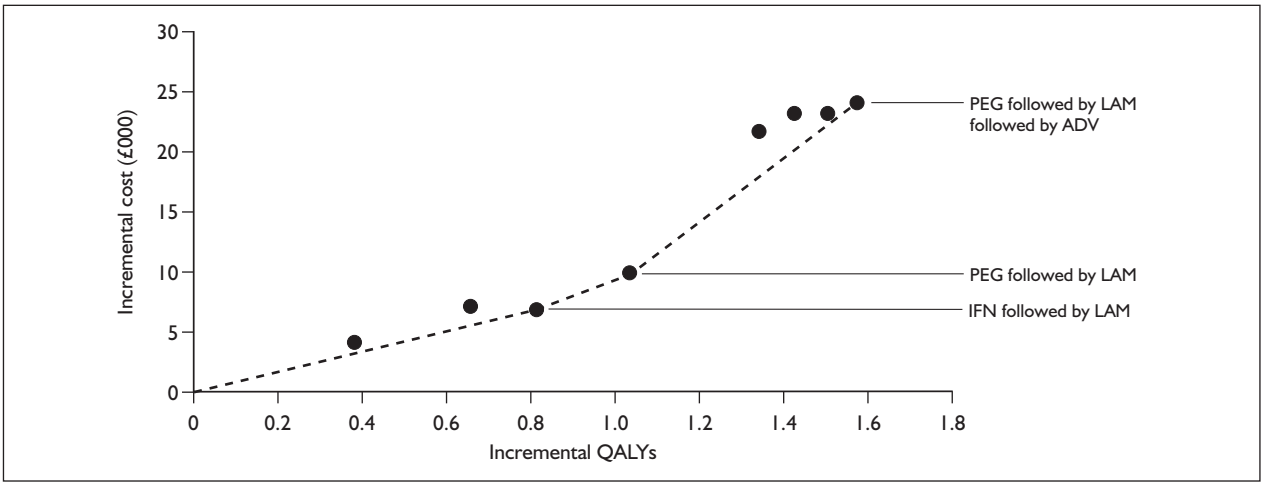

FIGURE 2 *Incremental cost-effectiveness and cost-effectiveness frontier, applying utility set 1.*

DOI: 10.3310/hta13350

TABLE 36 *Deterministic sensitivity analysis for sequential treatment strategies in updated model [ICERs (£)]*

	IFN-α	PEG-α-2a	IFN-α then LAM	PEG-α-2a then LAM	IFN-α then ADV	IFN-α then LAM then ADV	PEG-α-2a then ADV	PEG-α-2a then LAM then ADV
Baseline analysis			8552	12,801				26,379
Structural assumptions								
Zero transition probability from compensated cirrhosis to HBeAg-seroconverted state			8956	11,853				40,833
Zero transition probability from HBeAg-seroconverted state to HCC			8363	12,605				25,950
Zero transition probability to HBsAg-seroconverted state			8636	12,683				27,028
Methodological uncertainty								
Discount rates (6.0% for costs and 1.5% for outcomes)			5367	8192				12,171
Discount rates (0.0% for costs and 0.0% for outcomes)			4362	5672			16,206	16,601
Baseline cohort characteristics								
HBeAg-positive cohort, 50% male			8503	12,758				26,154
HBeAg-negative cohort, 50% male			8489	12,544				26,278
Baseline cohort, 50% HBeAg positive			8406	8933				30,559
Change age of cohort at start of simulation	−5 years		8135	11,892				24,886
	+ 5 years		9117	14,086				28,331
	+ 10 years		9895	15,932				30,921

continued

TABLE 36 *Deterministic sensitivity analysis for sequential treatment strategies in updated model [ICERs (£)] (continued)*

	IFN-α	PEG-α-2a	IFN-α then LAM	PEG-α-2a then LAM	IFN-α then ADV	IFN-α then LAM then ADV	PEG-α-2a then ADV	PEG-α-2a then LAM then ADV
Parameter uncertainty								
Varying rate of ADV resistance + 0.02			8552	12,801				26,116
+ 0.04			8552	12,801				25,911
+ 0.06			8552	12,801				25,751
+ 0.08			8552	12,801				25,626
No utility gain from seroconversion			10,425	14,712				31,114
No utility gain from HBeAg seroconversion, but 0.1 utility gain from HBsAg seroconversion			10,049	14,300				30,107
Utility gain (+ 0.04) from seroconversion			9585	13,883				29,030
Age-specific utilities (with health-state decrements based on Levy *et al.*[56])			8287	12,597				25,883
Age-specific utilities, as above (no utility gain from HBeAg or HBsAg seroconversion)			10,034	14,443				30,426
Age-specific utilities, as above (no gain from HBeAg, but 0.1 utility gain from HBsAg seroconversion)			9685	14,046				29,463
Double cost for compensated cirrhosis state (to £2683)			8062	11,974				26,122
Reduce PEG-α cost by 20%				8241				26,379
Reduce ADV cost by 20%			8552	12,801			21,981	26,487
Reduce ADV and PEG-α cost by 20%				8241			21,981	26,487
Reduce ADV and PEG-α cost by 30%				7629			18,827	33,354

HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio.

we report ICERs only for the optimal strategies in each analysis (using the methods for identifying the cost-effectiveness frontier and for excluding strategies using the principle of extended dominance, as described for *Figure 1*.

In this sensitivity analysis, the selection of optimal strategies is generally robust to changes in structural assumptions, baseline characteristics and parameter values. As with the base-case analysis, the optimal treatment sequence was generally identified as IFN-α or PEG-α-2a, followed by LAM, reserving ADV as a salvage strategy for patients who develop LAM resistance. The estimated ICERs are also generally robust to changes applied in the sensitivity analysis. However, changes in some key assumptions produce less favourable cost-effectiveness estimates than the base case adopted for this analysis:

- Assuming that patients with compensated cirrhosis cannot achieve HBeAg seroconversion produces a significantly less favourable ICER for the treatment strategy containing ADV as salvage for patients who develop LAM resistance. In contrast, the ICERs for IFN-α or PEG-α-2a followed by LAM are largely insensitive to this changed structural assumption.
- Reducing the proportion of the baseline cohort that has HBeAg-positive CHB also produces a less favourable ICER for the strategy including ADV (relative to PEG-α-2a followed by LAM), while the cost-effectiveness of PEG-α-2a followed by LAM improves (relative to IFN-α followed by LAM).
- Cost-effectiveness estimates for all treatment strategies are less favourable with increasing patient age at start of treatment. QALY gains from interventions are reduced by 15–20%, whereas incremental costs are reduced by 2–6%.
- Reducing the utility gain from seroconversion (to either no utility gain or using the lower value of 0.04 used in our previous report) gives a less favourable ICER than for the base case.

Reducing drug costs for PEG-α-2a leads to the elimination of 'IFN-α followed by LAM' from the sequence of optimal strategies and leads to an improvement in the cost-effectiveness of PEG-α-2a followed by LAM (relative to best supportive care).

Applying alternative discount rates (6% for costs and 1.5% for outcomes, as in our previous report, or 0% for both costs and outcomes) produces more favourable ICERs than the base case – reducing the ICER for PEG-α-2a followed by LAM with ADV as salvage from £26,379 to £12,171 (relative to PEG-α-2a followed by LAM).

Applying alternative utility sets – probabilistic sensitivity analysis

A probabilistic sensitivity analysis was undertaken using utility set 1 (see *Table 31*), updated costs (see *Tables 32* and *33*) and a discount rate of 3.5% for both costs and outcomes. The utilities were sampled from beta distributions with parameters calculated using the method of moments[63] (using the reported mean values and standard errors derived from 95% CIs reported for UK infected patients by Levy and colleagues[56]) (see Appendix 6 for full details). Health-state costs were sampled from gamma distributions with parameters calculated using the method of moments (see Appendix 6 for full details).

Table 37 reports the mean cost and QALYs (with percentile-based 95% CIs) and the ICERs for the sequential strategies from the probabilistic sensitivity analysis. The mean discounted QALYs are close to those in the deterministic base-case analysis. However, the mean costs are around £1500 lower for each strategy.

Figure 3 shows the cost-effectiveness acceptability curves (CEACs) for all interventions included in the analysis of sequential treatment strategies. As with our previous report, this suggests that IFN-α-2a or PEG-α-2a followed by LAM would be the optimal strategy at lower threshold values of willingness to pay, but as the threshold increases the sequential treatment strategy including ADV salvage is increasingly likely to be the optimal intervention.

In contrast with our previous report,[12] this strategy (interferon followed by LAM with ADV as salvage) becomes optimal only at the upper range of ICERs conventionally deemed as cost-effective from an NHS decision-making perspective. This is reinforced by *Figure 4* which shows the cost-effectiveness acceptability frontier[64] for the analysis based on our previous report (*Figure 4a*) and using the updated model (*Figure 4b*). The cost-effectiveness acceptability frontier comprises those portions of the CEAC where interventions are deemed optimal (using the maximum net benefit criterion) over a range of willingness-to-pay values. This clearly illustrates that interferon alpha followed by LAM is optimal, using the updated model, over a wider range of willingness-to-pay values (£9000–£12,000 for IFN-α followed by LAM

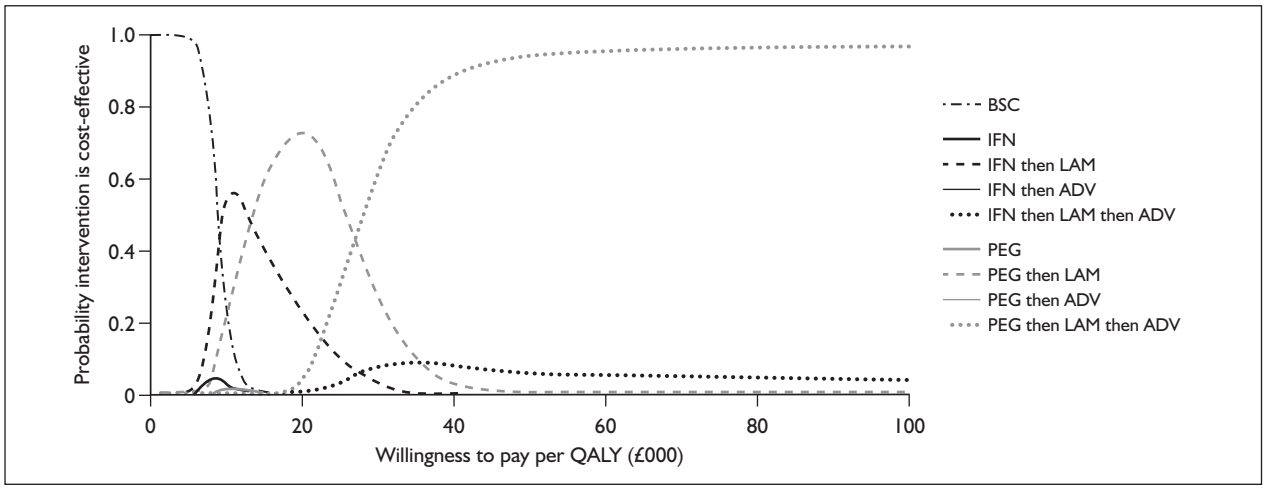

FIGURE 3 *Cost-effectiveness acceptability curves for sequential treatment strategies in overall cohort of patients with HBeAg-positive and HBeAg-negative CHB.*

and £13,000–£26,000 for PEG-α followed by LAM) than in the analysis based on the previous report (£5000–£6500 for conventional IFN followed by LAM and £7000–£11,500 for PEG-α followed by LAM). As discussed earlier, this arises largely as a result of the change in discount rates applied in the updated model.

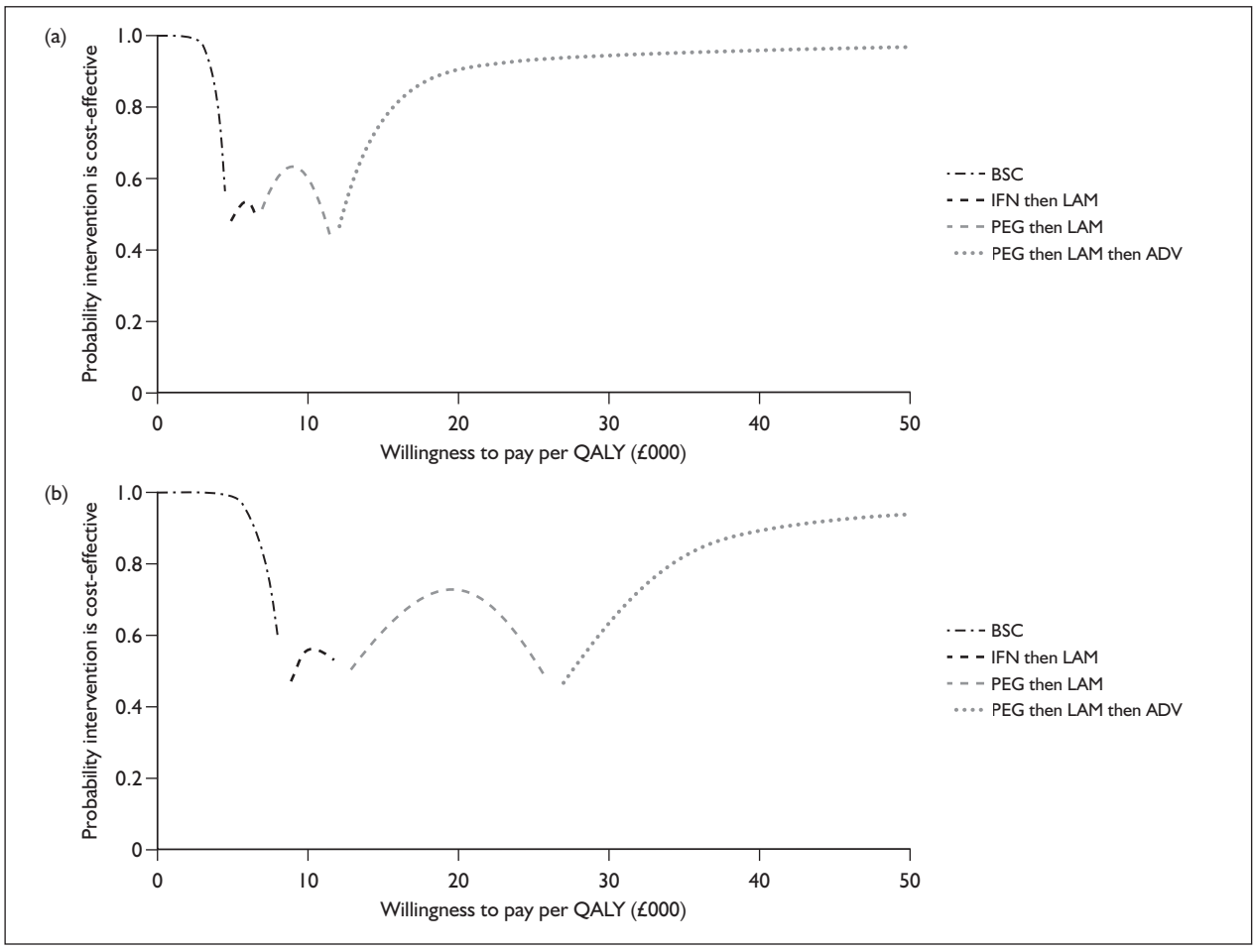

FIGURE 4 *Cost-effectiveness acceptability frontier based on analysis in original assessment report and on updated model. (a) Cost-effectiveness acceptability frontier based on analysis in original assessment report. (b) Cost-effectiveness acceptability frontier based on updated model.*

TABLE 37 *Costs and outcomes from probabilistic analysis of sequential strategies*

Strategy	Discounted costs [£ (95% CI)]	Discounted QALYs (95% CI)	ICER (£ per QALY gained)
Best supportive care	11,007 (9079–13,335)	11.99 (11.07–12.77)	
IFN-α	15,024 (13,164–17,289)	12.38 (11.46–13.16)	10,334
IFN-α followed by LAM	17,881 (15,881–20,184)	12.80 (11.86–13.61)	6759[a]
IFN-α followed by ADV	32,713 (28,737–37,153)	13.32 (12.40–14.11)	18,815[b]
IFN-α followed by LAM followed by ADV	33,946 (29,470–39,012)	13.40 (12.47–14.20)	26,762[c]
PEG-α-2a	18,128 (16,265–20,309)	12.65 (11.74–13.45)	11,336
PEG-α-2a followed by LAM	20,744 (18,745–23,119)	13.03 (12.09–13.86)	12,578[d]
PEG-α-2a followed by ADV	33,966 (29,677–38,788)	13.48 (12.56–14.29)	7412[e]
PEG-α-2a followed by LAM followed by ADV	34,810 (30,068–40,213)	13.55 (12.62–14.33)	5,732[f]

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
a Comparing IFN-α-2a followed by LAM with IFN-α-2a alone.
b Comparing IFN-α-2a followed by ADV with IFN-α-2a alone.
c Comparing IFN-α-2a followed by LAM followed by ADV salvage with IFN-α-2a followed by LAM.
d Comparing PEG-α-2a followed by LAM with IFN-α-2a followed by LAM.
e Comparing PEG-α-2a followed by ADV with IFN-α-2a followed by ADV.
f Comparing PEG-α-2a followed by LAM followed by ADV salvage with IFN-α-2a followed by LAM followed by ADV salvage.

Cost-effectiveness of PEG-α-2b – base case

Table 38 reports total cost, discounted life expectancy and discounted QALYs for a cohort of patients with HBeAg-positive CHB receiving 24 months of PEG-α-2b compared with 24 months of IFN-α-2b (based on HBeAg seroconversion rates reported by Zhao and colleagues[27]). This is based on the clinical effectiveness review (see Chapter 3).

The results suggest that PEG-α-2b is a cost-effective alternative to IFN-α-2b for the treatment of patients with CHB. In the absence of a comparison with best supportive care, this analysis implicitly assumes that IFN-α-2b is a cost-effective option and a current standard of care. Supportive care has not been included in this analysis as the trial reported by Zhao and colleagues[27] did not include a placebo or no treatment arm. No trials comparing IFN-α-2b with placebo or no treatment were included in the clinical effectiveness review reported in Chapter 3.

Cost-effectiveness of PEG-α-2b – deterministic sensitivity analysis

Table 39 reports a series of one-way sensitivity analyses based on the range of values and sources of uncertainty reported in sensitivity analyses in our previous review.[12]

The ICERs are generally robust to changes in structural assumptions, baseline characteristics and parameter values. However, changes in some key assumptions produce less favourable cost-effectiveness estimates than the base case adopted for this analysis:

TABLE 38 *Cost-effectiveness results for PEG-α-2b*

Strategy	Cost (£)	Discounted life expectancy	Discounted QALYs	ICER (£ per QALY gained)
IFN-α-2b	12,610	18.20	13.57	
PEG-α-2b	14,067	18.35	13.73	9169

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

TABLE 39 *Deterministic sensitivity analysis of cost-effectiveness of PEG-α-2b compared with IFN-α2b*

	IFN-α-2b		PEG-α-2b		
	Cost (£)	**QALY**	**Cost (£)**	**QALY**	**ICER (£ per QALY gained)**
Baseline analysis	12,610	13.57	14,067	13.73	9169
Structural assumptions					
Zero transition probability from compensated cirrhosis to HBeAg-seroconverted state	13,801	12.62	15,222	12.81	7454
Zero transition probability from HBeAg-seroconverted state to HCC	12,545	13.65	13,998	13.81	8805
Zero transition probability to HBsAg-seroconverted state	14,853	12.91	16,325	13.08	8935
Discount rates (6% for costs and 1.5% for outcomes)	10,267	19.08	11,745	19.32	6225
Discount rates (0% for costs and 0% for outcomes)	19,124	26.07	20,559	26.41	4218
Baseline cohort characteristics					
HBeAg-positive cohort, 50% male	12,646	13.66	14,103	13.82	9090
Change age of cohort at start of simulation −5 years	12,772	14.02	14,230	14.19	8779
Change age of cohort at start of simulation + 5 years	12,392	13.03	13,848	13.18	9673
Change age of cohort at start of simulation + 10 years	12,102	12.38	13,557	12.52	10,340
Parameter uncertainty					
No utility gain from seroconversion (HBeAg or HBsAg)	12,610	12.45	14,067	12.56	13,415
No utility gain from HBeAg seroconversion, but 0.1 utility gain from HBsAg seroconversion	12,610	12.89	14,067	13.01	12,647
Utility gain (+ 0.04) from seroconversion	12,610	12.90	14,067	13.03	11,311
Age-specific utilities (with health-state decrements based on Levy *et al*.[56])	12,610	14.91	14,067	15.07	8884
Age-specific utilities, as above (no utility gain from HBeAg or HBsAg seroconversion)	12,610	13.79	14,067	13.91	12,814
Age-specific utilities, as above (no gain from HBeAg but 0.1 utility gain from HBsAg seroconversion)	12,610	14.23	14,067	14.35	12,111
Double cost for compensated cirrhosis state (to £2683)	14,661	13.57	16,056	13.73	8780
Reduce PEG-α-2b cost by 20%	12,610	13.57	13,548	13.73	5906

HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

TABLE 40 *Costs and outcomes from probabilistic analysis of PEG-α-2b compared with IFN-α-2b*

Strategy	Discounted costs [£ (95% CI)]	Discounted QALYs (95% CI)	ICER (£ per QALY gained)
IFN-α-2b	12,669 (10,524–15,252)	13.58 (12.41–14.57)	
PEG-α-2b	14,119 (12,066–16,617)	13.74 (12.57–14.71)	8930

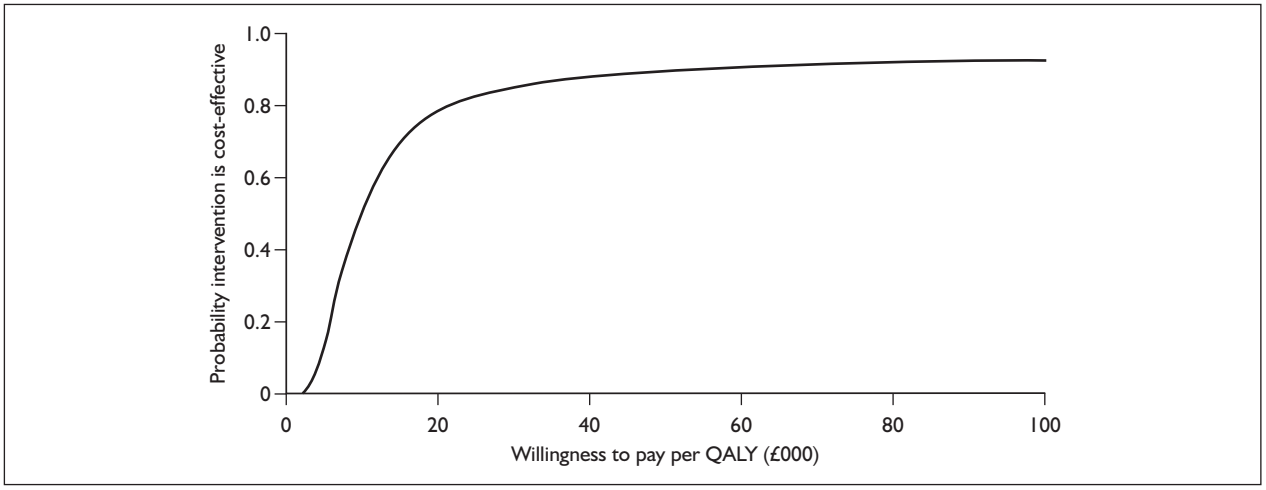

FIGURE 5 *Cost-effectiveness acceptability curve for PEG-α-2b in patients with HBeAg-positive CHB.*

- Cost-effectiveness estimates for all treatment strategies are less favourable with increasing patient age at start of treatment. QALY gains from interventions are reduced by 5–12%, whereas incremental costs reduce by less than 1%.
- Reducing the utility gain from HBeAg seroconversion (to either no utility gain or using the lower value of 0.04 used in our previous report) gives a less favourable ICER than for the base case.

Reductions in drug costs for PEG-α-2b and the use of alternative discount rates are associated with more favourable cost-effectiveness estimates in the sensitivity analysis. Reducing drug costs for PEG-α-2b by 20% leads to a 4% reduction in total costs associated with PEG-α-2b, reducing the ICER to £5906. Using discount rates that applied at the time we conducted our previous review (6% for costs and 1.5% for outcomes), the ICER reduces to £6225. Applying zero discount rates, the ICER reduces to £4218.

In all analyses the ICER is below the threshold usually taken to define cost-effectiveness from an NHS decision-making perspective.

Cost-effectiveness of PEG-α-2b – probabilistic sensitivity analysis

A probabilistic sensitivity analysis was undertaken using utility set 1 (see *Table 31),* updated costs (see *Tables 32* and 33) and a discount rate of 3.5% for both costs and outcomes. The utilities were sampled from beta distributions with parameters calculated using the method of moments[63] (using the reported mean values and standard errors derived from 95% CIs reported for UK infected patients by Levy and colleagues[56]) (see Appendix 6 for full details). Health-state costs were sampled from gamma distributions with parameters calculated using the method of moments (see Appendix 6 for full details).

Table 40 reports the mean discounted cost and mean discounted QALYs (with percentile-based 95% CIs) for IFN-α-2b and PEG-α-2b from the probabilistic evaluation of the model. *Table 40* also reports the ICER for PEG-α-2b compared with IFN-α-2b, based on the mean discounted cost and mean discounted QALYs. The results from the probabilistic evaluation of the model are similar to those in the deterministic base-case analysis.

Figure 5 shows the CEACs for PEG-α-2b for patients with HBeAg-positive CHB. This suggests that PEG-α-2b is likely to be a cost-effective option for the treatment of HBeAg-positive CHB, in comparison with IFN-α-2b.

In the probabilistic sensitivity analysis PEG-α-2b had a probability of being cost-effective (compared with IFN-α-2b) of 79% at a willingness-to-pay threshold of £20,000 per QALY, and 86% at a willingness-to-pay threshold of £30,000 per QALY.

Chapter 5
Discussion

Assessment of clinical effectiveness

The trials included in this report were diverse in terms of aims, comparators and design characteristics. This prohibited quantitative meta-analysis and also made it difficult to provide an overall narrative summary of outcomes. The general finding is that both ADV and PEG-α-2b are associated with benefits across a range of outcomes (virological, biochemical and histological), with relatively few adverse effects and, in the case of ADV, relatively low viral resistance. This finding is similar to that of our previous assessment report of ADV and PEG-α-2a.[12]

Although both drugs appeared to be superior to their comparators, there were no consistent statistically significant differences. In many cases, no statistical tests were reported to confirm superiority, and some trials were small and probably underpowered. Uncertainties therefore exist regarding comparative efficacy and safety.

Benefits were not always sustained after treatment cessation, suggesting the need for ongoing treatment. This report was able to include evidence on the durability of effects of continued treatment from follow-up studies included in our original report. The 5-year follow-up study, based on the RCT by Hadziyannis and colleagues,[20] reported that favourable changes in viral load, biochemical markers and liver histology were generally sustained. After 5 years of ADV, the cumulative resistance rate was 29%, lower than the 60% rate associated with LAM after 4 years of treatment.[20] The relatively low rates of resistance to ADV are encouraging, particularly as HBeAg-negative patients are likely to require maintenance treatment over a long period. However, caution is required in the interpretation of these results as they were derived from an observational cohort study arising from an RCT.

Other RCTs included in our original assessment report were ongoing and fully published results would have been expected at the time of our update search. For example, at the termination of the double-blind phase of the RCT of ADV versus placebo in HBeAg-positive patients (Marcellin and colleagues,[65] ADV Study 437, see Appendix 3), all patients were assigned to receive ADV for up to 5 years. This was similar in design to the follow-up study in HBeAg-negative patients conducted by Hadziyannis and colleagues. Fully published results of this study, if and when available, would complement those already reported, illustrating durability in HBeAg-positive patients. This is a group of patients who, in the absence of HBeAg seroconversion, are likely to require ongoing treatment.

This report identified fully published RCT evidence for the effectiveness of adding ADV to LAM in LAM-resistant HBeAg-negative patients.[18] Our previous report identified RCTs of this kind only in HBeAg-positive patients.[66,67] The RCT included in this update failed to identify any significant differences between treatments in clinical outcomes, although there was a statistically significant difference between groups favouring combination therapy in terms of ADV resistance (a zero rate). Caution is advised as the trial appeared to be small, underpowered and generally methodologically weak, in common with the previous trials.[66,67] Therefore, the evidence base for treatment of LAM-resistant patients is generally poor and good quality RCTs are needed.

PEG-α-2b is associated with some degree of benefit, although the results of the trials were inconsistent, which may be partly the result of variable methodological quality. In terms of HBeAg seroconversion, which expert clinical opinion suggests would be one of the goals of IFN-based treatment, PEG-α-2b appears broadly comparable to PEG-α-2a. For example, in the trial by Janssen and colleagues,[26] the proportion of seroconverted patients who received 1 year of PEG-α-2b and LAM was 25% at follow-up, compared to 27% for those who received 1 year of PEG-α-2a and LAM (Lau and colleagues[50]). Caution is advised as no head-to-head RCTs have been identified and this is not a formal statistical indirect comparison.

In terms of initiating therapy with a combination therapy, the only studies identified by our update search were those featuring PEG-α-2b and LAM.

Such trials have limited applicability as PEG-α is indicated only in patients with compensated liver disease, and may not be tolerated by all patients. There has been much interest in the initiation of therapy with combined nucleoside/nucleotide agents, particularly as a way of minimising the risk of drug resistance. No such trials were found in our search; however, as this report was being finalised, an RCT of LAM in combination with ADV, versus ADV and placebo in HBeAg-positive treatment-naive patients was published (Sung and colleagues[68]). (Note that a conference abstract reporting interim results of this trial was described in our previous report.) Combination therapy was more effective than monotherapy on some measures, including LAM resistance. This trial will be fully included in any future updates of this report.

It has been argued that use of sequential monotherapies increases the risk of drug resistance and may potentially limit treatment options, as has been the case in the management of other infectious diseases such as HIV.[69] Given the interest in de novo combination therapy as a means of reducing the likelihood of multidrug resistance in CHB, there is a need for further trials of this modality, particularly of nucleoside/nucleotide analogues. Fortunately, there is an increasing number of potential treatment options open to clinicians and patients. Newer nucleoside analogues are becoming available, including entecavir, telbivudine and tenofovir. Licensing trials of these drugs have tended to assess the efficacy and safety of their use as monotherapies.[70–73] High-quality RCTs are needed to assess appropriate combinations of these and other drugs in treatment-naive patients, and these should be carefully designed to minimise the risk of cross-resistance (e.g. entecavir and telbivudine in combination). Trials should be conducted in both HBeAg-positive and -negative patients, with long-term treatment, particularly for negative patients (e.g. at least 5 years).

Few other systematic reviews have been published to which the results of this review can be compared. None featuring ADV was identified in the production of this report, and only one of PEG-α was located (Hui and colleagues[74]). The latter included RCTs of both PEG-α-2a and -2b, and its results were comparable with our current and previous reports.[12]

A limitation of this report is the fact that only published evidence was considered for inclusion. Conference abstracts reporting long-term follow-up of some of the RCTs included in our original report are available, but have not been included in the current report. A more detailed discussion of uncertainties and limitations can be found in our previous assessment report.[12]

Assessment of cost-effectiveness

Systematic review of economic evaluations

The majority of the cost-effectiveness studies reviewed in this report were direct evaluations of PEG-α-2a versus LAM (Veenstra and colleagues[44] and Sullivan and colleagues[45]) or LAM (with or without ADV salvage for LAM-resistant patients) versus ADV (Buti and colleagues[47] and Kanwal and colleagues[38]). There are no published economic evaluations of the entire spectrum of alternative therapies for CHB (i.e. including the new pharmacotherapies entecavir and telbivudine) conducted from the NHS perspective, nor any evaluations of combinations of nucleotide/nucleoside analogues in LAM-naive patients. Evaluation of the new medications was outside the scope of this report. Contrary to expectations, our searches did not capture studies reporting the effectiveness (in terms of drug resistance) of nucleoside/nucleotide analogue combination therapy in LAM-naive (or non-resistant) patients on which to base further modelling.

The most comprehensive published economic evaluation that compares the broader range of alternative therapies in the general population of CHB patients was conducted in the US,[38] using a mix of health-care resources and prices that are unlikely to be applicable in the NHS context. The recently published adaptation of the unpublished Roche model,[44] while adopting an NHS perspective, includes only two medications (PEG-α-2a and LAM). There is, therefore, uncertainty remaining about the relative costs and effects of the entire range of treatment alternatives for CHB. A comprehensive economic evaluation of alternative antiviral treatments for CHB should be undertaken, from an NHS perspective, including new treatments [entecavir and telbivudine, which have received European marketing authorisation, and tenofovir, which has received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP)].

The recently published multinational study of assessment of quality of life by Levy and colleagues[56] is an important contribution to the

area. The study employed a preference-based method (standard gamble), based on patients' rather than clinicians' ratings. However, the UK sample size was small (about 200 people) and may not be representative of the entire population. While the results of the study are generally consistent with utility estimates used in previously published economic evaluations, this is mainly because of the large variation between the estimates used in previous studies, each of which involved a small number of clinicians to evaluate utility weight for each of the health states included in the model. There is a substantial disparity, in both absolute and relative terms, between utility values reported by Levy and colleagues[56] and those used in our previous economic evaluation.[12]

Update of SHTAC economic model

The model developed for our previous report[12] was updated to include:

- utility values based on those reported in Levy and colleagues[56]
- treatment monitoring and health-state costs updated to 2006–7 prices
- current discounting practice
- a separate analysis to include PEG-α-2b.

The ICERs in the updated analysis are generally less favourable than in our previous report. However, the same optimal treatment sequence [IFN (conventional or pegylated) followed by LAM with ADV salvage for patients who develop resistance] was identified in both analyses. Sensitivity analyses indicate that much of the difference between the results in the two reports arises from the change in discounting practice.

Key uncertainties in the model, identified in the sensitivity analyses, that affect the cost-effectiveness estimates were:

- Outcomes for patients with compensated cirrhosis who receive treatment – if the probability of HBeAg seroconversion is set to zero the ICER of strategies including ADV increases sharply.
- The size of utility gain from HBeAg seroconversion or loss of the surface antigen (HBsAg) – if there is no gain in utility, the incremental cost-effectiveness of all strategies is poorer.

While it is relatively common in trials of antiviral treatment for hepatitis C to report outcomes by stage of disease – identifying cirrhotic and non-cirrhotic patients separately – this is less common in CHB. Clearer identification of patients' outcome by stage of disease may enable more reliable and transparent modelling of the cost-effectiveness of antiviral treatments in this group of patients.

Uncertainty over the existence and size of the utility gain associated with response to treatment cannot be addressed using studies included in this review. The study by Levy and colleagues[56] did not include utility estimates for patients who HBeAg seroconverted or lost the surface antigen, nor did it consider quality of life for patients who remain chronically infected, but have low viral levels (which would characterise response to treatment in patients with HBeAg-negative CHB). Further research is required to derive utility estimates across the full range of health states relevant to HBeAg-negative and HBeAg-positive variants of CHB, using appropriate preference-based methods in a representative sample of the UK population.

A further source of uncertainty in the model concerns the relationship between patients with HBeAg-positive and HBeAg-negative CHB. The latter group have only recently been included in economic models of antiviral treatment and have traditionally had a limited evidence base on natural history and epidemiology. The two groups of patients have typically been enrolled in separate clinical trials or have been analysed separately, leading to them being included as two separate populations in economic models. However, it has been suggested that HBeAg-negative CHB may represent a late stage of CHB (reflected by the older average age for patients with HBeAg-negative CHB).[75] The implication of this for economic models of cohorts of CHB patients is that a proportion of patients who begin the model with HBeAg-positive CHB should move into the HBeAg-negative cohort. Currently, there is limited evidence on which to base such transitions. More robust evidence on the natural history of CHB and development of HBeAg-negative disease is needed to improve the robustness of economic models of antiviral treatments.

The absence of reliable evidence on the effectiveness (in terms of treatment resistance rather than HBeAg seroconversion or viral suppression) of combination treatments limits the scope for robust modelling of their long-term effectiveness and cost-effectiveness. Given that patients with HBeAg-negative CHB are likely to require long-term maintenance therapy, this is a major gap in knowledge and limits

reliable selection of optimal treatment strategies. The potential benefits offered by new antiviral treatments (in terms of reduced resistance profiles in comparison with LAM) may be compromised by the use of a well-tolerated, comparatively low-cost drug (LAM), with a poor resistance profile which may induce cross-resistance or promote more rapid development of resistance on switching to alternative therapies (such as ADV). However, in the absence of evidence of benefit, it is difficult to make a case for adopting a combination treatment that may cost up to four times as much as LAM monotherapy.

Chapter 6
Conclusions

Both ADV and PEG-α are beneficial for patients with CHB in terms of suppressing viral load, reducing liver damage-associated biochemical activity, inducing HBeAg seroconversion, and reducing liver fibrosis and necroinflammation. Emerging evidence suggests that benefits are durable when patients are treated with ADV for up to 5 years, with relatively low risk of resistance.

In terms of cost-effectiveness, the optimal treatment strategy is PEG-α followed by LAM, followed by ADV for patients developing LAM resistance. Further research should assess the clinical effectiveness and cost-effectiveness of newer antiviral agents in relation to existing drugs, including the role of initiating treatment with combination therapy.

Acknowledgements

We are grateful to Professor Geoffrey Dusheiko for commenting on a draft of this report.

We would also like to thank Emma Loveman of SHTAC for acting as internal editor of this report.

Contribution of authors

Jonathan Shepherd (Principal Research Fellow) developed the protocol. Alison Price (Information Scientist) undertook the literature searches. Jonathan Shepherd, Louise Baxter (Research Fellow), Debbie Hartwell (Research Fellow) and Petra Harris (Research Fellow) applied the inclusion criteria for the clinical effectiveness review. Jonathan Shepherd, Louise Baxter, Debbie Hartwell and Petra Harris performed the data extraction/quality assessment for the clinical effectiveness review. Elena Gospodarevskaya (Senior Research Fellow) applied the inclusion criteria and performed the data extraction/quality assessment for the cost-effectiveness review. Jeremy Jones (Principal Research Fellow) developed the economic modelling. Jonathan Shepherd, Louise Baxter, Debbie Hartwell, Petra Harris, Elena Gospodarevskaya, Jeremy Jones and Alison Price were involved in drafting the report.

References

1. Chu CM, Karayiannis P, Fowler MJ, Monjardino J, Liaw YF, Thomas HC. Natural history of chronic hepatitis B virus infection in Taiwan: studies of hepatitis B virus DNA in serum. *Hepatology* 1985;**5**:431–4.

2. Thomas HC. Best practice in the treatment of chronic hepatitis B: a summary of the European Viral Hepatitis Educational Initiative (EVHEI) 93. *J Hepatol* 2007;**47**:588–97.

3. De Franchis R, Hadengue A, Lau G, Lavanchy D, Lok A, McIntyre N, *et al*. EASL international consensus conference on hepatitis B. Switzerland: Geneva; 13–14 September 2002. Consensus statement (long version). *J Hepatol* 2003;**39**:S3–25.

4. Carman WF, Jacyna MR, Hadziyannis S, Karayiannis P, McGarvey MJ, Makris A, *et al*. Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection. *Lancet* 1989;**2**:588–91.

5. Lai CL, Ratziu V, Yuen MF, Poynard T. Viral hepatitis B. *Lancet* 2003;**362**:2089–94.

6. Department of Health. *Getting ahead of the curve*: *a strategy for combating infectious diseases (including other aspects of health protection)*. London: HMSO; 2002.

7. Pendleton S, Wilson-Webb P. Rising curve – chronic hepatitis B infection in the UK. Canterbury: Hepatitis B Foundation; 2007.

8. Wong JB, Koff RS, Tine F, Pauker SG. Cost-effectiveness of interferon-alpha 2b treatment for hepatitis B e antigen-positive chronic hepatitis B. *Ann Intern Med* 1995;**122**:664–75.

9. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis [see comment]. *Hepatology* 1998;**27**:209–12.

10. Pojoga C, Dumitrascu DL, Pascu O, Grigorescu M, Radu C, Damian D. Impaired health-related quality of life in Romanian patients with chronic viral hepatitis before antiviral therapy. *Eur J Gastroenterol Hepatol* 2004;**16**:27–31.

11. Nowak MA, Bonhoeffer S, Hill AM, Boehme R, Thomas HC, McDade H. Viral dynamics in hepatitis B virus infection. *Proc Natl Acad Sci USA*;1996;**93**:4398–402.

12. Shepherd J, Jones J, Takeda A, Davidson P, Price A. Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation. *Health Technol Assess* 2006;**10**(28).

13. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness*: *CRD's guidance for those carrying out or commissioning reviews*. CRD Report Number 4, 2nd edition. York: York Publishing Services; 2001.

14. Bonino F, Marcellin P, Lau GK, Hadziyannis S, Jin R, Piratvisuth T, *et al*. Predicting response to peginterferon alpha-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. *Gut* 2007;**56**:699–705.

15. Chow WC, Cooksley G, Chang WY, Manns M, Thongsawat S, Zhang HF, *et al*. Predicting response in a large, multinational trial of peginterferon alfa-2a (40 kDa + lamivudine vs lamivudine alone) in HBeAg-positive chronic hepatitis B. *Liver Int* 2005;**25**:1296–7.

16. Cooksley G, Manns M, Lau GKK, Liaw YF, Marcellin P, Chow WC, *et al*. Effect of genotype and other baseline factors on response to peginterferon alpha-2a (40 kDa) (PEGASYS) in HBeAg-positive chronic hepatitis B: results from a large, randomised study. *J Hepatol* 2005;**42**:30–1.

17. Hui CK, Zhang HY, Lee NP, Chan W, Yueng YH, Leung KW, *et al*. Serum adiponectin is increased in advancing liver fibrosis and declines with reduction in fibrosis in chronic hepatitis B. *J Hepatol* 2007;**47**:191–202.

18. Rapti I, Dimou E, Mitsoula P, Hadziyannis SJ. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B [see comment]. *Hepatology* 2007;**45**:307–13.

19. Zeng M, Mao Y, Yao G, Wang H, Hou J, Wang Y, *et al*. A double-blind randomized trial of adefovir dipivoxil in Chinese subjects with HBeAg-positive chronic hepatitis B. *Hepatology* 2006;**44**:108–16.

20. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, *et al*. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006;**131**:1743–51.

21. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, *et al*. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003;**348**:800–7.

22. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, *et al*. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B [see comment]. *N Engl J Med* 2005;**352**:2673–81.

23. Chan HL, Wong VW, Chim AM, Choi PC, Chan HY, Hui AY, *et al*. Virological response to different combination regimes of peginterferon alpha-2b and lamivudine in hepatitis B e antigen positive chronic hepatitis B. *Antivir Ther* 2007;**12**:815–23.

24. Chan HLY, Leung NWY, Hui AY, Wong VWS, Liew CT, Chim AML, *et al*. A randomized, controlled trial of combination therapy for chronic hepatitis B: comparing pegylated interferon-alpha 2b and lamivudine with lamivudine alone. *Ann Intern Med* 2005;**142**:240–50.

25. Kaymakoglu S, Oguz D, Gur G, Gurel S, Tankurt E, Ersoz G, *et al*. Pegylated interferon alfa-2b monotherapy and pegylated interferon alfa-2b plus lamivudine combination therapy for patients with hepatitis B virus e antigen-negative chronic hepatitis B. *Antimicrob Agents Chemother* 2007;**51**:3020–2.

26. Janssen HL, van ZM, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, *et al*. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2005;**365**:123–9.

27. Zhao H, Kurbanov F, Wan MB, Yin YK, Niu JQ, Hou JL, *et al*. Genotype B and younger patient age associated with better response to low-dose therapy: a trial with pegylated/nonpegylated interferon-alpha-2b for hepatitis B e antigen-positive patients with chronic hepatitis B in China. *Clin Infect Dis* 2007;**44**:541–8.

28. Chan HL, Hui AY, Wong VW, Chim AM, Wong ML, Sung JJ. Long-term follow-up of peginterferon and lamivudine combination treatment in HBeAg-positive chronic hepatitis B. *Hepatology* 2005;**41**:1357–64.

29. van Zonneveld M, Zondervan PE, Cakaloglu Y, Simon C, Akarca US, So TM, *et al*. Peg-interferon improves liver histology in patients with HBeAg-positive chronic hepatitis B: no additional benefit of combination with lamivudine. *Liver Int* 2006;**26**:399–405.

30. van Zonneveld M, Flink HJ, Verhey E, Senturk H, Zeuzem S, Akarca US, *et al*. The safety of pegylated interferon alpha-2b in the treatment of chronic hepatitis B: predictive factors for dose reduction and treatment discontinuation. *Aliment Pharmacol Ther* 2005;**21**:1163–71.

31. Buster EH, Hansen BE, Buti M, Delwaide J, Niederau C, Michielsen PP, *et al*. Peginterferon alpha-2b is safe and effective in HBeAg-positive chronic hepatitis B patients with advanced fibrosis. *Hepatology* 2007;**46**:388–94.

32. Flink HJ, van Zonneveld M, Hansen BE, de Man RA, Schalm SW, Janssen HL, *et al*. Treatment with Peg-interferon alpha-2b for HBeAg-positive chronic hepatitis B: HBsAg loss is associated with HBV genotype. *Am J Gastroenterol* 2006;**101**:297–303.

33. ter Borg MJ, van Zonneveld M, Zeuzem S, Senturk H, Akarca US, Simon C, *et al*. Patterns of viral decline during PEG-interferon alpha-2b therapy in HBeAg-positive chronic hepatitis B: relation to treatment response. *Hepatology* 2006;**44**:721–7.

34. Ghany MG, Doo EC. Management of chronic hepatitis B. *Gastroenterol Clin North Am* 2004;**33**:563–79.

35. Pai SB. Characterization of hepatitis B virus inhibition by novel 2´-fluoro-2´,3´-unsaturated beta-D- and L-nucleosides. *Antivir Chem Chemother* 2005;**16**:183–92.

36. Drummond M, O'Brien BJ, Stoddart G, Torrance GW. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press; 1997.

37. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36).

38. Kanwal F, Gralnek IM, Martin P, Dulai GS, Farid M, Spiegel BM. Treatment alternatives for chronic hepatitis B virus infection: a cost-effectiveness analysis. *Ann Intern Med* 2005;**142**:821–31.

39. Dusheiko GM, Roberts JA. Treatment of chronic type B and C hepatitis with interferon alfa: an economic appraisal. *Hepatology* 1995;**22**:1863–73.

40. Brooks EA, Lacey LF, Payne SL, Miller DW. Economic evaluation of lamivudine compared with interferon-alpha in the treatment of chronic hepatitis B in the United States. *Am J Manag Care* 2001;**7**:677–82.

41. Orlewska E. The cost-effectiveness of alternative therapeutic strategies for the management of chronic hepatitis B in Poland. *Value Health* 2002;**5**:404–20.

42. Crowley SJ. Cost-effectiveness analysis of lamivudine for the treatment of chronic hepatitis B. *PharmacoEconomics* 2000;**17**:409–277.

43. Crowley S, Tognarini D, Desmond P, Lees M, Saal G. Introduction of lamivudine for the treatment of chronic hepatitis B: expected clinical and economic outcomes based on 4-year clinical trial data. *J Gastroenterol Hepatol* 2002;**17**:153–64.

44. Veenstra DL, Sullivan SD, Dusheiko GM, Jacobs M, Aledort JE, Lewis G, *et al*. Cost-effectiveness of peginterferon alpha-2a compared with lamivudine treatment in patients with HBe-antigen-positive chronic hepatitis B in the United Kingdom. *Eur J Gastroenterol Hepatol* 2007;**19**:631–8.

45. Sullivan SD, Veenstra DL, Chen PJ, Chang TT, Chuang WL, Tsai C, *et al*. Cost-effectiveness of peginterferon alfa-2a compared to lamivudine treatment in patients with hepatitis B e antigen positive chronic hepatitis B in Taiwan. *J Gastroenterol Hepatol* 2007;**22**:1494–9.

46. Kanwal F, Farid M, Martin P, Chen G, Gralnek IM, Dulai GS, *et al*. Treatment alternatives for hepatitis B cirrhosis: a cost-effectiveness analysis. *Am J Gastroenterol* 2006;**101**:2076–89.

47. Buti M, Casado MA, Calleja JL, Salmeron J, Aguilar J, Rueda M, *et al*. Cost-effectiveness analysis of lamivudine and adefovir dipivoxil in the treatment of patients with HBeAg-negative chronic hepatitis B. *Aliment Pharmacol Ther* 2006;**23**:409–19.

48. Sun X, Qin WX, Li YP, Jiang XH. Comparative cost-effectiveness of antiviral therapies in patients with chronic hepatitis B: a systematic review of economic evidence. *J Gastroenterol Hepatol* 2007;**22**:1369–77.

49. Pwu RF, Chan KA. Cost-effectiveness analysis of interferon-alpha therapy in the treatment of chronic hepatitis B in Taiwan. *J Formos Med Assoc* 2002;**101**:632–41.

50. Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, *et al*. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B [see comment]. *N Engl J Med* 2005;**352**:2682–95.

51. Liaw YF, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, *et al*. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *Gastroenterology* 2000;**119**:172–80.

52. Leung NWY, Lai CL, Chang TT, Guan R, Lee CM, Ng KY, *et al*. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis e antigen seroconversion rates: results after three years of therapy. *Hepatology* 2001;**33**:1527–32.

53. Lok ASF, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, *et al*. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003;**125**:1714–22.

54. Wang CC, Kowdley K. Built to last? Durability of lamivudine-induced serocoversion in patients with chronic hepatitis B. *Gastroenterology* 2004;**126**:1917–19.

55. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997;**127**:855–65.

56. Levy AR, Kowdley K, Iloeje U, Tafesse E, Mukherjee J, Gish R, *et al*. The impact of chronic hepatitis B on quality of life: a multinational study of utilities from infected and uninfected persons. *Value in Health*. Online early. doi: 10.1111/j.1524–4733.2007.00297.x. 17–12–2007.

57. Kind P, Hardman G, Macran SUK. *Population norms for EQ-5D*. CHE Discussion Paper No. 172. York: Centre for Health Economics, University of York; 1999.

58. Wright M, Forton D, Main J, Goldin R, Torok E, Tedder R, *et al*. Treatment of histologically mild hepatitis C virus infection with interferon and ribavirin: a multicentre randomized controlled trial. *J Viral Hepat* 2005;**12**:58–66.

59. Chong CA, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, *et al*. Health-state utilities and quality of life in hepatitis C patients. *Am J Gastroenterol* 2003;**98**:630–8.

60. Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M, *et al*. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. *Liver Transpl* 2002;**8**:263–70.

61. Curtis L. *Unit costs of health and social care*. Canterbury: Personal Social Services Research Unit, University of Kent; 2007.

62. Joint Formulary Committee. *British national formulary*. No. 55. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2008.

63. Briggs AH, Claxton K, Sculpher M. *Decision modelling for health economic evaluation*. Oxford: Oxford University Press; 2006.

64. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–87.

65. Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, *et al*. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003;**348**:808–16.

66. Perrillo R, Hann HW, Mutimer D, Willems B, Leung N, Lee WM, *et al*. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. *Gastroenterology* 2004;**126**:81–90.

67. Peters MG, Hann HH, Martin P, Heathcote EJ, Buggisch P, Rubin R, *et al*. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology* 2004;**126**:91–101.

68. Sung JJ, Lai JY, Zeuzem S, Chow WC, Heathcote EJ, Perrillo RP, *et al*. Lamivudine compared with lamivudine and adefovir dipivoxil for the treatment of HBeAg-positive chronic hepatitis B. *J Hepatol* 2008;**48**:728–35.

69. Sasadeusz JJ, Locarnini SL, Macdonald G. Why do we not yet have combination chemotherapy for chronic hepatitis B? *Med J Aust* 2007;**186**:204–6.

70. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, *et al*. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006;**354**:1001–10.

71. Yao G, Chen C, Lu W, Ren H, Tan D, Wang Y, *et al*. Efficacy and safety of entecavir compared to lamivudine in nucleoside-naïve patients with chronic hepatitis B: a randomized double-blind trial in China 92. *Hepatol Int* 2007;**1**:365–72.

72. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, *et al*. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B [see comment]. [Erratum appears in *N Engl J Med* 2006;**354**:1863.] *N Engl J Med* 2006;**354**:1011–20.

73. Lai CL, Gane E, Liaw YF, Hsu C-W, Thongsawat S, Wang Y, *et al*. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007;**357**:2576–88.

74. Hui AY, Chan HL, Cheung AY, Cooksley G, Sung JJ. Systematic review: treatment of chronic hepatitis B virus infection by pegylated interferon [review; 26 refs]. *Aliment Pharmacol Ther* 2005;**22**:519–28.

75. Fattovich G. Natural history of hepatitis B. *J Hepatol* 2003;**39**:50–8.

76. Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, *et al*. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004;**351**:1206–17.

77. Cooksley WG, Piratvisuth T, Lee SD, Mahachai V, Chao YC, Tanwandee T, *et al*. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. *J Viral Hepat* 2003;**10**:298–305.

78. Sung JJY, Chan HLY, Hui AY, Chan FKL, Chim AML, Wong ML, *et al*. Combination of pegylated interferon and lamivudine is superior to lamivudine monotherapy in the treatment of chronic hepatitis B: a randomized trial [abstract]. *J Hepatol* 2003;**38**:33.

79. Liaw YF, Tai DI, Chu CM, Chen TJ. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *Hepatology* 1988;**8**:493–6.

80. van Nunen AB, Hansen BE, Suh DJ, Lohr HF, Chemello L, Fontaine H, *et al*. Durability of HBeAg seroconversion following antiviral therapy for chronic hepatitis B: relation to type of therapy and pretreatment serum hepatitis B virus DNA and alanine aminotransferase. *Gut* 2003;**52**:420–4.

81. Di Bisceglie A, Rustgi V, Hoofnagle J, Dusheiko G, Lotze MT. Hepatocellular carcinoma. NIH conference. *Ann Intern Med* 1988;**108**:390–401.

82. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, *et al*. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;**351**:1521–31.

83. Lok AS, Lai CL, Wu PC, Leung EK, Lam TS. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. *Gastroenterology* 1987;**92**:1839–43.

84. Liaw YF, Tai DI, Chu CM, Lin DY, Sheen IS, Chen TJ, *et al*. Early detection of hepatocellular carcinoma in patients with chronic type B hepatitis. A prospective study. *Gastroenterology* 1986;**90**:263–7.

85. Fattovich G, Brollo L, Giustina G, Noventa F, Pontisso P, Alberti A, *et al*. Natural history and prognostic factors for chronic hepatitis type B. *Gut* 1991;**32**:294–8.

86. Lau DT, Everhart J, Kleiner DL. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology* 1997;**113**:1660–7.

87. Liaw YF, Lin DY, Chen TJ, Chu CM. Natural course after the development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *Liver* 1989;**9**:235–41.

88. Marcellin P, Hadziyannis S, ES, Peters M, Benhamou Y, Brosgart C, *et al*. Adefovir dipivoxil 10 mg results in consistent efficacy in chronic hepatitis

B patients with diverse baseline characteristics. *J Hepatol* 2003;**38**:153–4.

89. Goodman Z, Dhillon AP, Wu PC, *et al*. Lamivudine treatment reduces progression to cirrhosis in patients with chronic hepatitis B. *J Hepatol* 1999;**30**:59.

90. Chen CH, Su WW, Yang SS, *et al*. Long-term trends and geographical variations in the survival rates of hepatocellular carcinoma: analysis of 11,312 patients in Taiwan. *J Gastroenterol Hepatol* 2006;**21**:1561–66.

Appendix 1

Data extraction and critical appraisal of included RCTs

Reference and design	Intervention	Participants	Outcome measures
Rapti *et al*., 2007[18] *Trial design:* RCT *Number of centres:* 1 *Country:* Greece *Funding:* Not specified; drugs supplied on compassionate basis by Gilead Sciences	*Group A* *n* = 14 Adefovir (ADV) Dose: 10 mg daily Duration: (Median) 30 months (range 23–48) (ongoing study) *Group B* *n* = 28 ADV Dose: 10 mg daily Duration: (Median) 40 months (range 9–53) Lamivudine (LAM) Dose: Not stated[a] Duration: (Median) 40 months (range 9–53) (ongoing study)	Total numbers involved: 42 Total randomised: 42 *n* in each group: 14 ADV monotherapy (Group A); 28 ADV + LAM (Group B) *Inclusion criteria:* Adult patients with HBeAg-negative chronic HBV; genotypical HBV resistance plus virological and biochemical breakthroughs to LAM. Criteria for the previous study:[a] HBsAG +ve or HbeAG –ve/anti-HBe +ve for ≥ 6 months, elevated ALT in 3 separate monthly occasions, HBV DNA > 10^5 copies/ml within last month before starting LAM therapy, compensated liver disease with histological findings of chronic hepatitis +/- histological evidence of cirrhosis *Exclusion criteria:* Antibody to hepatitis C or D virus or to HIV; had received a liver transplant or any antiviral drug other than IFN-α *Baseline measurements:* Median HBV DNA (range), copies/ml All: 8,040,500 (15,500 – 6.4×10^8) Group A: 1.5×10^7 (24,900 – 1.7×10^8) Group B: 7,148,150 (15,500 – 6.4×10^8) *p* = 0.873 (A vs B) Median ALT (range), IU/l All: 122.5 (52 – 1004) Group A: 135 (74 – 608) Group B: 108 (52 – 1004) *p* = 0.088 (A vs B) Male gender, *n/N* (%) All: 39/42 (92.8) Group A: 14/14 (100) Group B: 25/28 (89.3) *p* = 0.539 (A vs B)	*Primary outcomes:*[b] Biological response (ALT change from baseline and ALT normalisation) and virological response (non-detectability of HBV DNA levels) *Secondary outcomes:* HBV resistance to ADV Adverse effects *Length of follow-up:* Median duration of treatment 37.5 months (range 9–53) (ongoing)

	Median age (range), years All: 56 (39–76) Group A: 53 (39–76) Group B: 56.5 (42–70) $p = 0.173$ (A vs B) *Ethnic groups:* 100% white *Losses to follow up:* None to date *Compliance:* 2/28 patients in Group B had to reduce ADV dose because of adverse events *Treatment history:* LAM-resistant patients. Duration of previous LAM monotherapy, median (range): All: 32 (12–84) Group A: 42 (12–84) Group B: 30 (12–82) $p = 0.552$ (A vs B) *Patient characteristics:* All LAM resistant, had HBV genotype D infection and precore stop codon mutation with G1896A, and compensated liver disease *Cirrhosis, n/N* (%): All: 16/42 (38.1) Group A: 4/14 (28.5) Group B: 12/28 (42.9) $p = 0.505$ (A vs B)		
Outcome	**Group A (ADV) ($n=14$)**	**Group B (ADV + LAM) ($n=28$)**	***p*-value**
Median HBV DNA at 24 months, copies/ml (range)	1000 (1000–4,957,000)	1000 (1000–58,190)	0.321
% of patients with HBV DNA ≤ 1000 copies/ml at 24 months	75	82.6	0.670
HBeAg levels	Not reported	Not reported	Not reported

continued

Rate of seroconversion	Not reported	Not reported	Not reported
Median ALT at 24 months, IU/l (range)	24 (15–55)	24.5 (12–69)	0.863
% of patients with ALT ≤ 49 IU/l (upper limit of normal) at 24 months	72.7	91	0.304
Adverse events			
Dose discontinuation for any adverse event	0	0	
Dose reduction for any adverse event	0	2 (ADV reduced)	
Adverse events experienced			
Gastrectomy (due to gastric cancer)	1	0	
HCC	0	3	

Additional results

There were no statistically significant differences between groups in the cumulative probability of return of ALT to normal ($p = 0.6869$). However, biochemical relapse after return of ALT to normal was observed only in the ADV arm

There were no statistically significant differences between groups in the cumulative probability of HBV DNA becoming non-detectable ($p = 0.2559$)

When virological response was analysed according to baseline HBV DNA levels, there was a significantly earlier and more frequent decline to non-detectable levels by PCR among patients with $< 10^7$ copies/ml at baseline compared to those with $> 10^7$ copies/ml. The difference was statistically significant in each arm separately ($p = 0.0329$ and 0.0185 for groups A and B respectively) and for all patients in the study ($p = 0.0013$)

In both arms, optimal or suboptimal virological response at 12 months (undetectable HBV DNA or $< 10^4$ copies/ml) were more frequent in patients with $< 10^7$ copies/ml at baseline. Additionally, end of treatment virological response rates were found to be statistically different according to this cut-off – HBV DNA level of 10^4 copies/ml at month 12 ($p = 0.04$ Group A, $p = 0.009$ Group B and $p = 0.0001$ for all patients). Neither ALT at baseline ($p = 0.697$ Group A, $p = 0.487$ Group B and $p = 0.960$ for all patients) nor duration of prior LAM treatment ($p = 0.83$ Group A, $p = 0.77$ Group B and $p = 0.144$ for all patients) affected optimal or suboptimal response at month 12

After the first year of therapy, 21% of patients in Group A compared with 0% in Group B developed genotypic ADV resistance with virological breakthroughs ($p = 0.0182$)

ADV was generally well tolerated. No statistically significant difference was seen in the rate of HCC development between the two groups ($p = 0.545$)

Methodological comments

Allocation to treatment groups: Randomly assigned in a 1:2 ratio ADV : ADV + LAM. Randomisation method not specified

Allocation concealment: Not reported

Blinding of outcome assessors: Original long-term study from which these patients were taken was open-label. No further details regarding blinding were reported

Analysis by intention to treat: Yes. Not specified per se, but the analysis was performed on all 42 patients

Comparability of treatment groups at pre-treatment: Groups similar at baseline for all reported characteristics. *p*-values presented

DOI: 10.3310/hta13350

Method of data analysis: Mann–Whitney Test used for comparisons of quantitative variables between groups, Wilcoxon matched-pairs signed-ranks test for evaluation of changes of variables within the same group, and the corrected chi-squared or two-tailed Fisher's exact test for qualitative data. The Kaplan–Meier was used to estimate both virological and biochemical remission rates during the study period and Cox regression analysis to evaluate the association of several characteristics with the maintenance of remission. In all cases, a two-tailed $p < 0.05$ was considered statistically significant

Power analysis: Not reported

Attrition/drop-out: None reported to date; all patients still undergoing therapy

General comments

Generalisability: Patients with HBeAg-negative HBV chronic liver disease. Patients had no co-infections and were previously treated only with IFN-α

Conflict of interests: Funding not stated. ADV supplied on compassionate basis by Gilead Sciences; Roche Analytical donated Cobas TaqMan HBV reagents

Definitions: Upper limit of normal for ALT was 49 IU/l. Initial virological response was considered as non-detectable serum HBV DNA by PCR and initial biochemical response as the decline of ALT within the normal range in two consecutive determinations during therapy

a Patients were taken from a previous long-term study of LAM monotherapy and either switched to ADV or given added ADV – details of LAM dosage not provided in this publication.
b Not stated as primary outcomes per se.

Quality assessment for RCTs (quality criteria – CRD report 4)

Criterion	Judgement
1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Unknown
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partial
8. Did the analyses include an intention to treat analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Zeng *et al.*, 2006[19] *Trial design:* Multicentre, double-blind/open-label RCT *Number of centres:* 7 *Country:* China *Funding:* GlaxoSmithKline	*Group A:* PAA *n* = 120 Placebo Dose: n/a Duration: 12 weeks Adefovir dipivoxil Dose: 10 mg/day Duration: 28 weeks Adefovir dipivoxil Dose: 10 mg/day Duration: 12 weeks (Total ADV duration: 40 weeks) *Group B:* AAA *n* = 240 Adefovir dipivoxil Dose: 10 mg/day Duration: 12 weeks Adefovir dipivoxil Dose: 10 mg/day Duration: 28 weeks Adefovir dipivoxil Dose: 10mg/day Duration: 12 weeks Total ADV duration: 52 weeks	Total numbers involved: 480 Total randomised: 480 *n* in each group: Group A 120, Group B 240, Group C 120 *Inclusion criteria:* Patients ≥ 18 years who, at screening (up to 28 days prior to randomisation and, for HBsAg, ≥ 6 months prior to study enrolment), had detectable hepatitis B surface antigen (HBsAg); detectable hepatitis B e antigen (HBeAg); serum HBV DNA ≥ 10^6 copies/ml;[a] serum ALT level > 1 × ULN (and > 2 × ULN sometime within the previous 6 months) *Exclusion criteria:* Hepatocellular carcinoma; liver decompensation; serum creatinine > 1.5 mg/dl (≥ 130 μmol/L); ALT > 10 × ULN; seropositivity for hepatitis C or D virus or HIV; LAM therapy within 3 months prior to screening; and ADV therapy or any other anti-HBV therapy within the previous 6 months. Subjects were not permitted to receive systemic antiviral agents, immunomodulators, immunosuppressive therapy, Chinese traditional medicines, or agents known to lower ALT levels during the study *Baseline measurements:* HBV DNA [$\log_{10}$ copies/ml (mean ± SD)], median (range): PAA 8.6 ± 1.0, 8.8 (4.7–11.1) AAA 8.6 ± 1.0, 8.8 (4.5–11.9) AAP 8.5 ± 1.0, 8.8 (4.0–11.1) ALT (× ULN) [mean ± SD, median (range)]: PAA 3.8 ± 4.1, 2.5 (0.5–28.9) AAA 3.9 ± 3.8, 2.7 (0.4–29.5) AAP 3.3 ± 2.6, 2.6 (0.3–15.7) Sex (male): PAA 98 (82%) AAA 201 (84%)	*Primary outcomes:* Serum HBV DNA at week 12 ($\log_{10}$ reduction from baseline) *Secondary outcomes:* Virological response HBV DNA change from baseline[b] at weeks 40 and 52 HBV DNA < 10^5 copies/ml Undetectable HBV DNA (< 300 copies/ml) Biochemical response ALT normalisation[c] at weeks 12, 40 and 52 ALT flares[d] Serological response HBeAg loss HBeAg seroconversion[e] Quality of life Length of follow-up: 52 weeks' treatment, follow-up ongoing for an additional 4 years

DOI: 10.3310/hta13350

	Group C: AAP *n* = 120 Adefovir dipivoxil Dose: 10 mg/day Duration: 12 weeks Adefovir dipivoxil Dose: 10 mg/day Duration: 28 weeks Placebo Dose: NA Duration: 12 weeks Total ADV duration: 40 weeks *Study design:* 12 weeks double-blind and randomised to adefovir (ADV) or placebo, then 28 weeks open-label ADV. The original ADV group was then re-randomised to ADV or placebo for 12 weeks. The original placebo group remained on open-label ADV for 12 weeks	AAP 98 (82%) Age [mean ± SD (range)]: PAA 32 ± 10 (18–61) AAA 31 ± 9 (17–61) AAP 32 ± 10 (18–56) *Ethnic groups*: Chinese *Losses to follow-up:* 1.2%, *n* = 6 (adverse events = 3, withdrawal because of IgA nephritis diagnosis = 1, back pain = 1, alopecia = 1) *Compliance:* 45 patients had increased serum HBV DNA of at least 1 $\log_{10}$ copies/mL while on ADV, all were compliant *Treatment history:* 63% (*n* = 303) of patients had previously taken medication for CHB, including 32% (*n* = 154) who had received LAM and 37% (*n* = 176) who received treatment with traditional Chinese medicines *Patient characteristics:* Patients with cirrhosis excluded. Incidence of YMDD-mutant HBV reported to be similar between treatment groups. (PAA 20%, AAA 22% & AAP 15%)	

Outcome	**PAA (*n* = 120)[f]**	**AAA (*n* = 240)[f]**	**AAP (*n* = 120)[f]**
HBV DNA change ($\log_{10}$ copies/ml) from baseline week 12, median	–0.1	–3.4	–3.3
Range (25–75%)	–5.2 to 3.1 (–0.7 to 0.3)	–7.7 to 0.5 (–4.6 to 2.6)	–6.8 to –1.0 (–4.3 to –2.7)
HBV DNA < 10^5 copies/ml	4/115 (3%)	113/227 (50%)	55/116 (47%)
HBV DNA undetected[l]	0/119 (0%)	11/232 (5%)	7/120 (6%)

continued

Median decrease in serum HBV DNA levels week 12: 3.4 log_{10} copies/ml in ADV group; 0.1 log_{10} copies/ml in placebo group ($p < 0.001$)			
HBV DNA change (log_{10} copies/ml) from baseline week 40, median	–4.6	–4.2	–4.0
Range (25%, 75%)	–7.7 to 2.0 (–5.6 to –3.1)	–8.0 to 0.5 (–5.5 to –3.0)	–8.6 to 0.7 (–5.3 to –3.0)
HBV DNA < 10^5 copies/ml	75/115 (65%)	147/231 (64%)	68/115 (59%)
HBV DNA undetected[g]	23/119 (19%)	42/236 (18%)	23/119 (19%)
HBV DNA change (log_{10} copies/ml) from baseline at week 52, median	–5.0	–4.5	–0.2
Range (25%, 75%)	–8.0 to 2.1 (–6.0 to –3.3)	–8.0 to 0.7 (–5.8 to –3.1)	–6.1 to 2.1 (–1.6 to 0.3)
HBV DNA < 10^5 copies/ml	81/115 (70%)	155/231 (67%)	13/115 (11%)
HBV DNA undetected[g]	36/119 (30%)	67/236 (28%)	1/119 (1%)
HBeAg loss at week 52	24/118 (20%)	30/233 (13%)	10/114 (9%)
HBeAg seroconversion at week 52	21/118 (18%)	19/233 (8%)	8/114 (7%)
ALT normalisation from baseline[h]			
Week 12	15/108 (14%)	92/220 (42%)	48/110 (44%)
Week 40	69/106 (65%)	163/223 (73%)	81/109 (74%)
Week 52	74/107 (69%)	176/224 (79%)	23/109 (21%)
Serum ALT normalisation week 12: 140/330 (42%) patients in ADV group; 15/108 (14%) patients in placebo group ($p < 0.001$)			
Median (range) ALT (× ULN)			
Week 12	2.4 (0.1–14.4)	1.1 (0.3–9.1)	1.1 (0.2–5.9)
Week 40	0.8 (0.2–4.1)	0.7 (0.1–4.4)	0.9 (0.3–30)
Week 52	0.7 (0.2–4.0)	0.6 (0.2–5.1)	3.0 (0.2–36.4)
ALT flares[i]			
Week 12	5/120 (4%)	1/232 (0.5%)	1/120 (1%)
Week 40	0/118 (0%)	0/235 (0%)	1/119 (1%)
Week 52	0/119 (0%)	1/236 (0.5%)	34/119 (29%)

Adverse events			
Dose discontinuation for any adverse event		2	1
Dose reduction for any adverse event			
Incidence of hepatitis B-related adverse events[j]	< 1%	< 1%	11 (9%)
Adverse events after re-randomisation to placebo at week 40			
Reactivation of hepatitis B	1/120 (< 1%)	1/240 (< 1%)	11/120 (9%)
Upper respiratory infection	10/120 (8%)	20/240 (8%)	9/120 (8%)
Fatigue	7/120 (6%)	6/240 (3%)	8/120 (7%)
Nasopharyngitis	6/120 (5%)	11/240 (5%)	2/120 (2%)
Viral resistance at week 52[k]	PAA ($n = 11$)	AAA ($n = 28$)	AAP ($n = 6$)
N236T or A181V mutation	0	0	0

Methodological comments

Allocation to treatment groups: Participants randomised by central telephone randomisation system (RAMOS) for treatment assignment via random number generation in blocks of 8 (3:1 ratio for 12 weeks, re-randomisation at week 40, 2:1 ratio for 12 weeks; when considering the three groups, the ratio would appear to be 1:2:1). Placebo patients experiencing progression of liver disease were eligible to receive open-label ADV. All patients were randomised to placebo or ADV for 12 weeks, followed by open-label ADV for 28 weeks. Those who received ADV in the first 12 weeks were re-randomised to ADV or placebo, whereas those who received placebo in the first 12 weeks continued on open-label ADV

Allocation concealment: Double-blind study drug and open-label supplies were packaged, labelled and numerically coded for each treatment according to the computer-generated random code

Blinding of outcome assessors: Patients were blinded until week 12. All then received open-label ADV for 28 weeks. The PAA group received open-label ADV for the next 12 weeks, while the AAA and AAP groups were re-randomised and blinded to whether they were receiving ADV or placebo

Analysis by intention to treat: Study states that the primary population for efficacy analyses was all randomised subjects regardless of whether the study drug was taken or if the subject completed the study. However, results are not available for all subjects in the efficacy results table. The population for the safety analyses was all subjects for whom no clear evidence of failure to take study medication was available. No adjustment was made for missing data

Comparability of treatment groups at pre-treatment: Groups appear similar at baseline; only two *p*-values given, for ADV and placebo groups at week 12

Method of data analysis: Mean ± SD stated for baseline characteristics. Median (range 25–75%) stated for HBV DNA results. Results for the week 12 analysis are presented for the two treatment groups: ADV ($n = 360$) and placebo ($n = 120$). The results of subsequent analyses are presented for three treatment groups: PAA ($n = 120$), AAA ($n = 240$) and AAP ($n = 120$)

Power analysis: The study was designed to enrol 480 subjects and expected to provide greater than 95% power to detect a mean difference in the change in HBV DNA from baseline to week 12 between ADV and placebo of 1.5 $\log_{10}$ copies/ml

Attrition/drop-out: Six subjects discontinued study drug prematurely, three of these for adverse events. Some results missing from table

General comments

Generalisability: Predominantly male, HBeAg-positive CHB Chinese population without cirrhosis

Conflict of interests: GSK funded the study, and completed the statistical analysis; however they do not manufacture this drug

a Lower limit of detection 200 copies/ml, revised to 300 copies/ml during the course of the study.
b Log_{10} reduction copies/ml.
c Subjects with elevated serum ALT at baseline.
d $>5 \times$ ULN and $> 2 \times$ baseline (for first 12 weeks) or $> 2 \times$ nadir for subsequent intervals.
e Defined as a decrease in HBeAg to an undetectable level and an increase in HBeAb to a detectable level.
f No adjustment made for missing data.
g HBV DNA <300 copies/ml.
h Patients with elevated serum ALT at baseline.
i $> 5 \times$ ULN $> 2 \times$ baseline (for the first 12 weeks) or > 2 x nadir (for subsequent intervals).
j These events all occurred following re-randomisation of subjects to placebo at week 40. All eight cases of disease exacerbation occurred after subjects were re-randomised to placebo at week 40.
k A total of 45 subjects (28 from AAA, 11 from PAA and 6 from AAP) had an increase in serum HBV DNA of at least 1 log_{10} copies/ml while on adefovir from their lowest point during treatment, and therefore had isolates analysed for the presence of ADV-associated mutations at week 52. In the majority of subjects (28/45), this increase in serum HBV DNA was less than 2 log_{10} copies/ml.

Quality assessment for RCTs (quality criteria – CRD report 4)

Criterion	Judgement
1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Partial
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were outcome assessors blinded to the treatment allocation?	Partial
5. Was the care provider blinded?	Partial
6. Was the patient blinded?	Partial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an intention to treat analysis?	Inadequate
9. Were withdrawals and drop-outs completely described?	Partial

DOI: 10.3310/hta13350

Reference and design	Intervention	Participants	Outcome measures
Hadziyannis *et al.*[20–22] *Trial design:* Multicentre RCT; 96 weeks double-blind, 144 weeks open-label *Number of centres:* 32 *Country:* Greece (also Canada, Israel, France, Italy, Austria, Taiwan and Singapore) *Funding:* Gilead Sciences	*Group A* *n* = 123 Drug 1: ADV Dose: 10 mg/day Duration: 48 weeks *Ongoing phase* Drug 2: ADV or placebo (random reassignment) *Group A1:* Double-blind *n* = 80 Drug: ADV Dose: 10 mg/day Duration: 48 weeks *Group A2*: Double-blind *n* = 40 Drug: Placebo Dose: NA Duration: 48 weeks Total double-blind: 96 weeks *Open-label phase* *n* = 70 Drug: ADV Dose: 10 mg/day Duration: 144 weeks Overall total: 240 weeks Three of the original Group A did not receive treatment during the second period	HBeAg status: Negative Total randomised: 185; *n* in each group: (2:1 ratio): A: *n* = 123, B: *n* = 62 (one patient did not receive treatment and was excluded from all analyses) *Open-label phase* Total randomised: 125; placebo–ADV: 87% (48/55) for 192 weeks (one patient discontinued because of HBsAg seroconversion); ADV–ADV: 86% (60/70) for 240 weeks Nine patients did not enrol in the long-term safety and efficacy study. Genotypes: A 6%, B 17%, D 62%, E 2% and F < 1% Drop-outs: Weeks 0–48 = 4, weeks 49–96 = 8, weeks 97–240 = 17 *Inclusion criteria:* Aged 16–65 with HBeAg-negative chronic hepatitis B and compensated liver disease (CHB defined by the presence of detectable HBsAg for at least 6 months, undetectable HBeAg, detectable anti-HBe, a serum HBV DNA level of at least 10^5 copies per ml and an ALT level between 1.5 and 15 × ULN Patients had to have a total bilirubin level of no more than 2.5 mg/dl, a prothrombin time no more than 1 second above the normal range, a serum albumin level at least 3 g/dl, a serum creatinine level no more than 1.5 mg/day and an adequate blood count *Exclusion criteria:* A coexisting serious medical or psychiatric illness; immune globulin, interferon or other immune- or cytokine-based therapies with possible activity against HBV disease within 6 months before screening; recent treatment with systemic corticosteroids, immunosuppressants or chemotherapeutic agents; a serum alpha-fetoprotein level of at least 50 ng/ml; evidence of a hepatic mass; liver disease not caused by hepatitis B; prior therapy for more than 12 weeks with a nucleoside or nucleotide analogue with activity against HBV; seropositivity for HIV, HCV or HDV	*Primary outcomes:* Histological improvement, defined as a reduction of at least 2 points in the Knodell necroinflammatory score, with no concurrent worsening of the Knodell fibrosis score; ranked assessments of necro-inflammatory activity and fibrosis (improved, no change or worse) *Secondary outcomes:* Change from baseline in serum HBV DNA levels, ALT levels and proportion of patients with HBsAg seroconversion Adverse events *Long-term follow-up:* Changes from baseline in serum HBV DNA ALT levels at week 96 % of patients with undetectable serum HBV DNA % of patients with normalised ALT % of patients with HBsAg seroconversion Adverse events *Open-label phase end points:* % of patients with undetectable serum HBV DNA ≤ 1000 copies/ml Normalisation of ALT levels HBsAg seroconversion Histological improvement Histological improvement evaluated by rank assessments: improved, no change or worse; Knodell and Ishak fibrosis scores Genotypic analysis of entire HBV polymerase at baseline and for patients with serum HBV DNA ≥ the LLQ of the PCR assay weeks 48, 96, 144, 192 and 240

continued

Group B

n = 62

Drug 1: Placebo

Dose: NA

Duration: 48 weeks

Ongoing phase: Double-blind

Group B1

n = 60

Drug 2: ADV

Dose: 10 mg/day

Duration: 48 weeks

Total: 96 weeks

Open-label phase

n = 55

Drug: ADV

Dose: 10 mg/day

Duration: 144 weeks

Overall total: 240 weeks

Baseline measurements:

Characteristic	**Group A (*n* = 123)**	**Group B (*n* = 61)**
Age (year), mean ± SD (range)	46 ± 9.8 (18–65)	45 ± 10.4 (22–65)
Male gender, *n* (%)	102 (83)	50 (82)
Race, *n* (%)		
White	82 (67)	40 (66)
Black	5 (4)	1 (2)
Asian	36 (29)	20 (33)
Weight (kg), mean ± SD (range)	75 ± 11.5 (50–111)	73 ± 15.4 (46–135)
ALT		
Mean ± SD – U/l	143.5 ± 125.3	149.9 ± 195.2
Median – U/l	93	100
Range – U/l	24–742	29–1459
≤ ULN – no. (%)	7 (6)	2 (3)
> ULN – no. (%)	116 (94)	59 (97)
Multiples of ULN		
Mean ± SD	3.5 ± 3.0	3.6 ± 4.5
Median	2.3	2.4
Range	0.7–17.3	0.7–33.9
HBV DNA – log copies/ml[a]		
Mean ± SD	6.9 ± 3.3	6.0 ± 1.0
Median	7.1	7.1
Range	3.67–9.46	4.42–8.45
Knodell score		
Total		
Mean ± SD	9.6 ± 3.3	8.9 ± 3.4
Median	10	9
Range	2–17	2–16

Adverse events and lab tests 4-weekly to week 96; 12-weekly thereafter. Liver biopsies optional weeks 96, 144, 192 and 240

Length of follow-up: 240 weeks

Characteristic	Group A (*n* = 123)	Group B (*n* = 61)
Necroinflammatory activity		
Mean ± SD	7.7 ± 2.7	7.1 ± 2.7
Median	8	7
Range	1–14	1–12
Fibrosis		
Mean ± SD	1.9 ± 1.2	1.8 ± 1.1
Median	1	1
Range	0–4	1–4
Cirrhosis, no. (%)	14 (11)	6 (10)
Prior HBV medications, no. (%)[b]		
Interferon	48 (39)	28 (46)
Lamivudine	10 (8)	4 (7)
Famciclovir	7 (6)	7 (11)

ULN, upper limit of normal.
a Values were log-transformed with use of a base 10 scale.
b Some patients had received more than one type of medication.

Losses to follow-up: One placebo patient dropped out before receiving any drug and was excluded from analysis. Another is said to have dropped out after HIV infection was diagnosed. No other drop-outs are mentioned

Compliance: Not reported

Patient characteristics, e.g. carriers, those with liver disease, genotype, etc: No further details given

Full baseline data are provided for Groups A1, A2 and B1. No significant differences between the three groups are reported

continued

Baseline measurements (open-label phase):

	Placebo–ADV baseline (*n* = 55)	**Placebo–ADV, pre-treatment, week 48 (*n* = 55)**	**ADV–ADV, baseline pretreatment (*n* = 70)**
Age (year), mean ± SD (range)	46 ± 10 (22–65)		47 ± 10 (26–65)
Male gender, *n* (%)	46 (84)		57 (81)
Race, *n* (%)			
White	38 (69)		49 (70)
Black	1 (2)		3 (4)
Asian	16 (29)		18 (26)
Weight (kg)			
Mean ± SD	74 ± 15.4		75 ± 11.6
Median	74		76
HBV DNA level[a]			
Mean ± SD	6.93 ± 0.96	5.77 ± 1.18	6.87 ± 0.87
Median	7.16	5.85	7.08
ALT level, IU/l			
Mean ± SD	156 ± 204	83 ± 70	141 ± 124
Median	100	62	99
> ULN, *n* (%)	54 (98)	40 (73)	64 (91)
Multiples of ULN, median	2.5	1.5	2.3
Knodell score			
Mean ± SD	7.1 ± 2.8	7.3 ± 2.3	7.7 ± 2.7
Median	7.0	7.0	7.0
Ishak fibrosis score			
Mean ± SD	2.3 ± 1.6	2.6 ± 1.4	2.6 ± 1.4
Median	2.0	2.0	2.0

a values were log-transformed with use of a base 10 scale.

DOI: 10.3310/hta13350

	Lower HBV DNA and ALT levels for placebo patients prior to treatment				
Outcome	**Group A (ADV) (*n* = 117)**	**Group B (placebo) (*n* = 55)**	***p*-value**		
HBV DNA mean change from baseline at week 48 (log copies per ml)	3.91	1.35	< 0.001		
Patients with undetectable HBV DNA levels, *n* (%)	63/123 (51)	0/61(0)	< 0.001		
Comments: Graphs in Figure 2 show changes through time at 4-weekly intervals, but not data extracted at this stage as treatment end points already taken from tables					
% of patients enrolled (open-label phase)	*48 weeks (%)*	*96 weeks (%)*	*144 weeks (%)*	*192 weeks (%)*	*240 weeks (%)*[c]
HBV DNA < 1000 copies/ml[a]	72	80	77	73	67
HBV DNA < 1000 copies/ml[b]	71	71	73	62	53
a ITT, failure for resistance or HCC. b ITT, missing = failure. c Includes only patients in the ADV–ADV group.					
Comments: Patients enrolled in open-label phase, *n* = 125. Roche Amplicor PCR assay [lower limit of quantification (LLQ) 400 copies/ml until January 2002 then 1000 copies/ml) was used until May 2004 and then, because of its discontinuation, assay was changed to TaqMan PCR assay (LLQ 169 copies per ml; 5.82 copies/ml = 1 IU/ml) at week 240					
Long-term response	**Continued ADV group**		**ADV–placebo group**	**Placebo–ADV group**	
Long-term virological response	Week 96 (*n* = 79)	Week 144 (*n* = 70)	Week 96 (*n* = 40)	Week 96 (*n* = 60)	
No. of patients assessed	70	67	38	49	
Change in serum HBV/DNA (log copies/ml)					
Mean ± SD	–3.35 ± 1.18	–3.42 ± 1.27	–1.34 ± 1.24	–3.71 ± 1.05	
Median	–3.47	–3.63	–1.09	–3.85	
IQ range	–4.20 to –2.59	–4.23 to –3.11	–2.19 to –0.40	–4.31 to –3.18	
p-value compared with continued treatment at week 96	–	NA	< 0.001	0.12	
Serum HBV DNA <1000 copies/ml, *n*/total (%)	50/70 (71)	53/67(79)	3/38 (8)	37/49 (76)	
p-value compared with continued treatment at week 96	–	NA	< 0.001	0.68	

continued

Outcome	Group A (ADV; *n*=116)	Group B (placebo; *n*=55)	
ALT at 48 weeks			
Patients with normalised ALT levels, *n* (%)	84 (72)	17 (29)	$p < 0.001$
Median decrease from baseline (U/l)	55	38	$p = 0.01$

ALT normalisation, % of patients enrolled (open-label phase)	*48 weeks (%)*	*96 weeks (%)*	*144 weeks (%)*	*192 weeks (%)*	*240 weeks (%)*[c]
ITT[a]	75	74	71	73	69
ITT[b]	75	65	68	63	59

a ITT, failure for resistance or HCC.
b ITT, missing = failure.
c Includes only patients in the ADV–ADV group. ALT > ULN among patients with pre treatment.

Comments: Patients enrolled in open-label, *n* = 125

Long-term response	**Continued ADV group**		**ADV–placebo group**	**Placebo–ADV group**
Long-term biochemical response	*Week 96 (n = 79)*	*Week 144 (n = 70)*	*Week 96 (n = 40)*	*Week 96 (n = 60)*
No. of patients assessed	71	67	38	50
Change in serum ALT (IU/litre)				
Mean ± SD	–98 ± 118.4	–97 ± 120.13	–63 ± 131.0	–130 ± 213.2
Median	–59	–54	–29.5	–79.5
IQ range	–115 to –27	–121 to –28	–68 to 18	–134 to –46
p-value compared with continued treatment at week 96	–	NA	0.01	0.21
Normalisation of ALT, *n*/total (%)[a]	47/64 (73)	43/62 (69)	12/38 (32)	40/50 (80)
p-value compared with continued treatment at week 96	–	NA	<0.001	0.51

a Patients with baseline ALT levels exceeding the upper limit of the normal range were included in the analysis.

	Group A (ADV; *n*=121)	**Group B (placebo; *n*=57)**	
Histology (proportion with improvement, defined by a reduction of at least 2 points in Knodell necroinflammatory score, with no worsening of fibrosis)	(*n* = 121) 77 (64%)	(*n* = 57) 19 (33%)	$p < 0.001$; absolute difference (95% CI) 30.0% (15.4–45.2)

DOI: 10.3310/hta13350

	Group A (ADV; *n* = 112)	Group B (placebo; *n* = 55)	
Change in total Knodell score			p < *0.001*
Mean ± SD	–3.7 ± 3.1	0.4 ± 3.7	
Median	–4	1	
Range	–11 to 2	–9 to 8	
Change in Knodell necroinflammatory score			p < *0.001*
Mean ± SD	–3.4 ± 2.9	0.3 ± 3.2	
Median	–3	0	
Range	–9 to 2	–7 to 8	
Change in Knodell fibrosis score at week 48			p = *0.005*
Mean ± SD	–0.3 ± 0.7	0.1 ± 0.9	
Median	0	0	
Range	–3 to 1	–2 to 2	
Ranked assessment (%)			*Not reported*
Necroinflammatory activity			
Worse	3	51	
No change	17	7	
Improved	80	42	
Fibrosis			
Worse	4	38	
No change	47	36	
Improved	48	25	

Comments: Primary analysis based on 178 patients (97%) with assessable baseline liver biopsy specimens. 167 (91%) had assessable pre-treatment and post-treatment liver biopsy specimens. *p*-values were calculated with the Wilcoxon rank-sum test

Ranked assessment, % (open-label phase)	192 weeks placebo–ADV	240 weeks ADV–ADV
Improved necroinflammation	86	83
Improved fibrosis	73	75
Median change in Knodell necroinflammation score from baseline	–4.5 points	–5.0 points

continued

Median change in Ishak fibrosis score	–1.0 points	–1.0 points
% improvement in Ishak fibrosis score	55	71

Comments: Proportion of patients with at least 1-point improvement in Ishak fibrosis score increased from 35% after 48 weeks of ADV. 58% of patients (7 of 12) with pre-treatment bridging fibrosis or cirrhosis improved in Ishak fibrosis score by at least 2 points and three (of four) patients with cirrhosis improved by 4 points

Changes from baseline	**Continued ADV group (*n* = 19)**		**ADV–placebo group (*n* = 8)**		**Placebo–ADV group (*n* = 20)**	
Knodell scores	*Week 48*	*Week 96*	*Week 48*	*Week 96*	*Week 48*	*Week 96*
Overall						
Baseline	10.02 ± 2.07		12.3 ± 2.25		8.3 ± 3.31	
Change	–4.4 ± 2.39	–4.7 ± 2.7	–4.3 ± 1.49	–1.4 ± 1.92	0.9 ± 4.56	–2.4 ± 4.79
Inflammation						
Baseline	8.37 ± 1.50		10.0 ± 1.31		6.40 ± 2.76	
Change	–4.2 ± 2.32	–4.3 ± 2.71	–3.8 ± 1.83	–0.9 ± 1.96	0.6 ± 3.78	–2.3 ± 3.93
Fibrosis						
Baseline	1.84 ± 1.17		2.3 ± 1.39		1.9 ± 1.17	
Change	–0.2 ± 0.63	–0.4 ± 1.12	–0.5 ± 0.93	–0.5 ± 0.93	0.3 ± 1.17	–0.15 ± 1.27

Adverse events (AEs)	*n = 123*	*n = 61*
Dose discontinuation for any AE	0	0
Dose reduction for any AE	0	0
Severe (grade 3 or 4) AE, *n* (%)	7 (6)	6 (10)
Serious AE	4 (7)[a]	4 (3)[b]
AE, n *(%)*		
Any AE	94 (76)	45 (74)
Headache	29 (24)	10 (16)
Pharyngitis	23 (19)	14 (23)
Abdominal pain	18 (15)	3 (5)
Asthemia	16 13)	10 (16)
Influenza-like syndrome	13 (11)	13 (21)
Back pain	12 (10)	4 (7)
Pain	10 (8)	6 (10)
Increased cough	10 (8)	4 (7)
Insomnia	6 (5)	4 (7)
Dyspepsia	6 (5)	2 (3)
Rhinitis	6 (5)	1 (2)

DOI: 10.3310/hta13350

a Hip abscess, transient ischemic attack, acute hepatitis, sialadenitis.
b Perianal abscess, pain after liver biopsy, dengue fever, renal colic.
None of the serious AEs were considered to be related to treatmentt

Adverse events occurring in at least 10% of patients – long-term	**Weeks 49–96**			**Continued adefovir group**	
	Continued ADV group (n = 79)	*ADV-Placebo group (n = 40)*	*Placebo-ADV group (n = 60)*	*Baseline to week 48 (n = 79)*	*Baseline to week 96 (n = 70)*
Any event	58 (73)	32 (80)	41 (68)	67 (85)	60 (86)
General					
Headache	12 (15)	4 (10)	5 (8)	23 (29)	19 (27)
Abdominal pain	16 (20)	7 (18)	5 (8)	22 (28)	20 (29)
Asthenia	8 (10)	6 (15)	3 (5)	15 (19)	15 (21)
Flu-like syndrome	6 (8)	4 (10)	5 (8)	14 (18)	14 (20)
Back pain	4 (5)	5 (12)	3 (5)	9 (11)	9 (13)
Pain	4 (5)	2 (5)	4 (7)	11 (14)	12 (17)
Accidental injury	4 (5)	2 (5)	2 (3)	6 (8)	8 (11)
Digestive					
Diarrhoea	6 (8)	4 (10)	1 (2)	8 (10)	6 (9)
Dyspepsia	5 (5)	5 (12)[a]	1 (2)	7 (9)	7 (10)
Respiratory					
Pharyngitis	14 (18)	8 (20)	8 (13)	23 (29)	23 (36)
Increased cough	3 (4)	4 (10)	2 (3)	6 (8)	7 (10)
Bronchitis	2 (3)	1 (2)	1 (2)	6 (8)	9 (13)
Metabolic and nutritional					
Increased ALT levels	2 (3)[b]	6 (15)[a]	1 (2)	3 (4)	3 (4)
Musculoskeletal					
Arthralgia	6 (8)	5 (13)[a]	1 (2)	7 (9)	6 (9)

a $p < 0.05$ compared with the placebo–adefovir group.
b $p < 0.05$ compared with the adefovir–placebo group.

continued

Comments:

The study drug was discontinued because of adverse events in two patients in the continued ADV group (a protocol-defined increase in serum creatinine levels of ≥ 0.5 mg/dl and hepatocellular carcinoma) and in three patients in the ADV–placebo group (jaundice, elevated ALT and a skin disorder)

The safety profile over 144 weeks remained consistent with that seen earlier in the study

10% of patients suffered adverse events in the 144-week open-label phase; three patients discontinued because of adverse events; two patients (1.6%) appeared to have ADV-related adverse events (one elevated creatinine, one elevated ALT in the setting of mutations and virological resistance). Twenty-four serious adverse events (19%) were considered unrelated to ADV

Three per cent of patients (6 of 183) treated with ADV in the open-label phase developed hepatocellular carcinoma. Patients with hepatocellular carcinoma were diagnosed after 112–219 weeks of treatment with ADV, but one patient's tumour was diagnosed after 48 weeks of therapy

Additional outcomes:

Resistance: The polymerase–reverse transcriptase domain of the HBV polymerase gene was sequenced from serum samples obtained at baseline and week 48 from 117 patients with detectable serum HBV DNA levels. Four different novel substitutions occurred at conserved sites in the HBV polymerase in three patients, all of whom were in Group B (placebo). In vitro phenotypic analyses showed that viruses with the mutations remained fully susceptible to adefovir

Cumulative resistance probabilities (open-label phase)	*48 weeks (%)*[a]	*96 weeks (%)*[a]	*144 weeks (%)*[a]	*192 weeks (%)*[a]	*240 weeks (%)*[a]
Mutation	0	3	11	18	29
Mutation and virological resistance	0	3	8	14	20
Mutation, virological resistance and ALT elevation (clinical resistance)	0	2	6	10	11

a 48-week probabilities include all patients receiving ADV in the first 48 weeks; 96-week probabilities include all patients treated with ADV during the double-blind phase; 144- and 192-week probabilities include patients from placebo–ADV and ADV–ADV groups enrolled in the open-label phase; 240-week probability includes only patients in the ADV–ADV group

Comments: (Treatment year = 48 weeks.) Probabilities were calculated using all patients on ADV (n = 183) at risk for each of the three events. ('Mutations' are ADV-associated mutations regardless of HBV DNA and ALT levels; 'virological resistance' includes mutations with HBV DNA ≥ 1 – $\log_{10}$ copies/ml increased from nadir (confirmed or last measurement) or never suppressed to < 3 – $\log_{10}$ copies/ml; and 'clinical resistance' includes mutations with virological resistance and ALT > ULN (after normalising ALT) each treatment year. Cumulative probabilities were derived from the products of the current and all preceding annual probabilities by life-table analysis

Long-term serological response: HBsAg seroconversion occurred in one patient in the continued adefovir group at week 72 and one in the placebo–adefovir group at week 68 (approx 20 weeks after the start of treatment with ADV). In the open-label phase, six patients (5%) had HBsAg loss after a median of 196 weeks (range 20–260) of ADV; five of these had developed antibody to hepatitis B surface antigen (anti-HBs) at their last measurement

Methodological comments

Allocation to treatment groups: Patients assigned to ADV or placebo in a 2:1 ratio. Central randomisation was stratified according to five geographic regions. Permuted blocks (with a block size of 6) were used in each stratum. At week 48, treatment patients were randomly assigned to receive either continuing treatment or placebo for the remainder of the study and placebo patients were reassigned to treatment. This part of the study is ongoing and remains blinded. Weeks 97–240 of the long-term follow-up study were open-label

Blinding: Clinical data were collected, monitored and entered into a database by a contract research organisation. Lab tests were conducted by Covance and the sponsor held the data and conducted the statistical analyses. Knodell scores were assessed by an independent histopathologist who was unaware of the patients' treatment assignments and the timing of liver biopsy

Comparability of treatment groups: No significant differences are reported between groups' baseline values. For the long-term follow-up paper, baseline demographic characteristics and those related to hepatitis B infection were not statistically different among the three groups. For the open-label phase cohort, lower HBV DNA and ALT levels prior to treatment for placebo patients were reported. The authors suggest that this could be due to viral replication and disease activity fluctuations previously observed in HbeAg-negative patients

Method of data analysis: Statistical analyses included all patients who received at least 1 dose of the study drug. The analysis of histological end points included a subgroup of this population that had an assessable baseline biopsy specimen. Total *n* varies for each outcome measure, so true ITT was not performed. An unstratified Cochran–Mantel–Haenszel test was used for the primary efficacy end point, conducted as a nominal two-sided α level of 0.05. All confidence intervals, significance tests and resulting *p*-values were two-sided, with an α level of 0.05. Standard deviations are given for all mean values. For the long-term follow-up paper, statistical analyses included all patients who received at least 1 dose of the study drug in the second 2 weeks. All tests for significance and resulting *p*-values were two-sided with a 0.05 level of significance. Except for the trend test, this is the same for the open-label phase cohort. HBV DNA and ALT levels were analysed by ITT, missing equals failure (ITT; M = F), and ITT, missing equals failure for resistance or hepatocellular carcinoma, missing is excluded for other reasons (ITT; M = F R/HCC) to provide a more realistic view of efficacy (drop-outs unrelated to efficacy are expected in a 5-year trial). In this second analysis (ITT; M = F R/HCC), patients were considered failures if they (1) harboured HBV with an ADV-resistance mutation and either terminated the study or had lamivudine added (if a patient had HBV with a resistance mutation and remained in the study on ADV monotherapy, his or her serum HBV DNA and ALT values were included in analyses rather than being deemed failures) or (2) were diagnosed with hepatocellular carcinoma. Missing values from patients who left the study for other reasons were excluded. To assess statistical significance in the stepwise logistic regression, the Wald χ^2 test was used. It is assumed that patients have the same length of follow-up and potential predictors of resistance were evaluated for patients treated up to 192 weeks to maximise the number of analysed patients

Sample size/power calculation: The study was designed to enrol 180 patients and to have at least 90% power to detect an absolute difference of 30% between groups (60% vs 30%) with respect to the primary end point, assuming that 25% of patients would have missing biopsy specimens at week 48 or baseline Knodell scores < 2 and would therefore be counted as having no response, and that 8% would have missing biopsy specimens at baseline and would thus be excluded from the primary efficacy analysis

Attrition/drop-out: One placebo patient dropped out before receiving any drug and was excluded from analysis. Another is said to have dropped out after HIV infection was diagnosed. No other drop-outs are mentioned. For the long-term follow-up paper, one patient in Group A1 (i.e. continuation of ADV) withdrew from the study before taking medication in the second 48 weeks. Drop-outs for the open-label phase cohort weeks 0–48 were Group A: adverse event 1, patient request 1, lost to follow-up 1; Group B: patient request 1. Weeks 49–96, Group A1: adverse event 2, lost to follow-up 1, also 1 patient received no medication; Group B1: patent request 2. Weeks 97–240, Group A2: adverse event 3, patient request 2, disease progression 1, other 4; Group B1: HBsAg seroconversion 1, patient request 2, prohibited medication 1, death 1 (car accident), other 2

General comments

Generalisability: Male and female patients 16–65 years of age who had HBeAg-negative chronic hepatitis B and compensated liver disease were eligible

Inclusion/exclusion criteria: Clearly defined above

Outcome measures: Appropriate outcome measures are used

Intercentre variability: Not assessed

Conflict of interests: Supported by Gilead Sciences

No data provided for patient subgroups, e.g. genotype, ethnicity, gender

Quality assessment for RCTs (quality criteria – CRD report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported[a]
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate[b]
6. Was the care provider blinded?	Adequate
7. Was the patient blinded?	Partial[b]
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis?	Inadequate
10. Were losses to follow-up completely described?	Partial

a Not for placebo patients prior to treatment (lower HBV DNA and ALT levels) in open-label phase.
b Not in open-label phase.

DOI: 10.3310/hta13350

Reference and design	Intervention	Participants	Outcome measures
Chan *et al.*, 2007[23] *Trial design:* Open-label RCT (pilot study) *Number of centres:* 1 *Country:* China *Funding:* Research Fund for the Control of Infections Diseases, Health, Welfare and Food Bureau, Hong Kong	*Group A* *n* = 10 Drug 1: PEG-α-2b Dose: 1.5 μg/kg/week s.c. for body weight < 65 kg or 100 μg/kg/week for body weight > 65 kg Duration: 32 weeks Drug 2: LAM Dose: 100 mg daily orally Duration: 104 weeks[a] *Group B* *n* = 10 Drug 1: PEG-α-2b Dose: 1.5 μg/kg/week s.c. for body weight < 65 kg or 100 μg/kg/week for body weight > 65kg Duration: 32 weeks, starting 8 weeks prior to LAM Drug 2: LAM Dose: 100 mg daily orally Duration: 96 weeks[a] *Group C* *n* = 10 Drug 1: PEG-α-2b	Total numbers involved: 30 Total randomised: 30 (randomised 1:1:1) Total analysed in each group: Group A *n* = 9, Group B *n* = 9, Group C *n* = 10 *Inclusion criteria:* Aged 18–65 Positive HBsAg for at least 6 months HBeAg positive Serum HBV DNA of at least 1,000,000 copies/ml ALT 1.3–10 × ULN at screening *Exclusion criteria:* Co-infection of hepatitis C or HIV Decompensated liver disease History of hepatocellular carcinoma Other causes of liver disease Serious medical or psychiatric illness Concurrent use of corticosteroid or immunosuppressive agents or history of using interferon or antiviral agents Women of childbearing age had to have a negative pregnancy test *Baseline measurements:*	*Primary outcomes:* Reduction of serum HBV DNA at week 52 *Secondary outcomes:* HBV DNA reduction HBV DNA undetectable by PCR ALT normalisation Development of genotypic LAM resistance up to week 104 *Length of follow-up:* 128 weeks (24 weeks after end of treatment)

Characteristics	Group A, *n* = 10	Group B, *n* = 10	Group C, *n* = 10
Mean age, years (± SD)	35 ± 12	30 ± 6	30 ± 7
Male gender, *n* (%)	6 (60)	6 (60)	10 (100)
HBeAg positive, *n* (%)	9 (90)	10 (100)	10 (100)
Log HBV DNA, copies/ml, mean ± SD	9.01 ± 0.71[a]	7.62 ± 1.02[a]	8.68 ± 0.57[a]

Dose: 1.5 µg/kg/week s.c. for body weight < 65 kg or 100 µg/kg/week for body weight > 65 kg

Duration: 32 weeks, starting 8 weeks after commencement of LAM

Drug 2: LAM

Dose: 100 mg daily orally

Duration: 104 weeks[a]

Characteristics	Group A, *n* = 10	Group B, *n* = 10	Group C, *n* = 10
ALT, IU/l, mean ± SD	206 ± 76	365 ± 672	236 ± 187
Necroinflammation score, median (range)	8 (3–11)	5 (1–15)	5 (2–11)
Fibrosis score, median (range)	1.5 (1–5)	1 (0–2)	1 (0–4)
a Group A vs Group B, $p = 0.003$; Group B vs Group C $p = 0.011$.			

Age (mean ± SD): 31 ± 9 (for all patients)

Ethnic groups: Chinese

Losses to follow-up: 28 patients completed treatment and follow-up according to the protocol. Two losses (Group A *n* = 1, Group B *n* = 1)

Compliance: One patient (Group B) refused to continue treatment after the first dose of PEG

Treatment history: Patients were naive to IFN and other antiviral agents

Patient characteristics, e.g. carriers, those with compensated/decompensated liver disease, etc: HBeAg-positive CHB, compensated liver disease, not co-infected

a At week 104, HBeAg-positive patients could continue LAM for a further 28 weeks or discontinue therapy. HbeAg- negative patients at week 104 had treatment stopped.

Outcome	Group A (*n* = 9)	Group B (*n* = 9)	Group C (*n* = 10)
Median log HBV DNA reduction			
Week 4[a,b]	4.21	1.39	2.95
Week 8[a,c]	5.46	1.55	3.14
Week 52[d]	6.38	3.43	4.44
Week 104 (end of treatment)[e]	6.13	5.24	5.15

DOI: 10.3310/hta13350

Negative HBV DNA at week 52, *n* (%)	4 (44)	2 (22)[f]	1 (10)[g]
Negative HBV DNA at week 104, *n* (%)	3 (33)	5 (56)	4 (40)
Undetectable HBV DNA at follow-up (week 128), *n* (%)	2 (22%)	1 (11%)	2 (20%)

a Owing to staggered regimes, at weeks 4 and 8, Group A was PEG + LAM, Group B was PEG monotherapy and Group C was LAM monotherapy.
b Median difference between Groups A and B was 3.59 (95% CI 1.49–5.65, $p < 0.0001$) and between Groups A and C was 1.45 (95% CI 0.11–2.78, $p = 0.027$).
c Median difference between Groups A and B was 3.91 (95% CI 2.06–6.34, $p < 0.0001$) and between Groups A and C was 1.95 (95% CI 0.79–3.09, $p = 0.004$).
d Median difference between Groups A and B was 2.07 (95 CI 0.31–3.96, $p = 0.030$) and between Groups A and C was 1.61 (95 CI –0.07 to 2.08, $p = 0.060$).
e Median difference between Groups A and B was 0.90 (95% CI –1.05 to 2.63, $p = 0.20$) and between Groups A and C was 0.56 (95% CI –0.97 to 2.07, $p = 0.46$).
f Group b vs Group A, $p = 0.62$.
g Group C vs Group A, $p = 0.24$.

HBeAg levels

Rate of seroconversion			
At week 52, *n* (%)	6 (67)	3 (33)[a]	1 (10)[b]
At end of treatment (week 104), *n* (%)	5 (56)	3 (33)[c]	6 (60)[d]
At follow-up (week 128), *n* (%)	5 (56)	3 (33)[e]	4 (40)[f]

a Group A vs Group B, $p = 0.35$.
b Group A vs Group C, $p = 0.037$.
c Group A vs Group B, $p = 0.64$.
d Group A vs Group C, $p = 1.00$.
e Group A vs Group B, $p = 0.64$.
f Group A vs Group C, $p = 0.83$.

ALT/AST change from baseline at end point

Normal ALT levels at end of treatment (week 104), *n* (%)	9 (100)	9 (100)	9 (90)
Normal ALT levels at follow-up (week 128), *n* (%)	4 (44)	5 (56)	4 (40)

Comments: Four patients in Group A and two in Group B continued LAM beyond week 104, owing to failure to lose HBeAg at end of treatment. Two patients in Group B and two in Group C had post-treatment ALT reactivation > 5 × ULN (range 465–1980 IU/l) between weeks 120 and 128. One patient in Group B and 1 in Group C restarted LAM in week 124.

Histology response at week 104	*(n = 9)*	*(n = 8)*	*(n = 9)*
Necroinflammatory score, ≥ 2-point improvement, *n* (%)	8 (89)	6 (75)[a]	8 (89)[b]
Fibrosis score, ≤ 1-point change, *n* (%)	8 (89)	6 (75)[c]	9 (100)[d]

a Group A vs Group B, $p = 0.91$.
b Group C vs Group A, $p = 1.00$. No patients had a ≥ 2-point deterioration.
c Group B vs Group A, $p = 0.91$.
d Group C vs Group A, $p = 1.00$. One patient in Group A and two in Group B had ≥ 2-point deterioration in fibrosis score.

continued

Other viral response outcomes	***Group A (n = 10)***	***Group B (n = 10)***	***Group C (n = 10)***
Adverse events			
Dose reduction for any adverse event	2	0	2
Dose discontinuation for any adverse event[a]	0	1[b]	0
Serious adverse events			
Adverse events experienced, *n* (%)			
Upper respiratory tract symptoms[c]	5 (50)	1(10)	7 (70)
Fever	6 (60)	6 (60)	7 (70)
Alopecia	5 (50)	5 (50)	6 (60)
Abdominal discomfort	2 (20)	4 (40)	5 (50)
Malaise	3 (30)	3 (30)	6 (60)
Headache	4 (40)	6 (60)	3 (30)
Myalgia	6 (60)	2 (20)	3 (30)
Reduced appetite	1 (10)	2 (20)	4 (40)
Erythema at injection site	3 (30)	4 (40)	2 (20)
Allergic rashes	2 (20)	0	0
Weight loss >10%	1 (10)	0	0
Dizziness	4 (40)	1 (10)	2 (20)
Laboratory toxicity, *n* (%)			
Increased alanine aminotransferase	0	0	2 (20)
Increased creatine kinase	1 (10)	2 (20)	1 (10)
Increased amylase	1 (10)	1 (10)	0
Low phosphate	0	2 (20)	1 (10)
Hyperthyroidism	0	1 (10)	0

a PEG reduced to half due to neutropenia ($0.7–0.9 \times 10^9$/ml) at doses 6–19 (one patient in Group B resumed full dose of PEG after 2 weeks, three patients continued on half-dose of PEG).
b Patient had hysterectomy for menorrhagia week 21 – study medication was not interrupted.
c URT symptoms included cough, running nose and sore throat.

Resistance to lamivudine at week 104	*Group A (n = 9)*	*Group B (n = 9)*	*Group C (n = 10)*
rtM204V	1	1	1
rtL108M and rtM205I			1

No genotypic resistance was found to lamivudine in any of the three groups at week 52

DOI: 10.3310/hta13350

Additional results (e.g., early response factors, subgroup analysis, etc)

Also monitored liver biochemistry (within 4 weeks of start and at end of treatment, at end of histology), quantitation of covalently closed circular DNA and total intrahepatic HBC DNA

Methodological comments

Allocation to treatment groups: Randomisation was performed using random numbers generated through a computer. Randomised 1:1:1

Allocation concealment: The random numbers were placed in opaque envelopes by research staff not involved in patient management

Blinding of outcome assessors: Histological specimens were assessed by a single histopathologist who was unaware of the treatment assignments or the times at which the specimens were obtained. No information reported regarding the assessment of the primary or other secondary outcome measures

Analysis by intention to treat: Not ITT for efficacy analyses. Reports that assessment of efficacy end points was based on the patients who were on per protocol treatment and follow-up. Patients with spontaneous HBeAg seroconversion before commencement of treatment were excluded and patients who dropped out were treated as missing data on efficacy assessment. For the analysis of adverse events, all patients randomised to treatment groups and who received at least one dose of medication were included. One patient in Group A had spontaneous HBeAg conversion at baseline and one patient in Group B withdrew after the first dose of PEG – these patients were excluded from the efficacy assessments. ITT for adverse events

Comparability of treatment groups at pre-treatment: Baseline serum HBV DNA significantly lower in Group B than in Groups A and C. Mean ALT levels were higher in Group B than in Groups A and C, but not reported to be statistically different. Otherwise groups were comparable. No other *p*-values reported

Method of data analysis: Median log HBV DNA reduction of Group A (simultaneous administration) was compared with Groups B and C respectively. Continuous variables were expressed as median (range) owing to the small sample size and were compared by Mann–Whitney U-test. Categorical variables were compared by Pearson chi-squared test or Fisher's exact test as appropriate. Statistical significance was taken as p-value < 0.05. All statistical tests were two-sided

Power analysis: To detect a two-sided difference of 1.5 log steps with an estimated standard deviation of 1.0 after allowing an alpha error of 0.025 (Bonferroni's correction for two comparisons) and achieving a power of 0.8, eight patients were required in each treatment arm. A total of 30 patients with 10 patients in each treatment group were required, allowing for a drop-out rate of 20%

Attrition/drop-out: One drop-out (Group B) and one seroconversion at baseline (Group A)

General comments

Generalisability: Chinese HBeAg-positive CHB population without co-infection

Conflict of interests: One author is a member of the advisory board of Schering–Plough and Novartis. One other author has received consulting fees from the National Health Research Institutes of Taipie, the Hong Kong Police Force, Lippincott Williams & Wilkins and the Hong Kong College of Physicians, as well as lecture fees by AstraZeneca Hong Kong Ltd, GSK Pharmaceuticals International and the American Society for Gastrointestinal Endoscopy. PEG supplied by Schering–Plough, LAM by GlaxoSmithKline. Authors had final responsibility for study protocol, case report forms, progress of study, statistical analysis, reporting of data and manuscript submission, while having full access to the data files of the study

Definitions: ALT, alanine transaminase; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen, HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus DNA; LAM, lamivudine, PEG-α-2b, pegylated interferon α-2b; s.c., subcutaneously; ULN, upper limit of normal; URT, upper respiratory tract.

Quality assessment for RCTs (quality criteria – CRD report 4)

Criterion	Judgement
1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were outcome assessors blinded to the treatment allocation?	Partial
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Inadequate (open-label)
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analyses include an intention to treat analysis?	Inadequate
9. Were withdrawals and drop-outs completely described?	Adequate

DOI: 10.3310/hta13350

Reference and design	Intervention	Participants	Outcome measures
Chan et *al.*, 2005[24] and Chan et *al.*, 2005 (long-term follow-up)[28] *Trial design:* phase III, open-label RCT *Number of centres:* 1 *Country:* China *Funding:* Schering–Plough Corporation supplied PEG-α-2b and GlaxoSmithKline supplied LAM	*Group A:* PEG+LAM[a] *n* = 50 Drug 1: Pegylated IFN-α-2b[b] s.c. Dose: 1.5 μg/kg of body weight per week for patients < 65 kg; 100 μg for patients > 65 kg Duration: 32 weeks Drug 2: Lamivudine (oral) Dose: 100 mg daily Duration: 52 weeks[c] *Group B:* LAM *n* = 50 Drug 1: Lamivudine (oral) Dose: 100 mg daily Duration: 52 weeks No patients received additional antiviral or immunomodulator treatment other than study drugs	Total numbers involved: 168 Total randomised: 100 *n* in each group: 50 *Inclusion criteria:* 18–65 years with CHB Positive for HBsAg for at least 6 months HBeAg-positive; serum HBV DNA level of at least 500,000 copies/ml ALT level 1.3–5 × ULN *Exclusion criteria:* Decompensated liver disease or a history of IFN or antiviral agent use Co-infection with hepatitis C or D virus or HIV History of hepatocellular carcinoma Other causes of liver disease (including autoimmune hepatitis) Wilson disease Haemochromatosis and α_1 antitrypsin deficiency Serious medical or psychiatric illness Concurrent use of corticosteroid or immunosuppressive agents Pregnancy *Baseline measurements:*[a]	*Primary outcomes used:* SVR – HBeAg seroconversion and HBV DNA level < 500,000 copies/ml at 24 weeks after cessation of treatment Follow-up study: SVR – sustained HBeAg loss and HBV DNA < 100,000 copies/ml from treatment cessation until end of follow-up. *Secondary outcomes:* End of treatment virological and biochemical response; sustained biochemical response Reduction in HBV DNA levels and normalisation of ALT level Histological improvement (using Knodell and Ishak scoring systems) Adverse events Length of follow-up: 24 weeks after end of treatment Post-treatment follow-up: 117 ± 34 weeks Group A, 124 ± 29 weeks Group B (range 82–174, $p = 0.27$); all patients had post-treatment follow-up for at least 52 weeks

Characteristic[a]	Group A (*n* = 50)	Group B (*n* = 50)
Age, year (range)	32 (19–57)	34 (21–65)
Male gender, *n* (%)	31 (62)	36 (72)
Body weight, kg	64 (41–90)	68 (42–89)
BMI, kg/m_2 range	22 (16–33)	25 (18–32)
ALT level, *n* (%)[b]		
Normal	2 (4)	3 (6)
1–2 × ULN	13 (26)	21 (42)
2–5 × ULN	27 (54)	20 (40)
5 × ULN	8 (16)	6 (12)

continued

Characteristic[a]	Group A ($n = 50$)	Group B ($n = 50$)
ALT level, U/l(%)	144 (48–1179)	119 (36–461)
HBeAg-positive, %	100	98[c]
HBV DNA level > 500,000 copies/ml,%	100	100
HBV DNA level, log^{10}copies/mL, *n* (%)	8.04 (5.91–9.74)	7.67 (5.74–9.49)
HBV genotype		
B	15 (30)	16 (32)
C	32 (64)	31 (64)
B and C	3 (6)	3 (6)
Histology	($n = 46$)	($n = 47$)
Necroinflammatory score (range)	5 (1–11)	5 (1–12)
Fibrosis score (range)	1 (0–6)	1 (0–5)

a Continuous variables are shown as the median (range). Patients met entry criteria at screening but not at baseline.
b Group A: ALT level < 1.3 × ULN ($n = 2$, 6%); ALT > 5 times ULN ($n = 8$, 16%). Group B: ALT level < 1.3 × ULN ($n = 9$, 18%); ALT > 5 times ULN ($n = 6$, 12%).

Losses to follow-up: $n = 4$ (Group A = 2, Group B = 2) at EOT; $n = 16$ (Group A = 5, Group B = 11) at follow-up (24 weeks after EOT)

Compliance: Two patients (Group A = 1, Group B = 1) withdrew owing to lack of interest. Completed treatment = 96% (48 patients in each group); completed post-treatment follow-up = 80% (43 patients Group A; 37 patients Group B)

Treatment history: Treatment-naive patients

Patient characteristics: HBeAg-positive CHB, serum HBV DNA of at least 500,000 copies/ml and moderately elevated serum ALT levels (1.3–5 × ULN)

a Group A: 8 weeks PEG only, then 24 weeks PEG + LAM, followed by 28 weeks of LAM only; total treatment duration 60 weeks. Group A received 8 weeks therapy for 8 weeks longer than Group B.
b PEG reduced according to severity of adverse events.

DOI: 10.3310/hta13350

Outcome	Group A ($n = 50$)	Group B ($n = 50$)
HBV DNA median $\log_{10}$ reduction, copies/ml (range)		
End of treatment[a]	3.89 (1.59–6.35)	2.74 (–0.10–5.68)
Week 48[b]	4.65 (–0.84–7.83)	3.62 (1.32–7.33)
HBV DNA virological response, *n*/*N* (%)		
End of treatment[c]	30/50 (60)	14/50 (28)
Week 48[d]	25/50 (50)	14/50 (28)
Post-treatment viral relapse, *n*/*N* (%)	12/30 (40)	7/14 (50)
Virological relapse after week 76, *n*/*N* (%)	0/48	0/47
Rate of HBeAg seroconversion, *n*/*N* (%)		
Week 8 (before commencement of LAM in Group A)	9/50 (18)	0/50
Week 32 (after 24 weeks of LAM in both groups)	20/50 (40)	11/50 (22)
Last 28 weeks of extended LAM	30/50 (60)	14/50 (28)
SVR at follow-up (24 weeks after treatment)[e]	18/50 (36)	7/50 (14)
SVR at long-term follow-up	14/48 (29)	4/47 (8)
	(*n*=48)	(*n*=47)
HBeAg negative at EOT, *n*/*N* (%)	30/48 (63)	13/47 (28)
Viral relapse, *n*	16	97
HBeAg loss at last follow-up, *n*	7	5
HBeAg positive at EOT, *n*/*N* (%)[f]	18/48 (38)	34/47 (72)
HBeAg loss last follow-up, *n*	17	31
HBsAg clearance, *n*/*N* (%)	5	7

a Median difference 1.24 (95% CI 0.78–1.66).
b Median difference 1.10 (95% CI 0.55–1.65).
c Absolute difference 32% points (95% CI 14–50, $p = 0.001$).
d Absolute difference 22% points (95% CI 3–41).
e Absolute difference 22% points (95% CI 6–38, $p = 0.011$).
f $p = 0.001$.

continued

Normalisation of ALT levels, n/N *(%)*			
End of treatment[a]	45/50 (90)	39/50 (78)	
At follow-up (24 weeks after treatment)[b]	25/50 (50)	15/50 (30)	
Median ALT at 24 weeks follow-up, IU/l (range) (estimated from a graph by the reviewers)	60	69	
a Absolute difference 12% points (95% CI –2 to 26). b Absolute difference 20% points (95% CI 1–39).			
Histological response (EOT), n/N *(%)*	*(n = 40)*	*(n = 44)*	
≥ 2-point increase in necroinflammatory score[a]	24 (60%)	26 (59%)	
≥ 2-point decrease in necroinflammatory score	4 (10%)	4 (9%)	
≥ 2-point increase in fibrosis scores[b]	6 (15%)	4 (9%)	
≥ 2-point decrease in fibrosis scores[c]	4 (10%)	2 (5%)	
a Absolute difference 1% point (95% CI –20 to 22). b Absolute difference 6% points (95% CI –8 to 20). c Absolute difference 5% points (95% CI –6 to 17).			
LAM-resistant mutants, EOT, *n/N* (%)[a]	10/48 (21)	19/48 (40)	
a Absolute difference 19% points (95% CI 8–37).			
Adverse events, n *(%)*			
Dose discontinuation (PEG) for any adverse event	4 (8)	0	
Dose reduction (PEG) – any adverse event	5 (10)	0	
Serious adverse events, n *(%)*	4 (8)	0	
Open-label LAM for severe post-treatment biochemical relapse	7	14	
Ascites or hepatic encephalopathy	0	0	
Decompensation at post-treatment biochemical relapse	2	4	
Adverse events experienced, n *(%)*			*p-value*
Upper respiratory tract symptoms	37 (74)	19 (38)	0.001
Fever	36 (72)	2 (4)	< 0.001
Alopecia	24 (48)	2 (4)	< 0.001
Abdominal discomfort	22 (44)	13 (26)	0.093

DOI: 10.3310/hta13350

Malaise	22 (44)	7 (14)	0.002
Headache	21 (42)	2 (4)	< 0.001
Myalgia	13 (26)	2 (4)	0.006
Arthralgia	12 (24)	2 (4)	0.01
Reduced appetite	12 (24)	0 (0)	0.001
Local erythematous reaction	12 (24)	0 (0)	0.001
Allergic rashes	9 (18)	1 (2)	0.02
Dizziness	8 (16)	1 (2)	0.036
Vomiting or diarrhoea	7 (14)	3 (6)	> 0.2
Weight loss (> 10%)	7 (14)	1 (2)	0.065

a URT symptoms included cough, running nose and sore throat.

Additional results: Also reported are HBeAg loss at EOT – probabilities of sustained response and HBeAg at EOT – the subsequent probabilities of sustained response for both groups at weeks 24, 52 and 76

Virological

After adjustment for baseline ALT levels, the absolute difference in predicted probabilities of Groups A and B for end of treatment virological response was 31% points (95% CI 10–49, $p = 0.003$) and for SVR was 22% points (95% CI 3–47% points; $p = 0.015$)

Among patients with baseline ALT $< 5 \times$ ULN, the EOT virological response of PEG + LAM was still significantly higher than LAM therapy [25/42 (60%) vs 12/44 (27%), absolute difference 32% points (95% CI 12–52)]. The predicted probability for SVR also remained higher [15/42 (36%), 95% CI 21–50 Group A vs 6/44 (14%), 95% CI 4–24 Group B, absolute difference 22% points (95% CI 4–40)]

Among patients who developed HBeAg seroconversion during treatment, the median time for HBeAg seroconversion after commencement of treatment was 24 weeks (range 8–60 weeks) in Group A vs 24 weeks (range 0–40 weeks) in Group B ($p = 0.13$)

Five patients in Group A and two patients in Group B became HBV DNA-negative by PCR assay

Three patients in Group A and two in Group B were negative for HBV DNA by PCR assay at 24 weeks after treatment

All patients who had lost HBeAg developed antibodies to HBeAg

Follow-up study: Only 1/30 patients who had HBeAg loss after combination treatment did not develop anti-HBe antibody; otherwise all patients developed HBeAg seroconversion to +ve anti-HBe. Of patients achieving an SVR (Group A = 14, Group B = 4), all had +ve anti-HBe antibodies at post-treatment follow-up. Two sustained responders in the PEG + LAM group had transient elevation of HBV DNA to > 100,000 copies/ml at weeks 8 and 16 after treatment. All four SVR patients in the LAM group had transient elevation of HBV DNA > 100,000 copies/ml (three patients at week 8 and one patient at week 100 after treatment). If all patients who had a single transient HBV DNA elevation were regarded as non-responders, the probability of SVR of PEG + LAM was still higher than LAM (log-rank test, $p < 0.0001$). All non-sustained responders had HBV DNA 100,000 copies/ml at virological relapse. Among patients who had HBeAg loss at EOT, 12/16 (75%) PEG + LAM vs 8/9 (98%) LAM also had HBeAg reversion

continued

Biochemical

Of those with SVR, all except one patient in Group A had sustained normalisation of ALT levels (ALT 1.1 × ULN)

Histological

Among the 16 patients (10 in Group A, six in Group B) without evaluable paired liver biopsy specimens, six patients (four in Group A, two in Group B) had EOT virological response, and two patients (Group A) had an SVR

Drug-resistant mutants

Among patients receiving LAM, seven had a LAM-resistant mutant and 12 had both wide-type and LAM-resistant mutants. Among PEG + LAM patients, five had a LAM-resistant mutant and five had mixed wide-type and LAM-resistant mutants

Adverse events

Most AEs were transient and were related to the use of PEG-α-2b. No patients died or required liver transplantation

Serious AEs – one patient in each of the following: bipolar disorder requiring antidepressant therapy (week 21), pulmonary tuberculosis requiring anti-tuberculosis treatment (week 11), thyrotoxicosis requiring propyluracil treatment (week 17) and severe local reaction at injection sites (week 8) that resolved spontaneously. PEG was discontinued in all four cases; three patients continued with LAM through to week 60 while the fourth patient withdrew from the study and was considered a treatment failure

Reduction of PEG dose to 50 μg/week (if body weight > 65 kg) or 1.0 μg/kg/week if < 65 kg) was due to anaemia ($n = 1$), neutropenia ($n = 3$) and/or thrombocytopenia ($n = 4$)

One patient (Group A) had PEG withheld for two doses at weeks 4 and 5 owing to severe hepatitis flare-up (ALT level 1762 U/l) and resumed full dose at week 6 when ALT level decreased to a lower level (242 U/l)

Five patients (10%) in Group A and 11 patients (23%) in Group B developed severe post-treatment relapse of CHB (absolute difference –13% points (95% CI –27 to 2). Two Group B patients had post-treatment relapse leading to elevation of serum bilirubin levels to 82 μmol/l and 153 μmol/l. LAM was resumed and all patients responded

Follow-up study: Seven PEG + LAM vs 14 LAM patients received open-label LAM for severe post-treatment biochemical relapse – one patient (Group A) developed acute duodenal ulcer bleeding complicated by shock and aspiration pneumonia, and died at week 64 after treatment. No patients developed ascites or hepatic encephalopathy. Two PEG + LAM patients developed decompensation at post-treatment biochemical relapse with serum bilirubin elevated to 140 IU/l at week 32 and 138 IU/l at week 63; four LAM patients had elevated serum bilirubin from 52–153 IU/l at weeks 12–22 after treatment (five of these six patients had a histological fibrosis score of 1 and the remaining patients had a fibrosis score of 4 before commencement of treatment)

Methodological comments

Allocation to treatment groups: A computer-generated list was used for assignment to groups. Randomised 1:1

Allocation concealment: Research staff, who were not involved in patient management, placed the random numbers in opaque envelopes

Blinding of outcome assessors: A research nurse prescribed study drugs after receiving the information about treatment allocation at the baseline visit. One histopathologist, blinded to treatment assignments or the times at which the specimens were obtained, assessed all histological specimens. All lab assays were performed in-house. Investigators assessing adverse events were not blinded to treatment as they were able to reduce the PEG dose according to the AE experienced. No information reported regarding the assessment of the primary or other secondary outcome measures

Analysis by intention to treat: Modified ITT analysis for treatment responses, included all randomly assigned patients having received at least one drug dose. For assessment of virological and biochemical responses, or analyses of sustained responses, early withdrawals (week 52 for LAM and week 60 for PEG + LAM) or patients with missing data were classified as having a failed response. The analysis of adverse events included all patients randomly assigned to either treatment group, having received at least one drug dose. One patient in Group B had HBeAg seroconversion before commencement of treatment and was excluded from analysis

Comparability of treatment groups at pre-treatment: Baseline characteristics were well matched between the two groups (no *p*-values presented), but several patients had either normal ALT levels or levels that were greater than 5 × ULN at baseline randomisation visit. Median ALT levels for Group A were higher than those for Group B ($p = 0.02$), but proportion of patients ($p > 0.2$) in different ALT categories (1–2 ×, 2–5 × or > 5 × ULN) did not differ

Method of data analysis: Patients in Group A, who stopped pegylated interferon prematurely, had assessments of virological and biochemical responses if lamivudine treatment was continued to the end. Continuous variables were expressed as the median (range). Hepatitis B virus DNA was logarithmically transformed for analysis. Continuous variables, including patient age, liver biochemistry, $\log_{10}$ HBV DNA levels, and histological scores were compared using the Mann–Whitney U-test. Categorical variables and the proportions of patients with virological and biochemical responses, histological improvements, lamivudine-resistant mutants and adverse events were compared using the Pearson chi-squared test or Fisher's exact test, as appropriate. The timing of HBeAg seroconversion was compared using Kaplan–Meier survival analysis. A logistic regression model was used to compare virological response with adjustment for baseline imbalance in ALT levels. A *p*-value < 0.05 was considered statistically significant. All statistical tests were two-sided. HBV DNA was logarithmic transformed to normal distribution for analysis. Continuous variables with normal distribution were expressed as mean ± SD and variables with skewed distribution as median and range. Baseline categorical variables were compared using Pearson's chi-squared test, and continuous variables were compared by Student t-test and Mann-Whitney U-test as appropriate. Kaplan–Meier was used for survival analysis to compare the probability of SVR as well as HBeAg seroconversion among non-responders. The Cox proportional hazard model was used to assess the predictors of SVR among patients in Group A. Statistical tests and significance as above

Power analysis: The proportion of patients receiving monotherapy who achieve SVR was around 15% and for PEG + LAM up to 33%. It was anticipated that the use of PEG + LAM treatment had superior efficacy and that the rate of SVR was 30% higher than that of monotherapy (SVR in Group A vs Group B, 45% vs 15%). Given these estimated response rates, it was calculated that 94 patients would be required to provide a power of 80% at an α level of 0.05, allowing for a drop-out rate of 10%

Attrition/drop-out: Total = 20 (7 Group A, 13 Group B). Two patients in each group did not complete treatment – early withdrawal due to lack of interest = 2 (one Group A, one Group B), allergic reaction = 1 (Group A), pregnancy = 1 (Group B). A further 16 patients did not complete post-treatment follow-up because of severe relapse while receiving lamivudine (five Group A, 11 Group B). One patient in Group B had HBeAg seroconversion before commencement of treatment and was excluded from analysis

General comments

Generalisability: Chinese treatment-naive patients with hepatitis B e antigen (HBeAg), positive chronic hepatitis B and moderately elevated ALT levels

Conflict of interests: treatment drugs funded by Schering–Plough (pegylated interferon α-2b) and GlaxoSmithKlein (lamivudine). The study protocol, data collection and progress of the study were the authors' responsibility. The authors had full access to all of the study's data files and were responsible for statistical analysis, reporting of data, and manuscript submission. Representatives of the pharmaceutical companies supplying the drugs did not comment on the manuscript before submission. No potential conflicts of interest were disclosed by the authors

Other: Open-label LAM given to patients with severe post-treatment relapse of CHB (defined as an ALT level > 10×ULN and HBV DNA level > 500,000 copies/ml)

Definitions: ALT, alanine aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; EOT, end of treatment; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; SVR, sustained virological response; ULN, upper limit of normal. Necroinflammation score – reduction of at least 2 points clinically meaningful indicator of histological changes. Liver biopsy results with at least three portal tracts sufficient for histological scoring. ALT flare during treatment defined as pre-treatment baseline level plus ALT increase > 116 IU/l (i.e. 2×ULN) at any time during treatment. Virological relapse defined as either HBV DNA > 100,000 copies on any two or more occasions or HBeAg reversion during entire post-treatment follow-up period. Timing of virological relapse taken as timing of first HBV DNA elevation or HBeAg reversion, whichever was earlier. Biochemical relapse defined as ALT elevation to > 2 times upper limit of laboratory normal. Decompensation defined as elevated serum bilirubin > 50 IU/l accompanied by biochemical relapse

Quality assessment for RCTs (quality criteria – CRD report 4)

Criterion	Judgement
1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were outcome assessors blinded to the treatment allocation?	Partial
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Inadequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partial
8. Did the analyses include an intention to treat analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Adequate

DOI: 10.3310/hta13350

Reference and design	Intervention	Participants	Outcome measures
Janssen *et al.*, 2005,[26] van Zonneveld *et al.*, 2006[29] and van Zonneveld *et al.*, 2005[30] *Trial design:* Double-blind RCT *Number of centres:* 42 *Countries:* 15 (Netherlands, Belgium, Germany, Denmark, Poland, Spain, Italy, Greece, Turkey, Israel, Canada, Indonesia, Singapore and Malaysia) *Funding:* Rotterdam Foundation for Liver Research; financial support from Schering–Plough International and GlaxoSmithKline R&D	*Group A:* PEG/LAM *n* = 130 Drug 1: Pegylated interferon alpha-2b (PEG-IFN) Dose: 100 μg/week[a] Duration: 32 weeks Dose 2: 50 μg/week[a] Duration: 20 weeks (weeks 32–52) Drug 2: Lamivudine Dose: 100 mg/day Duration: 52 weeks *Group B:* PEG/placebo *n* = 136 Drug 1: Pegylated interferon alpha-2b Dose: 100 μg/week[a] Duration: 32 weeks Dose 2: 50 μg/week[a] Duration: 20 weeks (weeks 32–52) Drug 2: Placebo Duration: 52 weeks	Total numbers involved: 307 Total randomised: 307 (Group A, *n* = 152; Group B *n* = 155) *n* in each group: Group A 130; Group B 136 *n* in each group in histology study: Group A 52; Group B 58 (total = 110). *n* in each group in safety study: Group A 148; Group B 148 (total = 300) *Inclusion criteria:* Patients with CHB, ≥ 16 years. HBsAg positive longer than 6 months; positive HBeAg on two occasions within 8 weeks of randomisation; two episodes of raised serum concentrations of ALT (2 × ULN) within 8 weeks of randomisation Previous liver biopsy if taken < 1 year prior to treatment or biopsy at start of therapy (second optional biopsy EOT). Biopsy samples adequate for evaluation if at least 0.5 cm long, had at least four evaluable portal tracts and not so regimented as to preclude recognition of acinal architecture Safety study: Patients who had received at least one dose of study medication *Exclusion criteria:* Presence of serum antibodies against hepatitis C or D virus or HIV; antiviral therapy or immunosuppressive therapy within the preceding 6 months; pregnancy or inadequate contraceptive measures; substance abuse during the previous 2 years; other acquired or inherited causes of liver disease; coexisting serious medical or psychiatric illness; uncontrolled thyroid disease; inadequate counts of leucocytes (≤ 3×10^9/l), granulocytes (≤ 1.8×10^9/l) or platelets (≤ 100×10^9/L); radiological or imaging evidence of hepatocellular carcinoma or advanced liver disease with a prothrombin time prolonged by > 3 seconds; serum albumin concentration < 35g/l, bilirubin more than 35 μmol/l, or a history of ascites, variceal bleeding or hepatic encephalopathy	*Primary outcome:* Loss of HBeAg at EOT and end of follow-up (EOF-U) *Secondary outcomes at EOT and EOF-U:* Concentration of HBV DNA < 200,000 copies/ml and HBV DNA < level of detection;[b] return to normal of ALT concentrations; presence of mutations in YMDD motif of HBV polymerase HBsAg and HBV genotype were also assessed Baseline liver histology and optional biopsy sample at EOT *Histological activity index:* Necroinflammatory and fibrosis score[c] *Adverse events:* Histology study: liver biopsy overall sample lengths and number of portal tracts Length of follow-up: 26 weeks (treatment length 52 weeks, total 78 weeks)

continued

Baseline measurements:

Characteristics	Group A (*n* = 130)	Group B (*n* = 136)
Age, mean (SD)	34 (12)	36 (14)
	34 (12)[a]	33 (12)[a]
Sex (M), *n* (%)	98 (75)	107 (79)
M/F, *n* (%)	38/14 (73/27)[a]	47/11 (81/19)[a]
Weight (kg), mean (SD)	74 (16)	72 (13)
Ethnicity, *n* (%)		
White	95 (73)	101(74)
	37 (71)[a]	43 (74)[a]
Asian	24(18)	29 (21)
	10 (19)[a]	12 (21)[a]
Other/mixed	11(8)	6 (4%)
	5 (10)[a]	3 (5)[a]
HBV DNA[b]	9.1 (1.0)	9.1 (0.8)
	9.1 (0.9)[a]	9.1 (0.8)[a]
ALT[c]	4.4 (3.9)	4.3 (3.1)
	4.7 (3.3)[a]	4.1 (3.0)[a]
Cirrhosis, *n* (%)	13 (12)	11 (10)
	6 (12)[a]	7 (12)[a]
Previous PEG, *n* (%)	27 (21)	28 (21)
Previous LAM, *n* (%)	17 (13)	16 (12)
Necroinflammatory score[a,d]	5.4 ± 2.0	5.6 ± 2.2
Fibrosis score[a,d]	2.6 ± 1.5	2.3 ± 1.6

a Histology study.
b Mean (SD) log HBV DNA, copies/ml.
c Mean (SD), multiples of ULN.
d Mean ± SD.

DOI: 10.3310/hta13350

	No significant differences in baseline characteristics between patients with or without histological assessment (histology study) 228 (76%) male and 72 females in safety study; mean age = 35 years; 76% Caucasian. Of 230 evaluable biopsies, 26 patients (11%) had cirrhosis *Losses to follow-up:* Group A, *n* = 7; Group B, *n* = 3 *Compliance:* At the end of treatment 242 patients remained on treatment and 184 on full-dose treatment. No significant differences in dose reductions between the treatment groups *Treatment history*: Previous IFN Group A: 27 (21%)/10 (19%)[d]/; Group B: 28 (21%)/12 (21%).[d] Previous LAM Group A: 17 (13%)/3 (6%)[d]; Group B: 16 (12%)/6 (10%).[d] Previously treated with IFN in safety study: 71 (24%), with LAM 45 (16%) *Patient characteristics*, e.g. carriers, those with compensated/ decompensated liver disease etc: HBeAg-positive CHB positive patients, some with cirrhosis

a Patients of ≤ 55 kg body weight received weight-adjusted dose of PEG: 1.50 μg/kg weekly for first 32 weeks, 0.75 μg/kg weekly from weeks 32–52).
b Level of detection for HBV DNA defined as 400 copies/ml by in-house Taqman PCR assay based on the Eurohep standard.
c Improvement in histology was defined as a decrease of ≥ 2 points for the necroinflammatory score (range 0–18) and 1 point for the fibrosis score (range 0–6); worsening was defined as an increase by ≥ 2 points for the necroinflammatory score and 1 point for the fibrosis score using the histological activity index (Ishak).
d Histology study.

Outcome	**EOT**			**EOF-U**		
	Group A (*n* = 130)	**Group B (*n* = 136)**	***p*-value**	**Group A (*n* = 130)**	**Group B (*n* = 136)**	***p*-value**
HBeAg loss	57 (44%)	40 (29%)	0.01	46 (35%)	49 (36%)	0.91
HBeAg seroconversion	33 (25%)	30 (22%)	0.52	38 (29%)	39 (29%)	0.92
HBsAg loss	9 (7%)	7 (5%)	0.54	9 (7%)	9 (7%)	0.92
HBsAg seroconversion	8 (6%)	6 (4%)	0.53	9 (7%)	7 (5%)	0.54
HBV DNA < 200,000 copies/ml	96 (74%)	40 (29%)	< 0.0001	41 (32%)	37 (27%)	0.440.43
HBV DNA, 400 copies/ml	43 (33%)	13 (10%)	< 0.0001	12 (9%)	9 (7%)	
HBV DNA change from baseline	Not possible to calculate as EOT on chart is different to that reported in paper	Not possible to calculate as EOT on chart is different to that reported in paper		2.3 (estimated from figure in paper)	2.2 (estimated from figure in paper)	
ALT returned to normal	66 (51%)	46 (34%)	0.005	46 (35%)	44 (32%)	0.60

continued

Liver histology at EOT (histology study)	*Group A (n = 52)*	*Group B (n = 58)*
Fibrosis		
Improvement	17 (33%)	13 (22%)
No change	15 (29%)	23 (40%)
Deteriorated	20 (38%)	22 (38%)[a]
Inflammation		
Improvement	25 (48%)	31 (53%)
No change	22 (42%)	21 (36%)
Deteriorated	5 (10%)	6 (10%)[b]

a $p = 0.22$ for improvement or no change vs worsening.
b $p = 0.57$ for improvement or no change vs worsening. Authors advise caution as post-treatment biopsies were optional and selection may have occurred.

Histological changes at EOT (histology study)	*Group A (n = 52)*	*Group B (n = 58)*
Necroinflammatory score, mean ± SD (range)		
Pre-treatment	5.4 ± 2.0 (2–9)	5.6 ± 2.2 (1–10)
Post-treatment	3.7 ± 2.0 (1–8)	4.1 ± 1.8 (1–9)
p-value (pre- vs post-treatment)	< 0.001	< 0.001
Change	–1.7 ± 2.6 (–7/+3)	–1.5 ± 2.3 (–7/+4)
Fibrosis score, mean ± SD (range)		
Pre-treatment	2.6 ± 1.5 (0–6)	2.3 ± 1.6 (0–6)
Post-treatment	2.8 ± 1.8 (0–6)	2.7 ± 1.6 (0–6)
p-value (pre- vs post-treatment)	0.23	0.07
Change	0.2 ± 1.4 (–3/+3)	0.4 ± 1.5 (–2/+5)

Overall mean necroinflammatory score improved by 1.6 points, significant improvement in both groups ($p < 0.001$). Largest improvements in focal inflammation (mean 0.7 points) and in interface hepatitis (mean 0.6 points). Necroinflammation score improved in 51% of patients (decrease ≥ 2 points) and only 10% showed worsening (increase ≥ 2 points). Inflammation improved in 48% of patients in Group A and 53% of patients in Group B ($p = 0.57$)

Overall mean fibrosis score increased by 0.3 points ($p = 0.03$). Fibrosis score improved in 27% of patients (decrease ≥ 2 points). Mean fibrosis score increased by 0.2 points in Group A and 0.4 points in Group B ($p = 0.59$)

DOI: 10.3310/hta13350

Viral resistance, end of treatment[a]		*Group A (n = 130)*	*Group B (n = 136)*	
YMDD mutation (resistance to lamivudine), *n* (%)		14 (11)	Not applicable	
a Two of these patients responded to therapy with loss of HBeAg. Seven (50%) of them had been previously treated with lamivudine and had had a mutant from the start of therapy.				
Adverse events	Group A (*n* = 130)	Group B (*n* = 136)		
Dose discontinuation for any adverse event[a]			28 (9%) overall PEG discontinuation	24 discontinued blinded drug (lamivudine/placebo)
PEG dose reduction for any adverse event[b]			37 (54%) Group A	32 (47%) Group B
Common adverse events experienced, n *(%)*			*Reason for dose reduction, n (%)*	*Reason for early dis-continuation, n (%)*
Flu-like syndrome	96 (74%)	84 (62%)	7 (10)	3 (11)
Headache	59 (45%)	55 (40%)		
Fatigue	54 (42%)	59 (43%)	2 (3)	
Myalgia	42 (32%)	41 (30%)	1 (1)	
Abdominal pain	25 (19%)	26 (19%)		
Arthralgia	20 (15%)	22 (16%)		
Loss of > 10% body weight	25 (19%)	28 (21%)		
Anorexia	21 (16%)	22 (16%)		
Diarrhoea	14 (11%)	15 (11%)		
Nausea	14 (11%)	25 (18%)		
Dermatological-local reaction	38 (29%)	36 (27%)		
Alopecia	35 (27%)	26 (19%)		
Pruritus	18 (14%)	14 (10%)		
Depression (including mood changes and irritability)	28 (22%)	29 (21%)		
Insomnia	20 (15%)	11 (8%)		
Neutropenia (<1.5x 10^9/L)	34 (26%)	29 (21%)	36 (52)	1 (4)
Thrombocytopenia (<75 x 10^9/L)	14 (11%)	17 (13%)	7 (10)	1 (4)
Leucopenia			2 (3)	
Combined haematological			6 (8)	

continued

Psychiatric	4 (6)	10 (36)
Local reaction		
Anorexia	1 (1)	
Patients lost to follow-up	1 (1)	4 (14)
Anaemia		1 (4)
Flare		1 (4)
Seizures		1 (4)
Acute pancreatitis		1 (4)
Decompensated liver disease		1 (4)
Pneumonia		1 (4)
Other	2 (3)	3 (11)
Total	69 (23%)	

a 266 patients remained on treatment and 184 (69%) patients remained on full-dose treatment. There were no significant differences in dose reductions between the treatment groups. There were 33 serious adverse events (12% of patients) of which 17 (53%) were probably related to therapy [hepatitis flare 4, depression 3, severe neutropenia (grade III or IV) 3, and one each of psychosis, seizures, pancreatitis, anxiety, dizziness, diarrhoea and syncope]. All serious adverse events were reversible after treatment was stopped.
b Pre-existing cirrhosis and neutropenia were the most important predictors of dose reduction or early treatment discontinuation. Frequency of all side effects was reported as not significantly different between groups. There were no dose reductions of LAM or placebo. 50% of the dose reductions occurred within the first 10 weeks, with numbers of dose reductions decreasing thereafter and only two reported after week 32. Discontinuation of therapy was reported more frequently before the scheduled dose reduction of PEG at week 32. Flares: Group A, $n = 37/148$ (25%); Group B, $n = 34/152$ (22%); $p = 0.5$.
c Safety study

Additional results

Also reported HBeAg loss by HBV genotype and YMDD mutant at EOT. Two (14%) patients had responded to therapy with loss of HBeAg, while seven (50%) of had been previously treated with LAM and had had a mutant from the start of therapy. Results for treatment response by HBV genotype were also reported. Other baseline factors that were predictive of response with multivariate analysis were low viral load [1.6 (1.3–1.8), $p = 0.009$], high ALT concentrations [1.1 (1.0–1.2), $p = 0.02$] and absence of previous IFN therapy [2.2 (1.1–4.5), $p = 0.04$]. Low HBV DNA levels ($p = 0.002$) and low BMI ($p = 0.02$) were two baseline factors associated with improvement of necroinflammatory scores and stable or improved fibrosis stage. Also reported HBV genotype on histological response

Methodological comments:

Allocation to treatment groups: Eligible patients were randomised on a 1:1 basis to PEG/LAM or PEG/placebo. Randomisation was done centrally and stratified by study centre

Allocation concealment: Treatment was allocated in blocks of six per centre. Centres were monitored by an independent company, which led to the withdrawal of one centre where source data could not be verified. The trial was double-blinded. The placebo was similar in appearance to LAM and administrated daily

Blinding of outcome assessors: All HBV markers were assessed at central laboratory, with staff unaware of treatment allocation. Routine biochemical and haematological tests were done by automated techniques at participating centres. Histological samples were scored centrally by a pathologist unaware of treatment regimen; assessment of other outcomes was not discussed. Treating physician assessed and reported adverse events using standard case-record forms, verified by trial centre

DOI: 10.3310/hta13350

Analysis by intention to treat: Modified ITT $n = 266$, 87% (all randomised patients meeting inclusion criteria and having had at least one dose of study medication). One study centre was withdrawn because of 'misconduct' (see allocation concealment above) and 24 (8%) patients were excluded from ITT, but it is unclear how far into the study this occurred (assessment of primary and secondary end points was not possible for these patients, as a result of samples being thawed for a long period). A further 10 (3%) patients were excluded because they had lost HBeAg before the start of treatment and seven (2%) patients did not take any study medication. Patients excluded from the final analysis were reported to be equally distributed among assigned treatment groups

Comparability of treatment groups at pre-treatment: Groups appear similar at baseline, but no *p*-values are given. Population in histological study reported to be representative of the original study population, with not significant differences in baseline characteristics between those included and excluded from histological assessment (no *p*-values are given)

Method of data analysis: Withdrawals were classified as treatment failures. The effects of PEG and PEG/LAM therapy on response were compared by the chi-squared test. Response rates are those assessed by % HBeAg loss, HBV DNA concentration < 200,000 copies/ml, HBV DNA negative by PCR or normal ALT concentrations at EOT and EOF-U. Patients with missing data at week 52 or week 78 were classified as non-responders at EOT or EOF-U respectively. The relationship between patients baseline characteristics and HBeAg loss at EOF-U (sustained response) was examined by logistic regression analyses. Univariate analysis was used to assess the importance of prognostic factors. Multiple logistic regression analyses were done with baseline characteristics to check the independence of these factors. Independence of genotype as a prognostic factor was assessed using multivariate analysis. All *p*-values were two-sided. Comparisons between groups were made using the chi-squared test for categorical variables and the Mann–Whitney test for continuous variables. Logistic regression was used for multivariate analysis. Baseline variables (improvements of necroinflammation and fibrosis, worsening of fibrosis: sex, race, age, BMI, transmission route, genotype of HBV, ALT, log HBV DNA, previous therapy with LAM or PEG) were evaluated as prognostic factors. A separate multivariate analysis evaluated which treatment end points (ALT normalisation, HBV DNA < 200,000 copies/ml, HBV DNA PCR negativity, HBeAg loss and HBeAg seroconversion) were associated with improvement of necroinflammation and fibrosis, or with worsening of fibrosis. Kaplan–Meier analysis was used to assess time until dose reduction or premature discontinuation of therapy. Chi-squared analysis was carried out to compare frequencies of adverse events. For all analysis in the safety study, the data of the two groups were combined

Power analysis: The study was powered to account for a mixed population with 50% of patients previously non-responsive to IFN therapy and 50% who had not received IFN previously, with a baseline ALT concentration of > twice ULN. To obtain a power of more than 80% ($\alpha = 0.05$), an estimated 270 patients would be needed, on assumption of rates of HBeAg loss at the end of follow-up of 20% for PEG and 36% for PEG/LAM therapy. Sample-size calculation was based on an estimated withdrawal rate of 20%. Fewer PEG-experienced patients were recruited than expected ($n = 55$, 21%) but it is reported that with a total of 266 patients in the modified ITT population, the study remained adequately powered

Attrition/drop-out: 22 withdrawals from Group A (four did not start treatment, six HBeAg-negative at start of treatment and 12 in centre withdrawn for misconduct) and 19 withdrawals from Group B (three did not start treatment, four HBeAg negative at start of treatment and 12 in centre withdrawn for misconduct). These were not included in the modified ITT. Of those included in the modified ITT, 12 patients discontinued because of adverse events, one for other reasons and three were lost to follow up in Group A, while 11 patients discontinued as a result of adverse events and seven were lost to follow-up in Group B. Biopsy pairs: $n = 151$ patients (40% response), 41 patients were excluded (= 45 biopsies) for the following reasons: biopsy sample was too small (16), not enough portal tracts (12), too fragmented (14) or technical reasons (3). 115 patients had no follow-up biopsy (response 32%)

Safety paper reports 28 discontinuations for adverse events

General comments

Generalisability: HBeAg-positive CHB patients from Europe, East Asia and North America, some with cirrhosis. Authors advise caution with the histological results as post-treatment biopsies were optional and selection may have occurred

Conflict of interests: The study received financial support from Schering–Plough International and GlaxoSmithKline R&D. Three authors have served as consultants or received grants from Schering–Plough International and GlaxoSmithKline and other major pharmaceutical companies. The authors state that companies providing financial support to the Foundation for Liver Research (Funder) approved the study design. They state that no funding source had any role in the collection, management, analysis or interpretation of the data, writing of the report or decision to submit for publication. Data collection and management was carried out at the trial coordinating centre in the Netherlands

continued

Other: Because there was no difference in serious adverse events or need for dose reduction or premature treatment discontinuation, the data for the two groups were combined in the paper on safety

Definitions: ALT, alanine aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; EOF-U, end of follow-up; EOT, end of treatment; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen, HBV DNA, hepatitis B virus DNA; LAM, lamivudine; PEG-α-2b, peginterferon α-2b; ULN, upper limit of normal

Adverse events were graded according to the WHO recommendations as mild/moderate/severe/life-threatening, and reported in relation to therapy as unrelated/possibly related/probably related or related to therapy. The effect on study medication was none/dose reduction/treatment discontinuation. Serious adverse events were defined as events resulting in death, life-threatening, require/prolong patient hospitalisation, events which result in persistent/significant disability/incapacity, pregnancy, congenital anomaly, cancer or overdose. Hepatitis flares were defined as increase in serum ALT at least 3 × baseline level. Psychiatric side effects included mood changes, irritability and depression

Quality assessment for RCTs (quality criteria – CRD report 4)

Criterion	Judgement
1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the care provider blinded?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an intention to treat analysis?	Inadequate
9. Were withdrawals and drop-outs completely described?	Partial

DOI: 10.3310/hta13350

Reference and design	Intervention	Participants	Outcome measures
Kaymakoglu *et al.*, 2007[25] *Trial design:* Prospective, open-label RCT *Number of centres:* 8 *Country*: Turkey *Funding:* not reported-	*Group A:* PEG *n* = 19 Drug 1: PEG-α-2b Dose: 1.5 μg/kg of body weight/week Duration: 48 weeks *Group B:* PEG ± LAM *n* = 29 Drug 1: PEG-α-2b Dose: 1.5 μg/kg of body weight/week Duration: 48 weeks Drug 2: LAM Dose: 100 mg daily Duration: 48 weeks	Total numbers involved: 48 Total randomised: 48 Analysed in each group: Group A, *n* = 19; Group B, *n* = 29 *Inclusion criteria:* Aged 18+ HBsAg positive for minimum of 6 months HBeAg negative and anti-HBe positivity on two occasions in past 3 months Serum ALT levels > 1.3 × ULN on two occasions in previous 3 months HBV DNA positivity LLD 4pg/mL Compensated liver disease with histological evidence of chronic hepatitis *Exclusion criteria:* Any other cause of liver disease Immunosuppressive or antiviral treatment in previous 6 months Hepatocellular carcinoma *Baseline measurements:*	*Outcomes:* HBV DNA level and ALT level normalisation weeks 48 and 72 Length of follow-up: 24 weeks (total = 72 weeks)

Characteristics	Group A (*n* = 19)[a]	Group B (*n* = 29)[a]
Age, years ± SD	42.6 ± 10.9	43 ± 7.8
Male/female ratio	13/6	20/9
HBV DNA (pg/ml)	182.3 ± 175.4	209.6 ± 207.8
ALT (IU/l)	130.4 ± 45	161.5 ± 172.4
HAI	7.0 ± 3.2	8.3 ± 2.9
AST (IU/l)	80.3 ± 22.9	89.2 ± 47.5

Characteristics	Group A ($n = 19$)[a]	Group B ($n = 29$)[a]
Histological stage, fibrosis score (Knodell scoring system)		
Mild	10	15
Moderate	3	4
Severe	4	8
Cirrhosis	2	2
Total bilirubin mg/dl	0.8 ± 0.4	0.8 ± 0.4
Albumin (g/dl)	4.3 ± 0.3	4.5 ± 0.7
a Data are means ± SD unless otherwise stated.		

Ethnic groups: Not stated

Losses to follow-up: $n = 0$

Compliance: Not reported

Treatment history: Not reported

Patient characteristics (e.g. carriers, those with compensated/decompensated liver disease, etc.): HBeAg-negative CHB with compensated liver disease

Outcome	Group A	Group B
HBV DNA change from baseline		
HBV DNA (< 4pg/ml), EOT, *n* (%)	12 (63)	23 (79)
HBV DNA (< 4pg/ml), EOF-U, *n* (%)	7 (37)	10 (34)
< 400 copies/ml, EOF-U, *n* (%)	5 (26)	7 (24)
HBV DNA reduction	Not reported	Not reported
Comments: $p > 0.05$ for all parameters; proportion of patients who had serum HBV DNA negativity at EOT and EOF-U similar		
HBsAg levels		
Rate of seroconversion		
Seroconversion week 72, *n* (%)	2 (11)	1 (3)

DOI: 10.3310/hta13350

ALT/AST change from baseline at end point	Not reported	Not reported
ALT normalisation, EOT, *n* (%)	10 (53)	19 (66)
ALT normalisation, EOF-U, *n* (%)	8 (42)	14 (48)
Comments: Proportion of patients who had serum ALT normalisation at EOT and EOF-U similar		
Other viral response outcomes		
Adverse events		
Dose discontinuation for any adverse event	0	
Dose reduction for any adverse event	0	
Adverse events experienced, %		
Flu-like symptoms	71	
Cytopenia	23	
Injection site reactions	10	
Pruritus	8	
Depression	6	
Thyroiditis	2	
Comments: No patient discontinued as the result of an adverse event		
Additional results: The only variable influencing EOF-U response was female sex ($p < 0.05$)		
Methodological comments:		
Allocation to treatment groups: Randomised 1:1.5 ratio; no other details reported		
Allocation concealment: The study is open-label		
Blinding of outcome assessors: The study is open-label		
Analysis by intention to treat: Not reported. Results are given for the whole group		
Comparability of treatment groups at pre-treatment: Groups appeared to be similar, but PEG + LAM group had higher ALT level (including larger SD) at baseline		
Method of data analysis: Groups were compared using Fisher's exact test and Student's *t*-test where appropriate. Multiple logistical regression analyses were used to determine the independent variables influencing treatment response. A *p*-value of < 0.05 was considered statistically significant		
Power analysis: Not reported		
Attrition/drop-out: Group A, 3 early withdrawals and Group B, 2 early withdrawals; no other details given		

continued

General comments

Generalisability: HBeAg-negative CHB population with compensated liver disease

Conflict of interests: None reported

Definitions: ALT, alanine transferase; AST, asparatate amino transferase; CHB, chronic hepatitis B; EOF-U, end of follow-up; EOT, end of treatment; HAI, histological activity index; HBeAg, hepatitis B e antigen; HbsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus DNA; LAM, lamivudine, LLD, lower limit of detection; PEG-α-2b, peginterferon α-2b.

Quality assessment for RCTs (quality criteria – CRD report 4)

Criterion	*Judgement*
1. Was the assignment to the treatment groups really random?	Unclear
2. Was the treatment allocation concealed?	Unclear
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were outcome assessors blinded to the treatment allocation?	Inadequate
5. Was the care provider blinded?	Inadequate
6. Was the patient blinded?	Inadequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an intention to treat analysis?	Unclear
9. Were withdrawals and drop-outs completely described?	Inadequate

DOI: 10.3310/hta13350

Reference and design	Intervention	Participants	Outcome measures
Zhao *et al.*, 2007[27] *Trial design:* Open-label, parallel RCT *Number of centres:* 6 *Country:* China *Funding:* No funding stated	*Group A:* *n* = 115 PEG IFN-α-2b Dose: 1.0 μg/kg/once per week, s.c. Duration: 24 weeks *Group B:* *n* = 115 IFN-α-2b Dose: 3 MIU three times per week, s.c. Duration: 24 weeks	Total numbers involved: 412 patients screened Total randomised: 230 eligible Randomised to each group: Group A: 115; Group B: 115 *Inclusion criteria:* Patients 18–70 years of age; chronic HBV infection (defined as the presence of HBsAg and HBeAg for at least 6 months prior to enrolment); serum HBV DNA level $> 1\times10^5$ copies/ml; and ALT level within a range 2–10 ULN; WBC count $> 3.0\times10^9$ cells/l; granulocyte count $> 1.5\times10^9$ cells/l; platelet count $> 100\times10^9$ platelets/l *Exclusion criteria:* Any cause of liver disease other than chronic HBV infection, pregnant and/or breastfeeding women, use of immune regulators during the previous 6 months or receipt of antiviral therapy (nucleotide analogues and IFN) during the previous 3 months of commencement of the study *Baseline measurements:*	*Primary outcomes:* Virological,[a] serological[b] and biochemical[c] response at EOT and follow-up *Secondary outcomes:* Adverse effects Genotype- associated response Length of follow-up: 24 weeks after cessation of treatment

	Group A	Group B	*p*-value
Age (years), median (range)	31.0 (18.0–53.0)	31.0 (18.0–66.0)	0.51
Male gender, *n* (%)	93 (80.9)	96 (83.5)	0.61
Diagnosis established (months), median (range)	48.0 (2.0–372.0)	52.0 (0–272.0)	0.80
IFN therapy experience, *n* (%)	20 (17.4)	10 (8.7)	0.05
ALT, mean ± SD[a]	4.2 ± 2.0	3.8 ± 2.0	0.13
HBV DNA level (log copies/ml), mean ± SD	8.1 ± 0.8	8.0 ± 1.0	1.00
Genotype B, *n* (%)	31 (27)	29 (25.2)	0.90

continued

	Group A	Group B	*p*-value
Age (years), median (range)	28.0 (18.0–48.0)	25.0 (18.0–49.0)	0.90
Genotype C, *n* (%)	84 (73.0)	86 (74.8)	0.90
Age (years), median (range)	32.0 (19.0–53.0)	32.0 (18.0–66.0)	0.90
a Data are x-fold, exceeding upper limit of the normal range.			

Losses to follow-up: Group A, $n = 7$; Group B, $n = 14$

Compliance: Four patients in Group B discontinued treatment because of adverse effects

Treatment history: Previous IFN-α-2b therapy: Group A, $n = 20$ (17.4%); Group B, $n = 10$ (8.7%); $p = 0.05$

Patient characteristics: HBeAg and HBsAg positive, HBV DNA level $> 10^5$ copies/ml, elevated ALT level 2–10 × ULN.

a Rate of serum HBV DNA $< 10^5$ copies/ml and $< 10^3$ copies/ml, and mean reduction of serum HBV DNA level from baseline.
b Rate of HBeAg loss and seroconversion, rate of HBsAg seroconversion.
c Normalisation of ALT, sustained combined response (HBeAg –ve, HBV DNA < 5 $\log_{10}$ copies/ml and normal ALT level at week 48).

Response at week 48, *n* (%)[a]	**Group A, PEG-α-2b (*n* = 115)**	**Group B, IFN-α-2b (*n* = 115)**	***p*-value**
Mean reduction of HBV DNA level from baseline, $\log_{10}$ copies/ml			
Week 24 (EOT)	2.22	1.66	0.03
Week 48 (EOF-U), ± SD	–1.4 ± 2.2	–1.1 ± 2.1	0.34
HBV DNA level < 5 $\log_{10}$ copies/ml	34 (29.6)	22 (19.1)	0.06
HBV DNA level < 3 $\log_{10}$ copies/ml	14 (12.2)	14 (12.2)	1.00
HBeAg loss			
Week 24 (EOT)	26 (22.6)	20 (17.4)	Not significant
Week 48 (EOF-U)	28 (24.4)	16 (13.9)	0.04
HBeAg seroconversion	25 (21.7)	16 (13.9)	0.12
HBsAg seroconversion	0 (0)	2 (1.7)	0.50
ALT level normalisation	39 (33.9)	40 (34.8)	0.93
Sustained combined response	20 (17.4)	12 (10.4)	0.13

DOI: 10.3310/hta13350

Adverse events		
Dose discontinuation for any adverse event	0	4[b]
Dose reduction for any adverse event	0	0
Adverse events experienced[c]	75%	75%

a Data are *n* (%) of patients, unless otherwise indicated.
b Two patients with elevated ALT with nausea and vomiting, one patient with elevated ALT and total bilirubin levels, one patient with elevated total bilirubin levels.
c Various clinical forms of drug-related adverse effects, flu-like symptoms and fever were the most common.

Additional results: Results were also presented for HBV genotype-associated response, and predictive factors associated with sustained combined response

Rates of sustained combined response, HBeAg seroconversion and ALT normalisation were similar for both treatment arms at EOT (data not shown)

Two patients (Group B) seroconverted after 24 weeks; this was maintained to the 48-week follow-up

75% of patients in each treatment group experienced various clinical forms of drug-related adverse effects. Flu-like symptoms and fever were the most common adverse events

Methodological comments

Allocation to treatment groups: A central computerised randomisation method was used on a ratio of 1:1

Allocation concealment: No details reported

Blinding of outcome assessors: Biochemical and haematological lab assays were performed in-house at the participating centres. Investigators assessing adverse events were not blinded to treatment as they were able to reduce the PEG or IFN dose according to adverse event experienced. No information reported regarding the assessment of the other primary or secondary outcome measures

Analysis by intention to treat: the study was analysed by intention to treat, all 230 patients were included in the efficacy and safety analysis. Patients who discontinued were considered to be non-responders

Comparability of treatment groups at pre-treatment: Groups were similar at baseline for demographic and prognostic characteristics (*p*-values reported), with the exception of the proportion of patients who had previously received IFN therapy, which was significantly higher in Group A ($p = 0.05$). A higher number of patients had genotype C (73.9%) than genotype B (26.1%), and genotype B patients were significantly younger than genotype C patients (mean 26.5 vs 32.0 years, $p < 0.0001$), but these did not differ between treatment groups

Method of data analysis: Continuous variables were analysed using an unpaired t-test or Wilcoxon rank sum test, and a treatment group comparison of categorical variables was performed using Pearson's χ^2 test, or if data were sparse, Fisher's exact test. Differences between treatment groups of measurements of efficacy were examined using Cochran–Mantel–Haenszel statistics. A two-way analysis of variance, with treatment, centre and treatment-by-centre interaction as factors, was used to compare changes in HBV DNA levels from baseline to weeks 24 and 48 between the treatment groups. The incidence of adverse effects was compared between treatment groups using Cochran–Mantel–Haenszel statistics, controlling for centre ($p < 0.05$ was considered to be significant)

Power analysis: Not reported

Attrition/drop-out: Drop-outs were reported at each stage in a flow-chart. Reasons were given for four (Group B) who discontinued because of adverse events; two others (Group B) discontinued for non-study reasons. Reasons for loss to follow-up were not given. Completed treatment: Group A, 115; Group B, 109. Completed follow-up: Group A, 108; Group B, 95

continued

General comments

Generalisability: Chinese patients, HBeAg and HBsAg positive, previous IFN therapy, nearly three-quarters had genotype C

Conflict of interests: No funding source is stated. The authors state there are no conflicts of interest

Other: In this study patients received less than one-third of the recommended dose of IFN-α-2b. The patients receiving PEG-α-2b also received a lower dose (1.0 μg/kg/week) than had been administered in previous reports (1.5 μg/kg/week for patients with body weight < 65 kg or 100 μg/week for those with body weight ≥ 65 kg). Generally, EOT results were not presented

Definitions: ALT, alanine aminotransferase; EOF-U, end of follow-up; EOT, end of treatment; HBeAg hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; s.c., subcutaneously; ULN, upper limit of normal. Combined response and sustained combined response were defined as serum HBV DNA level < 10^5 copies/ml, HBeAg loss and normal ALT levels at EOT and EOF-U. Relapse was defined as a combined response at EOT, but with abnormal ALT levels and serum HBV DNA ≥ 10^5 copies/ml with or without HBeAg loss at EOF-U

Quality assessment for RCTs (quality criteria – CRD report 4)

Criterion	Judgement
1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Partial
4. Were outcome assessors blinded to the treatment allocation?	Inadequate
5. Was the care provider blinded?	Inadequate
6. Was the patient blinded?	Inadequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Partial
8. Did the analyses include an intention to treat analysis?	Adequate
9. Were withdrawals and drop-outs completely described?	Partial

Appendix 2

QUOROM flow chart of study inclusion (2007 update literature search)

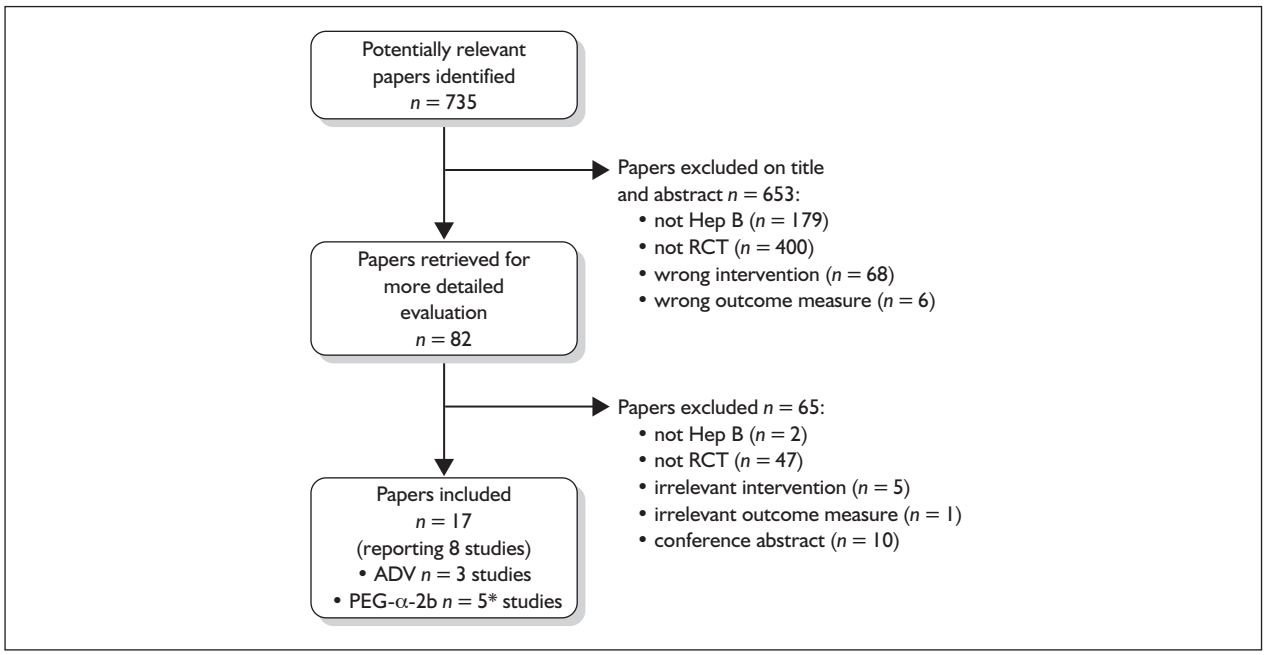

FIGURE 6 *QUORUM flow chart. Note: An additional PEG-α-2b study, published in 2005, was identified from the Reference Manager database used in our previous assessment report (although it was not actually included in that report). Therefore, the total number of PEG-α-2b included studies in the current report was five, and the total number of studies included in the review was eight.*

Appendix 3

Characteristics of RCTs included in original assessment report

Seven fully published RCTs were included in our original report:

- Four evaluated ADV. In two studies ADV was compared with placebo.[21,65] (A publication reporting long-term follow-up of one of these trials was identified by our update search.[20] In the other two studies, ADV, either as monotherapy or in combination with LAM, was compared with LAM monotherapy in patients with LAM resistance.[66,67]
- Three evaluated PEG-α-2a. In two studies, the combination of PEG-α-2a and LAM was compared with both agents separately (the difference being that one study included HBeAg-positive patients, the other HBeAg-negative patients).[50,76] The third study compared PEG-α-2a with IFN-α.[77]

Table 41 provides a general overview of the RCTs included in the original systematic review. For further detail on the study characteristics and results, please consult the original report.[12] The remainder of the current report focuses on studies included from the updated literature search.

TABLE 41 *Overview of RCTs included in original systematic review*

Study	HBeAg status	No. of participants, duration of trial (T_d), additional follow-up (F_d) and total duration	Arm 1	Arm 2	Arm 3	Arm 4
ADV studies						
Hadziyannis *et al.*, 2003[21] Study 438	Negative	*n* = 185 T_d = 48 weeks[a] F_d = 0 weeks Total = 48 weeks	ADV 10 mg/day (*n* = 123)	Placebo (*n* = 62)		
Marcellin *et al.*, 2003[65] Study 437	Positive	*n* = 515 T_d = 48 weeks[b] F_d = 0 weeks Total = 48 weeks	ADV 10 mg/day (*n* = 172)	ADV 30 mg/day (*n* = 173)	Placebo (*n* = 170)	
Perrillo *et al.*, 2004[66] Study 465	Positive	*n* = 95 T_d = 52 weeks[c] F_d = 0 weeks Total = 52 weeks	LAM 100 mg/day + ADV 10 mg/day (*n* = 46)	LAM 100 mg/day + placebo (*n* = 49)		
Peters *et al.*, 2004[67] Study 461	Positive	*n* = 59 T_d = 48 weeks F_d = 0 weeks Total = 48 weeks	ADV 10 mg/day + placebo (*n* = 19)	ADV 10 mg/day + LAM 100 mg/day (*n* = 20)	LAM 100 mg/day + placebo (*n* = 19)	
Sung *et al.*, 2003[78]	Positive	*n* = 115 T_d = 52 weeks[d] F_d = 0 weeks Total = 52 weeks	LAM 100 mg/day + ADV 10 mg/day (*n* = 55)	LAM 100 mg/day + placebo (*n* = 57)		

continued

TABLE 41 *Overview of RCTs included in original systematic review (continued)*

Study	HBeAg status	No. of participants, duration of trial (T_d), additional follow-up (F_d) and total duration	Arm 1	Arm 2	Arm 3	Arm 4
PEG-α-2b studies						
Marcellin *et al*., 2004[76] Study 241	Negative	*n* = 552 (of whom 537 were included in analyses) T_d = 48 weeks F_d = 24 weeks Total = 72 weeks	PEG 180 μg/week + placebo (*n* = 177)	PEG 180 μg/ week + LAM 100 mg/day (*n* = 179)	LAM 100 mg/ day (*n* = 181)	
Cooksley *et al*., 2003[77] Study 037	Positive	*n* = 194 T_d = 24 weeks F_d = 24 weeks Total = 48 weeks	IFN 4.5 MIU three times/week (*n* = 51)	PEG 90 μg/ week (*n* = 49)	PEG 180 μg/ week (*n* = 46)	PEG 270 μg/ week (*n* = 48)
Lau *et al*., 2005[50] Study 240	Positive	*n* = 814 T_d = 48 weeks F_d = 24 weeks Total = 72 weeks	PEG 180 μg/week + placebo/day (*n* = 271)	PEG 180 μg once weekly + LAM 100 mg once daily (*n* = 271)	LAM 100 mg once daily (*n* = 272)	

MIU, million international units.
a After 48 weeks, patients in the ADV group were re-randomised to receive placebo for 48 weeks, or 10 mg ADV for 192 weeks. Patients in the placebo group received 10 mg ADV for a further 192 weeks. Study due to end June 2005, when patients will have received 5 years of treatment.
b After 48 weeks, patients were reassigned so that the 30 mg ADV group received placebo, the 10 mg ADV group were re-randomised to receive either 10 mg ADV or placebo, and the placebo group received 10 mg ADV. After July 2001, the double-blind phase of the study was terminated and all groups were assigned to receive 10 mg ADV (open-label) up to March 2005, when patients will have received 5 years of treatment.
c 78 patients continued to receive treatment for a further 2 years (Study 493). Study is ongoing.
d Study continued for a further 52 weeks.

Appendix 4

Data extraction forms – economic evaluations

Reference

Veenstra and colleagues (2007) Cost-effectiveness of peginterferon alpha-2a compared with lamivudine treatment in patients with HBe-antigen-positive chronic hepatitis B in the United Kingdom.[44]

Study characteristics

Research question

What are the stated objectives of the evaluation?

- To assess the net health consequences, costs, and cost-effectiveness of peginterferon alpha-2a (40 kDa) for treatment of patients with HBeAg-positive CHB, compared with lamivudine treatment (p. 632).

Study population

What definition was used for chronic hepatitis B?

- The cohort was defined as those with a histological diagnosis of CHB, HBeAg +ve for more than 6 months, and detectable HBV DNA > 500,000 copies/ml.

What are the characteristics of the baseline cohort for the evaluation?

Age	32-year-old patients
Sex	78% male
Race (if appropriate)	87% Asian
Genotype	Not specified
Other characteristics	Characteristics of the cohort were based on patient population ($n = 542$) enrolled in a clinical trial (Lau *et al.*[50]). 100% HBeAg+ve 17% with compensated cirrhosis or transition to cirrhosis Mean baseline ALT was 110.6 U/l (> 2×ULN)

Interventions and comparators

What number of interventions/strategies were included?

- Two.

Was a no treatment/supportive care strategy included?

- No.

Describe interventions/strategies:

- Intervention/strategy 1: PEG-α-2a 180 mg daily monotherapy for 48 weeks
- Intervention/strategy 2: lamivudine 100 mg daily monotherapy up to a maximum of 4 years or until patients achieve HBeAg seroconversion.

Analytical perspective

What is the perspective adopted for the evaluation (health service, health and personal social services, third-party payer, societal (i.e. including costs borne by individuals and lost productivity)?

- UK NHS perspective.

Study type

Cost-effectiveness/cost-utility/cost-benefit analysis?

- CEA (incremental cost per additional life-year saved)
- CUA (incremental cost per QALY).

Institutional setting

Where is/are the intervention(s) being evaluated usually provided?

- Not identified. PEG-α-2a is administered intravenously, so for some patients the treatment may be provided at the institutional setting. LAM is an oral medication and can be self-administered.

Country/currency

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

- Currency is £ sterling in 2005. (Table 2, p. 635).

Data sources

Effectiveness

Were the effectiveness data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
Effectiveness data at 48 weeks of treatment were derived from a single study	✓	Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, *et al*. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005;**352**:2682–95
Long-term effectiveness data (seronversion, relapse and lamivudine resistance rates at 2-4 years,) were derived from combination of previous follow-up studies	✓	*Non-controlled studies* Liaw YF, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, *et al*. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *Gastroenterology* 2000;**119**:172–80. Leung NW, Lai CL, Chang TT, Guan R, Lee CM, Ng KY, *et al*. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy. *Hepatology* 2001;**33**:1527–32 Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, *et* al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003;**125**:1714–22
Expert opinion	×	

Give the definition of treatment effect used in the evaluation.

- Primary treatment effect (p. 633, also one of two primary outcomes in the pivotal clinical trial)
  - % of patients achieving seroconversion (transitioning from CHB state to seroconversion state). This can occur spontaneously or as a result of treatment.
- In addition the following outcomes are used
  - percentage of patients relapsing (transitioning from seroconversion state back to CHB state). Can occur on an annual basis (yet different rates apply at 6 months after the treatment and the subsequent intervals)
  - percentage of lamivudine patients developing resistance (used in the scenario analysis)
  - percentage of patients with AEs (from Lau and colleagues[50]).

Give the size of treatment effect used in the evaluation.

- Not applicable. Serocoversion, relapse and resistance are composite, qualitative measures of outcome.

Include values used for subgroups (if applicable). Indicate the source for individual treatment effects (if appropriate).

Intervention costs

Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
A single clinical trial used to estimate the proportion of patients with AEs	✓	Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, *et al*. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005;**352**:2682–95
A review/synthesis or combination of previous studies is used for health-state costs	✓	*Produced in* Shepherd J, Jones J, Takeda A, Davidson P, Price A. *Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation*. Southampton Health Technology Assessments Centre (SHTAC); 2005 Bennett WG, Inoue Y, Beck JR,Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997;**127**: 855–65.
Expert opinion estimates of resources used to treat AE associated with PEG-α-2a treatment	✓	

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

Resource category	Type of resources	Unit cost estimate	Source
Drug costs (weekly)	PEG-α-2a 180 mg	£132	BNF
	LAM 100 mg	£20	
	Health state	**Total annual management cost**	**Source**
Health-state costs (range)	Seroconversion	£267 (200–334)	Shepherd J, Jones J, Takeda A, Davidson P, Price A. *Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation*. Southampton Health Technology Assessments Centre (SHTAC); 2005 Bennett WG, Inoue Y, Beck JR,Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997;**127**:855–65
	Chronic hepatitis B	£537 (403–671)	
	Compensated cirrhosis	£1138 (854–1422)	
	Decompensated cirrhosis	£9120 (6840–11,400)	
	Hepatocellular carcinoma	£8127 (6095–10,159)	
	Liver transplantation	£36,788.00 (27,561–45,985)	
	Post-liver transplant	£1385 (1039–1731)	
Average costs of treating side effects per patient per year of treatment	Not elaborated	Unit costs are not presented PEG-α-2a £6.48 LAM £2.04	BNF unit costs are used for each component of treatment of AE

Other direct costs (used in scenario analysis)

Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
A single (observational) study	✓	Incidence of lamivudine resistance 26%/year (Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, *et al*. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003;**125**:1714–22
A review/synthesis or combination of previous studies	×	
Expert opinion	×	

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

- The cost of ADV used in the LAM arm as a salvage therapy for the patients who developed resistance (£73.50 per week).

Indicate the source for individual cost values (if appropriate).

Indirect costs (due to lost productivity, unpaid inputs to patient care)

Were indirect costs included?

- Not applicable.

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued).

- Not applicable.

Indicate the source for individual cost values (if appropriate).

Health-state valuations/utilities (if study uses quality of life adjustments to outcomes)

Were the utility data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
A single (observational) study	×	
A review/synthesis or combination of previous studies	✓	Wong JB, Koff RS, Tine F, Pauker SG. Cost-effectiveness of interferon-alpha 2b treatment for hepatitis B e antigen-positive chronic hepatitis B. *Ann Intern Med* 1995;**122**:664–75 Bennett WG, Inoue Y, Beck JR,Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997;**127**:855–65 Kind P, Hardman G, Macran S. *UK population norms for EQ-5D*. CHE Discussion Paper 172. York: York Centre for Health Economics, University of York; 1999
Expert opinion	×	

List the utility values used in the evaluation.

Seroconversion	UK age-specific utility (± 20%)
Chronic hepatitis B	0.87 (0.89–0.97)
Compensated cirrhosis	0.84 (0.82–0.86)
Decompensated cirrhosis	0.46 (0.36–0.56)
Hepatocellular carcinoma	0.41 (0.31–0.51)
Liver transplantation	0.42 (0.32–0.52)
Post-liver transplant	0.62 (0.52–0.72)
An absolute decrease in utility of 0.05 to PEG-α-2a arm compared with lamivudine arm was used (Wong JB, Koff RS, Tine F, Pauker SG. Cost-effectiveness of interferon-alpha 2b treatment for hepatitis B e antigen-positive chronic hepatitis B. *Ann Intern Med* 1995;**122**:664–75).	

Indicate the source for individual cost values (if appropriate).

Modelling

If a model was used, describe the type of model used (e.g. Markov state-transition model, discrete event simulation).

- Markov state-transition model.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

- Model structure was similar to previously published models by Crowley,[42] Crowley and colleagues[43] and Pwu and Chan,[49] except that Crowley and colleagues did not include health states to account for patients receiving a liver transplant.

What was the purpose of the model (i.e. why was a model required in this evaluation)?

- Not explained, but presumably to estimate long-term costs and benefits (expressed in terms of final rather than intermediate outcomes) beyond the timeframe of the clinical trial (48-week treatment).

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported? List them if reported.

- HBeAg seroconversion, HBeAg-positive CHB, compensated cirrhosis, decompensated

cirrhosis, HCC, liver transplantation, post-liver transplantation, and death.

Extract transition probabilities for [natural history/disease progression] model and show sources (refer to Table 1, p. 634).

Disease state from	To	% (range)
Chronic hepatitis B	Seroconversion, year 1, peginterferon a-2a (40 kDa)	32.0 (30.0–34.0)
	Seroconversion, year 1, lamivudine	19.0 (17.0–21.0)
	Seroconversion, year 2, lamivudine	10.0 (9.5–11.0)
	Seroconversion, year 3, lamivudine	6.0 (3.0–9.0)
	Seroconversion, year 4, lamivudine	5.0 (2.5–7.5)
	Seroconversion, spontaneous	9.0 (6.0–12.0)
	Compensated cirrhosis	6.0 (4.0–8.0)
	Hepatocellular carcinoma	0.40 (0.10–0.70)
HBeAg seroconversion	Chronic hepatitis B, year 5, lamivudine	25.0 (20.0–30.0)
	Chronic hepatitis B, year 2, peginterferon a-2a (40 kDa)	8.0 (3.0–13.0)
	Chronic hepatitis B, spontaneous relapse	2.9 (1.0–5.0)
	Compensated cirrhosis	1.0 (0.5–2.0)
Compensated cirrhosis	Decompensated cirrhosis	5.0 (3.8–9.5)
	Death	5.0 (3.0–6.5)
Decompensated cirrhosis	Hepatocellular carcinoma	2.5 (2.0–7.8)
	Liver transplantation	3.1 (1.0–10.0)
	Death	39.0 (30.0–50.0)
Hepatocellular carcinoma	Death	56 (45.0–65.0)
	Liver transplantation	Not reported
Liver transplantation	Post-liver transplantation	79.0 (tunnel state)
	Death	21.0 (15.0–25.0)
Post-liver transplant	Death	5.7 (3.0–9.0)

What is the model time horizon? Duration of the cycle?

- 12-month cycle, lifetime duration (not specified).

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

- All costs were discounted at a 6% annual rate and outcomes (e.g. QALYs) at 1.5%, in accordance with UK guidelines at the time of this analysis.

Results/analysis

What measure(s) of benefit were reported in the evaluation?

- Life-years (LYs), quality-adjusted life years (QALYs).

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation.

- Treatment with PEG-α-2a compared with treatment with LAM is associated with:
- Additional discounted life expectancy of 0.39 and additional quality-adjusted life expectancy of 0.30 years.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation.

- Lifetime (discounted) costs associated with treatment
- PEG-α-2a £14,900 per patient
- LAM £11,800 per patient.

Synthesis of costs and benefits –are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

- The comparative performance of alternative treatment strategies was measured by the ICER, defined as the additional cost of a specific strategy, divided by its additional clinical benefit, compared with the next least expensive strategy.
- Discounted ICER is equal to £7949 (£8000) per LY gained.
- Discounted ICER is equal to £10,333 (£10,400) per QALY gained.

Give results of any statistical analysis of the results of the evaluation.

- The cost-effectiveness acceptability curve generated from the probabilistic sensitivity analysis indicated that there was a greater than 95% probability that PEG-α-2a was cost-effective compared with lamivudine at the £30,000 per QALY threshold (95% central range of results, £6000–£26,500 per QALY gained).

Was any sensitivity analysis performed? If yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic]?

- One-way and probabilistic sensitivity analyses were performed.
- ICERs were most sensitive to variation in the probability of:
  - developing compensated cirrhosis from CHB
  - PEG-α-2a seroconversion rate as observed in the clinical trial (Lau and colleagues[50])
  - relapse after 4 years of lamivudine treatment (i.e. from year 5 on)
  - the probability of developing compensated cirrhosis from the seroconversion state.
- The ICER for PEGα-2a compared with lamivudine monotherapy ranged from £8300 to £15,400 per QALY when treatment efficacy, drug cost, the health state-transition probabilities, utility values and health-state cost estimates were varied.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

- A scenario analysis in which ADV salvage treatment was used for lamivudine-resistant patients was provided.
- Annual seroconversion rates and drug costs for lamivudine-treated patients were modified based on the proportion of patients (26%, Lok and colleagues[53]), with resistance each year rather than explicitly including a resistance health state.
- The increase in the HBeAg seroconversion rate for resistant patients who received ADV salvage therapy was obtained from a randomised controlled trial of ADV–lamivudine combination therapy versus lamivudine monotherapy in lamivudine-resistant patients (Perrillo and colleagues[66]) (8% versus 3% HBeAg seroconversion at end of 1 year of treatment respectively).
- Not relevant to structural uncertainty (no new state was added) or methodological uncertainty. Transition probabilities (parameters of the model) were altered.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base-case analysis. If so, what were the suggested causes?

- Treatment with PEG-α-2a compared with treatment with LAM and ADV salvage therapy is associated with:
  - additional discounted life expectancy of 0.33 and (versus 0.39 in the base-case analysis)
  - additional quality-adjusted life expectancy of 0.14 years (versus 0.30 in the base-case analysis)
  - the lifetime difference in cost between treatments with PEG-α-2a and LAM has decreased from £3100 to £875.
- The scenario analysis results are:
  - discounted ICER is equal to £2652 per LY gained
  - discounted ICER is equal to £6250 not (£6100 as reported) per QALY gained.

Conclusions/implications

Give a brief summary of the author's conclusions from their analysis.

- Authors suggest that use of PEG-α-2a is highly likely to be cost-effective, given certain assumptions about disease progression and the efficacy and cost of therapy. The ICERs were most sensitive to variation in the probability of developing compensated cirrhosis from CHB, PEG-α-2a seroconversion rate, lamivudine treatment durability and the probability of developing compensated cirrhosis from seroconversion. However, when these parameters were varied over a range of estimates using one-way and multiway sensitivity analyses, the ICER did not exceed the £30,000/QALY threshold.

What are the implications of the evaluation for practice?

PEG-α-2a is likely to be cost-effective in treatment of HBeAg +ve patients who do not develop HBeAg –ve disease variant.

  - Uncertainty in relation to applicability of the outcomes to HBeAg –ve patients (a shortcoming of the study is an exclusion of HBeAg –ve state in disease progression).
  - Uncertainty in relation to generalisability of the results to England and Wales population (87% Asian in the modelled cohort, although UK life tables are used). In particular, seroconversion rates used in years 2–4 are low in comparison to the rate reported elsewhere [27–35% at 2 years and 40% at 3 years (Shepherd and colleagues[12], Crowley[42])].
  - Uncertainty associated with terminating LAM maintenance (and hence HBV DNA suppression) after 4 years. In particular, applying transition probabilities beyond 4 years of lamivudine treatment. A 25% annual relapse rate appears to be a conservative estimate in comparison with the 35% rate reported in the literature; this is five times the rate observed in year 4. This may bias the result in favour of PEG-α-2a.

- Although scenario analysis more closely approximates the real clinical practice, no probabilistic sensitivity analysis was performed with respect to parameter estimates (seroconversion rates observed in LAM/ADV treatment versus LAM monotherapy).

Reference

Sullivan and colleagues (2007) Cost-effectiveness of peginterferon alfa-2a compared to lamivudine treatment in patients with hepatitis B e antigen positive chronic hepatitis B in Taiwan.[45]

Study characteristics

Research question

What are the stated objectives of the evaluation?

- The objective of our study was to assess the net health consequences, costs and cost-effectiveness of 48 weeks of peginterferon alfa-2a for treatment of patients with HBeAg-positive CHB, compared with 48 weeks of lamivudine treatment.

Study population

What definition was used for mild chronic hepatitis B?

- The hypothetical cohort of patients was based on the clinical and demographic characteristics of patients in the Lau and colleagues (2005) clinical trial.[50] The cohort was defined as those with a histological diagnosis of CHB, HBsAg-positive for more than 6 months, and detectable HBV DNA > 500,000 copies/ml.

What are the characteristics of the baseline cohort for the evaluation?

Age	32-year-old patients
Sex	78% male
Race (if appropriate)	87% Asian
Genotype	Not specified
Other characteristics	Characteristics of the cohort were based on the patient population ($n = 542$) enrolled in a clinical trial (Lau *et al.*, 2005[50]). 100% HBeAg+ve 17% with compensated cirrhosis or transition to cirrhosis Mean baseline ALT was 110.6 U/l (> 2×ULN)

Interventions and comparators

What number of interventions/strategies were included?

- Two

Was a no treatment/supportive care strategy included?

- No

Describe interventions/strategies.

- Intervention/strategy 1: PEG-α-2a 180 mg daily monotherapy for 48 weeks
- Intervention/strategy 2: Lamivudine 100 mg daily monotherapy for 48 weeks.

Analytical perspective

What is the perspective adopted for the evaluation [health service, health and personal social services, third-party payer, societal (i.e. including costs borne by individuals and lost productivity)]?

- Taiwan Bureau of National Health Insurance.

Study type

Cost-effectiveness/cost-utility/cost-benefit analysis?

- CEA (incremental cost per additional life-year saved)

- CUA (incremental cost per QALY).

Institutional setting
Where is/are the intervention(s) being evaluated usually provided?

- Not identified. PEG-α-2a is administered intravenously, so for some patients, the treatment may be provided at the institutional setting. LAM is an oral medication and can be self-administered.

Country/currency
Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

- The costs are initially expressed in NTD; the outcomes are also converted into US$. The base year to which all costs are related is not indicated, but unit costs for medical procedures and intervention medications were expressed in NTD as at 2004.

Data sources
Effectiveness
Were the effectiveness data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
Effectiveness data at 48 weeks of treatment were derived from a single study	✓	Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, *et al*. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005;**352**:2682–95.
A review/synthesis or combination of previous studies	✓	Lok *et al*., 1987[83] Crowley, 2000[42] Pwu and Chan, 2002[49] van Nunen et al., 2003[80] Wang *et al*., 2004[54] Liaw *et al*., 1988,[79] 1986,[84] 1989[87] Lau *et al*., 1997[86]
Expert opinion	✓	The data selected for use in the model were validated by eight clinical hepatology experts in Taiwan

Give the definition of treatment effect used in the evaluation.

- Primary treatment effect (p. 633, also one of two primary outcomes in the pivotal clinical trial) – percentage of patients achieving seroconversion (transitioning from CHB state to seroconversion state). This can occur spontaneously or as a result of treatment.
- In addition the following outcome is used:
- percentage of patients relapsing (transitioning from seroconversion state back to CHB state). Can occur first at year 2 (p. 1495). The paper did not report the probability of relapsing at year 2. After year 3 all patients could experience spontaneous seroconversion or relapse on an annual basis (Lok and colleagues,[83])

Give the size of treatment effect used in the evaluation.

- Not applicable. Seroconversion and relapse are composite, qualitative measures of outcome.

Include values used for subgroups (if applicable). Indicate the source for individual treatment effects (if appropriate).

Intervention costs
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
Cost of HCC was obtained from a single study	✓	Wang JD. *Estimation of life years lost and financial burden of major cancer in Taiwan*. Taipei: Australia–Taiwan Clinical Trial Symposium, 20–21 November 2004
A review/synthesis or combination of previous studies and the Taiwanese Government sources	✓	Liver transplantation costs were estimated based on the cost of a liver transplant surgical procedure and treatment costs to avoid infections in a Taiwanese hospital
Expert opinion	✓	The costs for the disease states of CHB, compensated cirrhosis and decompensated cirrhosis were based on the medical resource use reported by treating clinicians

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

Resource category	**Type of resources**	**Cost estimate for the overall treatment period of 48 weeks**	**Source**
Drug acquisition costs	PEG-α-2a 180 mg daily	NTD203,616	BNHI 2004 Reference List for Drugs
	LAM 100 mg daily	NTD30,912	
	Health state	**Total annual management cost (NTD)**	**Source**
Health-state costs	Seroconversion	Not reported (assumed to be zero?)	Unit costs from BNHI 2004 Fee Schedule for Medical Service and Reference List for Drugs Wang JD, 2004 (see above) BNHI 2004 Fee Schedule and Chang Gung Hospital data
	Chronic hepatitis B	$11,806 ($8855–14,758)	
	Compensated cirrhosis	$20,821 ($15,618–26,026)	
	Decompensated cirrhosis	$44,431 ($33,323–55,539)	
	Hepatocellular carcinoma	$96,510 ($72,383–120,638)	
	Liver transplantation	$1,720,632 ($1,290,474–2,150,790)	
	Post-liver transplant	$508,901 ($381,676–636,126)	

Indicate the source for individual cost values (if appropriate).

Other direct costs (incurred directly in treating patients)

Were the cost data derived from:

	Tick	**Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)**
A single (observational) study	×	
A review/synthesis or combination of previous studies	×	
Expert opinion	×	

- Not reported.

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

Indicate the source for individual cost values (if appropriate)

Indirect costs (due to lost productivity, unpaid inputs to patient care)

Were indirect costs included?

- Not used.

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued).

Indicate the source for individual cost values (if appropriate).

Health-state valuations/utilities (if study uses quality of life adjustments to outcomes)

Were the utility data derived from:

	Tick	**Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)**
A single (observational) study	×	
A review/synthesis or combination of previous studies	✓	Quality of life (utility) values associated with CHB disease states were based on data obtained from previously published economic evaluations (Pwu and Chan, 2002,[49] Wong *et al.*, 1995,[8] Bennett *et al.*, 1997[55]
Expert opinion	×	

List the utility values used in the evaluation.

Seroconversion	1.00 (0.98–1.00) (Pwu and Chan[49])
Chronic hepatitis B	0.95 (0.9–0.95) (Pwu and Chan[49])
Compensated cirrhosis	0.9 (0.8–0.92) (Pwu and Chan[49])
Decompensated cirrhosis	0.54 (0.5–0.65) (Wong *et al*., 1995[8])
Hepatocellular carcinoma	0.5 (0.3–0.5) (Bennett *et al*., 1997[55])
Liver transplantation	0.5 (0.5–0.6) (Bennett *et al*., 1997[55])
Post-liver transplant	0.7 (0.6–0.8) (Bennett *et al*., 1997[55])

Indicate the source for individual cost values (if appropriate).

Modelling

If a model was used, describe the type of model used (e.g. Markov state-transition model, discrete event simulation).

- Markov state-transition model

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

- Model structure was similar to previously published models by Crowley[42] and Pwu and Chan,[49] except that Crowley did not include health states to account for liver transplantation.

What was the purpose of the model (i.e. why was a model required in this evaluation)?

- Not explained, but presumably to estimate long-term costs and benefits (expressed in terms of final rather than intermediate outcomes) beyond the timeframe of the clinical trial (48-week treatment).

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported? List them if reported.

- HBeAg seroconversion, HBeAg-positive CHB, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplantation, postliver transplantation, and death.

Extract transition probabilities for [natural history/ disease progression] model and show sources (or refer to table in text).

Disease state from	To	% (range)	Source
Chronic hepatitis B	Seroconversion, year 1, peginterferon a-2a	32.1 (30.0–34.0)	Lau *et al*., 2005[50]
	Seroconversion, year 1, lamivudine	19.1 (17.0–21.0)	Lau *et al*., 2005[50]
	Seroconversion, spontaneous, years 3+	7.7 (5.0–9.0)	Lok *et al*., 1987[83]
	Compensated cirrhosis	4.4 (3.0–6.0)	Liaw *et al*., 1988[79]
	Hepatocellular carcinoma	0.83 (0.20–1.00)	Liaw *et al*., 1986[84]
HBeAg seroconversion	Chronic hepatitis B, year 2, lamivudine	35.0 (30.0–40.0)	van Nunen *et al*., 2003,[80] Wang *et al*., 2004[54]
	Chronic hepatitis B, year 2, peginterferon a-2a	8.0 (3.0–13.0)	van Nunen *et al*., 2003[80]
	Chronic hepatitis B, spontaneous relapse	3.0 (2.6–5.0)	van Nunen *et al*., 2003[80]
	Compensated cirrhosis	1.0 (0.5–1.6)	Crowley, 2000[42]
Compensated cirrhosis	Decompensated cirrhosis	4.6 (2.3–5.6)	Liaw *et al*., 1989[87]
	Hepatocellular carcinoma	2.8 (2.5–5.0)	Liaw *et al*., 1989[87]
	Death	5.1 (3.4–5.1)	Lau *et al*., 1997[86]
Decompensated cirrhosis	Hepatocellular carcinoma	2.5 (2.0–5.0)	Crowley, 2000[42]
	Liver transplantation	1.4 (10.05–3.10)	Taiwan Registry
	Death	39.0 (23.5–40.0)	Crowley, 2000[42]
Hepatocellular carcinoma	Death	37.2 (37.0–56.0)	Pwu and Chan, 2002[49]
	Liver transplantation	0.08 (0.02-0.08)	Chen, 2006[90]
Liver transplantation	Post-liver transplant	85.0 (79.0–90.0)	Taiwan Bureau of National Health Insurance
	Death	15.0 (10.0–21.0)	
Post-liver transplant	Death, year 2 and beyond	1.5 (1.0–5.7)	Taiwan Bureau of National Health Insurance

What is the model time horizon?

- Not reported, but appears to be life time.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

- All costs and outcomes were discounted at a 3% annual rate.

Results/analysis

What measure(s) of benefit were reported in the evaluation?

- Life-years (LYs), quality-adjusted life years (QALYs)

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation.

- Treatment with PEG-α-2a compared with treatment with LAM is associated with:
  - additional discounted life expectancy of 0.33
  - additional quality-adjusted life expectancy of 0.41 years.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation.

- Lifetime (discounted) costs associated with treatment
- PEG-α-2a NTD355,932 per patient
- LAM NTD200,016 per patient.

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

- The comparative performance of alternative treatment strategies was measured by the ICER, defined as the additional cost of a specific strategy, divided by its additional clinical benefit, compared with the next least expensive strategy.
- Discounted ICER is equal to NTD466,936 (NTD472,475) per LY gained.
- Discounted ICER is equal to NTD380,619 (NTD380,250) per QALY gained (US$12,000).

Give results of any statistical analysis of the results of the evaluation.

- No statistical analysis was reported.

Was any sensitivity analysis performed? If yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic].

- Deterministic (one-way) sensitivity analysis was performed and the most influential variables were identified with a 'tornado diagram'.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

- Parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates) were tested.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base-case analysis? If so, what were the suggested causes?

- Estimates of incremental cost-effectiveness were most sensitive to variation in the probability of developing compensated cirrhosis from CHB, the probability of developing compensated cirrhosis from the seroconversion state, and the peginterferon alfa-2a efficacy rate.
- The ICER for peginterferon alfa-2a compared with lamivudine monotherapy ranged from NTD313,819 to NTD485,262 per QALY (i.e. did not exceed US$15,000) gained despite variation in treatment efficacy, drug cost, the health-state transition probabilities, utility values and health-state cost estimates.

Conclusions/implications

Give a brief summary of the authors' conclusions from their analysis.

- The findings suggest that use of peginterferon alfa-2a is likely to be cost-effective, given certain assumptions about disease progression and the efficacy and cost of therapy. The cost-effectiveness ratios were most sensitive to variation in the probability of developing

compensated cirrhosis from CHB, the probability of developing compensated cirrhosis from seroconversion and peginterferon alfa-2a efficacy rates. However, when these parameters were varied over a range of estimates, the ICER did not exceed NTD485,000 per QALY.

What are the implications of the evaluation for practice?

- Although 48 weeks of treatment with peginterferon alfa-2a (40KD) compared with 48 weeks of treatment with lamivudine in CHB patients who are HBeAgpositive offers life expectancy benefits at a favourable cost-effectiveness ratio, the implication for clinical practice in Taiwan is not clear as the current reimbursement guidelines in Taiwan provide for 6 months of peginterferon alfa-2a and 12–18 months of lamivudine.

Reference

Kanwal and colleagues (2006) Treatment alternatives for hepatitis B cirrhosis: a cost-effectiveness analysis.[46]

Study characteristics

Research question

What are the stated objectives of the evaluation?

- An economic analysis is performed to estimate the cost-effectiveness of competing strategies for the management of cirrhosis as a result of chronic HBV with active viral replication.

Study population

What definition was used for mild chronic hepatitis B?

- No definition was provided for chronic HBV; however, the cohort of patients with cirrhosis was assumed to have active viral replication at the baseline.

What are the characteristics of the baseline cohort for the evaluation?

Age	50 years old
Sex	Not indicated
Race (if appropriate)	Not indicated
Genotype	Not indicated
Other characteristics	It was assumed that 50% of the cohort had compensated cirrhosis and the remainder had decompensated cirrhosis. Within each treatment strategy patients are stratified by stage of liver disease (i.e. compensated vs decompensated) and separate probability estimates are assigned to compensated vs decompensated groups

Interventions and comparators

What number of interventions/strategies were included?

- Six.

Was a no treatment/supportive care strategy included?

- Yes.

Describe interventions/strategies.

Strategy 1: no pharmacological treatment of chronic HBV ('do nothing' strategy).

Strategy 2: lamivudine monotherapy 100 mg once daily for an indefinite period.

Strategy 3: ADV monotherapy 10 mg once daily for an indefinite period.

Strategy 4: lamivudine with crossover to ADV on development of resistance ('ADV salvage' strategy).

Intervention/strategy 5: entecavir monotherapy 0.5 mg once daily for an indefinite period.

Intervention/strategy 6: lamivudine with crossover to entecavir on development of resistance ('entecavir salvage' strategy).

Analytical perspective

What is the perspective adopted for the evaluation (health service, health and personal social services, third-party payer, societal (i.e. including costs borne by individuals and lost productivity)?

- The perspective adopted was of a (US) third-party payer.

Study type

Cost-effectiveness/cost–utility/cost–benefit analysis?

- Cost–utility analysis. The results are reported as the incremental cost per QALY gained between the competing strategies.

Institutional setting

Where is/are the intervention(s) being evaluated usually provided?

- All pharmacotherapies are administered orally.

Country/currency

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

- 2005 US$ (p. 2080).

Data sources

Effectiveness

Were the effectiveness data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
A single study	×	
A combination of previous studies	✓	Yes. A systematic review of literature was conducted and assessed by three independent reviewers according to the predefined selection criteria. All available data into annual probability estimates and combined across studies by calculating a weighted mean using study sample size as the weight
Expert opinion	×	

Give the definition of treatment effect (outcomes) used in the evaluation.

- The following efficacy end points are relevant to probability estimates used in the evaluation: progression from compensated to decompensated cirrhosis
  - regression (recompensation) from decompensated to compensated cirrhosis
  - decomposition following initial recompensation
  - progression from cirrhosis to hepatocellular carcinoma (for compensated cirrhosis only?)
  - developing resistance to initial pharmacotherapy
  - developing severe renal side effects (seems to be used in ADV patients only)
  - progression to liver transplantation
  - progression to cirrhosis following liver transplantation
  - subsequent complications related to recurrent HBV post-liver transplantation.

Give the size of treatment effect used in the evaluation.

- Not applicable. Outcomes are assessed in a dichotomous variable (yes/no).

Include values used for subgroups (if applicable). Indicate the source for individual treatment effects (if appropriate).

Intervention costs

Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
A single (observational) study	×	
A review/synthesis or combination of previous studies and other sources	✓	Costs for physician services and procedures obtained from the 2005 American Medical Association Current Procedural Terminology codebook and the 2005 Medicare Fee Schedule, and derived our base-case pharmaceutical costs from the average wholesale prices (AWPs) listed in the 2006 Red Book. Because large buying consortiums are often capable of obtaining prices lower than the Red Book AWPs, we obtained cost estimates for cirrhosis and related health states from a published study of detailed itemised inpatient and outpatient direct costs incurred by patients with cirrhosis (Bennett *et al*.[55])
Expert opinion	×	

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

***Drug costs* (Red Book, *FDA*)**	***($)***
Cost per month of lamivudine	158
Cost per month of ADV	595
Cost per month of entecavir	720
Cost per 5 ml injection of hepatitis B immune globulin (HBIG)	684
Non-drug costs of treatment period (American Medical Association, 2004 prices)	
Cost per physician visit	52
Cost per set of laboratory tests	80
Cost per abdominal ultrasound	150
***Costs of cirrhosis care (Bennett* et al.[55])**	
Cost per year of compensated cirrhosis	964
Cost of first year following variceal haemorrhage (assuming survival)	22,444
Cost per subsequent year following variceal haemorrhage	4393
Cost per year of ascites	4058
Cost of first year of encephalopathy	14,406
Cost per subsequent year following encephalopathy	3337
Cost of liver transplantation	127,499
Cost per year of follow-up care post-liver transplant	22,266
Cost of hepatocellular carcinoma	38,715

Indicate the source for individual cost values (if appropriate).

Other direct costs (incurred directly in treating patients)

Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
A single study	✓	Cost estimates for cirrhosis and related health states were obtained from a published study of detailed itemised inpatient and outpatient direct costs incurred by patients with cirrhosis (Bennett *et al.*[55]) These 1997 costs were updated to 2005 dollars using the medical care component of the consumer price index
A review/synthesis or combination of previous studies	×	
Expert opinion	×	

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

Cost per year of compensated cirrhosis	$964
Cost of first year following variceal haemorrhage (assuming survival)	$22,444
Cost per subsequent year following variceal haemorrhage	$4393
Cost per year of ascites	$4058
Cost of first year of encephalopathy	$14,406
Cost per subsequent year following encephalopathy	$3337
Cost of liver transplantation	$127,499
Cost per year of follow-up care post-liver transplant	$22,266
Cost of hepatocellular carcinoma	$38,715

Indicate the source for individual cost values (if appropriate).

Indirect costs (due to lost productivity, unpaid inputs to patient care)

Were indirect costs included?

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued).

Indicate the source for individual cost values (if appropriate).

Health-state valuations/utilities (if study uses quality of life adjustments to outcomes)

Were the utility data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
A single study	✓	Previously established utilities for cirrhosis and related complications that were derived using standard gamble elicitations in patients with chronic hepatitis C were adopted (Chong *et al.*[59])
A review/synthesis or combination of previous studies	×	
Expert opinion	×	

List the utility values used in the evaluation.

Utility of compensated cirrhosis	0.82 (0.80), according to Table 3 (p. 2080)
Utility of decompensated cirrhosis	0.60
Utility following successful liver transplant	0.86
Utility of hepatocellular carcinoma	0.73

Indicate the source for individual cost values (if appropriate).

Modelling

If a model was used, describe the type of model used (e.g. Markov state-transition model, discrete event simulation).

- Markov state-transition model.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

- The authors used their previously published model (Kanwal and colleagues[38]) for cost-effectiveness analysis of treatment options in compensated hepatitis B to develop a current version for the subgroup of hepatitis B patients with cirrhosis.

What was the purpose of the model (i.e. why was a model required in this evaluation)?

- To determine whether and under what circumstances the greater therapeutic benefits of newer antiviral agents, such as adefovir and entecavir, offset their greater cost versus lamivudine in the management of chronic hepatitis B cirrhosis (by extrapolating the outcomes of the clinical trial over the long term) (p. 2077), and also to permit comparisons between different interventions in medicine, using QALYs as a final outcome to allow for these comparisons to be made (p. 2080).

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported? List them if reported.

- The base-case patient has chronic HBV infection, active viral replication and clinical cirrhosis (either compensated or decompensated) and no previous treatment for hepatitis B (see Figure 1, p. 2077, although it is a bit confusing, as there is no transition from chronic HBV with cirrhosis to either decompensated or compensated cirrhosis).
- The following health states are used in the model:
  - compensated cirrhosis
  - decompensated cirrhosis
  - successful liver transplant
  - hepatocellular carcinoma
  - death.

Extract transition probabilities for [natural history/ disease progression] model and show sources (or refer to table in text).

	Estimate, %	**Weighted averages across the following studies (references as reported in Kanwal *et al.*[46] are presented)**
Transition probabilities used in 'no treatment' strategy		
Annual rate of mortality in compensated cirrhosis	4.9	21–31
Annual rate of progression from compensated to decompensated cirrhosis	7.3	21, 23, 29, 31–34
Annual rate of recompensation in decompensated cirrhosis	8	37–39
Annual rate of decomposition following initial recompensation	20	40, 41
Annual rate of mortality in decompensated cirrhosis	19	21–23, 26, 27, 35
Annual rate of progression from cirrhosis to hepatocellular carcinoma	3.4	21, 25, 29, 35, 36, 42–45
Annual rate of mortality in hepatocellular carcinoma	43.3	46–48
Annual rate of receiving a liver transplant in decompensated cirrhosis	25	49
Annual rate of receiving a liver transplant in hepatocellular carcinoma	30	49
Annual rate of development of recurrent HBV following successful transplant (assuming patients on lamivudine and HBIG therapy post-transplant)	4.7	50–64
Annual rate of progression to decompensated cirrhosis in patients with recurrent HBV following successful transplant	24	52, 56, 66
Annual rate of progression to decompensated cirrhosis in patients without recurrent HBV following successful transplant	7	Not reported
Annual rate of receiving a second liver transplant in patients with recurrent HBV	13	Not reported

	Estimate, %	Weighted averages across the following studies (references as reported in Kanwal *et al.*[46] are presented)
Annual rate of receiving a second liver transplant in patients without recurrent HBV	1	Not reported
Annual rate of mortality following successful transplant in patients with HBV recurrence (adjusted to account for decreasing mortality over time from transplant)	18.8	52, 66–70
Annual rate of mortality following successful transplant in patients with recurrent HBV (adjusted to account for decreasing mortality over time from transplant)	5.4	52, 66, 67
Transition probabilities used in LAM monotherapy strategy and combination treatment strategy in patients receiving LAM		
Annual rate of developing resistance on long-term lamivudine	23	71–85
Annual rate of progression from compensated to decompensated cirrhosis with lamivudine resistance	8	5, 7, 10, 11, 38, 86, 87
Annual rate of progression from compensated to decompensated cirrhosis without lamivudine resistance	2	5, 11, 38, 86, 87
Annual rate of recompensation in decompensated cirrhosis with lamivudine resistance	8	Assumption
Annual rate of recompensation in decompensated cirrhosis without lamivudine resistance	35	7, 38, 87
Annual rate of decomposition following initial recompensation in decompensated cirrhosis with lamivudine resistance	25	Assumption
Annual rate of decomposition following initial recompensation in decompensated cirrhosis without lamivudine resistance	4	7
Annual rate of progression from cirrhosis to hepatocellular carcinoma	1.5	7, 87
Recurrent HBV following successful transplant with lamivudine resistance	80	5, 50, 70, 88
Annual rate of developing recurrent HBV following successful transplant without lamivudine resistance	4.7	88
Transition probabilities used in ADV monotherapy strategy and ADV salvage therapy		
Annual rate of developing resistance on long-term adefovir		
Year 1	0	89
Year 2	2	89
Year 3	5	89
Year 4	8	89
Annual rate of developing severe renal side effects	2	13, 88, 90, 91
Annual rate of progression from compensated to decompensated cirrhosis with adefovir resistance	8	Assumption
Annual rate of progression from compensated to decompensated cirrhosis without adefovir resistance	2	14, 91, 92
Annual rate of recompensation in decompensated cirrhosis with adefovir resistance (equal to corresponding variable in LAM arm)	8	Assumption

	Estimate, %	Weighted averages across the following studies (references as reported in Kanwal *et al.*[46] are presented)
Annual rate of recompensation in decompensated cirrhosis without adefovir resistance	33	14, 93
Annual rate of decomposition following initial recompensation in decompensated cirrhosis with adefovir resistance (equal to corresponding variable in LAM arm)	25	Assumption
Annual rate of decomposition following initial recompensation in decompensated cirrhosis without adefovir resistance	4	91
Annual rate of progression from cirrhosis to hepatocellular carcinoma	1.5	93
Annual rate of development of recurrent HBV following successful transplant with adefovir resistance (equal to corresponding variable in LAM arm)	80	Assumption
Annual rate of development of recurrent HBV following successful transplant without adefovir resistance (equal to corresponding variable in LAM arm)	4.7	Assumption
Transition probabilities used in entecavir monotherapy strategy and entecavir salvage therapy		
Annual rate of developing resistance on long-term entecavir		
Treatment-naive patients (years 1 and 2)	0	12, 109
Treatment-naive patients (years 3–10)	1	Assumption
Lamivudine-resistant patients years 3–14	7	100
Annual rate of progression from compensated to decompensated cirrhosis without entecavir resistance(equal to corresponding variable in LAM/ADV arm)	2	Assumption
Annual rate of progression from compensated to decompensated cirrhosis with entecavir resistance (equal to corresponding variable in LAM/ADV arm)	8	Assumption
Annual rate of recompensation in decompensated cirrhosis with entecavir resistance (equal to corresponding variable in LAM/ADV arm)	8	Assumption
Annual rate of recompensation in decompensated cirrhosis without entecavir resistance (equal to corresponding variable in LAM arm)	35	Assumption
Annual rate of progression from cirrhosis to hepatocellular carcinoma (equal to corresponding variable in LAM/ADV arm)	4.7	Assumption

What is the model time horizon?

- Lifetime horizon.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

- All costs and utility estimates were discounted at a rate of 3% per year.

Results/analysis

What measure(s) of benefit were reported in the evaluation?

- QALYs.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation.

- Not reported separately.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation.

- Not reported separately.

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

- Adefovir monotherapy versus 'doing nothing' ICER is $19,731($14,342–$24,224).
- Adefovir monotherapy versus entecavir monotherapy ICER is $25,626 ($19,637–$31,184).
- 'Adefovir salvage' strategy is dominated.
- 'Entecavir salvage' strategy is dominated.
- Lamivudine monotherapy is dominated.

Give results of any statistical analysis of the results of the evaluation.

- A probabilistic (Monte Carlo) simulation under the assumption that all variables were triangular.
- In distribution was performed to estimate the 2.5 and 97.5 percentiles for estimated ICERs comparing alternative strategies.

Was any sensitivity analysis performed? If yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic].

- Base-case probability estimates were varied within the plausible range reported in the literature or taken as an assumption. In particular, proportion of patients with decompensated hepatitis B at baseline was varied within 0–100% range. In the sensitivity analysis the medication prices from the Red Book were substituted for the acquisition costs of the Veteran's Administration (VA) used as a proxy for the discounts achieved by large third-party payers.
- A multivariable sensitivity analysis ('tornado analysis') was performed and the most influential variables were rank ordered. One-way sensitivity analyses on the most influential variables were subsequently performed to identify the threshold values at which the cost-effectiveness order between the strategies changes (Table 5, p. 2081).

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

- Parameter uncertainty was tested (ie. assumptions about costs, quality of life and disease progression rates).

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base-case analysis? If so, what were the suggested causes?

- The model outcomes were found to be sensitive to the following variables:
  - cost per month of adefovir
  - cost per month of entecavir
  - annual rate of progression from compensated to decompensated cirrhosis with lamivudine resistance
  - annual rate of progression from compensated to decompensated cirrhosis with entecavir (no resistance)
  - annual rate of progression from compensated to decompensated cirrhosis with adefovir (no resistance)
  - annual rate of progression from compensated to decompensated cirrhosis with adefovir resistance.

Conclusions/implications

Give a brief summary of the authors' conclusions from their analysis.

The most cost-effective strategy in the management of HBV cirrhosis remains unclear. We performed a comprehensive decision analysis to identify the

most cost-effective therapeutic approach under varying clinical and budgetary conditions. Our analysis has four key findings:

1. We found that the newer generation of antiviral therapies in HBV, including adefovir and entecavir, are cost-effective in patients with HBV cirrhosis and should be preferred over lamivudine monotherapy.
2. Of the competing new-generation antiviral therapies, entecavir appears to be more effective yet more expensive than adefovir. Specifically, compared with adefovir, treating with upfront entecavir cost an additional $25,626 to gain one additional QALY – a value that falls well within the range of many commonly accepted medical interventions.
3. Selecting between adefovir and entecavir is highly dependent on available budgets and 'willingness to pay'. For third-party payers willing to pay $50,000 per QALY gained for entecavir, most (> 60%) patients receiving entecavir will fall within the budget. In contrast, entecavir is generally not cost-effective for third-party payers willing to pay less than $25,000 per QALY gained.
4. Our analysis found that initiating upfront lamivudine with crossover to adefovir or entecavir as 'salvage' on emergence of viral resistance is not cost-effective in HBV patients with cirrhosis. However, when faced with a patient who has already developed lamivudine resistance, using 'adefovir salvage' appears more effective and less expensive than 'entecavir salvage' on the basis of current viral resistance data.

What are the implications of the evaluation for practice?

1. Both adefovir and entecavir seem to be cost-effective in hepatitis B patients with cirrhosis.
2. Of the new agents, entecavir appears more effective yet more expensive than adefovir. Selecting between these agents completely depends upon the available health care budget and willingness to pay.
3. In patients with pre-existing lamivudine resistance, it appears more cost-effective to start with adefovir than with entecavir, as entecavir is associated with higher viral resistance than adefovir in the face of previous lamivudine resistance.

Critical appraisal

- Whether indirect comparison is used appropriately, i.e. only the studies that used the 'no treatment' arm as a common comparator were included in obtaining probability estimates.
- Whether homogeneity was addressed in calculating probability estimates across the studies?
- Whether assumptions about transitioning from compensated to decompensated cirrhosis are well justified?

Reference

Buti and colleagues (2006) Cost-effectiveness analysis of lamivudine and adefovir dipivoxil in the treatment of patients with HBeAg-negative chronic hepatitis B.[47]

Study characteristics

Research question

What are the stated objectives of the evaluation?

- The objective of this study was to analyse the cost-effectiveness of long-term therapy (over 4 years) with adefovir dipivoxil or lamivudine in patients with HBeAg-negative CHB in Spain. *However, the study compared LAM with ADV as a salvage therapy treatment algorithm with algorithms based on ADV monotherapy.*

Study population

What definition was used for mild chronic HBeAg-negative hepatitis B?

- No definition is provided. However from Figure 1 (p. 411) it appears that the cohort consisted of CHB patients with HBeAg-negative disease variant and compensated liver function.

What are the characteristics of the baseline cohort for the evaluation?

- The clinical effectiveness data for 100 patients with chronic HBeAg-negative CHB were obtained from the range of trials that enrolled patients with different demographic characteristics at baseline.

Age	Mean age of patients varied from 45 to 49 years
Sex	Proportion of males varied from 74% to 83%
Race (if appropriate)	
Genotype	
Other characteristics	Proportion of patients with cirrhosis, wherever reported, varied from 23% to 54% across four studies that were used to obtain estimates of the outcome

Interventions and comparators

What number of strategies were included?

- Two.

Was a no treatment/supportive care strategy included?

- No.

Describe interventions/strategies.

- Intervention/strategy 1: Lamivudine (100 mg daily) followed by adefovir dipivoxil (10 mg daily) as a salvage therapy for patients developing resistance to LAM treatment.
- Intervention/strategy 2: Adefovir dipivoxil (10 mg daily).

Analytical perspective
What is the perspective adopted for the evaluation (health service, health and personal social services, third-party payer, societal (i.e. including costs borne by individuals and lost productivity)?

- Spanish Public Health System.

Study type
Cost-effectiveness/cost–utility/cost–benefit analysis?

- Cost-effectiveness (incremental cost per additional patient with response).
- Cost-effectiveness ratios were also calculated.

Institutional setting
Where is/are the intervention(s) being evaluated usually provided?

- Not applicable. Both interventions are administered orally.

Country/currency

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

- Spain, 2003 Euros (p. 413).

Data sources
Effectiveness
Were the effectiveness data derived from:

	Tick	**Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)**
A single study	×	
Combination of previous studies	✓	See transition probabilities in Table 1 (pp. 412–13)
Expert opinion	✓	See transition probabilities in Table 1 (pp. 412–13). The methods for obtaining expert opinion were not elaborated

Give the definition of treatment effect used in the evaluation.

- 'Response to treatment' defined as a 'decrease of serum HBV DNA to undetectable levels by polymerase chain reaction (PCR) assay' (p. 411).
- In addition, 'resistance to treatment' as another outcome was used in the model. This was defined as as 'reappearance of HBV DNA in serum due to the emergence of drug resistant HBV mutants' (p. 411).
- Although not stated anywhere, 'progressing to decompensated liver disease' is an implicit outcome that is applied only to patients who received no treatment owing to development of resistance to LAM and/or ADV. This outcome is not associated with a defined health state but is associated with additional costs (Table 2, p. 414).

Give the size of treatment effect used in the evaluation.

- Not applicable. Outcomes are assessed in a dichotomous variable (yes/no).

Include values used for subgroups (if applicable). Indicate the source for individual treatment effects (if appropriate).

Intervention costs

Were the cost (resource use) data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
A single (observational) study	×	
A review/synthesis or combination of previous studies	✓	The European consensus conference and other international recommendations were taken into consideration in estimating the amount of resource use
Expert opinion	✓	Was used to estimate the frequency of outpatient visits and the laboratory tests required for each strategy

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

Resource category	Type of resources	Unit cost estimate	Source
Drug cost (monthly)	Lamivudine (100 mg, 28 tablets)	€55.59	Medicinal Product Catalogue
	Adefovir dipivoxil (10 mg, 30 tablets)	€428.40	
Specialist hepatologist consultation	Initial consultation	€154.24	Not indicated
	Successive consultations	€77.41	
Pathology investigation	Analyses	€23.66	Not indicated
	Serology	€43.73	SOIKOS database 2004
	α-fetoprotein	€14.29	Not indicated
Radiology investigations	Ultrasound scan	€62.94	SOIKOS database 2004
Diagnostic tests	Biopsy	€319.19	SOIKOS database 2004, Hospital Vall d'Hebron
	HBV DNA	€101.18	
	Resistance test	€18.00	

Indicate the source for individual cost values (if appropriate).

The resources listed in the table above are combined in different quantities to obtain the aggregated cost of initial assessment, annual treatment with LAM, annual treatment with ADV and costs incurred when no intervention therapy is administered (no active treatment state). See Table 3, p. 415.

Other direct costs
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
A single (observational) study		Not clear. Apparently average [weighted?] costs associated with progressing to a decompensated liver disease stage were derived using epidemiological data from unidentified source (footnote to Table 2, p. 414). Note: Decompensated CHB health state is not included in the model as presented in Figure 1 (p. 411)
A review/synthesis or combination of previous studies	×	
Expert opinion	×	

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

- Decompensation costs €172.50 applied only to a percentage of non-treated patients who develop decompensation because of cirrhosis (7.3%/year), hepatic encephalopathy (0.4%/year), varicose haemorrhage (1.1%/year), ascites (2.5%/year), hepatocarcinoma (1.6%/year); the source of these data is not provided.

Indicate the source for individual cost values (if appropriate).

Indirect costs (due to lost productivity, unpaid inputs to patient care)
Were indirect costs included?

- Indirect costs were not included.

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued).

Indicate the source for individual cost values (if appropriate).

Health-state valuations/utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	Were the methods for deriving these data adequately described? (Give sources if using data from other published studies)
A single (observational) study		Not applicable
A review/synthesis or combination of previous studies	×	
Expert opinion	×	

List the utility values used in the evaluation.

Indicate the source for individual cost values (if appropriate).

Modelling
If a model was used, describe the type of model used (e.g. Markov state-transition model, discrete event simulation).

- A decision-analytic model.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

- Appears to be a newly developed model.

What was the purpose of the model (i.e. why was a model required in this evaluation)?

- Not clearly indicated. Apparently, to help decision making in order to optimise resources by providing information regarding the costs associated with CHB and its progression towards more advanced stages, in particular with respect to treating HBeAg-negative patients with either LAM or AVD (summary of objective of the study as described on p. 410).

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported? List them if reported.

During 4 years the patient may progress through the following stages:

- Initial treatment with LAM
  - receiving LAM treatment with response
  - continuing LAM treatment with response
  - developing resistance to LAM treatment
  - receiving ADV treatment and continue with response (applies to LAM patients who developed resistance)
  - developing resistance and no response to ADV treatment
  - no active treatment

Also implicitly assumed is the state of decompensated liver disease for the proportion of patients who receive no treatment.

- Initial treatment with ADV
  - receiving ADV treatment and continue with response
  - developing resistance and no response to ADV treatment
  - no active treatment

Also implicitly assumed is the state of decompensated liver disease for the proportion of patients who receive no treatment.

Source of data: Expert opinion (not elaborated) and published clinical trials.

Extract transition probabilities for [natural history/ disease progression] model and show sources (or refer to table in text).

See Table 1, pp. 412–13

Lamivudine as initial treatment
What is the model time horizon?
- 4 years.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

- A 3% discount rate was applied to costs in the base-case scenario. Sensitivity analysis used undiscounted costs. No discount rate was applied to the efficacy and response results as these were obtained from figures published in clinical studies.

Results/analysis
What measure(s) of benefit were reported in the evaluation?

- Proportion of patients with response.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation.

- The proportion of patients with response in the lamivudine/adefovir arm at the end of year 4 was 40.4%.
- The proportion of patients with response in the adefovir dipivoxil arm at the end of year 4 was 78.0%.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation.

- The estimated discounted total cost of 4 years of treatment with lamivudine as an initial therapy was €11,457.
- The estimated discounted total cost of 4 years of treatment with adefovir dipivoxil as an initial therapy was €21,939.

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

- CER (average cost per patient with successful therapy response at year 4)
  - €28,375 for the LAM/ADV arm
  - €28,132 for the ADV arm.
- ICER (additional cost per patient with response in ADV monotherapy arm)
  - €27 872.

Give results of any statistical analysis of the results of the evaluation.

- No statistical analysis was performed.

Was any sensitivity analysis performed? If yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic].

- Deterministic one-way sensitivity analysis was performed (see Table 5, p. 417).

Disease state from	To	Transition probability	Source of transition probability
Initial LAM treatment	Continued LAM treatment with response (year 1)	0.73	Tassopoulos NC, *et al*. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precoremutant) chronic hepatitis B. *Hepatology* 1999;29:889–96
	Continued LAM treatment with response (year 2)	0.58	Lai CL, *et al*. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. *Clin Infect Dis* 2003;36:687–96
	Continued LAM treatment with response (year 3)	0.47	Lai *et al*., 2003
	Continued LAM treatment with response (year 4)	0.37	Di Marco, 2004; Gaia, 2004; Papatheodoridis, 2005
	Developing resistance to LAM (year 1)	0.27	Tassopoulos *et al*., 1999
	Developing resistance to LAM (year 2)	0.42	Lai *et al*., 2003
	Developing resistance to LAM (year 3)	0.53	Lai *et al*., 2003
	Developing resistance to LAM (year 4)	0.63	Di Marco, 2004; Gaia, 2004; Papatheodoridis, 2005
Develop resistance to LAM	Receive ADV treatment and continue with response (first year after initiation)	0.571	Vassiliadis T, *et al*. Adefovir dipivoxil added to ongoing lamivudine therapy in patients with lamivudine resistant hepatitis B e antigen negative chronic hepatitis B. *Aliment Pharmacol Ther* 2005;21:531–7
Receive ADV treatment	Continue ADV treatment with response into the second and subsequent years	0.71	Hadziyannis *et al*. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005;352:2673–81 and panel of experts
	Developing resistance and no response to ADV (first year after initiation)	0.429	Vassiliadis *et al*., 2005
	Developing resistance and no response to ADV into the second and subsequent years	0.29	Hadziyannis *et al*., 2005
Develop ADV resistance	No treatment	1.0	Panel of experts

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

- No sensitivity analysis in relation to structural uncertainty was performed.

Methodological uncertainty was tested by not applying a discount rate to the costs (0%), which is consistent with the choice of not discounting the outcomes.

The uncertainty in relation to the following resource use (but not the associated outcomes) was investigated:

1. the dosage of lamivudine was increased from 100 to 150 mg/day

2. decompensation costs were set to be equal to zero
3. the number of visits and laboratory tests investigating adefovir resistance was increased from two to four times per year to be equal to those treated with lamivudine
4. the cost of the diagnostic test of HBV drug resistance was reduced by half.

In addition a threshold analysis was undertaken by varying a single parameter of the model associated with clinical effectiveness – the lamivudine arm response rate at year 4.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base-case analysis? If so, what were the suggested causes?

- Considering €30,000 a threshold for a acceptability of a treatment strategy.
- CER and ICER were sensitive (i.e. > threshold) to the number of consultations in the ADV monotherapy arm and to the size of LAM dose in the combination therapy arm.

Conclusions/implications

Give a brief summary of the authors' conclusions from their analysis.

- The results indicate that at the end of the 4-year treatment, suppression of viral replication is achieved in almost twice the number of HBeAg-negative patients treated with adefovir dipivoxil (monotherapy) compared with patients treated with lamivudine (as initial treatment followed by adefovir as a salvage therapy in patients who developed resistance to LAM). Although the costs associated with 4 years of therapy with adefovir dipivoxil are moreorless double those of lamivudine/(ADV), the cost per responding patient with adefovir dipivoxil is slightly less than with lamivudine/(ADV). This study demonstrates that long-term therapy, over a period of 4 years, with adefovir dipivoxil as first-line treatment for HBeAg-negative patients can be considered a cost-effective strategy (p. 417).

What are the implications of the evaluation for practice?

- Hard to tell considering that the model does not adequately describe the natural disease progression.
- In addition to assumptions listed on pp. 411–412, many other assumptions were made in the model.
- Meta-analysis of the clinical outcomes across the studies using the same end point does not seem to have been conducted (simple averages are used). This means that the likely sources of homogeneity (e.g. differences in the baseline characteristics of the patients enrolled in the trials that provided inputs in the model) were not analysed.
- Indirect comparison of alternative therapies is used inappropriately. Clinical outcomes of LAM and ADV that were evaluated independently are used in two arms of the model.
- To check whether conditional probabilities (i.e. observed in LAM-resistant patients) were consistently applied to subsequent ADV treatment.

Appendix 5

Transition probabilities used in published economic evaluations

		Intervention			
From	**To**	**BSC (SHTAC)**	**BSC (Veenstra *et al.*, 2007[44])**	**BSC (Sullivan *et al.*, 2007[46])**	**BSC (Kanwal *et al.*, 2005[38])[a]**
'Cured' state (HBsAg)	HBsAg	#	Not used	Not used	Not used
	HCC	0.00005 (Wong *et al.*, 1995[8])			
	Dead of all causes	Life tables			
Seroconversion (HBeAg)	HBsAg	0.02 (de Franchis *et al.*, 2003[3])	Not used	Not used	Not used
	HBeAg	#	#	#	1.0
	CHB	0.03 (Wong *et al.*, 1995[8])	0.029 (0.1–5.0) (Wong *et al.*, 1995[8])	0.03 (0.1–5.0) (van Nunen *et al.*, 2003[80])	0
	CC	0.01 (Liaw *et al.*, 1988[79])	0.01 (0.5–2.0) (Crowley, 2000[42])	0.01 (0.5–2.0) (Crowley, 2000[42])	0
	HCC	0.001 (Wong *et al.*, 1995[8])	Not used	Not used	Not used
	Dead of all causes	Life tables	Life tables	Life tables	Life tables
Chronic hepatitis B (CHB)	HBsAg	0.0175 (Wong *et al.*, 1995[8])	Not used	Not used	Not used
	Seroconversion, spontaneous	0.09 (Wong *et al.*, 1995[8])	0.09 (6.0–12.0) (Wong *et al.*, 1995[8])	Seroconversion, year 3 + 0.077 (5.0–9.0) (Lok *et al.*, 1987[83])	0.069 (HBeAg +ve), 0.016 (HBeAg –ve)
	CHB	#	#	#	#
	Compensated cirrhosis	0.05 (Liaw *et al.*, 1988[79])	0.06 (0.04–0.08) (Liaw *et al.*, 2004[82])	0.044 (0.03–0.06) (Liaw *et al.*, 1988[79])	0.03 (HBeAg +ve), 0.046 (HBeAg –ve)
	Hepatocellular carcinoma	0.005 (Di Bisceglie *et al.*, 1988[81] and Wong *et al.*, 1995[8])	0.004 (0.001–0.007) (Crowley, 2000[42])	0.083 (0.2–01) (Liaw *et al.*, 1986[84])	0.015 (0.0- 0.1)
	Dead (excess mortality risk)	0.0035 (Gilead Sciences, Shepherd *et al.* 2006[12])	Not used	Not used	Not used
	Dead of all causes	Life tables	Life tables	Life tables	Life tables
Compensated cirrhosis (CC)	Seroconversion, spontaneous	0.09 (Wong *et al.*, 1995[8])	Not used	Not used	Not used
	Compensated cirrhosis	#	#	#	#
	Decompensated cirrhosis	0.05 (Fattovich *et al.*, 1991[85])	0.05 (0.038–0.095) (Fattovich *et al.*, 1991[85])	0.046 (0.023–0.056) (Liaw *et al.*, 1989[87])	0.073 (0.035–0.1)
	Hepatocellular carcinoma	0.025 (Wong *et al.*, 1995[8])	0.025 (0.02–0.078) (Wong *et al.*, 1995[8])	0.028 (0.025–0.05) (Liaw *et al.*, 1989[87])	0.034 (0.01- 0.12)
	Dead (excess mortality risk)	0.051 (Lau *et al.*, 1997[86])	0.05 (0.03–0.065) (Lau *et al.*, 1997[86])	0.051 (0.03–0.065) (Lau *et al.*, 1997[86])	0.049 (0.02–0.14)

		Intervention			
From	**To**	**BSC (SHTAC)**	**BSC (Veenstra et *al*., 2007[44])**	**BSC (Sullivan et *al*., 2007[46])**	**BSC (Kanwal et *al*., 2005[38])[a]**
	Dead of all causes	Life tables	Life tables	Life tables	Life tables
Decompensated cirrhosis (DC)	Decompensated cirrhosis	#	#	#	#
	Liver transplant	0.03 (Bennett *et al*., 1997[55])	0.031 (0.01–0.1) (Bennett *et al*., 1997 [55])	0.014 (0.10–0.3) (Taiwan Registry)	0.25 (0.0–0.4) (US registry for organ sharing)
	Hepatocellular carcinoma	0.025 (assumed the same as CC)	0.025 (0.02–0.078) (assumed the same as CC)	0.025 (0.02–0.05) (Crowley, 2000[42])	
	Dead (excess mortality risk)	0.39 (Wong *et al*., 1995[8])	0.39 (0.3–0.5) (Wong *et al*., 1995[8])	0.39 (0.23–0.4) (Wong *et al*., 1995[8])	0.19 (0.06–0.25)
	Dead of all causes	Life tables	Life tables	Life tables	–
Hepatocellular carcinoma	Liver transplant	0	0	0	0.3 (0.0–0.4) (US registry for organ sharing)
	Hepatocellular carcinoma	#	#	#	#
	Dead (excess mortality risk)	0.56 (Wong *et al*., 1995[8])	0.56 (0.45–0.65) (Wong *et al*., 1995[8])	0.37 (0.37–0.56) (Pwu and Chan, 2002[49])	0.433 (0.2–0.6)
	Dead of all causes	Life tables	Life tables	Life tables	Life tables
Liver transplant	Post-liver transplantation state	–	0.79	0.85 (Taiwan Bureau of National Health Insurance)	Not used
	Dead	0.21 (Bennett *et al*., 1997[55])	0.21 (Bennett *et al*., 1997[55])	0.15 (Taiwan Bureau of National Health Insurance)	
Post-liver transplantation state	Post-liver transplantation state	#	#	#	#
	Dead	0.057 (Bennett *et al*., 1997[55])	0.057 (Bennett *et al*., 1997[55])	0.015 (Taiwan Bureau of National Health Insurance)	Annual mortality rate 0.069 (0.02–0.12) (US registry for organ sharing)

BSC, best supportive care.
a Transition probabilities used in Kanwal *et al*.[48] are the weighted mean values across various relevant publications.
# indicates the residual probability, i.e. one minus the sum of all the other probabilities for the given health state.

		Intervention		
From	**To**	**PEG-α-2a (Veenstra *et al*., 2007[44])**	**PEG-α-2a (SHTAC)**	**PEG-α-2a (Sullivan *et al*., 2007[46])**
'Cured' state (HBsAg)	HBsAg	Not used	#	Not used
	HCC		0.00005 (Wong *et al*., 1995[8])	
	Dead of all causes		Life tables	
Seroconversion (HBeAg)	HBsAg	Not used	0.02 (de Franchis *et al*., 2003[3])	Not used
	HBeAg	#	#	#
	CHB	0.08 (0.3–0.13) (van Nunen *et al*., 2003[80])	0.09 (as in IFN) (van Nunen *et al*., 2003[80])	0.08 (0.3–0.13) (van Nunen *et al*., 2003[80])
	CC	0.01 (0.5–2.0) (Crowley, 2000[42])	0.01 (Liaw *et al*., 1988[79])	0.01 (0.5–1.6) (Crowley, 2000)[42]
	HCC	Not used	0.001 (Wong *et al*., 1995[8])	Not used
	Dead of all causes	Life tables	Life tables	Life tables
Chronic hepatitis B (CHB)	HBsAg	Not used	0.0175	Not used
	Seroconversion, spontaneous	Seroconversion, year 1, 0.32 (0.3–0.34) (Lau *et al*., 2005[50])	Seroconversion, year 1, 0.32 (Lau *et al*., 2005)[50]	Seroconversion, year 1, 0.32 (0.3–0.34) (Lau *et al*., 2005[50])
	CHB	#	#	#
	Compensated cirrhosis	0.06 (0.04–0.08) (Liaw *et al*., 2004[82])	0.05 (Liaw *et al*., 1988[79])	0.044 (0.03–0.06) (Liaw *et al*., 1988[79])
	Hepatocellular carcinoma	0.004 (0.001–0.007) (Crowley, 2000[42])	0.005 (Wong *et al*., 1995,[8] Di Bisceglie *et al*., 1988[81])	0.083 (0.02–0.1) (Liaw *et al*., 1986[84])
	Dead (excess mortality risk)	Not used	0.0035 (Shepherd *et al*., 2006[12])	Not used
	Dead of all causes	Life tables	Life tables	Life tables
Compensated cirrhosis (CC)	Seroconversion, spontaneous	Not used	0.09 (Wong *et al*., 1995[8])	Life tables
	Compensated cirrhosis	#	#	#
	Decompensated cirrhosis	0.05 (0.038–0.095) (Fattovich *et al*., 1991[85])	0.05 (0.038–0.095) (Fattovich *et al*., 1991[85])	0.046 (0.023–0.056) (Liaw *et al*., 1989[87])
	Hepatocellular carcinoma	0.025 (0.02–0.078) (Wong *et al*., 1995[8])	0.025 (Wong *et al*., 1995[8])	0.028 (0.025–0.05) (Liaw *et al*., 1989[87])
	Dead (excess mortality risk)	0.05 (0.03–0.065) (Lau *et al*., 1997[86])	0.051 (Lau *et al*., 1997[86])	0.051 (0.03–0.065) (Lau *et al*., 1997[86])
	Dead of all causes	Life tables	Life tables	Not used

		Intervention		
From	**To**	**PEG-α-2a (Veenstra *et al*., 2007[44])**	**PEG-α-2a (SHTAC)**	**PEG-α-2a (Sullivan *et al*., 2007[46])**
Decompensated cirrhosis (DC)	Decompensated cirrhosis	#	#	#
	Liver transplant	0.031 (0.01–0.1) (Bennett *et al*., 1997[55])	0.03 (Bennett *et al*., 1997[55])	0.014 (0.10–0.3) (Taiwan Registry)
	Hepatocellular carcinoma	0.025 (0.02–0.078) (assumed the same as CC)	0.025 (assumed the same as CC)	0.025 (0.02–0.05) (Crowley, 2000[42])
	Dead (excess mortality risk)	0.39 (0.3–0.5) (Wong *et al*., 1995[8])	0.39 (Wong *et al*., 1995[8])	0.39 (0.23–0.4) (Wong *et al*., 1995[8])
	Dead of all causes	Life tables	Life tables	Life tables
Hepatocellular carcinoma	Liver transplant	0	0	0
	Hepatocellular carcinoma	#	#	#
	Dead (excess mortality risk)	0.56 (0.45–0.65) (Wong *et al*., 1995[8])	0.56 (Wong *et al*., 1995[8])	0.37 (0.37–0.56) (Pwu and Chan, 2002[49])
	Dead of all causes	Life tables	Life tables	Life tables
Liver transplant	Post-liver transplantation state	0.79	–	0.85 (Taiwan Bureau of National Health Insurance)
	Dead	0.21 (Bennett *et al*., 1997[55])	0.21 (Bennett *et al*., 1997[55])	0.15 (Taiwan Bureau of National Health Insurance)
Post-liver transplantation state	Post-liver transplantation state	#	#	#
	Dead	0.057 (Bennett *et al*., 1997[55])	0.057 (Bennett *et al*., 1997[55])	0.015 (Taiwan Bureau of National Health Insurance)

		Intervention			
From	**To**	**LAM (Veenstra et al., 2007[44])**	**LAM (SHTAC)**	**LAM (Sullivan et al., 2007[46])**	**LAM (Kanwal et al., 2005[38])[a]**
'Cured' state (HBsAg)	HBsAg	Not used	#	Not used	Not used
	HCC		0.00005 (Wong *et al.*, 1995[8])		
	Dead of all causes		Life tables		
Seroconversion (HBeAg)	HBsAg	Not used	0.02 (de Franchis *et al.*, 2003[3])	Not used	Not used
	HBeAg	#	#	#	1.0
	CHB	0.25 (0.2–0.3) (van Nunen *et al.*, 2003[80])[b]	0.25 (0.2–0.3) (van Nunen *et al.*, 2003[80])[b]	0.25 (0.2–0.3) (van Nunen *et al.*, 2003[80])[b]	0
	CC	0.01 (0.5–2.0) (Crowley, 2000[42])	0.01 (Liaw *et al.*, 1988[79])	0.01 (0.5–1.6) (Crowley, 2000[42])	0
	HCC	Not used	0.001 (Wong *et al.*, 1995[8])	Not used	Not used
	Dead of all causes	Life tables	Life tables	Life tables	Life tables
Chronic hepatitis B (CHB)	HBsAg	Not used	0.0175 (Wong *et al.*, 1995[8])	Not used	Not used
	Seroconversion, spontaneous	Seroconversion, year 1, 0.19 (0.17–0.21) (Lau *et al.*, 2005[50])	Seroconversion 0.18 (Marcellin *et al.*, 2003)[88]	Seroconversion, year 1, 0.19 (0.17–0.21) (Lau *et al.*, 2005[50])	0.2 (HBeAg +ve), 0.1 (HBeAg –ve)
		Seroconversion, year 2, 0.1 (0.095–0.11) (Liaw *et al.*, 2000[51])			
		Seroconversion, year 3, 0.06 (0.03–0.09) (Liaw *et al.*, 2000[52])			
		Seroconversion, year 4, 0.05 (0.025–0.075) (Liaw *et al.*, 2000[53])			
	CHB	#	#	#	#
	Compensated cirrhosis	0.06 (0.04–0.08) (Liaw *et al.*, 2004[82])	0.02 additional Tx effect (Goodman *et al.*, 1999[89])	0.044 (0.03–0.06) (Liaw *et al.*, 1988[79])	0.03 (HBeAg +ve), 0.046 (HBeAg –ve)
	Hepatocellular carcinoma	0.004 (0.001–0.007) (Crowley, 2000[42])	0.005 (Di Bisceglie *et al.*,[81] Wong *et al.*, 1995[8])	0.083 (0.02–0.1) (Liaw *et al.*, 1986[84])	0.015 (0.0–0.1)
	Dead (excess mortality risk)	Not used	0.0035 (Shepherd *et al.*, 2006[12])	Not used	Not used
	Dead of all causes	Life tables	Life tables	Life tables	Life tables
Compensated cirrhosis (CC)	Seroconversion, spontaneous	Not used	0.09 (Wong *et al.*, 1995[8])	Not used	Not used
	Compensated cirrhosis	#	#	#	#

		Intervention			
From	**To**	**LAM (Veenstra *et al.*, 2007[44])**	**LAM (SHTAC)**	**LAM (Sullivan *et al.*, 2007[46])**	**LAM (Kanwal *et al.*, 2005[38])[a]**
	Decompensated cirrhosis	0.05 (0.038–0.095) (Fattovich *et al.*, 1991[85])	0.018 additional effect	0.046 (0.023–0.056) (Liaw *et al.*, 1989[87])	0.073 (0.035–0.1)
	Hepatocellular carcinoma	0.025 (0.02–0.078) (Wong *et al.*, 1995[8])	0.025 (Wong *et al.*, 1995[8])	0.028 (0.025–0.05) (Liaw *et al.*, 1989[87])	0.034 (0.01–0.12)
	Dead (excess mortality risk)	0.05 (0.03–0.065) (Lau *et al.*, 1997[86])	0.051 (Lau *et al.*, 1997[86])	0.051 (0.03–0.065) (Lau *et al.*, 1997[86])	0.049 (0.02–0.14)
	Dead of all causes	Life tables	Life tables	Life tables	Life tables
Decompensated cirrhosis (DC)	Decompensated cirrhosis	#	#	#	#
	Liver transplant	0.031 (0.01–0.1) (Bennett *et al.*, 1997[55])	0.03 (Bennett *et al.*, 1997[55])	0.014 (0.10–0.3) (Taiwan Registry)	0.25 (0.0–0.4) (US registry for organ sharing)
	Hepatocellular carcinoma	0.025 (0.02–0.078) (assumed the same as CC)	0.025 (assumed the same as CC)	0.025 (0.02–0.05) (Crowley, 2000[47])	
	Dead (excess mortality risk)	0.39 (0.3–0.5) (Wong *et al.*, 1995[8])	0.195	0.39 (0.23–0.4) (Wong *et al.*, 1995[8])	0.19 (0.06–0.25)
	Dead of all causes	Life tables	Life tables	Life tables	
Hepatocellular carcinoma	Liver transplant	0	0	0	0.3 (0.0–0.4) (US registry for organ sharing)
	Hepatocellular carcinoma	#	#	#	#
	Dead (excess mortality risk)	0.56 (0.45–0.65) (Wong *et al.*, 1995[8])	0.56 (Wong *et al.*, 1995[8])	0.37 (0.37–0.56) (Pwu and Chan, 2002[49])	0.433 (0.2–0.6)
	Dead of all causes	Life tables	Life tables	Life tables	Life tables
Liver transplant	Post-liver transplantation state	0.79	–	0.85 (Taiwan Bureau of National Health Insurance)	Not used
	Dead	0.21 (Bennett *et al.*, 1997[55])	0.021 additional effect	0.15 (Taiwan Bureau of National Health Insurance)	–
Post-liver transplantation state	Post-liver transplantation state	#	#	#	#
	Dead	0.057 (Bennett *et al.*, 1997[55])	0.057 (0.6) (Bennett *et al.*, 1997[55])	0.015 (Taiwan Bureau of National Health Insurance)	Annual mortality rate 0.069 (0.02–0.12) (US registry for organ sharing)

a Transition probabilities used in Kanwal *et al.*[38] are the weighted mean values across various relevant publications.
b According to van Nunen *et al.*[80] an additional 35% of LAM patients relapsed beyond 6 months of treatment. Veenstra *et al.*[44] considered this to be an overestimate and reduced the figure to 25% to account for the potential impact of extended (up to 4 years') therapy on seroconversion durability. In the SHTAC model these rates applied only to patients who underwent seroconversion while on LAM treatment and are only applied in the year immediately following seroconversion.
# indicates the residual probability, i.e. one minus the sum of all the other probabilities for the given health state.

Appendix 6

Updated parameters in probabilistic sensitivity analysis

TABLE 42 *Utility decrements to age-specific health-state utilities: values used in probabilistic analysis*

	Mean	SE	Distribution	Alpha	Beta
HBsAg/HBeAg seroconverted	0.79	0.0102	Beta	558.6160	148.4929
CHB	0.69	0.0128	Beta	1416.7219	636.4982
Compensated cirrhosis	0.68	0.0128	Beta	908.7808	427.6615
Decompensated cirrhosis	0.35	0.0128	Beta	489.0519	908.2392
Hepatocellular carcinoma	0.42	0.0153	Beta	628.4237	867.8233
Liver transplantation	0.57	0.0128	Beta	595.7397	449.4176
Post-liver transplantation	0.66	0.0153	Beta	909.6367	468.6007

TABLE 43 *Health-state cost distributions*

	Mean	SE	Distribution	Alpha	Beta
HBsAg seroconverted	0.00	–	–	–	–
HBeAg seroconverted	289.65	57.93	Gamma	25.0000	11.5861
CHB	583.58	116.72	Gamma	25.0000	23.3433
Compensated cirrhosis	1341.42	231.17	Gamma	33.6726	39.8372
Decompensated cirrhosis	10,750.25	1519.47	Gamma	50.0553	214.7674
Hepatocellular carcinoma	9579.74	1909.83	Gamma	25.1606	380.7444
Liver transplantation	32,215.38	2884.79	Gamma	124.7094	258.3237
	11,148.67	2547.97	Gamma	19.1451	582.3234
Post-liver transplantation	1632.58	355.02	Gamma	21.1461	77.2046

Standard error (SE) for HBeAg seroconversion and CHB costs assumed to be 20% of mean value.
Costs of transplant and first year care are estimated separately. Liver transplant cost is the sum of the two values.

TABLE 44 *Effectiveness of IFN- α and PEG-α in probabilistic analysis*

Parameter	Intervention	Mean	Distribution	Parameters
CHB to HBeAg seroconverted	IFN-α-2b	13.9%	Beta	$n = 115$; $r = 16$
	PEG-α-2b	21.7%	Beta	$n = 115$; $r = 25$

Appendix 7

Costs and outcomes of sequential treatment strategies – HBeAg-positive and HBeAg-negative cohorts

TABLE 45 *Costs and outcomes of sequential treatment strategies for patients with HBeAg-positive CHB*

Strategy	Cost (£)	Life expectancy	Discounted QALYs	ICER (£ per QALY gained)
Best supportive care	10,676	18.12	13.48	
Conventional IFN-α	14,632	18.43	13.80	12,215
Conventional IFN-α followed by lamivudine	17,232	18.87	14.22	6179
Conventional IFN-α followed by adefovir dipivoxil	29,163	19.46	14.76	15,186
Conventional IFN-α followed by lamivudine with adefovir salvage	28,961	19.51	14.80	20,412
Pegylated IFN-α	17,972	18.56	13.94	24,873
Pegylated IFN-α followed by lamivudine	20,473	18.99	14.35	26,647
Pegylated IFN-α followed by adefovir dipivoxil	31,882	19.55	14.86	27,636
Pegylated IFN-α followed by lamivudine with adefovir salvage	31,628	19.60	14.89	27,866

Optimal treatment sequence, using the principle of extended dominance:

IFN followed by LAM (ICER = £8804 per QALY gained relative to best supportive care), IFN followed by LAM followed by ADV (ICER = £20,413 relative to IFN followed by LAM) and PEG followed by LAM followed by ADV (ICER = £27,856 relative to IFN followed by LAM followed by ADV).

TABLE 46 *Costs and outcomes of sequential treatment strategies for patients with HBeAg-negative CHB*

Strategy	Cost (£)	Life expectancy	Discounted QALYs	ICER (£ per QALY gained)
Best supportive care	16,532	12.46	8.43	
Conventional IFN-α	20,799	13.19	8.96	8040
Conventional IFN-α followed by lamivudine	24,378	13.78	9.40	8172
Conventional IFN-α followed by adefovir dipivoxil	46,181	14.49	9.92	26,648
Conventional IFN-α followed by lamivudine with adefovir salvage	50,737	14.75	10.11	37,419
Pegylated IFN-α	23,279	13.98	9.55	4251
Pegylated IFN-α followed by lamivudine	26,323	14.41	9.86	4239
Pegylated IFN-α followed by adefovir dipivoxil	44,132	14.92	10.24	–6432
Pegylated IFN-α followed by lamivudine with adefovir salvage	47,529	15.11	10.37	–12,114

Optimal treatment sequence, using the principle of extended dominance:

PEG (ICER = £6056 per QALY gained relative to best supportive care), PEG followed by LAM (ICER = £9714 relative to PEG) and PEG followed by LAM followed by ADV (ICER = £41,560 relative to PEG followed by LAM).

This contrasts with the ICERs for the optimal treatment sequences derived from the original model, which were: PEG (ICER = £2950 per QALY gained relative to best supportive care), PEG followed by LAM (ICER = £4955 relative to PEG) and PEG followed by LAM followed by ADV (ICER = £18,039 relative to PEG followed by LAM).

As with the majority of the analyses reported in this update, the scale of difference in the ICERs (particularly that for the sequence of PEG followed by LAM followed by ADV) is largely accounted for by the change in discounting practice. Using the same discount rates as in our previous report (6% for costs and 1.5% for outcomes), the ICERs for these sequences (which remain the optimal sequences) are: PEG (ICER = £3914 per QALY gained relative to best supportive care), PEG followed by LAM (ICER = £5715 relative to PEG) and PEG followed by LAM followed by ADV (ICER = £20,175 relative to PEG followed by LAM).

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 Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 4, 2000

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 5, 2001

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 6, 2002

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 7, 2003

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 8, 2004

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 9, 2005

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 10, 2006

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 11, 2007

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 12, 2008

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 13, 2009

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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, Woolacott 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.

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 Science Support, NETSCC, HTA

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,
Director of NHS Support, 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

Dr Ruairidh Milne,
Director of Strategy and Development, NETSCC

Ms Kay Pattison,
Section Head, NHS R&D Programme, 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

Chair,
Professor Jon Nicholl,
Director, Medical Care Research Unit, University of Sheffield

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 Statisitics, Department of Primary Health Care, Univeristy 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

Professor Hywel Williams,
Professor of Dermato-Epidemiology, University of Nottingham

Observers

Ms Kay Pattison,
Section Head, NHS R&D Programme, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Medical Research Council

Diagnostic Technologies & 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

Ms Jane Bates, Consultant Ultrasound Practitioner, Ultrasound Department, Leeds Teaching Hospital NHS Trust

Dr Stephanie Dancer, Consultant Microbiologist, Hairmyres Hospital, East Kilbride

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales

Dr Ron Gray, Consultant Clinical Epidemiologist, Department of Public Health, University of Oxford

Professor Paul D Griffiths, Professor of Radiology, University of Sheffield

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medicines & Healthcare Products Regulatory Agency, London

Dr Anne Mackie, Director of Programmes, UK National Screening Committee

Dr Michael Millar, Consultant Senior Lecturer in Microbiology, Barts and The London NHS Trust, Royal London Hospital

Mr Stephen Pilling, Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, Service User Representative

Dr Phil Shackley, Senior Lecturer in Health Economics, School of Population and Health Sciences, University of Newcastle upon Tyne

Dr W Stuart A Smellie, Consultant in Chemical Pathology, Bishop Auckland General Hospital

Dr Nicholas Summerton, Consultant Clinical and Public Health Advisor, NICE

Ms Dawn Talbot, Service User Representative

Dr Graham Taylor, Scientific Advisor, Regional DNA Laboratory, St James's University Hospital, Leeds

Professor Lindsay Wilson Turnbull, Scientific Director of the Centre for Magnetic Resonance Investigations and YCR Professor of Radiology, Hull Royal Infirmary

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

Pharmaceuticals Panel

Members

Chair,
Professor Robin Ferner,
Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Deputy Chair,
Professor Imti Choonara,
Professor in Child Health, University of Nottingham

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

Dr Ben Goldacre, Research Fellow, Division of Psychological Medicine and Psychiatry, King's College London

Mrs Barbara Greggains, Service User Representative

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

Professor Jonathan Ledermann, Professor of Medical Oncology and Director of the Cancer Research UK and University College London Cancer Trials Centre

Dr Yoon K Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia

Professor Femi Oyebode, 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

Dr Lesley Wise, Unit Manager, Pharmacoepidemiology Research Unit, VRMM, Medicines & Healthcare Products Regulatory Agency

Observers

Ms Kay Pattison, Section Head, NHS R&D Programme, 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

Therapeutic Procedures Panel

Members

Chair,
Dr John C Pounsford,
Consultant Physician, North Bristol NHS Trust

Deputy Chair,
Professor Scott Weich,
Professor of Psychiatry, Division of Health in the Community, University of Warwick, Coventry

Professor Jane Barlow,
Professor of Public Health in the Early Years, Health Sciences Research Institute, Warwick Medical School, Coventry

Ms Maree Barnett,
Acting Branch Head of Vascular Programme, Department of Health

Mrs Val Carlill,
Service User Representative

Mrs Anthea De Barton-Watson,
Service User Representative

Mr Mark Emberton,
Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital, London

Professor Steve Goodacre,
Professor of Emergency Medicine, University of Sheffield

Professor Christopher Griffiths,
Professor of Primary Care, Barts and The London School of Medicine and Dentistry

Mr Paul Hilton,
Consultant Gynaecologist and Urogynaecologist, Royal Victoria Infirmary, Newcastle upon Tyne

Professor Nicholas James,
Professor of Clinical Oncology, University of Birmingham, and Consultant in Clinical Oncology, Queen Elizabeth Hospital

Dr Peter Martin,
Consultant Neurologist, Addenbrooke's Hospital, Cambridge

Dr Kate Radford,
Senior Lecturer (Research), Clinical Practice Research Unit, University of Central Lancashire, Preston

Mr Jim Reece
Service User Representative

Dr Karen Roberts,
Nurse Consultant, Dunston Hill Hospital Cottages

Observers

Dr Phillip Leech,
Principal Medical Officer for Primary Care, Department of Health

Ms Kay Pattison,
Section Head, NHS R&D Programme, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Medical Research Council

Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells,
Principal Research Officer, Department of Health

Disease Prevention Panel

Members

Chair,
Dr Edmund Jessop,
Medical Adviser, National Specialist, National Commissioning Group (NCG), London

Deputy Chair,
Dr David Pencheon,
Director, NHS Sustainable Development Unit, Cambridge

Dr Elizabeth Fellow-Smith,
Medical Director, West London Mental Health Trust, Middlesex

Dr John Jackson,
General Practitioner, Parkway Medical Centre, Newcastle upon Tyne

Professor Mike Kelly,
Director, Centre for Public Health Excellence, NICE, London

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Corfe Mullen, Dorset

Ms Jeanett Martin,
Director of Nursing, BarnDoc Limited, Lewisham Primary Care Trust

Dr Julie Mytton,
Locum Consultant in Public Health Medicine, Bristol Primary Care Trust

Miss Nicky Mullany,
Service User Representative

Professor Ian Roberts,
Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine

Professor Ken Stein,
Senior Clinical Lecturer in Public Health, University of Exeter

Dr Kieran Sweeney,
Honorary Clinical Senior Lecturer, Peninsula College of Medicine and Dentistry, Universities of Exeter and Plymouth

Professor Carol Tannahill,
Glasgow Centre for Population Health

Professor Margaret Thorogood,
Professor of Epidemiology, University of Warwick Medical School, Coventry

Observers

Ms Christine McGuire,
Research & Development, Department of Health

Dr Caroline Stone,
Programme Manager, Medical Research Council

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 Counsell, 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 & Ptnrs), 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 Levvy, 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, Ashtead

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) 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.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

ISSN 1366-5278