

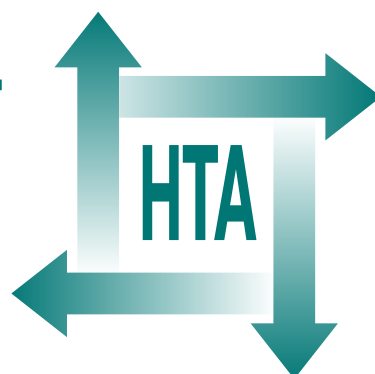
Non-occupational postexposure prophylaxis for HIV: a systematic review

J Bryant,* L Baxter and S Hird



February 2009
DOI: 10.3310/hta13140

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.

Non-occupational postexposure prophylaxis for HIV: a systematic review

J Bryant,* L Baxter and S Hird

Southampton Health Technology Assessments Centre (SHTAC), Wessex Institute for Health Research and Development, University of Southampton, Southampton, UK

*Corresponding author

Declared competing interests of authors: none

Published February 2009

DOI: 10.3310/hta13140

This report should be referenced as follows:

Bryant J, Baxter L, Hird S. Non-occupational postexposure prophylaxis for HIV: a systematic review. *Health Technol Assess* 2009; **13**(14).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index 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 by the HTA Programme as project number 07/40/01. The contractual start date was in December 2007. The draft report began editorial review in May 2008 and was accepted for publication in August 2008. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley

Series Editors: Dr Aileen Clarke, Dr Peter Davidson, Dr Chris Hyde, Dr John Powell, Dr Rob Riemsma and Professor Ken Stein

ISSN 1366-5278

© 2009 Queen's Printer and Controller of HMSO

This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to: NCCHTA, Alpha House, Enterprise Road, University of Southampton Science Park, Southampton SO16 7NS, UK.

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

Printed on acid-free paper in the UK by the Charlesworth Group.



Abstract

Non-occupational postexposure prophylaxis for HIV: a systematic review

J Bryant,* L Baxter and S Hird

Southampton Health Technology Assessments Centre (SHTAC), Wessex Institute for Health Research and Development, University of Southampton, Southampton, UK

*Corresponding author

Objective: To review the evidence on the clinical effectiveness and cost-effectiveness of non-occupational postexposure prophylaxis (PEP) for HIV.

Data sources: Eleven electronic databases were searched from inception to December 2007.

Review methods: Selected studies were assessed, subjected to data extraction using a standard template and quality assessment using published criteria. Studies were synthesised using a narrative approach with full tabulation of results from all included studies.

Results: One clinical effectiveness study meeting the inclusion criteria was identified, a cohort study of PEP in a high-risk HIV-negative homosexual male cohort in Brazil. The quality of the study was generally weak. Seroincidence in the cohort as a whole (2.9 per 100 person-years) was very similar to that expected in this population (3.1 per 100 person-years, $p > 0.97$), despite the seroconversion to HIV being 1/68 in the PEP group and 10/132 in the group not receiving PEP. High-risk sexual activities declined over time for both PEP and non-PEP users. Four economic evaluations met the inclusion criteria of the review. The methodological quality of the studies was mixed. The studies are constrained by a lack of published data on the clinical effectiveness of PEP after non-occupational exposure, with effectiveness data derived from one study of occupational PEP. Their generalisability to the UK is not clear. Results suggest that PEP following non-occupational exposure to HIV was cost saving for

men who have unprotected receptive anal intercourse with men, whether the source partner is known to be HIV positive or not; heterosexuals after unprotected receptive anal intercourse; and intravenous drug users sharing needles with a known HIV-positive person. PEP following non-occupational exposure to HIV was cost-effective for all male–male intercourse (unprotected receptive and insertive anal intercourse, unprotected receptive oral sex, and ‘other’) and was possibly cost-effective for intravenous drug users and high-risk women. Four additional studies were identified giving further information about adverse events associated with PEP after non-occupational exposure to HIV. The majority of participants experienced adverse events with the most common being nausea and fatigue. Rates were generally higher in participants receiving triple therapy than in participants receiving dual therapy. Completion of PEP therapy was variable, ranging from 24% to 78% of participants depending on type of therapy. Toxicity was the main reason for discontinuation of treatment.

Conclusions: It is not possible to draw conclusions on the clinical effectiveness of non-occupational PEP for HIV because of the limited evidence available. The review of cost-effectiveness suggests that non-occupational PEP may be cost-effective, especially in certain population subgroups; however, the assumptions made and data sources used in the cost-effectiveness studies mean that their results should be used with caution.



Contents

List of abbreviations	vii	6 Adverse events	23
Executive summary	ix	Completion of treatment	23
1 Aim of the review	1	Assessment of toxicity	25
2 Background	3	Summary of adverse events of PEP for non-occupational exposure to HIV	27
Description of underlying health problem	3	7 Discussion	29
Epidemiology	4	Statement of principal findings	29
Description of the intervention	4	Strengths and limitations of the assessment	30
Current UK practice	5	Other relevant issues	30
Costs	6	8 Conclusions	33
Issues specific to non-occupational HIV exposure	6	Non-occupational PEP for HIV	33
Rationale for the study	8	Research priorities	33
3 Methods	9	Acknowledgements	35
Search strategy	9	References	37
Inclusion and data extraction process	9	Appendix 1 Review methods from the research protocol	39
Quality assessment	9	Appendix 2 Sources of information, including databases searched and search terms	41
Inclusion criteria	10	Appendix 3 List of excluded studies	45
Data synthesis	10	Appendix 4 Data extraction of clinical effectiveness study	47
4 Clinical effectiveness	11	Appendix 5 Data extraction of cost-effectiveness studies	51
Quantity and quality of research available	11	Health Technology Assessment reports published to date	61
Assessment of effectiveness	12	Health Technology Assessment Programme	79
Summary of clinical effectiveness of PEP for non-occupational exposure to HIV	14		
5 Cost-effectiveness	15		
Quantity and quality of research available	15		
Assessment of cost-effectiveness	17		
Economic evaluation	21		
Summary of cost-effectiveness of PEP for non-occupational exposure to HIV	21		



List of abbreviations

3TC	lamivudine	MSA	metropolitan statistical areas
AIDS	acquired immunodeficiency syndrome	MSM	men who have sex with men
ART	antiretroviral therapy	Nfv	nelfinavir
BASHH	British Association for Sexual Health and HIV	PEP	postexposure prophylaxis
CCT	controlled clinical trial	PEPSE	PEP following potential sexual exposure to HIV
d4T	stavudine	PI	protease inhibitor
ddI	didanosine	RCT	randomised controlled trial
HIV	human immunodeficiency virus	QALY	quality-adjusted life-year
IDU	injecting/intravenous drug user	ZDV	zidovudine

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

Human immunodeficiency virus (HIV) is a sexually transmitted and bloodborne virus found primarily in the blood, semen or vaginal fluid of an infected person. It is transmitted in two main ways: by having unprotected sex (anal, vaginal or oral) with someone infected with HIV or by sharing needles and syringes with someone infected with HIV. Postexposure prophylaxis (PEP) for HIV is the prompt administration of antiretroviral therapy following known or potential exposure to HIV infection in an attempt to prevent the establishment of infection. The effectiveness of PEP in preventing seroconversion (i.e. converting from HIV negative to HIV positive, with the detection in the blood of antibodies to HIV) after non-occupational exposure to HIV is unclear.

Objectives

The main aim of this study was to review the evidence on the clinical effectiveness and cost-effectiveness of non-occupational PEP for HIV.

Methods

A systematic review of the evidence was undertaken using *a priori* methods.

Data sources

Eleven electronic databases were searched from inception to December 2007. Bibliographies of related papers were assessed for relevant studies and experts contacted to identify additional published references.

Study selection

Studies were included if they fulfilled the following criteria:

- Intervention: any antiretroviral drug regimen administered as non-occupational PEP for a short period (28 days) to HIV-negative

people potentially exposed to HIV through unprotected sexual contact or use of a potentially contaminated needle or potentially contaminated biological fluid.

- Participants: humans with non-occupational exposure to HIV through unprotected sexual exposure (oral, vaginal, anal), either voluntary or rape, with an HIV-infected partner or partner of unknown HIV status; humans with exposure to a needle contaminated by a known or potentially infected substance in a non-occupational setting.
- Comparator: no intervention; group not receiving PEP; a different PEP regimen.
- Outcomes: HIV seroconversion frequency; adverse effects and complications of PEP; adherence to PEP; health-related quality of life; costs or some measure of cost-effectiveness.
- Design: randomised controlled trial, controlled clinical trial, cohort study or case-control study; cost-effectiveness/utility studies; economic evaluations; prospective observational studies for adverse events.

Studies identified were assessed for inclusion in two stages with titles and abstracts and full papers of retrieved studies assessed independently by two reviewers, with differences in decisions resolved through discussion or through recourse to a third independent reviewer.

Data extraction and quality assessment

Data were extracted by two reviewers using a data extraction form developed *a priori*. Any disagreements were resolved through discussion or through recourse to independent assessment by a third reviewer. The methodological quality of the studies included in the systematic review was assessed by means of modified quality assessment tools using individual components of methodological quality rather than relying on summary scores. The quality criteria were applied by two reviewers, with any disagreements resolved through discussion or through recourse to a third independent reviewer.

Data synthesis

Studies were synthesised using a narrative approach with full tabulation of results from all included studies.

Results

Number and quality of studies

One clinical effectiveness study meeting the inclusion criteria for the review was identified. This was a cohort study of PEP in a high-risk HIV-negative homosexual male cohort in Brazil. The methodological quality and the quality of reporting of the study were generally weak.

Four economic evaluations met the inclusion criteria of the review (three conducted in the US and one in France). The methodological quality of the studies is mixed. Each of the studies is constrained by a lack of published data on the clinical effectiveness of PEP after non-occupational exposure, with effectiveness data derived from one study of occupational PEP. Their generalisability to the UK is not clear.

Summary of clinical effectiveness

Seroincidence in the cohort as a whole (2.9 per 100 person-years) was very similar to that expected by the study authors in this population (3.1 per 100 person-years, $p > 0.97$), despite the seroconversion to HIV being 1/68 in the PEP group and 10/132 in the group not receiving PEP. The study reported that, on average, high-risk sexual activities declined over time for both PEP and non-PEP users. The study authors concluded that a public health PEP programme would not have a major impact on HIV transmission in the study population.

Summary of cost-effectiveness

Results from the included economic studies suggest that PEP following non-occupational exposure to HIV is cost saving for men who have unprotected receptive anal intercourse with men, whether the source partner is known to be HIV positive or not; heterosexuals after unprotected receptive anal intercourse; and intravenous drug users sharing needles with a known HIV-positive person.

PEP following non-occupational exposure to HIV was cost-effective for all male–male intercourse (unprotected receptive and insertive anal intercourse, unprotected receptive oral sex, and ‘other’). PEP following non-occupational exposure to HIV was possibly cost-effective for intravenous drug users and high-risk women.

Adverse events

Four additional studies (two comparative studies and two observational studies) were identified that supplied further information about adverse events associated with PEP after non-occupational exposure to HIV. The majority of participants experienced adverse events with the most common being nausea and fatigue. Rates were generally higher in participants receiving triple therapy than in participants receiving dual therapy. Completion of PEP therapy was variable, ranging from 24% to 78% of participants depending on type of therapy. Toxicity was the main reason for discontinuation of treatment.

Conclusions

It is not possible to draw conclusions on the clinical effectiveness of non-occupational PEP for HIV because of the limited evidence in terms of quantity and quality of studies. Only one cohort study was identified that met the inclusion criteria for the systematic review. Cost-effectiveness has been assessed in four economic evaluations using evidence on effectiveness taken from the use of PEP in the occupational setting. Results are consistent across studies and suggest that non-occupational PEP may be cost-effective, especially in certain population subgroups. Although the studies have been conducted in an appropriate way and may have internal validity in terms of the structure of the model and plausible results, the assumptions and data sources mean that results should be used with caution. The generalisability to the UK of studies conducted in the US is not clear as sexual behaviour and HIV incidence may not be similar.

Suggested research priorities

The most important research need is to establish the clinical effectiveness of non-occupational PEP within the UK. Ongoing research in the form of the NONOPEP project, an MRC-funded surveillance programme of PEP for non-occupational exposure to HIV, will address aspects of clinical effectiveness in terms of seroconversion rates in people who take PEP compared with those who do not and evaluate problems associated with taking antiretroviral medications. This project is due for submission shortly. Data generated from this study can then be assessed and used to inform future economic modelling of the cost-effectiveness of non-occupational PEP in the UK.

Chapter I

Aim of the review

The aim of this project is to evaluate the effects of non-occupational postexposure prophylaxis (PEP) for human immunodeficiency virus (HIV) with a course of antiretroviral therapy.

The main objectives are as follows:

- to review the evidence on the clinical effectiveness of non-occupational PEP for HIV
- to summarise the best relevant evidence on the harms of non-occupational PEP for HIV
- to review the evidence on the costs and cost-effectiveness of non-occupational PEP for HIV
- to make recommendations for future research.

If appropriate, and if sufficient time and resources allow, an additional aim will be to develop an economic evaluation or adapt an existing one to model costs and cost-effectiveness in preventing seroconversion after non-occupational PEP for HIV.

Chapter 2

Background

Description of underlying health problem

Human immunodeficiency virus is a sexually transmitted and bloodborne virus found primarily in the blood, semen or vaginal fluid of an infected person. HIV is transmitted in two main ways:

- by having unprotected sex (anal, vaginal or oral) with someone infected with HIV
- by sharing needles and syringes with someone infected with HIV.

Human immunodeficiency virus can also be transmitted through blood infected with HIV and being exposed as a fetus or infant to HIV before/during birth or through breastfeeding. Any person is at risk of infection with the virus if he or she is exposed to HIV through unprotected sex, contaminated blood products or HIV-infected bodily fluids.¹

Seroconversion (converting from HIV negative to HIV positive) occurs when antibodies to HIV can be detected in the blood after infection with the virus. In individuals who become infected with HIV after exposure to the virus, about 30–70% experience an acute seroconversion illness, typically between 2 and 6 weeks after exposure to the virus. The onset is acute and the illness lasts for 1–2 weeks. Its severity varies from a mild glandular fever-like illness with fever, sore throat, lymphadenopathy and a non-itchy maculopapular rash to a severe illness associated with mucocutaneous ulceration and neurological manifestations that requires treatment in hospital.²

Human immunodeficiency virus has a prolonged 'silent' period during which it often remains undiagnosed, particularly as the seroconversion illness (if present) may have been very mild. More persistent or severe symptoms may not appear for 10 years or more after HIV first enters the body in adults, or within 2 years in children born with HIV infection. This period of asymptomatic infection varies greatly in each person. Some people may begin to have symptoms within a few months whereas others may be symptom-free for more than 10 years.³

Human immunodeficiency virus acts by attacking and destroying CD4 (cluster of differentiation) cells. These cells are a type of white blood cell called T lymphocytes (or helper/inducer cells), which are important in the body's immune system. Their depletion during HIV infection results in susceptibility to infection from opportunistic diseases such as tuberculosis, pneumonia and some cancers.⁴ A CD4 cell count (a measure of the number of CD4 cells in a specified volume of blood) gives a measure of the degree to which an individual's immune system is 'compromised'. It helps to identify periods in which an individual is more vulnerable to opportunistic infections, consequently helping inform decisions to initiate antiretroviral treatment and therapies to prevent these infections.⁴ Acquired immunodeficiency syndrome (AIDS) is diagnosed in the UK when an HIV-infected individual presents with an AIDS-defining illness, such as *Pneumocystis carinii* pneumonia, pulmonary tuberculosis or extrapulmonary tuberculosis.⁵

The seroprevalence of HIV is the number of cases of HIV present in a specific population at a designated time, where a case is defined as someone who has HIV antibodies in their serum.⁶ Information on the seroprevalence of HIV in the UK relies on case and test result reporting. However, this can only give information on diagnosed infections. It is therefore supplemented by a programme of unlinked anonymous surveys (using the residue of specimens collected for routine testing for other purposes), which provide information about the total seroprevalence, including both diagnosed and undiagnosed infections, in population subgroups.⁶

The most effective methods for preventing HIV infection are preventive behaviours including sexual abstinence, having sexual relations only with a non-infected partner, correct condom use, abstinence from drug-injection use and consistent use of sterile equipment when using injection drugs. However, secondary prevention measures such as prophylactic antiretroviral drugs have been used to reduce the risk of HIV infection after occupational or non-occupational exposure.⁷

Epidemiology

Globally there are an estimated 39.5 million people living with HIV. There were 4.3 million new infections in 2006, with 2.8 million (65%) of these occurring in sub-Saharan Africa and important increases in Eastern Europe and Central Asia, where there are some indications that infection rates have risen by more than 50% since 2004. In 2006, 2.9 million people died of AIDS-related illnesses.⁸

The most recent figures for the UK estimate that in 2006 there were 73,000 people living with HIV in the UK, around one-third of whom had not yet been diagnosed. There were an estimated 7800 reports of new diagnoses of HIV infection in 2006. A total of 59% of these were among heterosexuals, 36% in men who have sex with men (MSM) and 2.5% in intravenous drug users. In terms of ethnic group, 46% of persons newly diagnosed were black African and 42% were white.⁹

There are certain groups in the UK who are at higher risk of infection than others:

- homosexual men (MSM)
- injecting drug users (IDUs)
- men and women who have lived as adults in countries where heterosexual transmission of HIV is common (notably South, East and Central Africa)
- children, from their infected mothers during pregnancy and birth.¹

Table 1 shows the prevalence of HIV infection in different population subgroups in the UK.¹⁰

Description of the intervention

Postexposure prophylaxis for HIV is the prompt administration of antiretroviral therapy following known or potential exposure to HIV infection in an attempt to prevent the establishment of infection.¹¹

TABLE 1 HIV seroprevalence in different population subgroups in the UK

Community group	HIV seroprevalence (%)	
Homosexual men		
London	20.3	
Scotland	3.2	
Elsewhere	3.6	
Heterosexuals (region of birth)		
	Male	Female
UK	0.5	0.2
Rest of Europe	2.0	0.2
North America	2.9	0.1
Central and South America	2.4	0.9
Caribbean	1.2	1.0
North Africa and Middle East	0.5	0.4
Sub-Saharan Africa	6.9	11.3
South Asia	0.5	0.6
East and South-East Asia	0.5	0.7
Australasia	0.8	0.1
Injecting drug users		
London	2.9	
Elsewhere in the UK	0.5	

Animal models show that, after initial exposure, HIV replicates within dendritic cells of the skin and mucosa before spreading through lymphatic vessels and developing into a systemic infection. This delay in systemic spread leaves a 'window of opportunity' for PEP using antiretroviral drugs designed to block replication of HIV.¹² However, the evidence for the effectiveness of PEP in preventing seroconversion after non-occupational exposure to HIV is unclear.

Current UK guidance on PEP for non-occupational potential or actual exposure to HIV, based on the limited evidence available on the effectiveness of PEP after occupational exposure,^{10,12,13} recommends combination therapies. Although there is no direct evidence that they are more effective in preventing HIV post exposure than monotherapies, combination therapies are more efficacious in treating HIV-infected patients and in preventing perinatal transmission than monotherapies and so it is theorised that a combination of drugs would enhance the effectiveness of PEP.¹² As yet, no antiretroviral drug has been licensed for use after non-occupational exposure to HIV in the UK.¹³ The current drug regimen recommended for HIV PEP starter packs after non-occupational exposure¹⁴ is:

- one Combivir® (GlaxoSmithKline) tablet (300 mg zidovudine + 150 mg lamivudine) twice daily, plus
- two Kaletra® (Abbott) film-coated tablets (200 mg lopinavir + 50 mg ritonavir) twice daily.

Current UK guidance suggests that other drug combinations could be used when the physician considers them more appropriate for individual patients, such as including in the regimen ritonavir-boosted lopinavir, saquinavir or amprenavir.¹³ However, the current evidence on which drug regimen to use, the effectiveness of that regimen in preventing seroconversion following non-occupational exposure to HIV and adherence rates to different regimens is unclear. The guidance is based upon effectiveness of antiretroviral therapy in individuals chronically infected with HIV and on limited data of toxicity in PEP.

There are potential risks associated with PEP following non-occupational exposure or potential exposure to HIV. The drugs used have side effects such as gastrointestinal upset (nausea and diarrhoea), diabetic exacerbation, dangerous interactions with other drugs and nephrolithiasis.¹² These side effects can increase non-adherence,

which in turn can lead to seroconversion of the patient and the development of drug-resistant strains.¹² There is also the potential for an increase in risk behaviours if PEP is perceived as preventing HIV infection.⁷

Current UK practice

Current UK practice for prescribing PEP after non-occupational exposure to HIV is based on guidance issued by the Department of Health¹³ and guidelines from the British Association for Sexual Health and HIV (BASHH).¹⁰

The Department of Health guidance (2004) states that the lack of evidence of effectiveness of PEP following non-occupational exposure to HIV prevents a recommendation either in favour of or against its use.¹³ It suggests that expert advice should be sought urgently from a physician experienced in the treatment of HIV (or a paediatrician in the case of a child) in the event of any non-occupational exposure to HIV that is considered to carry a high risk of HIV infection.¹³ For optimal efficacy PEP should ideally be started within an hour of exposure, but as this time frame is unlikely to be met in non-occupational exposures to HIV the risk of PEP failure is increased. However, longer periods from exposure should not be considered an absolute contraindication to PEP.¹³ A risk assessment of the circumstances surrounding the exposure should be made by the physician considering prescribing PEP, to determine the risk of infection.¹³ The guidance states that all of the considerations that apply to the prescription of PEP after occupational exposure apply equally to non-occupational PEP from the point of a decision being reached that it is appropriate to prescribe it.¹³ The current recommended drug regimen has been outlined in the previous section.

The BASHH guidelines make recommendations for the use of PEP following potential sexual exposure to HIV (PEPSE).¹⁰ The recommendation is that PEPSE is given within 72 hours following unprotected vaginal or anal intercourse with an HIV-positive source or receptive anal intercourse with a source of unknown HIV status but from a group of > 10% HIV prevalence. It is suggested that patients complete 4 weeks of antiretroviral therapy and reattend for HIV testing at 3 months and 6 months post exposure.¹⁰ The recommended drug regimen has been outlined in the previous section.

A recent audit of practice against these guidelines suggests that PEPSE is being prescribed and dispensed as the BASHH guidelines recommend, but that completion rates for the full course of medication [53%, 95% confidence interval (CI) 40.84–64.21] and attendance for 3 and 6 months postexposure HIV testing (12%, 95% CI 5.56–21.29) are low.¹⁵

A survey of UK genitourinary medicine clinics in 1999 found that there were 242 requests for prophylactic antiretroviral drugs made at 56 clinics following a potential non-occupational exposure to HIV.¹¹ In total, 60% of these requests were made to nine clinics, six of which were located in the London area. The survey also found that there had been a fourfold increase in the number of requests for prophylactic antiretroviral drugs and a sevenfold increase in the number of prescriptions between 1997 and 1999.¹¹ Most of the requests had come from HIV-serodiscordant couples who had either had unprotected sex (13 cases, 29%) or had condom breakage during sex (10 cases, 22%).

Costs

One cost estimate suggests that the drug cost of a full 28-day course of PEP is approximately £600 (not including staff time,) whereas the lifetime costs of treatment for an HIV-positive individual are estimated to be between £135,000 and £181,000.¹⁰

Issues specific to non-occupational HIV exposure

There are a number of factors specific to non-occupational HIV exposure that impact on establishing the effectiveness of PEP in this situation or that have particular implications which are different from those in occupational exposures.¹⁶

Ethical issues

The study types available to investigate the efficacy of PEP for non-occupational exposures are limited as it is not deemed ethical to randomly allocate subjects to an intervention or a control group after such an exposure. No controlled trials are likely to take place for this reason.⁷

Time from exposure to PEP initiation

As mentioned in the section on current UK practice, current UK guidance on the use of PEP for non-occupational exposure to HIV recommends that PEP should be considered when individuals present within 72 hours of exposure.¹⁰ This contrasts with guidance for initiation of treatment within 1 hour of occupational exposure.¹³ The average length of time between non-occupational exposure and presentation at health services is unknown. One study of requests for PEP from UK genitourinary medicine clinics found that the time interval between exposure and request was known for 141 out of 242 requests for PEP.¹¹ Out of these 141 requests, 116 (82%) were made within 48 hours.

Potential multiple exposures to HIV pre- and post-PEP initiation

Unlike occupational exposure to HIV in which the exposure incident will usually be a single exposure, non-occupational exposures to HIV can be multiple.¹⁶

There is a possibility that HIV infection could take place as a result of another exposure immediately before the exposure that led to PEP being sought.¹⁶ Individuals presenting for PEP after non-occupational exposure who subsequently seroconvert have reported additional potential exposures (with partners known to be HIV positive or with unknown HIV status) between initiating the PEP regimen and their subsequent seroconversion.¹⁶ This, combined with potential multiple exposures before PEP, makes it difficult to determine whether seroconversion resulted from failure of PEP or from other exposures.¹⁶

Virus concentration

A high plasma viral load in the source may increase the risk of transmission.¹⁰ Although low or undetectable plasma viral loads probably reduce the risk, transmission may still be possible.¹⁰ Although viral loads in the genital tract normally correlate with plasma viral loads, it is possible to have a detectable genital viral load with an undetectable plasma viral load.¹⁰ This may be important in non-occupational exposures, where the exposures may be repeated.

Knowledge of HIV status of source

In many circumstances the estimated risk of HIV transmission following non-occupational exposure is greater than that following occupational exposure in which PEP is routinely considered (*Table 2*).¹⁰ Homosexual men having unprotected receptive anal intercourse with a known HIV-positive source have an estimated risk of transmission of 3% (or a 1 in 33 chance of infection).¹⁰ This compares with an estimated risk of transmission of 0.3% (1 in 333 chance of infection) following a needlestick injury when the source is HIV positive.¹⁰

In occupational exposure the HIV status of the source may already be known or there may be an opportunity to establish the HIV status of the source. In non-occupational exposure the HIV status of the source may also be known, for example in known HIV-discordant partners. However, the HIV status of the source may not be known and it may be very difficult or impossible to find out. This could make calculating the estimated risk of transmission after non-occupational exposures less accurate. The proportion of requests for PEP after non-occupational exposure for which the HIV status of the source is unknown is not currently established.

Furthermore, knowledge of the HIV status of the source is important because it may lead to better prescribing of antiretrovirals, for example in cases in which the source is known to have a drug-resistant strain of HIV. This can lead to higher adherence to medication and potentially greater effectiveness in preventing seroconversion.

Concomitant exposures to other pathogens

Risky sexual behaviour places individuals at risk of sexually transmitted infections other than HIV, such as gonorrhoea and syphilis.¹³ Exposure through sharing drug-injecting equipment can expose a person to the risk of other bloodborne infections such as hepatitis B and C.¹³ Epidemiological studies have shown that the presence of other sexually transmitted infections enhances HIV transmission.¹⁰

The impact of local trauma on the risk of transmission

Breaches in the mucosal barrier as a result of trauma (e.g. following sexual assault or first intercourse) may increase the risk of HIV acquisition.¹⁰ Menstruation or other bleeding may also facilitate transmission.¹⁰

Non-compliance with therapy and follow-up testing

As mentioned previously in the section on description of the intervention, the drugs used to prevent HIV seroconversion have side effects such as gastrointestinal upset (nausea and diarrhoea), diabetic exacerbation, dangerous interactions with other drugs and nephrolithiasis.¹² Because of this the BASHH guidelines state that these potential side effects need to be considered in situations in which the presenting patient is in a state of acute anxiety but the assessment of risk of transmission is low.¹⁰

TABLE 2 Risk of HIV transmission following an exposure from a known HIV-positive individual¹⁰

Type of exposure	Estimated risk of HIV transmission per exposure (%)
Blood transfusion (one unit)	90–100
Receptive anal intercourse	0.1–3.0
Receptive vaginal intercourse	0.1–0.2
Insertive vaginal intercourse	0.03–0.09
Insertive anal intercourse	0.06
Receptive oral sex (fellatio)	0–0.04
Needlestick injury	0.3 (95% CI 0.2–0.5)
Sharing injecting equipment	0.67
Mucous membrane exposure	0.09 (95% CI 0.006–0.5)
CI, confidence interval.	

Patients have cited side effects as a reason for discontinuing PEP after sexual exposure.¹⁵ The BASHH guidelines recommend that at least 75% of people receiving PEP following sexual exposure to HIV should complete the 4-week course of HIV therapy, and at least 75% should attend for a 3- and 6-month follow-up HIV test.¹⁰ However, one study¹⁵ found that only 53% (95% CI 40.84–64.21) of patients completed therapy and only 12% (95% CI 5.56–21.29) attended for both a 3- and 6-month follow-up HIV test. They speculate that this low completion rate may reflect recipients independently clarifying their source's HIV status, poor documentation of adherence and/or a high default rate from follow-up, with patient-perceived low risk, inadequate recall of non-attendees and a mobile population also contributing.¹⁵

Poor adherence to PEP regimens is important as it may theoretically result in the acquisition of a drug-resistant virus should the individual become HIV infected.¹⁰

Behavioural impact of PEP availability and programmes

There are concerns that the availability of PEP for non-occupational exposure to HIV will reduce commitment to primary prevention strategies such as using a condom during sex or avoiding needle sharing when injecting drugs. This could lead to a rise in the frequency of high-risk behaviours, thereby adding to, rather than lessening, HIV transmission.^{10,17} The most desirable outcome is that promoting PEP will cut rates of HIV infection in exposed individuals and reinforce safer sexual behaviour.¹⁷

A number of possible scenarios have been envisaged including:

- no impact of availability of PEP on behaviour
- negative impact: availability of PEP results in an increase in risky behaviours
- positive impact: the 'close call' may act to motivate and sustain risk reduction in individuals who have engaged in risk behaviour.¹⁰

Currently there is conflicting evidence with different studies providing evidence for each of the three scenarios.¹⁰ At the moment there are no data suggesting that a significant number of individuals will repeatedly present for PEP following non-occupational exposure.¹⁰

Another possible outcome of PEP for non-occupational exposures is that the overall number of HIV infections remains unchanged because the numbers protected by PEP are counterbalanced by additional infections in individuals whose risk behaviour is increased by awareness of PEP but who then fail to use it.¹⁷ There is the potential for PEP to cause net harm by protecting only a few individuals at the expense of adverse effects on behaviour and increased HIV transmission in the wider community.¹⁷ There are also implications for the cost and cost-effectiveness of non-occupational PEP, particularly if the awareness of availability of PEP for non-occupational exposures leads to increased demand from those with a low-risk exposure.¹⁷ Although these are important concerns there does not appear to be much evidence to support or refute them.

Rationale for the study

There is growing clinical and patient enthusiasm for the use of non-occupational PEP to prevent HIV infection, although the reduction in the risk of seroconversion may be small, therapy can have unpleasant side effects and other issues as described may impact on effectiveness. No systematic review of the existing literature has been identified. Research is therefore needed to synthesise the available evidence on the effectiveness, harms and cost-effectiveness of non-occupational PEP for HIV.

From the perspective of the patient the pressing clinical issue is to prevent HIV infection. The wider NHS perspective is the most appropriate and cost-effective use of expensive antiretroviral drugs.

Chapter 3

Methods

The a priori methods used for the review are outlined in the research protocol (see Appendix 1). This was sent to members of the advisory group for the review for expert comments (see Acknowledgements). Helpful comments were received relating to the general content of the research protocol; no specific problems with the proposed methods of the review were identified.

Some changes, additions or points of clarification were made to the methods discussed in the original protocol.

- It was felt important that a comparator group of some sort was included in any study that was considered for inclusion as evidence of clinical effectiveness. This could be either a group not receiving PEP, either through study design or by individual choice not to receive medication, or a group receiving an alternative drug regimen. As such, several studies that initially appeared to meet the inclusion criteria were excluded on the basis of not reporting relevant outcomes for comparator groups.
- The main outcome of interest to assess the clinical effectiveness of non-occupational PEP for HIV was the HIV seroconversion rate. However, adverse events are also an important outcome measure and to supplement the limited adverse event data from the clinical effectiveness section of the report additional studies were sought. Studies that did not report the main outcome of interest (seroconversion rates) but which did present adverse event data for both an intervention group and a comparator group were included for adverse events, as were prospective observational studies that met the inclusion criteria in terms of population and intervention.

The research methods used for the systematic reviews are summarised below.

Search strategy

The following databases were searched for published studies and ongoing research, from inception to December 2007: the Cochrane

Library (Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials), MEDLINE (Ovid), EMBASE (Ovid), PubMed, NHS Economic Evaluations Database (NHS EED), NHS Health Technology Assessment database (NHS HTA), Database of Abstracts of Reviews of Effectiveness (DARE), EconLit, National Research Register (NRR), Current Controlled Trials and ClinicalTrials.gov. Grey literature and conference proceedings were also searched. Searches were restricted to the English language and to human studies. Bibliographies of identified papers were assessed for other relevant studies. Investigators of studies were not contacted because of time constraints. Further details, including key search terms, can be found in Appendix 2.

Inclusion and data extraction process

Titles and abstracts of studies identified by the search strategy were screened independently for inclusion by two reviewers. The full text of potentially eligible studies was obtained and examined independently for inclusion by two reviewers. Data from each of the included studies were extracted by two reviewers on standard data extraction forms. Any disagreements were resolved by consensus or arbitration by a third reviewer if necessary.

The process for identifying and including studies is illustrated in Appendix 2, *Figure 1*. The primary reason for excluding studies was that they did not meet the inclusion criteria; for example they did not have a comparator group or results were not presented separately for the intervention and comparator groups. A list of studies excluded at various stages of the process can be found in Appendix 3.

Quality assessment

The methodological quality of included studies was assessed using modified formal tools specific to the design of the study and focusing on possible sources of bias. The clinical effectiveness study

was assessed for quality using criteria developed by Spitzer *et al.*¹⁸ Quality assessment of economic evaluations was conducted using a checklist adapted from those developed by Drummond and Jefferson¹⁹ and Philips and colleagues.²⁰

Quality criteria were applied to each included study independently by two reviewers. At each stage any differences in opinion were resolved through discussion or if necessary by arbitration by a third reviewer.

Inclusion criteria

The inclusion criteria used for studies of the clinical and cost-effectiveness of non-occupational PEP for HIV are shown below.

Intervention

- Any antiretroviral drug regimen administered as non-occupational PEP for a short period (28 days) to HIV-negative people potentially exposed to HIV through unprotected sexual contact or use of a potentially contaminated needle or potentially contaminated biological fluid.

Population

- Humans with non-occupational exposure to HIV. This may be by:
 - unprotected sexual exposure (oral, vaginal, anal), either voluntary or rape, with an HIV-infected partner or partner of unknown HIV status

- exposure to a needle contaminated by a known or potentially infected substance in a non-occupational setting.

Comparator

- No intervention.
- Group not receiving PEP.
- A different PEP regimen.

Outcomes

- HIV seroconversion frequency.
- Adverse effects and complications of PEP.
- Adherence to PEP.
- Health-related quality of life.
- Costs or some measure of cost-effectiveness.

Study type

- Randomised controlled trial (RCT), controlled clinical trial (CCT), cohort study or case-control study.
- Cost-effectiveness/utility studies.
- Economic evaluations.
- Prospective observational studies for adverse events.

Data synthesis

Synthesis of data was through narrative review with full tabulation of results of all included studies. Full data extraction forms are shown in Appendices 4 and 5. Meta-analysis was not possible because of the limited data found.

Chapter 4

Clinical effectiveness

Quantity and quality of research available

One published study met the inclusion criteria for the review, which was a cohort study conducted by Schechter and colleagues²¹ in Brazil (*Table 3, Figure 1* in Appendix 2 and Appendix 4).

The methodological quality and the quality of reporting of the included study were generally weak (*Table 4*).

Significant selection bias may have occurred during the recruitment of study participants. Participants were recruited from an unreported number of eligible participants of a previous HIV seroincidence study of MSM. A total of 250 of those deemed eligible were contacted by telephone and the first 200 to agree to participate were included in this study. The authors do not report the total number of eligible participants in the previous study or how the 250 eligible participants that were telephoned were selected, nor do they

TABLE 3 Details of included study

Study	Population	Intervention	Comparison	Outcome measures
Schechter et al. 2004 ²¹	Brazilian cohort of 200 high-risk men who have sex with men (MSM)	28-day course of PEP after potential high-risk exposure to HIV (zidovudine 300 mg and lamivudine 150 mg orally, fixed-dose combination tablet twice daily)	Non-PEP users	Reported behaviour, PEP utilisation, adverse events, incident HIV infection

TABLE 4 Quality assessment of included study

	Yes	U/I/S ^a	No	DK/NR ^b	N/A	Comments
Proper random assignment			No			
Proper sampling		U				250 potential participants invited to participate by telephone; first eligible 200 who agreed were enrolled. Participants were given PEP to begin after an eligible exposure
Adequate sample size		U				Authors comment that the 109 exposures for which PEP was taken represent a small proportion of the total eligible exposures that occurred during the study
Objective outcomes		I				Self-reported high-risk sexual activity
Blind assessment			No			
Objective eligibility criteria	Yes					
Reported attrition	Yes					
Comparability of groups	Yes					
Generalisability		U				Limited to men who have sex with men from a previously known high-risk cohort, aged 18–35 years
^a U/I/S, uncertain/incomplete/substandard. ^b DK/NR, don't know/not reported.						

report any attempt to minimise volunteer bias. No power calculation is provided to justify why 200 participants were needed.

Participants allocated themselves to the intervention or the control group depending on whether or not they initiated chemoprophylaxis after an eligible exposure by taking the 4-day supply of PEP that they had been given. If PEP was initiated, after 4 days the participant was assessed by study personnel to establish whether the exposure was considered a high enough risk to warrant a further 24 days of PEP. Further selection bias may have occurred at this point as the authors do not report what was considered to be a high-risk exposure or the procedure by which study personnel made such decisions. However, the authors do report the demographic and behavioural characteristics of all study participants, which suggests that there were no significant differences between those who did and those who did not use PEP over the course of the study.

The authors do not report blinding of study participants or personnel. Although it would not have been possible to have fully blinded both study personnel and participants, it may have been possible at the routine follow-up appointments to have blinded personnel to PEP use by participants. This could have reduced potential detection bias.

In the analysis the authors report that two participants had no follow-up data and were therefore excluded from analysis, meaning that an intention to treat analysis was not conducted. The authors report the seroincidence rate (incidence of seroconversions per 100 person-years) for all of the study participants together, compared with the expected number of incident HIV cases in the absence of PEP (modelled from the previous HIV incidence study). The authors state that they did this because of a lack of a control group (participants not taking PEP). However, the reported results seem to suggest that there is a control group with follow-up data (participants who

did not initiate PEP after an eligible exposure). It is therefore not clear why the authors did not calculate the incidence of seroconversion for those who took PEP and for those who did not take PEP, to give an estimate of the effectiveness of PEP in preventing seroconversion for non-occupational exposures.

This study reports the use of PEP amongst a well-established cohort of high-risk sexually active MSM, aged 18–35 years, in Rio de Janeiro, Brazil. The study cohort may have some similarities with populations of MSM living in other big cities, although the limited age range of study participants prevents generalisation to populations of MSM as a whole. It is also not possible to generalise the findings of this study to the population as a whole, in which potential exposure to HIV may also occur through heterosexual sex or non-occupational needlestick injuries.

Assessment of effectiveness

Tables 5–9 present the results of the included cohort study²¹ in terms of seroincidence of HIV within the cohort, PEP use, non-completion of PEP, adverse events and reports of risky behaviours.

Seroconversion to HIV

The HIV seroincidence is presented in Table 5. One incidence of seroconversion to HIV was reported in the group of participants that took PEP, compared with 10 from the ‘no PEP’ group. No *p*-value was reported. Over the course of the study the overall incidence of HIV was 2.9 per 100 person-years (95% CI 1.4–5.1). The authors report that, based on the risk profile of the participants and experience from a previous study, the expected number of new HIV infections overall was 11.8 (*p* > 0.97 compared with the observed 11 infections) and the expected seroincidence was 3.1 per 100 person-years (*p* > 0.97 compared with the seroincidence of 2.9 found in this study).

TABLE 5 HIV seroincidence

	PEP (n = 68)	No PEP (n = 132)	<i>p</i> -value
Seroconversion to HIV	1	10	Not reported

TABLE 6 PEP use (28-day course)

	PEP (n = 68)	No PEP (n = 132)
Prescribed once, n (%)	49 (72.1)	–
Prescribed twice, n (%)	14 (20.6)	–
Prescribed three times, n (%)	2 (2.9)	–
Prescribed four times, n (%)	2 (2.9)	–
Prescribed nine times, n (%)	1 (1.5)	–

PEP use

The PEP use in the cohort is presented in *Table 6*. In the majority of cases the full 28-day course was prescribed once per participant (72.1%). In total, 100 out of 109 exposures for which PEP was initiated by participants were considered eligible and received the 4-week course. The authors report that the most common reasons for not initiating PEP (\geq one possible response per participant) were sex with a steady partner ($n = 150$), the participant did not consider the exposure to be of sufficiently high risk to warrant PEP ($n = 94$) and concerns about side effects ($n = 23$).

Adverse events and adherence

The number of non-completed PEP courses is shown in *Table 7*. The authors report that the full 28-day regimen of PEP was completed for 89 (89%) of the eligible exposures, including the participant who seroconverted, and that the 11 discontinuations correspond to nine participants.

Two of the participants did not come back to the study site to complete their visits at 28 days.

There were seven discontinuations of PEP because of adverse events. At least one side effect was reported in 82% of episodes of PEP use. Nausea was the most commonly reported side effect: six of the discontinuations for adverse events were due to this. Apart from one patient with a history of

pancreatitis who had to stop taking PEP because of an asymptomatic increase in pancreatic enzymes, it is reported that there were no clinically significant laboratory abnormalities among those receiving PEP.

Risk behaviours and PEP use

The median numbers of male partners reported by participants are presented in *Table 8*. These remained the same from the baseline visit to the last visit at 24 months for both groups, although the range was increased in both groups at the last visit.

Table 9 shows the types of risk behaviours that participants were asked to report and the changes from the 6 months previous to the baseline visit to the 6 months previous to the last follow-up visit at 24 months. Reported unprotected anal intercourse decreased in both groups; in the no PEP group this decrease was statistically significant. Reported unprotected oral intercourse decreased significantly in both the PEP and the no PEP groups. Unprotected vaginal intercourse increased; this was not statistically significant.

Self-reported results should be viewed with some caution where there is the possibility that high-risk behaviour has been under-reported or where reports may be inconsistent.

TABLE 7 Non-completed PEP courses

	PEP (n = 68)	No PEP (n = 132)
Did not return to complete course	2	–
Discontinued because of adverse events	7	–

TABLE 8 Numbers of male partners and PEP use

	PEP (n = 68)	No PEP (n = 132)
Median number of male partners 6 months before baseline (range)	4 (0–50) ^a	2 (0–40) ^b
Median number of male partners 6 months before last visit (range)	4 (0–180) ^a	2 (0–100) ^b
a $p = 0.43$.		
b $p = 0.46$.		

TABLE 9 Risk behaviours and PEP use

	PEP (n = 68)			No PEP (n = 132)		
	6 months before baseline	6 months before last visit	p-value	6 months before baseline	6 months before last visit	p-value
Unprotected anal intercourse, n (%)	32 (47.1)	27 (39.7)	$p = 0.35$	48 (36.4)	32 (24.2)	$p = 0.008$
Unprotected oral intercourse, n (%)	16 (23.5)	8 (11.8)	$p = 0.06$	32 (24.4)	16 (12.2)	$p = 0.002$
Unprotected vaginal intercourse	1.6%	4.7%	$p = 0.16$	6.1%	8.3%	$p = 0.26$

Summary of clinical effectiveness of PEP for non-occupational exposure to HIV

- One cohort study of PEP in a high-risk HIV-negative homosexual male cohort in Brazil met the inclusion criteria of the review. The methodological quality and the quality of the reporting of the study were generally weak.
- The seroconversion to HIV rate in this study was one in the PEP group and 10 in the non-PEP group.
- The results suggest that PEP made no difference to the expected seroconversion to HIV for this cohort.
- Over the course of the study the overall seroincidence (combining the PEP and non-PEP groups) was 2.9 per 100 person-years (95% CI 1.4–5.1). This was compared with the authors expected seroincidence of 3.1 per 100 person-years ($p > 0.97$ compared with the observed seroincidence of 2.9).
- PEP was rarely prescribed on more than two occasions per participant, with the majority (72.1%) receiving just one course.
- The number of non-completed courses appears to be low, with only 2 out of 68 not returning to complete the course and 7 out of 68 discontinuing because of adverse events.
- The authors report that, on average, high-risk sexual activities declined over time for both PEP and non-PEP users. This does not appear to be related to the decision to initiate PEP; both groups had access to interventions designed to prevent/reduce risk behaviour, including at each visit pre- and post-test counselling, provision of condoms and safer sex workshops.
- The authors conclude that the results from their study 'argue against establishing a public health PEP programme in our population with the aim of having a major impact on HIV transmission' because of the observed overall seroincidence of 2.9% being so similar to that expected for this population.

Chapter 5

Cost-effectiveness

The aim of this chapter is to evaluate the cost-effectiveness of non-occupational PEP for HIV. A systematic review of the literature was conducted to identify economic evaluations of the use of PEP in people with non-occupational exposure to HIV. The feasibility of developing an economic model was also considered.

The methods used for the systematic review are described in Chapter 3. The details of the inclusion and exclusion criteria are shown in Appendix 1 and the search strategies are shown in Appendix 2.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by two reviewers. The full text of relevant papers was obtained and inclusion criteria were applied to each study independently by two reviewers. Differences in opinion were resolved through discussion or by arbitration by a third reviewer if necessary.

Economic evaluations were eligible for inclusion if they reported on the cost or cost-effectiveness of any antiviral drug regimen administered as PEP in people with non-occupational exposure to HIV (unprotected sexual exposure or needle contamination) compared with another PEP regimen or a group of people not receiving PEP (Appendix 1).

Quantity and quality of research available

Four economic evaluations^{22–25} met the inclusion criteria for the review and are shown in *Table 10* (details in *Figure 2* in Appendix 2 and Appendix 5).

A summary of the methodological quality of reporting in the four included studies is shown in *Table 11*. Each of the cost-effectiveness studies outlined a well-defined question: to assess the cost-effectiveness of PEP for HIV following a non-occupational exposure.^{22–25} The patient group was clearly stated in three of the four studies.^{23–25} In the study by Pinkerton and colleagues²² the patient group is less clear as the authors have referred to

a hypothetical cohort of 10,000 ‘patients’ (a cohort that includes women) but have used this term interchangeably with 10,000 ‘men who have sex with men’.

All of the studies clearly stated that their perspective was societal, with the analysis including all identifiable costs, regardless of who bore them. However, Pinkerton and colleagues²² stated only the monetary costs of PEP drugs and of treating a patient with HIV/AIDS. Herida and colleagues²⁵ referred only to health sector costs in their study, despite employing a societal perspective.

Two of the studies^{23,25} gave a clear description of the interventions considered. One study²⁴ does not describe the PEP programme employed, whereas in the other²² the intervention applied to a hypothetical cohort was assumed to be zidovudine, lamivudine and indinavir, or zidovudine and lamivudine only, but no further details are given. Three of the four studies^{22,24,25} employed the comparator of ‘no PEP’ whereas in the fourth study²³ the comparator used is unclear.

The study types used were appropriate for economic analysis in each case; three of the four studies included both cost-effectiveness and cost-utility analyses^{22,23,25} and one employed a cost-utility analysis alone.²⁴

Each of the four studies is limited as the effectiveness of the intervention, PEP in non-occupational exposure to HIV, has not been established. The effectiveness parameter in each of the papers is based on the results of a case-control study undertaken in health-care workers who were prescribed zidovudine monotherapy. The dual or triple drug regimens considered in these cost-effectiveness studies are assumed to be as effective as zidovudine alone in this study of occupational exposure. Pinkerton and colleagues²² have taken their effectiveness parameter, the probability that PEP is effective, from the original study,²⁶ set at 79%. The remaining three studies^{23–25} have taken their effectiveness parameter from the update of that study,²⁷ in which effectiveness is set at 81%, although one of these studies²⁵ reports that an effectiveness of 80% is used.

TABLE 10 Study characteristics of economic evaluations

	Pinkerton et al. 1998²²	Pinkerton et al. 2004²³	Pinkerton et al. 2004²⁴	Herida et al. 2006²⁵
Country of origin	US	US	US	France
Base year prices	1996 US\$	2000 US\$	2000 US\$	2002 Euros
Intervention	PEP following potential HIV exposure through sexual contact with a partner who may or may not be infected vs a 'no programme option'. PEP was assumed to consist of a 4-week regimen of triple combination therapy with ZDV, 3TC and the protease inhibitor indinavir	Initial 7-day PEP with additional 21 days supplied at follow-up visit. Also medical evaluation, HIV risk assessment, risk-reduction counselling. Response to medication of HIV-infected sources was obtained if possible to tailor PEP to that most appropriate	Hypothetical PEP programme in 96 US metropolitan statistical areas (MSA), based on San Francisco PEP programme	PEP programme vs 'no PEP' alternative. Clinicians prescribe drugs of their choice (usually tri-therapy containing protease inhibitor). Antiretroviral drugs and counselling provided at each visit
Study type	Cost-utility analysis; decision-analytical model to evaluate cost-effectiveness	Cost-effectiveness and cost-utility study	Cost-utility analysis	Cost-effectiveness analysis based on decision trees and cost-utility study
Study group	A hypothetical cohort of 10,000 patients who reported sexual intercourse with a partner of unknown HIV status	401 participants with possible non-occupational exposure to HIV (sexual, needle sharing, non-occupational needlestick injury, other (bite or assault))	Information on PEP clients taken from the San Francisco PEP programme, which was used to estimate the number of potential PEP clients in each group in each MSA	12,551 individuals who sought PEP between July 1999 and December 2003; 8958 (71%) were prescribed PEP and included in a national hospital-based voluntary surveillance of PEP programme for both occupational and non-occupational exposure
Perspective	Societal	Societal	Societal	Societal
Industry role	None stated	None stated (one of the authors has received honorariums from GlaxoSmithKline, Bristol-Myers Squibb and Agouron Pharmaceuticals)	Not stated	Not stated

3TC, lamivudine; ZDV, zidovudine.

The effectiveness of PEP and its effects on the cost-utility ratios presented in the studies, along with other parameters, are clearly explored in sensitivity analyses in each of the studies.²²⁻²⁵ Authors of two of the studies reported multivariate and threshold analyses in addition to the univariate sensitivity analysis.^{22,23}

Costs and consequences were judged to have been valued credibly in three of the four included studies.^{22,23,25} Pinkerton and colleagues²⁴ have

calculated the costs of providing PEP from a previously published cost analysis.

Three of the four studies have used a lifetime horizon for analysis.^{22,24,25} A shorter time horizon of 10 years has been employed for estimating long-term infection, but no justification has been given.²³ Discount rates are clearly reported in three studies. In two studies^{23,25} an annual rate of 3% was used to discount both costs and benefits, such as future savings in averted HIV-related

TABLE 11 Summary of the methodological quality of reporting of the cost-effectiveness studies

Quality criteria	Pinkerton et al. 1998 ²²	Pinkerton et al. 2004 ²³	Pinkerton et al. 2004 ²⁴	Herida et al. 2006 ²⁵
Is there a well-defined question?	Yes	Yes	Yes	Yes
Is there a clear description of alternatives (i.e. who did what to whom, where and how often)?	Unclear	Yes	No	Yes
Has the correct patient group/population of interest been clearly stated?	No	Yes	Yes	Yes
Is the correct comparator used?	Yes	Unclear	Yes	Yes
Is the study type reasonable?	Yes	Yes	Yes	Yes
Is the perspective of the analysis clearly stated?	Yes	Yes	Yes	Yes
Is the perspective employed appropriate?	Unclear	Yes	Yes	Unclear
Is the effectiveness of the intervention established?	No	No	No	No
Has a lifetime horizon been used for analysis? If not, has a shorter time horizon been justified?	Yes	No	Yes	Yes
Are the costs and consequences valued credibly?	Yes	Yes	Unclear	Yes
Is differential timing considered?	Yes	Yes	Unclear	Yes
Is incremental analysis performed?	Yes	No	No	No
Is sensitivity analysis undertaken and presented clearly?	Yes	Yes	Yes	Yes

medical costs. Pinkerton and colleagues²² used a 3% annual rate (applied to both costs and benefits) and altered this to 0% (undiscounted) and 5% in the sensitivity analysis. It is unclear if discounting has been applied in one of the 2004 Pinkerton and colleagues studies.²⁴

Incremental analysis was reported by only one of the studies.²² The remaining three papers report cost-utility ratios but no incremental ratios. Pinkerton and colleagues²³ compare their results with previously published papers.

Table 12 presents a summary of the external validity of the included cost-effectiveness studies. Three of the four studies are set in the US^{22–24} and the fourth in France,²⁵ where the institutional health-care arrangements and resource costs, and access to them, are not comparable to those in England and Wales. It is unclear whether the patient groups are similar to those of interest in England and Wales as these studies are set in differing health-care systems but are conducted among the relevant population: those taking PEP after a non-occupational exposure.

Either the intervention in each of the four studies was not sufficiently clear for a judgement to be made of treatment comparability^{24,25} or the research protocol included such elements as counselling and adherence counselling that may not be a feature of clinical management.²³ Pinkerton and colleagues²² have assumed that the PEP in their study consists of triple combination therapy, which is comparable to that recommended in the UK, but no further details are given.

Assessment of cost-effectiveness

Summaries of the results of the four published economic evaluations in terms of cost-utility ratios for different population subgroups are shown in Tables 13–15.

Herida and colleagues²⁵ found that the French PEP programme did not appear to be cost-effective overall, with a cost-effectiveness ratio of €996,104 per infection averted and €88,692 per quality-adjusted life-year (QALY) saved.

TABLE 12 Summary of the external validity of the cost-effectiveness studies

Quality criteria	Pinkerton et al. 1998 ²²	Pinkerton et al. 2004 ²³	Pinkerton et al. 2004 ²⁴	Herida et al. 2006 ²⁵
Patient group – are the patients in the study similar to those of interest in England and Wales?	Unclear	Unclear	Unclear	Unclear
Health-care system/setting – comparability to England and Wales; comparability of available alternatives; similar levels of resources; institutional arrangements comparable?	No	No	No	No
Treatment – comparability with clinical management?	Unclear	Unclear	Unclear	Unclear
Resource costs – comparability between study and setting/population of interest?	No	No	No	No

TABLE 13 Base-case cost–utility ratios for men who have sex with men

Type of exposure	Probability PEP effective	HIV transmission probability	Probability source is HIV positive	Estimated or actual PEP compliance	Cost per QALY	Study
Unprotected receptive anal intercourse	0.80	0.02	1.00	0.83	–€22,141	Herida et al. 2006 ²⁵
	0.80	0.02	0.14	0.74	€31,862	Herida et al. 2006 ²⁵
	0.81	0.02	0.293	1.00 ^a	Cost saving (actual cost per QALY not reported)	Pinkerton et al. 2004 ²³
	0.81	0.02	Not reported	0.778	US\$ < 0 (actual figure not reported)	Pinkerton et al. 2004 ²⁴
	0.79	0.02	0.18	0.69	US\$6354	Pinkerton et al. 1998 ²²
Unprotected insertive anal intercourse	0.80	0.0006	1.00	0.83	€241,716	Herida et al. 2006 ²⁵
	0.80	0.0006	0.14	0.80	€1,952,497	Herida et al. 2006 ²⁵
	0.81	0.0006	0.293	1.00 ^a	US\$686,525	Pinkerton et al. 2004 ²³
	0.81	0.0006	Not reported	0.778	US\$554,814	Pinkerton et al. 2004 ²⁴
	0.79	0.0006	0.18	0.69	US\$773,785	Pinkerton et al. 1998 ²²
All exposures combined ^b					US\$8607	Pinkerton et al. 2004 ²³
					US\$4907	Pinkerton et al. 2004 ²⁴

QALY, quality-adjusted life-year.

a PEP was assumed to be effective only if the patient was known to have completed the regimen; otherwise effectiveness was set to 0.

b Receptive or insertive anal intercourse, receptive oral sex and 'other'. References for sources of data can be found in the individual papers.^{22–25}

TABLE 14 Base-case cost–utility ratios for heterosexuals

Type of exposure	Probability PEP effective	HIV transmission probability	Probability source is HIV positive	Estimated or actual PEP compliance	Cost per QALY	Study
Unprotected receptive anal intercourse	0.80	0.02	1.00	0.81	–€22,031	Herida <i>et al.</i> 2006 ²⁵
	0.80	0.02	0.005	0.60	€1,943,685	Herida <i>et al.</i> 2006 ²⁵
	0.81	0.02	0.041	1.00 ^a	US\$165,289	Pinkerton <i>et al.</i> 2004 ²³
	0.81	0.02	Not reported	0.778	US\$ < 0 (actual figure not reported)	Pinkerton <i>et al.</i> 2004 ²⁴
	0.79	0.02	0.18	0.69	US\$6354	Pinkerton <i>et al.</i> 1998 ²²
Unprotected receptive vaginal intercourse	0.80	0.001	1.00	0.81	€135,111	Herida <i>et al.</i> 2006 ²⁵
	0.80	0.001	0.005	0.62	€38,653,452	Herida <i>et al.</i> 2006 ²⁵
	0.81	0.001	0.041	1.00 ^a	US\$262,562	Pinkerton <i>et al.</i> 2004 ²³
	0.81	0.001	Not reported	0.778	US\$380,891	Pinkerton <i>et al.</i> 2004 ²⁴
	0.79	0.001	0.02	0.69	US\$4,254,916	Pinkerton <i>et al.</i> 1998 ²²
All exposures combined: heterosexual females ^b					US\$161,114	Pinkerton <i>et al.</i> 2004 ²⁴
All exposures combined: heterosexual males ^c					US\$685,560	Pinkerton <i>et al.</i> 2004 ²⁴

QALY, quality-adjusted life-year.

a PEP was assumed to be effective only if the patient was known to have completed the regimen; otherwise effectiveness was set to 0.

b Male–female receptive anal intercourse, male–female receptive vaginal intercourse.

c Male–female insertive anal intercourse, male–female insertive vaginal intercourse, male–female other sexual exposure.

TABLE 15 Base-case cost–utility ratios for intravenous drug users (IDUs)

Type of exposure	Probability PEP effective	HIV transmission probability	Probability source is HIV positive	Estimated or actual PEP compliance	Cost per QALY	Study
IDU	0.80	0.0067	1.00	0.61	–€1141	Herida <i>et al.</i> 2006 ²⁵
	0.81	0.003	0.214	1.00	US\$86,462	Pinkerton <i>et al.</i> 2004 ²³
	0.81	0.003	Not reported	0.778	US\$97,867	Pinkerton <i>et al.</i> 2004 ²⁴

QALY, quality-adjusted life-year.

However, the authors report major differences in the cost-effectiveness ratio according to the type of exposure. PEP after receptive anal intercourse with an HIV-infected individual (men –€22,141, women –€22,031 per QALY saved) and PEP to an intravenous drug user (IDU) after sharing a needle with an HIV-infected person (–€1141 per QALY saved) were cost saving. PEP was cost-effective for MSM having receptive anal intercourse with a partner of unknown status (€31,862 per QALY saved). PEP was not considered cost-effective (cost per QALY €50,000) for all other exposures considered in the analysis.

One-way sensitivity analyses were performed on the compliance and life expectancy of HIV-infected individuals in this study.²⁵ PEP after receptive anal intercourse with an HIV-infected individual remained cost saving (–€17,778 and –€18,860 per QALY saved for MSM and heterosexual women respectively). PEP to an IDU after needle sharing with an HIV-infected person remained cost-effective but was no longer cost saving (€18,445 per QALY saved). Further sensitivity analyses incorporating higher lifetime HIV costs resulting from longer survival resulted in the three exposure risks with negative ratios in the base case remaining cost saving but with higher cost ratios.

Herida and colleagues²⁵ also performed threshold analyses for exposures with cost-effectiveness ratios under €200,000 per QALY saved, using minimum values of prevalence, per-contact HIV transmission or compliance required to achieve the cost-saving threshold (€0 per QALY saved) or the cost-effective threshold (€50,000 per QALY saved). The authors reported that PEP for MSM after receptive anal intercourse with a partner of unknown HIV status was cost saving for a per-contact transmission risk of at least equal to 0.0411 or an HIV prevalence of at least 0.208. For needle sharing with an individual of unknown serostatus the authors reported that cost-effectiveness occurred with a compliance of ≥ 0.92 with both the highest values of prevalence (0.21) and of the per-contact transmission risk (0.0092). The cost-effectiveness ratio was reached for a per-contact transmission risk equal to 0.0208 for receptive vaginal intercourse with an HIV-infected partner.

Pinkerton and colleagues²³ cost-utility analysis of a PEP programme for 401 participants with possible non-occupational exposure to HIV found that the use of PEP prevented an estimated 1.59 HIV infections (1.26 infections after adjusting for continuing risk behaviours over the subsequent

10 years), with an overall cost-utility ratio of US\$14,449 per QALY saved. In total, 96% of averted infections were among men who reported exposure through receptive anal intercourse with other men.

The authors report that the PEP programme was cost saving amongst men who have receptive anal intercourse with other men, and when the partner was known to be HIV positive.²³ The overall cost-utility ratio for men reporting exposure through male–male sex (receptive or insertive anal intercourse, receptive oral intercourse or ‘other’) was US\$8607 per QALY saved, whereas the cost-utility ratio for all other exposures combined was US\$258,667 per QALY saved. The cost per QALY saved for exposure by injecting drugs and male–female receptive anal sex was US\$86,462 and US\$165,289 respectively.

The results of the sensitivity analyses reported by the authors suggest that the PEP programme remained cost-effective when the effectiveness of PEP was set as low as 48% (base case 81%) and as long as PEP completion rates were greater than 29%.²³ The programme also remained cost-effective regardless of the percentage of partners known to be infected with HIV or the prevalence of infection among partners whose HIV status was unknown.

The cost-utility ratio was most sensitive to the receptive anal intercourse transmission probability.²³ The authors report that the PEP programme would be cost saving overall if this probability exceeded 0.033 and would be cost-effective (defined by the authors as a cost-utility ratio of US\$60,000 per QALY saved) for probabilities as small as 0.009 (the base case was set at 0.02).

The Pinkerton and colleagues study²⁴ of PEP in 96 metropolitan statistical areas in the US estimated the respective mean and median cost-utility ratios to be US\$15,728 and US\$15,367 per QALY saved, with 63.9 HIV infections averted. PEP was cost saving for male–male and male–female receptive anal intercourse exposures (see *Tables 13–15*). Cost-utility ratios for needle sharing and needlestick exposures were US\$97,867 and \$159,686 per QALY saved respectively. The cost-utility ratio exceeded \$380,000 per QALY saved for all other types of exposure.

The authors report²⁴ that the sensitivity analysis suggests that the results are moderately sensitive to PEP effectiveness and somewhat sensitive to the

proportion of people completing the PEP regimen, the proportion of PEP clients with known infected source partners and the lifetime costs of medical care and lost QALYs associated with a case of HIV infection.

The authors²⁴ conclude that PEP is only cost-effective in limited circumstances such as following receptive anal intercourse with a partner at high risk of infection and possibly following other high-risk exposures with a partner known to be infected. The authors state that PEP was highly cost-effective for MSM, less cost-effective for IDUs and high-risk women, and probably not cost-effective for general population exposures or heterosexual men.²⁴

The study by Pinkerton and colleagues²² evaluating the cost-effectiveness of PEP for a hypothetical cohort of 10,000 patients reporting sexual intercourse with a partner of unknown HIV status estimated that 19.62 HIV infections would be averted following receptive anal intercourse, 0.59 following insertive anal intercourse, 0.11 following receptive vaginal intercourse and 0.07 following insertive vaginal intercourse.

In this study²² the base-case analysis suggested that PEP is only cost-effective for receptive anal intercourse (all other cost-utility ratios exceeded US\$750,000 per QALY saved). The cost-utility ratio following receptive anal intercourse among MSM was US\$6354 per QALY saved. This became cost saving if the probability that the source partner was HIV positive was greater than 0.25 (see *Tables 13–15*).

The sensitivity analysis reported by Pinkerton and colleagues²² showed that PEP following receptive anal intercourse was always cost-effective across a range of values. PEP following receptive vaginal intercourse became cost-effective when the probability that the source partner was HIV positive was at least 0.73. The authors report that triple therapy was unlikely to be cost-effective relative to double therapy as the additional drug costs were not offset by treatment savings. The results did not appear to be sensitive to repeated exposure to HIV and PEP.²²

Economic evaluation

One of the aims of the current report was to draw together the best available evidence to estimate the cost-effectiveness of non-occupational PEP for HIV in a UK setting. The current authors

explored the feasibility of developing a de novo economic model, either by adapting an existing cost-effectiveness model or by constructing a new one. However, the available data to inform any cost-effectiveness analysis are very sparse, making it inappropriate to model the cost-effectiveness of non-occupational PEP for HIV at the present time. The limitation in the extent of the evidence for the clinical effectiveness of non-occupational PEP for HIV is the main reason for arriving at this conclusion, that is, the effectiveness of non-occupational PEP is unknown. Only one study met the systematic review criteria for assessing the clinical effectiveness of non-occupational PEP, and the authors state that the study design and relatively small number of seroconversions do not allow conclusions about the effectiveness of PEP in preventing infection. In addition, there were limited data for other model parameters, such as per-exposure transmission probabilities, prevalence of HIV among different population groups and treatment compliance. Any modelling using such data inputs will be of limited value.

However, should better quality and more relevant data become available, the modelling frameworks presented by Pinkerton and colleagues²³ and Herida and colleagues²⁵ may be useful starting points for cost-effectiveness analysis. Although these studies should be viewed with caution, because the clinical effectiveness was informed from one study of the use of PEP in an occupational setting and was based on assumptions that the same conditions exist in a non-occupational setting, they have been conducted in an appropriate way and appear to have internal validity in terms of model structure. Any model should incorporate PEP adverse events and completion rates as these have important economic consequences.

Summary of cost-effectiveness of PEP for non-occupational exposure to HIV

- Four economic evaluations met the inclusion criteria of the review.
- The methodological quality of the four studies is mixed. Each had a well-defined question, stated a reasonable study type and perspective and undertook a clear sensitivity analysis. However, each of the studies is constrained by a lack of published data on the clinical effectiveness of PEP after non-occupational

exposure, the per-exposure transmission risk, the compliance with medication and the prevalence of HIV infection amongst different population subgroups.

- In addition, external validity appears to be poor. None of the studies was clearly generalisable to the UK. Lack of detailed information on the PEP regimes used in all of the studies prevented comparison with UK clinical management, as did the lack of information on study participants.
- Results from the included studies suggest that PEP following non-occupational exposure to HIV is cost saving for:
 - men who have unprotected receptive anal intercourse with men, whether the source partner is known to be HIV positive or not
 - heterosexuals after unprotected receptive anal intercourse
 - intravenous drug users sharing a needle with a known HIV-positive person.
- PEP following non-occupational exposure to HIV was cost-effective for all male–male intercourse (unprotected receptive and insertive anal intercourse, unprotected receptive oral sex and ‘other’).
- PEP following non-occupational exposure to HIV was possibly cost-effective for intravenous drug users and high-risk women.
- In general, sensitivity analyses did not greatly alter the base-case findings. Some sensitivity to the following parameters was noted:
 - transmission probability following receptive anal intercourse
 - effectiveness of PEP
 - proportion of clients completing PEP
 - proportion of clients with known HIV-positive partners
 - lifetime costs of treatment and number of lost QALYs
 - receptive vaginal intercourse (which became cost-effective) when the probability of the source partner being HIV positive was ≥ 0.73 .
- In summary, although the results of the studies are consistent and suggest that non-occupational PEP may be cost-effective, the results should be treated with caution. It may not be appropriate to make assumptions that the same conditions exist in a non-occupational setting as in an occupational setting. The generalisability to the UK of studies conducted in the US and France is not clear. Although transmission risks for specific sexual practices are likely to be the same, sexual behaviour and HIV incidence may not be similar and local costs may be different.
- Because of limited data, especially on the effectiveness of non-occupational PEP for HIV, no de novo economic evaluation was conducted in the present study.

Chapter 6

Adverse events

Four additional studies were identified that report data on adverse events and they are presented here to provide further information on this issue. Two comparative studies^{28,29} consider different non-occupational PEP interventions and two prospective observational studies^{30,31} in relevant populations report data on toxicity and completion of medication. Details of the four studies are shown below (*Table 16*). Study results are presented in *Tables 17* and *18*.

In one prospective comparative study²⁸ of sexual assault victims who sought treatment within 72 hours of sexual exposure, participants were assigned to either medium or high severity groups according to factors that could influence HIV transmission. Those in the medium severity group ($n = 141$) were given zidovudine plus lamivudine and those in the high severity group ($n = 137$) were given zidovudine plus lamivudine plus protease inhibitor. Follow-up was at 6 months and toxicity and compliance are reported. In the other comparative study²⁹ PEP was provided within 72 hours to individuals with exposures from partners known to have been or to be at risk for HIV infection through sexual exposure or injecting drug use. In total, 97% of participants were treated exclusively with dual reverse transcriptase inhibitors. Rates of completion of PEP and toxicities after 4 weeks are reported.²⁹

In one 18-month prospective observational study³⁰ sexual assault survivors attending one of 24 Sexual Assault Treatment Centres (SATCs) within 72 hours of the assault were offered PEP if considered to be at high or unknown risk of HIV infection. The primary outcomes in this study were acceptance and completion rate, and adverse events were also reported. All participants were prescribed Combivir (zidovudine + lamivudine) and Kaletra (lopinavir + ritonavir) and received counselling regarding dosing, adherence and adverse events. Follow-up visits were scheduled for days 2–4 and weeks 1, 2, 3 and 4. The second prospective observational study³¹ enrolled patients presenting after sexual exposure to HIV from source partners known to be, or suspected of being, infected with HIV. The participants were prescribed zidovudine plus lamivudine if reporting the exposure within 72 hours and also received risk reduction counselling.

Follow-up visits were scheduled for weeks 1, 2, 4, 6, 12 and 26. The primary outcomes for this study were enrolment into concurrent behavioural risk reduction interventions, demand for non-occupational PEP and characteristics of those treated. Completion and adverse events were also reported.

All of the studies have methodological limitations in that, although there were objective criteria for the eligibility of subjects, subjects were self-referring and there was non-blinded assessment of self-reported outcomes. Not all outcomes are reported separately for all treatment groups in the comparative studies and it is not clear whether the different groups within each study are comparable; participants were also allowed to switch between treatment groups. The observational studies are limited by the lack of control groups. Although all of the sexual assault survivors attending SATCs were offered PEP,³⁰ 25.9% of health-care providers prescribing PEP reported strongly encouraging or encouraging participants to accept and 3.1% reported strongly discouraging or discouraging acceptance, which could affect both acceptance and possibly completion. Selected outcomes were reported separately for the high-risk and unknown-risk groups.³⁰ The recruitment by Shoptaw and colleagues³¹ focused on an underserved area and participants then self-referred to the study, meaning that the generalisability of the study findings is unclear.

Completion of treatment

Completion of treatment rates in the four studies are shown in *Table 17*. Garcia and colleagues²⁸ found that participants who received dual therapy were more likely to complete PEP (68%) than those who received three drugs (53%) ($p = 0.01$). In the high severity group 21% interrupted the use of protease inhibitor and completed PEP with two drugs, with the main reason for interruption being toxicity. Compliance at 6 months of follow-up was similar in both the medium and the high severity groups [odds ratio (OR) 1.0, 95% CI 0.8–1.3].²⁸ In the San Francisco PEP study,²⁹ over all groups, 78% of participants completed 4 weeks of treatment. Significantly more patients treated

TABLE 16 Studies reporting adverse event/compliance data

Study	Population	Interventions
Garcia et al. 2005 ²⁸	Sexual assault victims	
Brazil		
Prospective cohort study		
	Medium-risk group (<i>n</i> = 141) (vaginal/oral intercourse with ejaculation but without trauma)	ZDV + 3TC
	High-risk group (<i>n</i> = 137) [anal penetration; vaginal exposure with genital trauma; exposure to many aggressors; presence of factors that increase risk (inflammation, ulcers, bleeding, trauma, laceration, menstruation); aggressor known to be HIV positive]	ZDV + 3TC + PI
	All patients offered psychological and supportive counselling	
Kahn et al. 2001 ²⁹	Sexual or injecting drug use exposure	
San Francisco	Source HIV status/ART history unknown (<i>n</i> = 351)	ZDV + 3TC (combined pill twice daily)
PEP study	As above with source plasma HIV RNA levels on treatment above the limits of detection (<i>n</i> = 8)	ZDV + 3TC + Nfv (combined pill twice daily + Nfv three times daily)
	Source receiving or participant refused ZDV (<i>n</i> = 31)	ddl + d4T (two pills twice daily)
	As above with source plasma HIV RNA levels on treatment above the limits of detection (<i>n</i> = 5)	ddl + d4T + Nfv (two pills twice daily + Nfv three times daily)
	If source was receiving Nfv and had detectable plasma HIV RNA levels, alternative to Nfv given (<i>n</i> = 2)	Other ART
	All groups received risk reduction counselling and medication adherence counselling	
Loutfy et al. 2008 ³⁰	Sexual assault survivors (<i>n</i> = 798): 69 high risk; 729 unknown risk	Combivir (ZDV + 3TC) (one pill twice daily) and Kaletra (lopinavir/ritonavir) (three capsules orally twice a day) for 28 days
Canada		
Prospective observational study		
	Counselling regarding dosing, the importance of adherence and adverse events was provided	
Shoptaw et al. 2008 ³¹	Patients presenting post sexual exposure to persons known or suspected to be infected with HIV (<i>n</i> = 100)	ZDV + 3TC (twice daily)
US		
Prospective observational study		
	Risk reduction counselling provided	

3TC, lamivudine; ART, antiretroviral therapy; d4T, stavudine; ddl, didanosine; Nfv, nelfinavir; PI, protease inhibitor (indinavir or nelfinavir); RNA, ribonucleic acid; ZDV, zidovudine.

with didanosine plus stavudine completed 4 weeks of therapy than did those receiving zidovudine plus lamivudine (94% versus 76%, *p* = 0.01). However, the higher rates of completion seen in participants using didanosine plus stavudine may have been due to the study protocol. This discouraged participants from changing to zidovudine plus lamivudine if they developed

tolerable adverse events, in an attempt to provide treatment against a possibly resistant strain. In contrast, those taking zidovudine plus lamivudine who experienced adverse events were encouraged to switch to didanosine plus stavudine to complete their treatment course. Among participants who completed 4 weeks of therapy, the percentage of participants reporting complete adherence during

TABLE 17 Assessment of completion of treatment

Study	Compliance	Intervention			
Garcia et al. 2005 ²⁸		Medium severity group (dual therapy, n = 141)		High severity group (triple therapy, n = 137)	
	Completed 6 months of follow-up and 28 days of PEP, n (%)	69 (48.9)		53 (38.7)	
	Completed 6 months of follow-up, interruption of PEP, n (%)	11 (7.8)		23 (16.8)	
	Abandoned follow-up but completed 28 days of PEP, n (%)	27 (19.2)		20 (14.6)	
	Abandoned follow-up and 28 days of PEP, n (%)	34 (24.1)		41 (30)	
	Total, n (%)	141 (100)		137 (100)	
Kahn et al. 2001 ²⁹		ZDV + 3TC (n = 351)	ZDV + 3TC + Nfv (n = 8)	ddl + d4T (n = 31)	ddl + d4T + Nfv (n = 5)
	Completed 4 weeks of assigned PEP, n (%)	267 (76)	6 (75)	29 (94)	5 (100)
	Completed 4 weeks but changed initial PEP, n (%)	3 (1)	0	0	0
	Discontinued PEP, n (%)	47 (13)	0	1 (< 1)	0
	Toxicity, n (%)	27 (8)	–	0	–
	Source not infected, n (%)	10 (3)	–	0	–
	Participant preference, n (%)	6 (2)	–	1 (< 1)	–
	Participant HIV infected, n (%)	4 (1)	–	0	–
Loutfy et al. 2008 ³⁰	Non-adherent (%)	76.0 high-risk group 66.7 unknown-risk group			
	28-day course completed (%)	23.9 high-risk group 33.2 unknown-risk group			
Shoptaw et al. 2008 ³¹	Non-adherent (%)	36			
	28-day course completed (%)	64			
n = 100					
3TC, lamivudine; d4T, stavudine; ddl, didanosine; Nfv, nelfinavir; ZDV, zidovudine.					

the 4 days before the clinic visit ranged from 78% to 84%.²⁹

The percentage of participants receiving Combivir and Kaletra who completed the course of PEP was 23.9% in the high-risk group and 33.2% in the unknown-risk group in the study of sexual assault survivors by Loutfy and colleagues.³⁰ This study found that health-care provider-perceived moderate or high participant anxiety at the initial visit, assault by a stranger or an assailant known to the participant less than 24 hours previously or absence of concomitant physical assault were predictors of completion. Reasons for discontinuation included adverse events (81.2%), interference with usual routine (42%), inability

to take time away from work, school or other commitments (21.7%) and reassessment of HIV risk (18.8%). In the study by Shoptaw and colleagues³¹ 86% of participants were dispensed the full 28-day supply of PEP and 64% of participants receiving zidovudine plus lamivudine completed treatment.

Assessment of toxicity

Toxicity results are shown in *Table 18*. In one study²⁸ 93% of the participants receiving three drugs reported at least one side effect, compared with 66% of the participants receiving two drugs ($p < 0.01$). Digestive discomfort was the most common side effect and was statistically more

TABLE 18 Assessment of toxicity

Study	Side effect			
Garcia et al. 2005 ²⁸		Medium severity group (dual therapy, <i>n</i> = 141)	High severity group (triple therapy, <i>n</i> = 137)	<i>p</i> -value
	Any referred intolerance, <i>n</i> (%)	76 (66)	106 (93)	<i>p</i> < 0.01
	Digestive intolerance, <i>n</i> (%)	70 (60)	101 (89)	<i>p</i> < 0.01
	Nausea, <i>n</i> (%)	62 (53)	93 (82)	<i>p</i> < 0.01
	Vomiting, <i>n</i> (%)	23 (20)	55 (48)	<i>p</i> < 0.01
	Dyspepsia, <i>n</i> (%)	20 (17)	40 (35)	<i>p</i> < 0.01
	Malaise, <i>n</i> (%)	26 (12)	60 (53)	<i>p</i> < 0.01
	Headache, <i>n</i> (%)	14 (12)	19 (17)	<i>p</i> = 0.35
	Fever, <i>n</i> (%)	–	6 (5)	<i>p</i> = 0.01
	Asthenia, <i>n</i> (%)	4 (3)	13 (11)	<i>p</i> = 0.02
	Dizziness, <i>n</i> (%)	7 (6)	20 (18)	<i>p</i> < 0.01
	Myalgia, <i>n</i> (%)	2 (2)	5 (4)	<i>p</i> = 0.28
	Cutaneous rash, <i>n</i> (%)	3 (3)	16 (14)	<i>p</i> < 0.01
	Nephrolithiasis, <i>n</i> (%)	–	9 (8)	<i>p</i> < 0.01
	Laboratorial abnormalities, <i>n</i> (%)	18 (16)	39 (33)	<i>p</i> < 0.01
	Premature interruption of PEP (all drugs), <i>n</i> (%)	12 (10)	35 (29)	<i>p</i> < 0.01
Kahn et al. 2001 ²⁹	Adverse events experienced:	Combined treatment groups		
<i>n</i> = 396	Nausea	52%		
	Fatigue	44%		
	Headache	24%		
	Diarrhoea	15%		
	Anorexia	12%		
Loutfy et al. 2008 ³⁰	Adverse events resulting in drug discontinuation, <i>n</i>	3		
<i>n</i> = 798	Participants reporting at least one adverse event, any grade, <i>n</i> (%)	265 (96.4)		
	Participants reporting at least one adverse event grade 2–4 (median 3, range 1–8), <i>n</i> (%)	212 (77.1)		
	Adverse events experienced:			
	Fatigue	58.5%		
	Nausea	49.5%		
	Diarrhoea	22.5%		
	Headache	20.7%		
	Mood changes	20.7%		
	Vomiting	20.4%		
	Stomach problems	16.4%		

common in participants who received three drugs (*p* < 0.01).²⁸ Severe side effects were seen in patients receiving three drugs and hospitalisation occurred in six cases, as a result of Stevens–Johnson syndrome (*n* = 1), nephrolithiasis (*n* = 2) and severe gastrointestinal symptoms (*n* = 3).²⁸ In

the San Francisco study²⁹ subjective toxicity for all study groups included nausea (52%), fatigue (44%), headache (24%), diarrhoea (15%) and anorexia (12%). Toxicity was the main reason for discontinuing treatment (*n* = 27, 8%).²⁹

TABLE 18 Assessment of toxicity (continued)

Study	Side effect	
Shoptaw et al. 2008 ³¹	Participants reporting at least one adverse event, <i>n</i> (%)	79 (79)
<i>n</i> = 100	Adverse events experienced:	
	Fatigue	48%
	Nausea	45%
	Diarrhoea	7%
	Headache	20%
	Stomach problems	11%
	Malaise	8%
	Insomnia	6%
	Difficulty in concentrating	4%
	Depression	4%

The most common adverse events experienced in both observational studies were also fatigue (58.5%³⁰ and 48%³¹) and nausea (49.5%³⁰ and 45%³¹). Loutfy and colleagues³⁰ report that the majority of sexual assault survivors (77.1%) reported at least one adverse event (median 3, range 1–8) of grade 2–4 severity [adverse events were graded 1–4 using the US National Institute of Allergy and Infectious Diseases standardised toxicity grading system (grade 4 most severe)]. Three participants discontinued PEP because of adverse events, but no further details were given. The authors reported that participants who experienced vomiting were less likely to complete PEP than those who did not (OR 0.27, 95% CI 0.12–0.6, $p = 0.0007$).³⁰ Shoptaw and colleagues³¹ describe one participant requiring hospitalisation for suicide ideation, but this was not thought to be as a result of the study medication.

Summary of adverse events of PEP for non-occupational exposure to HIV

- There is limited evidence in terms of quantity and quality, with two comparative studies and two prospective observational studies reporting adverse events and/or treatment completion rates for non-occupational PEP for HIV.
- One comparative study reported a significantly higher degree of toxicity and therapy discontinuation among sexual assault victims

taking a three-drug regimen compared with those taking a two-drug therapy. Digestive discomfort was the most common side effect and was significantly higher in participants who received three drugs. PEP therapy was completed by 68% of participants receiving dual therapy and 53% of those receiving triple therapy.

- A second comparative study reported statistically higher completion rates among participants taking didanosine plus stavudine compared with those taking zidovudine plus lamivudine, although this may have been due to the study protocol. Complete adherence at 4 weeks was 78% overall, ranging from 40% to 79% for different drug combinations. Toxicity was the main reason for discontinuation of treatment, with nausea and fatigue being the most common side effects.
- One prospective observational study reported low completion of treatment rates, with 23.9% in the high-risk group and 33.2% in the unknown-risk group completing the course of PEP. The most common adverse events experienced by the participants were fatigue and nausea.
- A second prospective observational study also found that fatigue and nausea were the most commonly experienced adverse events and that the majority of participants experienced adverse events. PEP therapy was completed by 64% of participants.

Chapter 7

Discussion

Statement of principal findings

Clinical effectiveness

One cohort study²¹ met the inclusion criteria for the review of clinical effectiveness.

This study had methodological limitations and limitations in the quality of the reporting: it was unclear how the sample was selected, whether the sample size was adequate and whether the study is generalisable beyond the specific cohort among which it was conducted. Dropouts are reported but are not included in the analysis and there is no blind assessment of outcomes. The authors do report objective eligibility criteria and the groups are comparable at baseline.

The study reported seroconversion to HIV, drug use and risk behaviours in a group receiving non-occupational PEP for HIV. The participants in the study were a Brazilian cohort of 200 high-risk MSM.

Seroincidence in the cohort as a whole (2.9 per 100 person-years) was very similar to that expected by the study authors in this population (3.1 per 100 person-years, $p > 0.97$), despite the seroconversion to HIV being 1 out of 68 in the PEP group and 10 out of 132 in the group not receiving PEP. The study reported that, on average, high-risk sexual activities declined over time for both PEP and non-PEP users. The study authors concluded that a public health PEP programme would not have a major impact on HIV transmission in this population.

Cost-effectiveness

Four studies^{22–25} met the inclusion criteria for the review of cost-effectiveness.

The methodological quality of the cost-effectiveness studies was mixed, with each employing well-defined questions, the appropriate perspective, appropriate methods of analysis and clear sensitivity analyses. Each study is, however, limited by the unknown effectiveness of the intervention,

both the dual/triple drug regimen and the use of PEP in a non-occupational exposure patient group.

All four studies evaluated 28 days of PEP post non-occupational exposure to HIV, but full details are not given. Two of the studies considered hypothetical cohorts.^{22,24}

Results from the studies suggest that PEP following non-occupational exposure to HIV is cost saving for men who have unprotected receptive anal intercourse with men, whether the source partner is known to be HIV positive or not; heterosexuals after unprotected receptive anal intercourse; and intravenous drug users sharing needles with a known HIV-positive person.

PEP following non-occupational exposure to HIV was cost-effective for all male–male intercourse (unprotected receptive and insertive anal intercourse, unprotected receptive oral sex and ‘other’). PEP following non-occupational exposure to HIV was possibly cost-effective for intravenous drug users and high-risk women.

In general, sensitivity analyses did not greatly alter the base-case findings.

In summary, although the results of the studies are consistent and suggest that non-occupational PEP may be cost-effective, the results should be treated with caution. It may not be appropriate to make assumptions that the same conditions exist in a non-occupational setting as in an occupational setting and the generalisability to the UK of studies conducted in the US and France is questionable as sexual behaviour and HIV incidence may not be similar.

Adverse events

Additional studies were sought to supply further information on adverse events. The evidence was limited in terms of quantity and quality, with two comparative studies and two observational studies reporting adverse events and/or treatment completion rates for non-occupational PEP.

One comparative study²⁸ reported a significantly higher degree of toxicity and therapy discontinuation among rape victims taking a three-drug regimen compared with those taking a two-drug regimen. Completion of PEP therapy was low in both dual and triple therapy. A second comparative study²⁹ reported statistically higher completion rates among participants taking didanosine plus stavudine compared with those taking zidovudine plus lamivudine, although this may have been due to the study protocol.

One prospective observational study reported low rates of completion of treatment, with 23.9% in the high-risk group and 33.2% in the unknown-risk group completing the course of PEP. The most common adverse events experienced by the participants were fatigue and nausea.³⁰ A second prospective observational study³¹ also found that fatigue and nausea were the most commonly experienced adverse events and that the majority of participants experienced adverse events. PEP therapy was completed by 64% of participants.

Strengths and limitations of the assessment

The review has certain strengths:

- It is independent of any vested interest.
- The review brings together the evidence for the clinical effectiveness and the cost-effectiveness of non-occupational PEP for HIV and adverse event data by applying consistent methods of critical appraisal, presentation and transparency.
- The review was guided by the principles of undertaking a systematic review. Before undertaking the review the methods were set out in a research protocol (Appendix 1) and this was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods employed to undertake the different stages of the review.
- An advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.

In contrast, there were certain limitations placed upon the review:

- The number and type of studies available for inclusion in the review was limited. No RCTs

were identified and the economic evaluations were not conducted in the UK.

- Synthesis of the included studies was through narrative review. Because of the limitations of the literature, meta-analysis was not possible.
- Time and resource constraints for this short report together with the lack of effectiveness data for the use of non-occupational PEP for HIV prevented the development of an economic evaluation and so the assessment of cost-effectiveness was limited to a systematic review of existing cost-effectiveness studies.

Other relevant issues

- Only one cohort study met the systematic review inclusion criteria for the assessment of the clinical effectiveness of non-occupational PEP for HIV. The study design and relatively small number of seroconversions do not allow conclusions to be made about the effectiveness of PEP in preventing infection. However, results suggest that PEP made no difference to the expected HIV seroconversion rate for a high-risk HIV-seronegative homosexual male cohort in Rio de Janeiro, Brazil.
- One of the issues of concern is that PEP may be relied upon as a primary form of HIV prevention and will fail to reduce or may actually increase high-risk exposures because it is perceived to fully prevent virus transmission. In the included study PEP was not associated with an increase in reported high-risk behaviour. Reported high-risk behaviour declined slightly for the cohort as a whole but these results should be viewed with caution because of the potential for under-reporting of self-reported high-risk activities.
- Various assumptions were made in the studies considering the cost-effectiveness of non-occupational PEP for HIV. Of most concern is the use of the estimate of effectiveness from the occupational PEP setting, which is based on the assumption that the same conditions exist in the non-occupational setting as in the occupational setting.
- Other assumptions are acknowledged in the studies. For example, in the study conducted in France²⁵ compliance could only be estimated from the database for 47% of PEP prescriptions and so overall compliance was estimated at 0.75. However, overestimation of compliance would improve the cost-effectiveness ratio. There were no available data for lifetime HIV/AIDS costs in France and so these were

estimated by the authors. The model did not take into account the possibility that some patients seeking PEP may continue at-risk behaviour. The study also did not consider PEP adverse events. The authors state that taking these into account would further reduce the cost-effectiveness ratio of the overall PEP programme. The number of HIV infections predicted by the model was higher than that actually seen; however, HIV serology 6 months after PEP initiation was only available for 18% of patients and so the authors suggest that the true number of PEP failures may be higher.

- Pinkerton and colleagues²⁴ acknowledge that there are a number of issues of uncertainty in their study of non-occupational PEP in US metropolitan statistical areas. The results were most sensitive to the effectiveness of PEP and the per-exposure transmission probability for receptive anal intercourse. The lack of evidence of effectiveness of PEP for non-occupational exposures to HIV means that the results should be interpreted with caution. With regard to per-exposure transmission probabilities, the probabilities used in this study did not take into account variations in infectiousness over the

course of HIV disease, interpersonal variability or potential reductions from the use of highly active antiretroviral therapy.

- Pinkerton and colleagues conclude from their hypothetical cohort study²² that, from an economic effectiveness perspective, PEP should be restricted to partners of infected persons (e.g. serodiscordant couples), patients reporting unprotected receptive anal intercourse (including condom breakage) and possibly cases in which there is a substantial likelihood that the partner is infected.
- Various uncertainties, such as HIV prevalence rates, per-exposure transmission rates, completion of treatment and the impact of the number of pills prescribed daily, HIV status of partner and incomplete suppression of virus, some of which may vary in different locales, must be considered when modelling cost-effectiveness. Also, the potential for PEP programmes to incorporate risk counselling and the opportunity for intensive prevention counselling at the time of medication with PEP to influence future exposures must also be considered.

Chapter 8

Conclusions

Non-occupational PEP for HIV

It is not possible to draw conclusions on the clinical effectiveness of non-occupational PEP for HIV because of the limited evidence in terms of the quantity and quality of studies. Only one small cohort study was identified that met the inclusion criteria for the systematic review. Cost-effectiveness has been assessed in four economic evaluations using evidence on effectiveness taken from the use of PEP in the occupational setting. Results are consistent across studies and suggest that non-occupational PEP may be cost-effective, especially in certain population subgroups. Although the studies have been conducted in an appropriate way and have internal validity in terms of the structure of the model and plausible results, the assumptions and data sources mean that the results should be treated with caution. The generalisability to the UK of studies conducted in the US and France is not clear. Although transmission risks for specific sexual practices are likely to be the same, sexual behaviour and HIV incidence may not be similar and local costs may be different.

Research priorities

The most important research need is a comparative study to establish the effectiveness of using non-occupational PEP compared with not using PEP,

preferably within the UK using the currently recommended intervention. Data are also needed on HIV prevalence, seroconversion rates, per-exposure transmission, adverse events, treatment compliance rates, viral resistance rates, high-risk behaviours and effects of intensive counselling in different population groups. Some of these issues will be addressed by the NONOPEP project, which is an MRC-funded surveillance programme of PEP for non-occupational exposure to HIV. The study aims to describe current PEP prescribing practices and the demographic and exposure characteristics of individuals presenting for PEP; to evaluate the problems associated with taking antiretroviral therapy such as adverse events; to assess whether seroconversion has occurred and within which groups; and to contribute to a wider European study on the efficacy of PEP in the non-occupational setting. Data have been collected on individuals by means of a paper questionnaire, submitted to the Communicable Disease Surveillance Centre at baseline (presentation at clinic) and at three follow-up intervals (4 weeks, 3 months and 6 months). This study is due for submission shortly. Although there are challenges in conducting this research because of factors such as self-referral and follow-up of participants and self-reported outcomes, data generated from this study will be useful for informing any future economic modelling of the cost-effectiveness of non-occupational PEP in the UK.



Acknowledgements

Various people contributed to the project, including members of the advisory group who commented on the protocol and/or draft of the report, and we are grateful for their help: Paul Benn, Consultant in HIV/Genitourinary Medicine, Camden Primary Care Trust; Andrew Clegg, Professor and Director of SHTAC, WIHRD, University of Southampton; Martin Fisher, Consultant Physician in HIV/Genitourinary Medicine, Brighton and Sussex University Hospitals NHS Trust; Elizabeth Hodson, Information Assistant, WIHRD, University of Southampton; Alison Price, Information Scientist, WIHRD, University of Southampton; Jonathan Shepherd, Principal Research Fellow, SHTAC, WIHRD, University of Southampton; Kim Wherry, Finance Officer, WIHRD, University of Southampton.

Contribution of authors

Jackie Bryant was responsible for protocol development, the screening of the clinical effectiveness studies for inclusion, analysis and

interpretation of the clinical effectiveness studies, the screening of the cost-effectiveness studies for inclusion, analysis and interpretation of the cost-effectiveness studies, writing the report and project management and report editing. Susan Hird was responsible for protocol development, the screening of the clinical effectiveness studies for inclusion, data extraction and critical appraisal of the clinical effectiveness studies, analysis and interpretation of the clinical effectiveness studies, screening of the cost-effectiveness studies for inclusion, data extraction and critical appraisal of the cost-effectiveness studies, analysis and interpretation of the cost-effectiveness studies and report writing. Louise Baxter was responsible for the screening of the clinical effectiveness studies for inclusion, data extraction and critical appraisal of the clinical effectiveness studies, analysis and interpretation of the clinical effectiveness studies, the screening of the cost-effectiveness studies for inclusion, data extraction and critical appraisal of the cost-effectiveness studies, analysis and interpretation of the cost-effectiveness studies and report writing.



References

1. Health Protection Agency. *General information: HIV and AIDS*. URL: www.hpa.org.uk/infections/topics_az/hiv_and_sti/hiv/general.htm. Accessed 26 November 2007.
2. McCarthy GA, Mercey D. The changing clinical features of HIV-1 infection in the UK. *Commun Dis Rep Rev* 1994;**4**:R53–8.
3. National Institute of Allergy and Infectious Diseases. *HIV infection and AIDS: an overview*. URL: www.niaid.nih.gov/factsheets/hivinf.htm. Accessed 26 November 2007.
4. Health Protection Agency. *The national CD4 surveillance scheme*. URL: www.hpa.org.uk/infections/topics_az/hiv_and_sti/hiv/epidemiology/cd4.htm. Accessed 26 November 2007.
5. The UK Collaborative Group for HIV and STI Surveillance. *A complex picture. HIV and other sexually transmitted infections in the United Kingdom: 2006*. URL: www.hpa.org.uk/publications/2006/hiv_sti_2006/pdf/a_complex_picture_2006_last.pdf. Accessed 26 November 2007.
6. Evans B, McHenry A, Mortimer J. *HIV and AIDS in the UK. An epidemiological review: 2000*. London: Communicable Disease Surveillance Centre; 2001.
7. Martin NV, Almeda J, Casabona J. Effectiveness and safety of HIV post-exposure prophylaxis after sexual, injecting-drug-use or other non-occupational exposure (Protocol). *Cochrane Database Syst Rev* 2005;**2**:CD005273.
8. WHO and UNAIDS. *AIDS epidemic update: December 2006*. Geneva: UNAIDS; 2006.
9. The UK Collaborative Group for HIV and STI Surveillance. *Testing times. HIV and other sexually transmitted infections in the United Kingdom*. London: Health Protection Agency, Centre for Infections; 2007.
10. Fisher M, Benn P, Evans B, Pozniak A, Jones M, Maclean S, *et al*. UK guideline for the use of post-exposure prophylaxis for HIV following sexual exposure. *Int J STD AIDS* 2006;**17**:81–92.
11. Giele CM, Maw R, Carne CA, Evans BG, British Co-operative Clinical Group of the Medical Society for the Study of Venereal Diseases. Post-exposure prophylaxis for non-occupational exposure to HIV: current clinical practice and opinions in the UK. *Sex Transm Infect* 2002;**78**:130–2.
12. Young TN, Arens FJ, Kennedy GE, Laurie JW, Rutherford GW. Antiretroviral post-exposure prophylaxis (PEP) for occupational HIV exposure. *Cochrane Database Syst Rev* 2007;**1**:CD002835.
13. Department of Health (Expert Advisory Group on AIDS). *HIV post-exposure prophylaxis: guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS*. London: Department of Health; 2004.
14. Chief Medical Office. *Update to HIV post-exposure prophylaxis (PEP) guidance from the Expert Advisory Group on AIDS (EAGA) following the recent recall of Viracept (gateway reference 8562)*. London: Department of Health; 2007.
15. Day S, Mears A, Bond K, Kulasegaram R. Post-exposure HIV prophylaxis following sexual exposure: a retrospective audit against recent draft BASHH guidance. *Sex Transm Infect* 2006;**82**:236–7.
16. Roland ME, Neilands TB, Krone MR, Katz MH, Franes K, Grant RM, *et al*. Seroconversion following nonoccupational postexposure prophylaxis against HIV. *Clin Infect Dis* 2005;**41**:1507–13.
17. Richens J, Edwards SG, Sadiq ST. Can the promotion of post-exposure prophylaxis following sexual exposure to HIV (PEPSE) cause harm? *Sex Transm Infect* 2005;**81**:190–1.
18. Spitzer WO, Lawrence V, Dales R, Hill G, Archer MC, Clark P. Links between passive smoking and disease: a best evidence synthesis. *Clin Invest Med* 1990;**13**:17–42.
19. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *Br Med J* 1996;**313**:275–83.
20. 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).
21. Schechter M, do Lago RF, Mendelsohn AB, Moreira RI, Moulton LH, Harrison LH, *et al*. Behavioral impact, acceptability, and HIV incidence among homosexual men with access to postexposure chemoprophylaxis for HIV. *J Acquir Immune Defic Syndr* 2004;**35**:519–25.

22. Pinkerton SD, Holtgrave DR, Bloom FR. Cost-effectiveness of post-exposure prophylaxis following sexual exposure to HIV. *AIDS* 1998;**12**:1067–78.
23. Pinkerton SD, Martin JN, Roland ME, Katz MH, Coates TJ, Kahn JO. Cost-effectiveness of postexposure prophylaxis after sexual or injection-drug exposure to human immunodeficiency virus. *Arch Intern Med* 2004;**164**:46–54.
24. Pinkerton SD, Martin JN, Roland ME, Katz MH, Coates TJ, Kahn JO. Cost-effectiveness of HIV postexposure prophylaxis following sexual or injection drug exposure in 96 metropolitan areas in the United States. *AIDS* 2004;**18**:2065–73.
25. Herida M, Larsen C, Lot F, Laporte A, Desenclos JC, Hamers FF. Cost-effectiveness of HIV post-exposure prophylaxis in France. *AIDS* 2006;**20**:1753–61.
26. Centers for Disease Control and Prevention (CDC). Case-control study of HIV seroconversion in health care workers after percutaneous exposure to HIV-infected blood – France, United Kingdom, and United States, January 1988–August 1994. *MMWR Morb Mortal Wkly Rep* 1995;**44**:929–33.
27. Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, *et al.* A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. *N Engl J Med* 1997;**337**:1485–90.
28. Garcia MT, Figueiredo RM, Moretti ML, Resende MR, Bedoni AJ, Papaioordanou PM. Postexposure prophylaxis after sexual assaults: a prospective cohort study. *Sex Transm Dis* 2005;**32**:214–19.
29. Kahn JO, Martin JN, Roland ME, Bamberger JD, Chesney M, Chambers D, *et al.* Feasibility of postexposure prophylaxis (PEP) against human immunodeficiency virus infection after sexual or injection drug use exposure: the San Francisco PEP Study. *J Infect Dis* 2001;**183**:707–14.
30. Loutfy MR, Macdonald S, Myhr T, Husson H, Du Mont J, Balla S, *et al.* Prospective cohort study of HIV post-exposure prophylaxis for sexual assault victims. *Antivir Ther* 2008;**13**:87–95.
31. Shoptaw S, Rotheram-Fuller E, Landovitz RJ, Wang J, Moe A, Kanouse DE, *et al.* Non-occupational post exposure prophylaxis as a biobehavioral HIV-prevention intervention. *AIDS Care* 2008;**20**:376–81.

Appendix I

Review methods from the research protocol

The a priori methods used for the review are outlined below. The sources of information used are outlined in Appendix 2.

Study inclusion

Specific inclusion criteria will be defined. The full literature search results will be screened by one reviewer and checked by a second reviewer to identify all citations that may meet the inclusion criteria. Full manuscripts of all selected citations will be retrieved and assessed by two reviewers against the inclusion criteria. Disagreements over study inclusion will be resolved by consensus or if necessary by arbitration by a third reviewer.

The planned inclusion/exclusion criteria for the systematic review are as follows.

Population

Humans with non-occupational exposure to HIV. This may be by:

- unprotected sexual exposure (oral, vaginal, anal), either voluntary or rape, with an HIV-infected partner or partner of unknown HIV status
- exposure to a needle contaminated by a known or potentially infected substance in a non-occupational setting.

Intervention

Any antiretroviral drug regimen administered as PEP for a short period (28 days) to HIV-negative people potentially exposed to HIV through unprotected sexual contact or use of a potentially contaminated needle or potentially contaminated biological fluid.

Comparator

- No intervention.
- Group not receiving PEP.
- A different PEP regimen.

Outcomes

- HIV seroconversion frequency.
- Adverse effects and complications of PEP.

- Adherence to PEP.
- Health-related quality of life.
- Costs or some measure of cost-effectiveness.

Design

- RCT, CCT, cohort study or case-control study.
- Cost-effectiveness/utility studies.
- Descriptive studies with no control group will be excluded.

Data extraction

The extraction of study findings will be conducted by two reviewers using a predesigned and piloted data extraction form to avoid any errors. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

Quality assessment

The methodological quality of included studies will be assessed using formal tools specific to the design of the study and focusing on possible sources of bias. Quality assessment of RCTs will be conducted using criteria developed by the NHS Centre for Reviews and Dissemination; observational studies will be assessed using criteria developed by Spitzer *et al.*¹⁸ Quality assessment of economic evaluations will be conducted using a checklist adapted from those developed by Drummond and Jefferson¹⁹ and Philips *et al.*²⁰ Study quality will be assessed by two reviewers. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration involving a third reviewer.

Data synthesis

The methods of data synthesis will be determined by the nature of the studies identified through searches and included in the review. Quantitative synthesis of results, for example meta-analysis, will be considered if there are several high-quality studies of the same design and sources of heterogeneity will be investigated by subgroup analyses if applicable. The results of any included studies suitable for quantitative synthesis will also

be summarised in a narrative form along with a narrative synthesis of the results from studies for which quantitative synthesis is not possible. All results will also be tabulated.

Economic evaluation

When appropriate, and if time and resources allow, an economic model will be devised by adapting an existing cost-effectiveness model or constructing a new one using the best available evidence to determine cost-effectiveness in a UK setting. Data on resource use and costs will be taken from the published literature and from NHS sources

when appropriate and available. The perspective of the economic analysis will be that of the NHS and Personal Social Services. Effectiveness data will be taken from published studies and used in conjunction with other relevant data (e.g. resource use, unit costs) to populate the model to obtain measures of cost-effectiveness. If available, quality of life information will be obtained from the literature or other sources to calculate cost-utility estimates in terms of cost per QALY. The robustness of the results to the assumptions made in the model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

Appendix 2

Sources of information, including databases searched and search terms

The following search strategy was used in Ovid MEDLINE(R) from 1950 to November Week 2 2007 and adapted for other databases. Results were obtained for English language and non-English language papers. Bibliographies of related papers were assessed for relevant studies. *Tables 19 and 20* outline the databases and issues/dates searched. *Figures 1 and 2* provide flowcharts of the clinical effectiveness and cost-effectiveness studies respectively.

The search strategy used for non-occupational PEP was as follows:

- | | |
|--|--|
| <ol style="list-style-type: none"> 1 exp HIV/ (59429) 2 exp hiv-1/ (46463) 3 exp hiv-2/ (3192) 4 exp HIV Infections/ (169604) 5 exp hiv antibodies/ (7992) 6 (hiv or human immunodeficiency virus\$.ti,ab. (140649) 7 exp Acquired Immunodeficiency Syndrome/ (68119) 8 or/1–7 (214277) Population set 1 9 (post?exposure prophylax\$or PEP or nPEP or PEPSE).ti,ab. (4037) 10 post-exposure prophylax\$.ti,ab. (475) 11 post exposure prophylax\$.ti,ab. (475) 12 postexposure prophylax\$.ti,ab. (483) 13 or/9–12 (4402) Population set 2 14 (highly active antiretroviral therapy or haart).ti,ab. (7126) | <ol style="list-style-type: none"> 15 exp antiviral agents/ (210658) 16 exp anti-retroviral agents/ (40013) 17 exp anti-hiv agents/ (34216) 18 exp hiv fusion inhibitors/ (438) 19 exp hiv integrase inhibitors/ (470) 20 exp hiv protease inhibitors/ (7818) 21 (combivir or zidovudine or lamivudine or kaletra or lopinavir or ritonavir).ti,ab. (9741) 22 or/14–21 (215377) Intervention 1 set 1 23 non?occupational.ti,ab. (506) 24 nonoccupational.ti,ab. (506) 25 non occupational.ti,ab. (671) 26 or/23–25 (1169) Population set 3 27 Occupational Exposure/ (28336) Population set 4 28 8 and 13 (514) Combined population set 5 29 28 and 22 (345) PEP population with intervention 30 29 not 27 (212) Non-occupational set 31 limit 30 to (humans and english language) (182) Non-occupational set English language download A 32 30 not 31 (30) Non-occupational set non-English download B 33 29 not 30 (133) Occupational set all languages download C 34 from 31 keep 1–182 (182) 35 from 32 keep 1–30 (30) 36 from 33 keep 1–133 (133) |
|--|--|

The search strategies were translated to run in the databases listed above. Full search strategies are available upon request.

TABLE 19 *Clinical effectiveness and cost-effectiveness searches*

Databases searched	Clinical effectiveness: issues or dates searched	Cost-effectiveness: issues or dates searched
Cochrane Library – CDSR	Issue 4 2007; searched 13 September 2007	
Cochrane Library – CENTRAL	Issue 4 2007	
Ovid MEDLINE(R)	1950–November Week 2 2007	1950–November Week 2 2007
EMBASE	1980–2007 Week 49	1980–2007 Week 49
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	12 December 2007	12 December 2007
DARE (Database of Abstracts of Reviews of Effectiveness)	12 December 2007	
HTA database (on CRD databases)	12 December 2007	
NRR (National Research Register)	12 December 2007	
ClinicalTrials.gov (http://clinicaltrials.gov/)	12 December 2007	
NHS Economic Evaluations Database 2005–2007		12 December 2007

TABLE 20 *Adverse events searches*

Databases	Years/dates searched
Ovid MEDLINE(R)	1996–September Week 3 2007; searched 2 October 2007
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	28 September 2007
EMBASE	1996–2007 Week 38

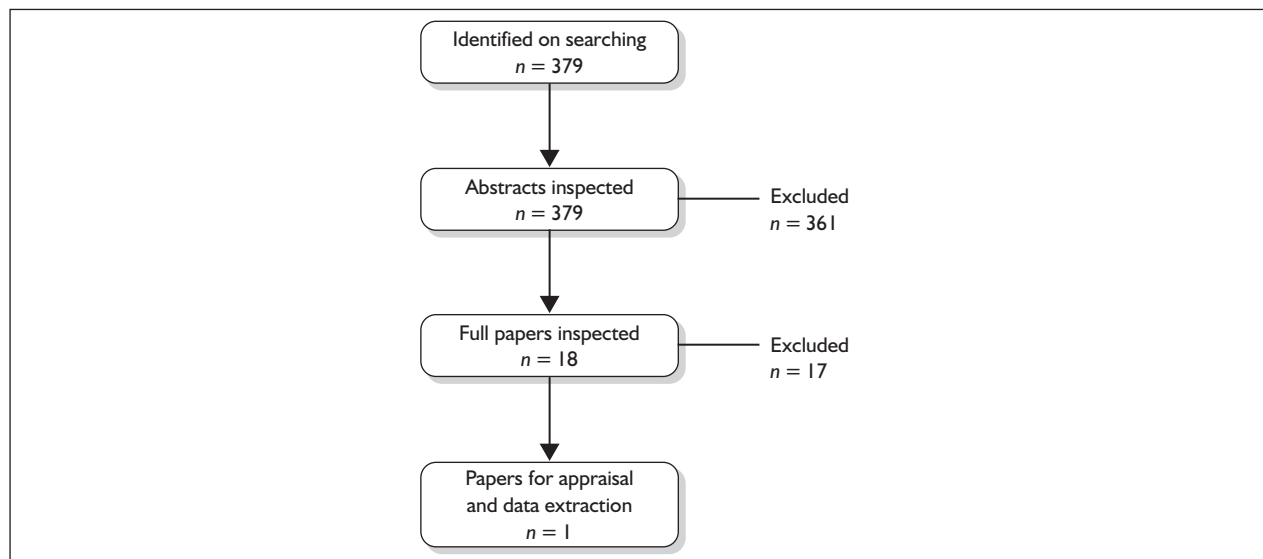


FIGURE 1 Flowchart of clinical effectiveness studies.

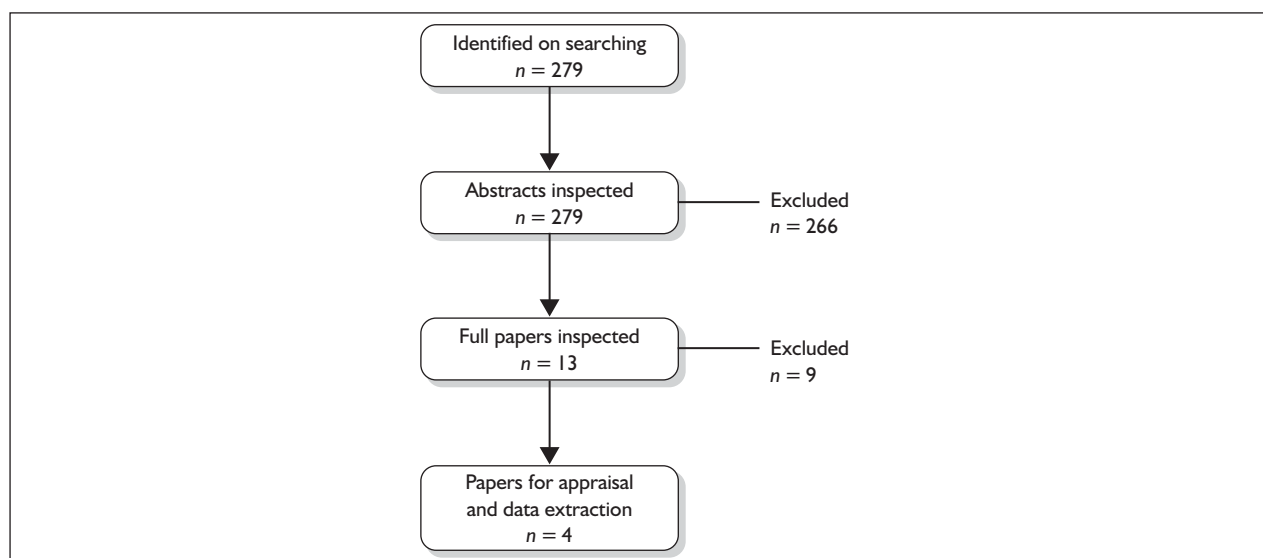


FIGURE 2 Flowchart of cost-effectiveness studies.

Appendix 3

List of excluded studies

Clinical effectiveness studies

Bernasconi E, Jost J, Ledergerber B, Hirschel B, Francioli P, Sudre P. Antiretroviral prophylaxis for community exposure to the human immunodeficiency virus in Switzerland, 1997–2000. *Swiss Med Wkly* 2001;**131**:433–7. (Questionnaire.)

Braitstein P, Chan K, Beardsell A, McLeod A, Montaner JS, O'Shaughnessy MV, *et al.* Prescribing practices in a population-based HIV postexposure prophylaxis program. *AIDS* 2002;**16**:1067–70. (No comparison group and prescribing practice as outcome.)

Luque A, Hulse S, Wang D, Shahzad U, Tanzman E, Antenozzi S, *et al.* Assessment of adverse events associated with antiretroviral regimens for postexposure prophylaxis for occupational and nonoccupational exposures to prevent transmission of human immunodeficiency virus. *Infect Control Hosp Epidemiol* 2007;**28**:695–701. (Chart review.)

Martin JN, Roland ME, Neilands TB, Krone MR, Bamberger JD, Kohn RP, *et al.* Use of postexposure prophylaxis against HIV infection following sexual exposure does not lead to increases in high-risk behavior. *AIDS* 2004;**18**:787–92. (No comparison group.)

Meel BL. HIV/AIDS post-exposure prophylaxis (PEP) for victims of sexual assault in South Africa. *Med Sci Law* 2005;**45**:219–24. (No comparison group.)

O'Sullivan BG, Levy MH, Dolan KA, Post JJ, Barton SG, Dwyer DE, *et al.* Hepatitis C transmission and HIV post-exposure prophylaxis after needle- and syringe-sharing in Australian prisons. *Med J Aust* 2003;**178**:546–9. (Study design.)

Poynten IM, Smith DE, Cooper DA, Kaldor JM, Grulich AE. The public health impact of widespread availability of nonoccupational postexposure prophylaxis against HIV. *HIV Med* 2007;**8**:374–81. (No comparison group.)

Puro V, Soldani F, De Carli G, Lazarevic Z, Mattioli F, Ippolito G, *et al.* Drug-induced aminotransferase alterations during antiretroviral HIV post-exposure prophylaxis. *AIDS* 2003;**17**:1988–90. (Occupational exposure.)

Puro V, De Carli G, Orchi N, Palvarini L, Chiodera A, Fantoni M, *et al.* Short-term adverse effects from and discontinuation of antiretroviral post-exposure prophylaxis. *J Biol Regul Homeost Agents* 2001;**15**:238–42. (Includes health-care workers.)

Rabaud C, Bevilacqua S, Beguinot I, Dorvaux V, Schuhmacher H, May T, *et al.* Tolerability of postexposure prophylaxis with zidovudine, lamivudine, and nelfinavir for human immunodeficiency virus infection. *Clin Infect Dis* 2001;**32**:1494–5. (Included occupational exposure.)

Rabaud C, Burty C, Grandidier M, Christian B, Penalba C, Beguinot I, *et al.* Tolerability of postexposure prophylaxis with the combination of zidovudine-lamivudine and lopinavir-ritonavir for HIV infection. *Clin Infect Dis* 2005;**40**:303–5. (No comparator.)

Rey D, Partisani M, Hess-Kempf G, Krantz V, Priester M, Cheneau C, *et al.* Tolerance of a short course of nevirapine, associated with two nucleoside analogues, in postexposure prophylaxis of HIV. *J Acquir Immune Defic Syndr* 2004;**37**:1454–6. (Chart review.)

Roland ME, Neilands TB, Krone MR, Katz MH, Franes K, Grant RM, *et al.* Seroconversion following nonoccupational postexposure prophylaxis against HIV. *Clin Infect Dis* 2005;**41**:1507–13. (No comparison group.)

Schechter M. HIV vaccine evaluation center in Rio de Janeiro, Brazil. *Vaccine* 2002;**20**:1909–11. (Note.)

Sonder G, Regez R, Brinkman K, Prins J, Mulder J, Coutinho R, *et al.* Postexpositiebehandeling tegen HIV buiten het ziekenhuis in Amsterdam, januari-december 2000. *Ned Tijdschr Geneesk* 2002;**146**:629–33. (Non-English.)

Timset F, Maillard A, Spindler E, Taquin Y, Deniaud, Ferchal F, *et al.* Traitement antirétroviral prophylactique après exposition sexuelle au VIH: 93 cas. *Ann Dermatol Venerol* 2002;**129**:866–9. (Non-English.)

Winston A, McAllister J, Amin J, Cooper DA, Carr A. The use of a triple nucleoside-nucleotide regimen for nonoccupational HIV post-exposure prophylaxis. *HIV Med* 2005;**6**:191–7. (Case note review.)

Cost-effectiveness studies

Allen UD, Read S, Gafni A. Zidovudine for chemoprophylaxis after occupational exposure to HIV-infected blood: an economic evaluation. *Clin Infect Dis* 1992;**14**:822–30. (Occupational exposure.)

Barham L, Lewis D, Latimer N. One to one interventions to reduce sexually transmitted infections and under the age of 18 conceptions: a systematic review of the

economic evaluations. *Sex Transm Infect* 2007;**83**:441–6. (Not PEP.)

Creese A, Floyd K, Alban A, Guinness L. Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence [erratum appears in *Lancet* 2002;**360**:880]. *Lancet* 2002;**359**:1635–43. (Not PEP.)

Forst LS, Fletcher B. HIV prophylaxis for health care workers. *J Occup Environ Med* 1997;**39**:1212–19. (Occupational exposure.)

Greub G, Gallant S, Zurn P, Vannotti M, Burgisser P, Francioli P, *et al.* Spare non-occupational HIV post-exposure prophylaxis by active contacting and testing of the source person. *AIDS* 2002;**16**:1171–6. (Not an economic evaluation.)

Hornberger J. A systematic review of cost–utility analyses in HIV/AIDS: implications for public policy. *Med Decis Making* 2007;**27**:789–821. (Not an economic evaluation of PEP.)

Marin MG, Van LJ, Yee A, Bonner E, Glied S. Cost-effectiveness of a post-exposure HIV chemoprophylaxis program for blood exposures in health care workers. *J Occup Environ Med* 1999;**41**:754–60. (Occupational exposure.)

Pinkerton SD, Holtgrave DR, Pinkerton HJ. Cost-effectiveness of chemoprophylaxis after occupational exposure to HIV. *Arch Intern Med* 1997;**157**:1972–80. (Occupational exposure.)

Scheid DC, Hamm RM, Stevens KW. Cost-effectiveness of human immunodeficiency virus postexposure prophylaxis for healthcare workers. *Pharmacoeconomics* 2000;**18**:355–68. (Occupational exposure.)

Appendix 4

Data extraction of clinical effectiveness study

Reference and design	Intervention	Participants	Outcome measures
<p>Author: Schechter <i>et al.</i>²¹</p> <p>Year: 2004</p> <p>Country: Brazil</p> <p>Study design: cohort study</p> <p>Number of centres: one</p> <p>Funding: GlaxoSmithKline, Conselho Nacional de Desenvolvimento Científico e Tecnológico, National Institute of Allergy and Infectious Diseases (research career award), Fogarty International Center (grant)</p>	<p>Intervention: postexposure prophylaxis (PEP): zidovudine 300 mg and lamivudine 150 mg orally, fixed dose combination tablet, twice daily for 28 days</p> <p>Initial 4-day supply of zidovudine and lamivudine to be taken post eligible exposure; additional 24-day supply provided for exposures deemed eligible by study personnel</p> <p>Subjects were instructed to begin taking the study regimen immediately after eligible exposures and in no circumstances > 48 hours after the exposure</p> <p>Control: no PEP</p>	<p>Number of participants: 200 enrolled in the study</p> <p>Intervention: 68 took PEP at least once; control: 132</p> <p>Sample attrition/dropout: 94% ($n = 187$) followed up for 24 months or until seroconversion; two excluded immediately because they had no follow-up data; seven (53.9%) had last interview at 6 months; two (15.4%) had last interview at 12 months; four (30.8%) had last interview at 18 months</p> <p>Inclusion criteria for study entry: male gender, confirmed HIV seronegativity, reported homosexual or bisexual behaviour, sexually active, defined as anticipated sexual activity in the next 6 months, willingness to use PEP after high-risk exposures, age 18–35 years</p> <p>Exclusion criteria for study entry: high-risk exposures for HIV in the previous 48 hours, anaemia, leukopenia or hepatic enzyme abnormalities at baseline, history of allergy or intolerance to any of the study medications</p> <p>Characteristics of participants: the cohort was recruited from former participants of an HIV seroconversion study conducted among high-risk men who have sex with men</p> <p>Intervention: see baseline characteristics table below</p> <p>Control: 132 did not take PEP – 86 did not take PEP despite reporting at least one instance of high-risk behaviour, 46 denied any high-risk behaviours during the study period</p> <p>Study participants were recruited from a well-characterised HIV incidence study cohort. The authors took the relationships between follow-up time, previously identified risk factors for new HIV infection and HIV incidence and applied them to the current cohort to produce an expected number of incident HIV cases in the absence of PEP</p> <p>Participants who did not start PEP were instructed to return every 6 months for an evaluation</p>	<p>Outcomes: reported behaviour, PEP utilisation, adverse events, incident HIV infection</p> <p>Observed and expected incidences were compared</p> <p>Method of assessing outcomes: detailed history taken at each visit, physical examination with focus on the presence of sexually transmitted diseases. Laboratory evaluation to assess for potential medication toxicity at baseline, 12- and 24-month visits. Participants to report symptoms consistent with severe toxicity. For participants who seroconverted during the study and who previously used PEP, polymerase chain reaction was performed on blood samples at the beginning and end of the PEP course to ensure that the seroconversion was unrelated to that exposure. Additional laboratory evaluations were undertaken for persons who took PEP based on symptoms that could have been caused by the study medications or if there were other medical reasons to suspect an increased likelihood of PEP-related side effects</p> <p>HIV seroconversion was defined as HIV enzyme-linked immunoabsorbent assay (ELISA) seronegativity at the baseline visit with a subsequent positive ELISA and western blot during a follow-up visit</p> <p>Drug-resistant HIV was assessed for the one participant in whom PEP failed</p> <p>Recruitment dates: July 1995–June 1998</p> <p>Follow up: median 24.2 months</p>

continued

Baseline characteristics	PEP (n = 68)	No PEP (n = 132)	Total (n = 200)	p-value
Age (years), median	28	28	28	$p = 0.83$
Race, n (%):				
White	34 (50)	60 (45)	94 (47)	$p = 0.69$
Black	15 (22)	26 (20)	41 (21)	
Mixed	3 (4)	11 (8)	14 (7)	
Other	16 (24)	35 (27)	51 (26)	
Completed high school, n (%)	55 (81)	93 (70)	148 (74)	$p = 0.11$
Income per month (Brazilian reais), median	445	480	465	$p = 0.57$
Receptive anal sex last 6 months, n (%)	48 (71)	84 (64)	132 (66)	$p = 0.33$
Unprotected receptive anal sex last 6 months, n (%)	23 (34)	34 (26)	57 (29)	$p = 0.23$
Insertive anal sex last 6 months, n (%)	46 (68)	93 (70)	139 (70)	$p = 0.68$
Unprotected insertive anal sex last 6 months, n (%)	20 (29)	39 (30)	59 (30)	$p = 0.98$
History of gonorrhoea last 6 months, n (%)	7 (10)	32 (24)	39 (20)	$p = 0.02$
Illicit drug use, n (%)	8 (12)	17 (13)	25 (13)	$p = 0.82$
Hepatitis B core antibody positive, n (%)	23 (34)	34 (26)	57 (29)	$p = 0.22$

Comments: The two groups were comparable on age, race, education, income, risk behaviours at enrolment, illicit drug use and hepatitis B seroprevalence

Outcomes: HIV incidence	PEP (n = 68)	No PEP (n = 132)	p-value
Seroconversion to HIV	1	10	Not reported

Comments: 11 subjects had new HIV infections during the course of the study, for an overall seroincidence of 2.9 per 100 person-years (95% CI 1.4–5.1). Based on the risk profile of the study participants and the experience of the authors' previous cohort study the expected number of new HIV infections was 11.8 ($p > 0.97$ compared with the observed 11 infections), for an expected seroincidence of 3.1 per 100 person-years ($p > 0.97$ compared with the observed seroincidence of 2.9)

Outcomes: PEP use (28-day course)	PEP (n = 68)	No PEP (n = 132)	p-value
Prescribed once, n (%)	49 (72.1)	—	—
Prescribed twice, n (%)	14 (20.6)	—	—
Prescribed three times, n (%)	2 (2.9)	—	—
Prescribed four times, n (%)	2 (2.9)	—	—
Prescribed nine times, n (%)	1 (1.5)	—	—

PEP utilisation: PEP was initiated a total of 109 times by 68 participants. A total of 100 were considered eligible exposures, for which a 4-week course was prescribed (see above). The most common reasons for not initiating PEP (\geq one possible response per participant) were sex with a steady partner ($n = 150$), participant did not consider the exposure to be of sufficiently high risk to warrant PEP ($n = 94$) and concerns about side effects ($n = 23$)

Outcomes: non-completed PEP courses

	PEP (n = 68)	No PEP (n = 132)	p-value
Did not return to complete course, n	2	–	–
Discontinued because of adverse events, n	7	–	–

Adverse events: At least one side effect was reported in 82% of episodes of PEP use; nausea was the most commonly reported side effect and six discontinuations (of those for adverse events) were due to this. One patient with a history of pancreatitis was instructed to stop taking PEP because of an asymptomatic increase in pancreatic enzymes. Apart from this there were no clinically significant laboratory abnormalities among participants who took PEP.

Adherence: The full 28-day regimen of PEP was completed for 89 (89%) of the eligible exposures, including the participant who seroconverted.

Outcomes: risk behaviours

	PEP (n = 68)	No PEP (n = 132)	p-value
Median number of male partners 6 months before baseline (range)	4 (0–50)	2 (0–40)	PEP: $p = 0.43$; no PEP: $p = 0.46$
Median number of male partners 6 months before last visit (range)	4 (0–180)	2 (0–100)	PEP: $p = 0.43$; no PEP: $p = 0.46$

Authors state that, on average, reported high-risk sexual activities declined over time for both PEP and non-PEP users

Risk behaviours	PEP (n = 68)			No PEP (n = 132)		
	6 months before baseline	6 months before last visit	p-value	6 months before baseline	6 months before last visit	p-value
Unprotected anal intercourse, n (%)	32 (47.1)	27 (39.7)	$p = 0.35$	48 (36.4)	32 (24.2)	$p = 0.008$
Unprotected oral intercourse, n (%)	16 (23.5)	8 (11.8)	$p = 0.06$	32 (24.4)	16 (12.2)	$p = 0.002$
Unprotected vaginal intercourse (%)	1.6	4.7	$p = 0.16$	6.1	8.3	$p = 0.26$

Additional comments

- The study regimen was chosen because, at the time of the study, a two-drug regimen was recommended for most HIV exposures that warrant PEP
- PEP failure was defined as a documented HIV seroconversion that occurred within 2 months after the exposure for which PEP was taken. Seroconversions that occurred ≥ 2 months after the exposure for which PEP was taken were not considered as PEP failures

Methodological comments

- Allocation to treatment groups: Participants decided whether to initiate PEP after a high-risk exposure. For seroconversion to HIV PEP users were compared with non-users
- Blinding: No blinding of assessors at follow-up visits
- Comparability of treatment groups: The groups that were compared within this study for seroconversions, PEP vs no PEP, were comparable at baseline

continued

- Method of data analysis: Data analysis was performed using SAS version 6.12. Comparisons between groups were analysed using chi-squared tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Comparisons of numbers of male partners at 6 months before baseline and at last interview were analysed using the signed rank test. Behaviour practices over time were examined using the McNemar test. Authors used the final interview that individuals participated in for those participants who did not have a 24-month interview. Incidence rates are expressed as the incidence of seroconversions per 100 person-years of follow-up and exact 95% confidence limits were calculated.
- The 'control' was modelled by fitting a binomial regression model to the first cohort data with a complementary log (–log) link function that accounts for previously identified risk factors for incidence of HIV in that cohort. The coefficients from that model were applied to the covariate and follow-up patterns of current participants to calculate the expected number of HIV seroconversions and expected HIV seroincidence
- Sample size/power calculation: No power calculation was performed
- Attrition/dropout: A cohort of 200 was enrolled; of these 68 took the study drug 109 times

General comments

- Generalisability: The cohort was recruited from former participants of an HIV seroincidence study conducted among high-risk men who have sex with men aged 18–35 years
- Outcome measures: The outcome measures were relevant to the study area
- Intercentre variability: N/A
- Conflicts of interest: Study was funded by GlaxoSmithKline, Conselho Nacional de Desenvolvimento Científico e Tecnológico, National Institute of Allergy and Infectious Diseases (research career award), Fogarty International Center (grant)

Appendix 5

Data extraction of cost-effectiveness studies

Study characteristics	
Study	Pinkerton <i>et al.</i> 1998 ²²
Country of origin	US
Base year prices	1996 US\$
Intervention	Postexposure prophylaxis (PEP) following potential HIV exposure through sexual contact with a partner who may or may not be infected, compared with a 'no programme option'. PEP was assumed to consist of a 4-week regimen of triple combination therapy with zidovudine (ZDV), lamivudine (3TC) and the protease inhibitor indinavir and was assumed to be as effective as ZDV monotherapy in the occupational setting
Study type	Cost-utility analysis; decision-analytical model to evaluate cost-effectiveness
Study group	A hypothetical cohort of 10,000 patients who reported sexual intercourse with a partner of unknown HIV status
Perspective	Societal
Industry role	None stated
Effectiveness parameter	Probability PEP effective 0.79 from occupational study ²⁶
Costs assessment	Primary cost of PEP is drug therapy: cost of PEP triple therapy per patient: US\$619. Obtained from published literature (references given)
Utilities assessment	Quality-adjusted life-years (QALYs) saved per infection prevented: 11.23. Obtained from published literature (references given)
Ranges for sensitivity analyses	Effectiveness: 0.43–0.94 Costs: US\$400–955 QALYs saved: 13.18–9.34
Study base case 'headline' predictions/findings	PEP should be restricted to partners of infected persons, to patients reporting unprotected receptive anal intercourse and possibly to cases where there is substantial likelihood that the partner is infected
Results	
Base case	<p>Authors use predetermined threshold of US\$50,000 per QALY saved</p> <p>The base-case analysis for a cohort of 10,000 patients receiving PEP reported: 19.62 HIV infections averted following receptive anal intercourse; 0.59 HIV infections averted following insertive anal intercourse; 0.11 HIV infections averted following receptive vaginal intercourse; and 0.07 HIV infections averted following insertive vaginal intercourse</p> <p>Authors report that prophylaxis is not cost-effective for sex act/role combinations other than receptive anal intercourse (all cost-utility ratios exceed US\$750,000 per QALY saved)</p> <p>They also report that PEP following receptive vaginal intercourse appears to be cost-effective if certain that the partner is infected [HIV prevalence (probability of HIV infection) has to be > 0.73]</p> <p>PEP following insertive exposures is reported to be marginally cost-effective at best (the cost-utility ratio is > US\$100,000 per QALY saved regardless of the probability of HIV infection)</p> <p>The cost-utility ratio for ZDV/3TC PEP following receptive anal intercourse among men who have sex with men is US\$6354 per QALY saved</p>
continued	

Study characteristics**Sensitivity analysis**

The sensitivity analyses indicated that the results for the receptive anal case were not sensitive to changes in the parameter values and PEP was always cost-effective across a range of values

Both the insertive anal and insertive vaginal cases were not sensitive and were not cost-effective across a (plausible) range of values. The receptive vaginal case was sensitive to the probability of the sexual partner of the patient being HIV infected. In this case, if the probability of infection is > 0.73 then PEP may be cost-effective

PEP is cost saving for receptive anal intercourse if the probability that the partner is infected is > 0.25

Triple PEP therapy was unlikely to be cost-effective relative to dual combination PEP (the additional drug costs will not be offset by treatment savings)

The results did not appear to be sensitive to repeated exposure and PEP

Conclusions

PEP following suspected sexual exposure to HIV is only cost-effective for receptive anal intercourse or receptive vaginal intercourse with a partner who is likely to be infected

If the probability that the partner is infected is very small then PEP may not be cost-effective following receptive anal intercourse

PEP after insertive vaginal intercourse or insertive anal intercourse is probably not cost-effective, regardless of the partner's risk status

The authors report that from a purely economic standpoint PEP should be restricted to partners of infected persons (e.g. serodiscordant couples), to patients reporting unprotected receptive anal intercourse (including condom breakage) and possibly to cases in which there is a substantial likelihood that the partner is infected. Providing PEP to all who request it does not appear to be an economically efficient use of limited HIV prevention and treatment resources

Caveats

Uncertainty in the effectiveness of PEP has implications for its cost-effectiveness

Authors have assumed that PEP is completely ineffective when the antiretroviral regimen is discontinued prematurely

Analysis assumes that all individuals receiving PEP are uninfected and that PEP therefore can prevent an infection. Therefore, the above results may disproportionately overstate the cost-effectiveness of PEP in high prevalence communities

PEP for receptive anal intercourse may not be cost-effective (authors state US\$100,000 per QALY) if the probability that the partner is infected is quite small

There are limitations with the per-contact probabilities: they are not known with certainty and the probable ranges may overlap. Stage of disease, viral load, genetics and facilitation by sexually transmitted diseases are believed to also affect the risk of transmission; even greater uncertainty surrounds the probability of transmission for oral sex

Study characteristics	
Study	Pinkerton <i>et al.</i> 2004 ²³
Country of origin	US
Base year prices	2000 US\$
Intervention	An initial 7-day supply of antiretroviral medication; additional 21 days supplied at follow-up visit 7 days later
	The protocol for this study included discussion of potential benefits and negative consequences of PEP, medical evaluation, HIV risk assessment, risk reduction counselling and medication adherence counselling, and information on previous antiretroviral use and response to medication of HIV-infected sources was obtained if possible to tailor the regimen offered as PEP to one to which the infection would most likely be susceptible. Base-case values were assigned to these parameters
Study type	Cost–utility study
Study group	401 participants with possible non-occupational exposure to HIV [sexual, needle sharing, non-occupational needlestick injury, other (bite or assault)]. Distribution of patients was by exposure type, percentage of patients who completed PEP in each exposure group and proportion of completers with a known HIV-infected source. Patients who reported multiple exposures were classified according to the highest risk exposure. In total, 312 patients (78%) were known to have completed the PEP regimen; 46% reported that they knew that their source was infected with HIV
Perspective	Societal: included all identifiable costs, regardless of who bore these
Industry role	None stated (one of the authors has received honorariums from GlaxoSmithKline, Bristol-Myers Squibb and Agouron Pharmaceuticals)
Effectiveness parameter	Probability PEP effective 0.81 from occupational study ²⁷
Costs assessment	Five drug costs (for the five different drugs): US\$312, US\$267, US\$222, US\$280 and US\$679 from published literature (reference given)
	Itemised laboratory and clinic costs from published literature (reference given)
	Wages and travel costs from financial records kept by study investigators
Utilities assessment	Quality-adjusted life-years (QALYs) lost per HIV infection: 9.31. Obtained from published literature (reference given)
Ranges for sensitivity analyses	Effectiveness: 0.48–1.0 Costs: least expensive regimen US\$502 and most expensive regimen US\$1258 QALYS saved: 4.28–18.23
Study base case ‘headline’ predictions/findings	For this study population, HIV PEP was cost-effective by conventional standards and cost saving for persons seeking PEP after male–male receptive intercourse
continued	

Study characteristics**Results****Base case**

Use of PEP reduced the expected number of infections to 0.77 and therefore prevented an estimated 1.59 infections (expected infections in the absence of PEP in the exposures reported by the 401 patients would be 2.36). The authors have adjusted for continuing risk behaviours over the subsequent 10 years and report that PEP in this case would have averted 1.26 infections and saved US\$281,323 medical care costs and 11.74 associated QALYs

PEP effectiveness was set at 81%

The overall cost–utility ratio was US\$14,449 per QALY saved

The authors used thresholds of US\$40,000–\$60,000 per QALY for cost-effectiveness and US\$200,000 for non-cost-effectiveness

In total, 96% of averted infections were among men who reported exposure through receptive anal intercourse (RAI) with other men. When restricted to this subgroup the PEP programme was cost saving

Exposure through injection drugs: US\$86,462 per QALY saved; male–female RAI: US\$165,289 per QALY saved

Overall cost–utility ratio for men reporting exposure through male–male sex (receptive or insertive anal sex, receptive oral sex or 'other') was US\$8607 per QALY saved. Cost–utility ratio for all other exposures combined was US\$258,667 per QALY saved

The PEP programme was cost saving for patients who reported that their partner was HIV positive. The cost–utility ratio was US\$58,025 when the HIV status of the partner was unknown. The authors state that these results are mainly driven by the men with exposures through RAI as these were cost-saving; the cost–utility ratio for the 93 patients who were exposed through other routes was US\$278,671

Authors assumed that patients remained at risk of infection for 10 years after participating in the PEP programme, with an annual risk equal to the incidence of infection in the associated exposure group

Sensitivity analysis

The programme remained cost-effective when the PEP effectiveness parameter was set to 48%

The programme would not be cost saving even if the antiretroviral regimen was 100% effective

The programme was cost-effective for PEP completion rates > 29%

The programme remained cost-effective regardless of the percentage of partners known to be infected with HIV or the prevalence of infection among partners whose HIV status was unknown

The results were not sensitive to the HIV-related treatment cost and QALYs saved parameters

The programme was cost-effective provided that at least 2.24 QALYs were saved per averted infection and was cost-effective regardless of the cost of treating HIV and AIDS

Study characteristics**Sensitivity analysis**

The programme was still cost-effective if a 5% discount rate was used. When a 0% discount rate was used the cost–utility ratio decreased to US\$2385 per QALY saved

The cost–utility ratio was most sensitive to RAI transmission probability. The threshold analysis indicated that the PEP programme would be cost saving overall if this probability exceeded 0.033 and would be cost-effective (cost–utility ratio of US\$60,000 per QALY saved) for probabilities as small as 0.009 (base case was 0.02)

The programme would not be cost-effective (cost–utility ratio > US\$200,000 per QALY saved) if the per-exposure transmission probability for RAI was less than 0.003

Using alternative published HIV incidence and prevalence rates for San Francisco: US\$11,081 per QALY saved, lower than the base-case value

Cost–utility ratio increased to US\$71,381 when the transmission probabilities were set to their smallest values and decreased to less than zero (cost saving) when they were set to their largest values

Conclusions

HIV PEP was cost-effective by conventional standards (here defined as between US\$40,000 and US\$60,000) and cost saving for men seeking PEP after male–male RAI. It is possibly cost-effective for injection drug exposures and women reporting RAI but probably not cost-effective for other exposures. Although fewer than half of the patients reported male–male RAI, the PEP programme was cost-effective overall and authors suggest an economically sound use of societal health promotion resources

Caveats

The effectiveness of PEP after sexual exposures is unknown: authors assumed that dual and triple drug PEP was as effective as zidovudine PEP in a case–control study of occupational exposures

Differences in the transmission dynamics of sexual (mucosal) and occupational (percutaneous) exposures may also impact on PEP effectiveness

Study characteristics	
Study	Pinkerton <i>et al.</i> 2004 ²⁴
Country of origin	US
Base year prices	2000 US\$
Intervention	Hypothetical PEP programme in 96 US metropolitan statistical areas (MSAs), based on San Francisco PEP programme (no further detail provided in this paper)
Study type	Cost-effectiveness analysis
Study group	Information on PEP clients was taken from the San Francisco PEP programme. Potential PEP clients were divided into four risk groups based on exposure type: men who have sex with men (MSM), intravenous drug users (IDUs), male/female heterosexuals and other non-occupational exposures (bites, assaults involving mucosal exposure). It was assumed that the same proportion of each group would access PEP in each MSA as they had in the San Francisco PEP study. This was then used to estimate the number of potential PEP clients in each group in each MSA. Previously published estimates of HIV prevalence in the 96 MSAs for each risk group were used. It was assumed that the distribution of PEP-prompting exposures (e.g. receptive anal intercourse, injection-related exposure, etc.) in each MSAs would mimic the distribution observed in San Francisco. It was also assumed that risk group exposure could be inferred from exposure type (e.g. man reporting vaginal intercourse is in heterosexual group and source partner belongs to same group; one exception: non-occupational needlestick injuries usually come from discarded needles and so the HIV prevalence in IDUs was used to estimate the prevalence of infection among needlestick exposure sources)
Perspective	Societal
Industry role	Not stated
Effectiveness parameter	Probability PEP effective 0.81 from occupational study ²⁷
Costs assessment	Total cost of PEP programme in a particular MSA was calculated using a formula (given) including: drug costs for completers US\$597 (non-completers US\$454); laboratory work completers US\$26 (non-completers US\$14); other clinical services completers US\$523 (non-completers US\$240). Obtained from published literature (references given) and data from San Francisco PEP programme data
Utilities assessment	Quality-adjusted life-years (QALYs) saved per infection prevented: 9.31. Obtained from published literature (references given)
Ranges for sensitivity analyses	Effectiveness: 0.48–0.94 Costs: not used QALYs lost: 10.29–8.37
Study base case 'headline' predictions/findings	Proportion of clients completing therapy was set at 77.8% (based on San Francisco PEP study). The effectiveness of PEP in preventing HIV infection was assumed to be 81%, based on the findings of a case-control study in health-care workers (HCWs) exposed occupationally. Across the 96 MSAs the hypothetical PEP programmes would serve 19,154 clients at a total cost of US\$21.7m, averting 63.9 HIV infections (primarily MSM – 96.1% of the averted infections, constituting 75.9% of PEP clients)
Results	
Base case	<p>The combined cost-utility ratio (CUR) for the 96 MSA was US\$12,567 per QALY saved. This ranged from US\$4137 (San Francisco) to US\$39,101 (Stockton-Lodi MSA) per QALY saved. Only two MSAs had CUR greater than US\$30,000. The mean and median CUR were US\$15,728 and US\$15,367 respectively</p> <p>PEP was cost saving (CUR < US\$0) for male-male and male-female receptive anal intercourse exposures</p> <p>The CUR for needle-sharing exposures and needlestick exposures was US\$97,867 and US\$159,686 respectively</p> <p>CUR exceeded \$380,000 per QALY saved for all other types of exposure</p>

Study characteristics**Sensitivity analysis**

Key parameters were varied one at a time in univariate sensitivity analyses. Only one of the parameter manipulations (reducing the per-exposure transmission probability for receptive anal intercourse from 0.02 to 0.008) resulted in a CUR > US\$60,000 per QALY saved.

Individually varying the other transmission probabilities within plausible ranges produced < 4% deviation from the base CUR

Several prevalence-related measures were moderately to strongly correlated with the inverse of the CUR values for individual MSAs (although overall the CUR across the 96 MSAs was not especially sensitive to the prevalence of infection)

The authors report that the results were moderately sensitive to the effectiveness of PEP and somewhat sensitive to the proportions of persons who completed the PEP regimen, the proportion of PEP clients with known infected source partners and the lifetime costs of medical care and lost QALYs associated with a case of HIV infection

In particular, the proportion of the 'high-risk' MSM, IDUs, heterosexual subpopulation classified as HIV-infected MSM was strongly correlated with the inverse CUR

Conclusions

PEP for HIV could be a cost-effective adjunct to existing HIV prevention efforts

Overall across the 96 MSAs, PEP was cost saving for receptive anal intercourse and possibly cost-effective for needle sharing and non-occupational needlestick injuries, but of questionable economic value for all other types of exposure

PEP was highly cost-effective for MSM, less so for IDUs and high-risk women, and probably not cost-effective for general population exposures or heterosexual men

Caveats

The effectiveness of PEP in preventing infection and the per-exposure transmission probability are not established. HIV prevalence and population size estimates were based on a study published in 1996 (therefore reflecting HIV epidemiology in the early 1990s). Analysis did not take into account the ages of clients (which would affect the number of QALYs lost to infection) or whether or not a particular client completed the PEP regimen or was known to have been exposed to HIV by an HIV-positive partner. The analysis assumed that the distribution of client exposure groups in each MSA would mimic that observed in the San Francisco study. Implementation of PEP services in a given locale is likely to differ from the San Francisco experience

Study characteristics	
Study	Herida et al. 2006 ²⁵
Country of origin	France
Base year prices	2002 Euros
Intervention	Comparison of PEP programme with 'no PEP' alternative. For patients in PEP programme clinicians prescribe drugs of their choice (usually tri-therapy containing protease inhibitor). HIV/hepatitis B/hepatitis C serology tests, a pregnancy test and 'other' laboratory tests carried out at the baseline visit. Three follow-up visits scheduled at days 15, 30 and 90 after exposure. Laboratory tests scheduled at day 15. HIV and hepatitis serology is repeated at day 30 (end of treatment), 120 and 180. PEP physician provides patient with 4-week supply of antiretroviral drugs and counselling at each visit. Information on patients' characteristics, risk of exposure, treatments prescribed, serology and potential adverse effects were recorded by clinicians during follow-up visits and entered in an anonymous database. A total of 15 drugs were used in various two-drug (9%), three-drug (90%) and four-drug (1%) combinations
Study type	Cost-effectiveness analysis based on decision tree. As parameters vary according to exposure risks, a separate decision tree was built for each type of exposure event
Study group	12,551 individuals sought PEP between July 1999 and December 2003. Of these, 8958 (71%) were prescribed PEP and included in a national hospital-based voluntary surveillance of PEP programme for both occupational and non-occupational exposure (set up in 1999); 6812 (76%) of those prescribed PEP had a sexual exposure event, 2092 (23.4%) had an occupational exposure event (68.9% of these were HCWs) and 54 (0.6%) were exposed through sharing drug injection equipment. In the sexual exposure group, 2546 (28.4%) were men who have sex with men (MSM) and 4266 (47.6%) were heterosexual. The source was known to be HIV infected for 2413 individuals (27.1%)
Perspective	Societal
Industry role	Not stated
Effectiveness parameter	Probability PEP effective 0.80 from occupational study ²⁷ (in fact, 0.81 from reference)
Costs assessment	Total cost: €988; cost of PEP therapy per patient: €745; physician visits: €80; laboratory costs: €163. Obtained from PEP treatment prescribed between 1999 and 2003 using published prices (reference given)
Utilities assessment	Quality-adjusted life-years (QALYs) saved per infection prevented: 8.34. Obtained from published literature (references given)
Ranges for sensitivity analyses	Effectiveness: 0.48–0.94 Costs: not used QALYs saved: 11.58–4.31
Study base case 'headline' predictions/findings	Number of infections averted and number of QALYs saved during 1999–2003. On the basis of the model it was estimated that among 8958 treated individuals, 12 cases of HIV infection would have occurred if none had received PEP and 4.3 cases would have occurred if all had received PEP
Results	
Base case	<p>Five individuals became infected during follow-up – two were considered PEP failures (receptive anal intercourse in a gay man and a women); the three remaining patients (all MSM) were considered by physicians to have seroconversions resulting from high-risk sexual behaviour after the PEP treatment</p> <p>Cost of the PEP programme (providing PEP to 8958 individuals) was estimated at €7,670,002 and the cost-effectiveness ratio (CER) at €996,104 per infection averted</p> <p>The total cost of the programme (including the cost of caring for the estimated 4.3 cases of HIV infection that occurred among the 8958 treated individuals) was €3,035,075</p> <p>The cost of caring for the estimated 12 cases of HIV infection that would have occurred without the PEP programme was €8,752,150</p> <p>The estimated marginal cost was €5,717,075 and the CER was €88,692 per QALY saved</p>

Study characteristics**Sensitivity analysis**

There were major differences in the CER according to the type of exposure. PEP after receptive anal intercourse with an HIV-infected individual was cost saving in men and women (negative ratio of €22,141 and €22,031 per QALY saved respectively). PEP after an intravenous drug user (IDU) sharing needle with an HIV-infected person was cost saving (€1141 per QALY saved). PEP is cost-effective (< €50,000 per QALY saved) for HCW after percutaneous exposure to material from an HIV-infected patient, and for MSM having receptive anal intercourse with a partner of unknown status. These five exposures accounted for 15.7% of prescriptions. In other exposures PEP was not considered cost-effective: 72% of exposures had CER > €200,000 per QALY saved and 52% of cases had CER > €2m per QALY saved

One-way sensitivity analyses were performed on compliance according to the low estimation of the compliance, and on life expectancy of HIV-infected individuals according to the higher lifetime HIV cost resulting from longer survival (other parameters were kept fixed at base-case values)

Patients with missing follow-up information were considered as compliant as those known to have attended the 1-month follow-up (this compliance was used in the base case); patients with missing follow-up information were considered as lost to follow-up with a compliance = 0 (this estimated compliance was used in the sensitivity analysis). In this case the programme would prevent 3.8 infections and save 31.7 QALYs at a marginal cost of €5,087,998, resulting in a CER of €160,382 per QALY saved. As before, PEP after receptive anal intercourse with an HIV-infected individual remains cost saving (–€17,778 and –€18,860 per QALY saved for MSM and heterosexual women respectively). PEP to an IDU after needle sharing with an HIV-infected person remains cost-effective but is no longer cost saving (€18,445 per QALY saved)

One-way sensitivity analyses were performed on the life expectancy of HIV-infected individuals according to the higher value of life expectancy and higher lifetime HIV cost resulting from longer survival (16.82 QALYs compared to base case of 12.79, and €331,869 lifetime HIV/AIDS care costs compared to base case of €252,768; both costs and QALYs are discounted at 3%). According to this scenario the programme is less cost-effective than the base case (33.3 QALYs prevented at marginal cost of €5,105,998; CER = €153,241 per QALY saved). The three exposure risks with negative ratios in the base-case analysis remain cost saving but with higher cost ratios

Threshold analyses were performed for exposures with CER under €200,000 per QALY saved, using minimum values of prevalence, per-contact HIV transmission or compliance required to achieve the cost-saving threshold (€0 per QALY saved) or the cost-effective threshold (€50,000 per QALY saved). PEP for MSM after receptive anal intercourse with a partner of unknown HIV status would be cost saving for a per-contact transmission risk of at least equal to 0.0411 or an HIV prevalence of at least 0.208. After needle sharing with an individual of unknown serostatus, to achieve cost-effectiveness (€50,000 per QALY saved) the compliance should be ≥ 0.92 with both the highest values of prevalence (0.21) and of the per-contact transmission risk (0.0092). For receptive vaginal intercourse with an HIV-infected partner, a per-contact transmission risk equal to 0.0208 would allow the CER to be reached

Conclusions

According to international standards that use US\$50,000 per QALY saved as a threshold, the French PEP programme appears not to be a cost-effective intervention; only 15.7% of PEP courses in the French programme can be considered cost-effective

The PEP programme is less cost-effective than other French prevention or screening programmes

continued

Study characteristics**Caveats**

The authors list several limitations. They had to make several initial assumptions (and used sensitivity analyses to overcome this). Compliance could only be estimated for 47% of PEP prescriptions and so overall compliance was estimated at 0.75. Any overestimation of compliance would improve the CER (demonstrated in the sensitivity analysis by using low estimate of compliance)

There are no available data for lifetime HIV/AIDS costs in France and so the authors estimated these

The model did not take into account the possibility that some patients seeking PEP may continue at-risk behaviour

The study did not consider PEP adverse events. The authors state that taking these into account would further reduce the CER of the overall PEP programme: 65% of 2138 treated patients in the French PEP programme had clinical adverse events and 8% presented with biological abnormalities

The number of HIV infections predicted by the model was higher than that seen; however, HIV serology 6 months after PEP initiation was only available for 18% of patients and so the true number of PEP failures may be higher

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, Simmet 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, Towler G.

No. 33

Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.

By Shepherd J, Waugh N, Hewitson P.

No. 34

A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.

By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35

Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.

By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al.*

No. 36

A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.

By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37

Systematic review of treatments for atopic eczema.

By Hoare C, Li Wan Po A, Williams H.

No. 38

Bayesian methods in health technology assessment: a review.

By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39

The management of dyspepsia: a systematic review.

By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al.*

No. 40

A systematic review of treatments for severe psoriasis.

By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1

Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.

By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al.*

No. 2

The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.

By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al.*

No. 3

Equity and the economic evaluation of healthcare.

By Sassi F, Archard L, Le Grand J.

No. 4

Quality-of-life measures in chronic diseases of childhood.

By Eiser C, Morse R.

No. 5

Eliciting public preferences for healthcare: a systematic review of techniques.

By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al.*

No. 6

General health status measures for people with cognitive impairment: learning disability and acquired brain injury.

By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7

An assessment of screening strategies for fragile X syndrome in the UK.

By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8

Issues in methodological research: perspectives from researchers and commissioners.

By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al.*

No. 9

Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetism therapy.

By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10

Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.

By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al.*

No. 11

Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.

By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12

Statistical assessment of the learning curves of health technologies.

By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13

The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.

By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.

By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15

Home treatment for mental health problems: a systematic review.

By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al.*

No. 16

How to develop cost-conscious guidelines.

By Eccles M, Mason J.

No. 17

The role of specialist nurses in multiple sclerosis: a rapid and systematic review.

By De Broe S, Christopher F, Waugh N.

No. 18

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.

By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19

The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.

By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20

Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.

By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al.*

No. 21

Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.

By Marshall M, Crowther R, Almaraz-Serrano A, Creed F, Sledge W, Kluiters H, *et al.*

No. 22

The measurement and monitoring of surgical adverse events.

By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23

Action research: a systematic review and guidance for assessment.

By Waterman H, Tilden 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 Woolcott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al.*

No. 17

A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.

By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18

Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.

By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al.*

No. 19

Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.

By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al.*

No. 20

Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.

By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freemantle N, Vail A.

No. 21

The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.

By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22

A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.

By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23

A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.

By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, 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, Hohenstein F, Sterne J.

No. 2

Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.

By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al.*

No. 3

Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.

By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4

A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.

By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al.*

No. 5

Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.

By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al.*

No. 6

The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.

By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al.*

No. 7

The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.

By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al.*

No. 8

A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.

By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al.*

No. 9

Clinical effectiveness and cost-utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.

By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10

Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.

By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al.*

No. 11

First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).

By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12

The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.

By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13

A systematic review of atypical antipsychotics in schizophrenia.

By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al.*

No. 14

Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.

By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al.*

No. 15

Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.

By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al.*

No. 16

Screening for fragile X syndrome: a literature review and modelling.

By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17

Systematic review of endoscopic sinus surgery for nasal polyps.

By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18

Towards efficient guidelines: how to monitor guideline use in primary care.

By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19

Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.

By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20

Prioritisation of health technology assessment. The PATHS model: methods and case studies.

By Townsend J, Buxton M, Harper G.

No. 21

Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.

By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al.*

No. 22

The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.

By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23

The role of modelling in prioritising and planning clinical trials.

By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24

Cost-benefit evaluation of routine influenza immunisation in people 65–74 years of age.

By Allsup S, Gosney M, Haycox A, Regan M.

No. 25

The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.

By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26

Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.

By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27

Evaluating non-randomised intervention studies.

By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovich 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, Gribsch I, Taylor FC, Burke M, West RR, *et al.*

No. 42

Involving South Asian patients in clinical trials.

By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43

Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.

By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44

Identification and assessment of ongoing trials in health technology assessment reviews.

By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al.*

No. 45

Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine

By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46

Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.

By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al.*

No. 47

Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.

By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48

Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.

By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al.*

No. 49

Generalisability in economic evaluation studies in healthcare: a review and case studies.

By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al.*

No. 50

Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.

By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al.*

Volume 9, 2005

No. 1

Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.

By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al.*

No. 2

Do the findings of case series studies vary significantly according to methodological characteristics?

By Dalziel K, Round A, Stein K, Garside R, Castelnovo E, Payne L.

No. 3

Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.

By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Hailes 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, Sakarovich C, Deeks JJ, D'Amico R, *et al.*

No. 27

Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.

By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al.*

No. 28

Outcomes of electrically stimulated gracilis neosphincter surgery.

By Tillin T, Chambers M, Feldman R.

No. 29

The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.

By Garside R, Stein K, Castelnovo 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, Cogan 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 Castelnovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44

Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.

By Knowles R, Griebisch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45

The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.

By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al.*

No. 46

The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.

By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47

Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.

By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al.*

No. 48

Systematic review of effectiveness of different treatments for childhood retinoblastoma.

By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49

Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.

By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al.*

No. 50

The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.

By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al.*

Volume 10, 2006

No. 1

The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.

By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al.*

No. 2

FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.

By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3

The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.

By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al.*

No. 4

A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.

By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al.*

No. 5

Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.

By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6

Systematic review and evaluation of methods of assessing urinary incontinence.

By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al.*

No. 7

The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.

By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al.*

No. 8

Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.

By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9

Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.

By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al.*

No. 10

Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.

By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11

Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.

By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al.*

No. 12

A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.

By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al.*

No. 13

Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).

By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al.*

No. 14

The cost-effectiveness of screening for oral cancer in primary care.

By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, *et al.*

No. 15

Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.

By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al.*

No. 16

Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.

By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al.*

No. 17

Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.

By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al.*

No. 18

Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.

By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al.*

No. 19

Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.

By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al.*

No. 20

A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.

By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al.*

No. 21

Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.

By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22

Pressure relieving support surfaces: a randomised evaluation.

By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al.*

No. 23

A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.

By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al.*

No. 24

The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.

By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al.*

No. 25

Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.

By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al.*

No. 26

A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.

By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al.*

No. 27

A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost-utility for these groups in a UK context.

By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al.*

No. 28

Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.

By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29

An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.

By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al.*

No. 30

Accurate, practical and cost-effective assessment of carotid stenosis in the UK.

By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al.*

No. 31

Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.

By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al.*

No. 32

The cost-effectiveness of testing for hepatitis C in former injecting drug users.

By Castelnuevo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al.*

No. 33

Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.

By Kaltenthaler E, Brazier J, De Nigris E, Tumor I, Ferriter M, Beverley C, *et al.*

No. 34

Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.

By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al.*

No. 35

Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.

By Brazier J, Tumor I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al.*

No. 36

Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.

By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al.*

No. 37

Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.

By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38

A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.

By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, *et al.*

No. 39

The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.

By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40

What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).

By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al.*

No. 41

The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.

By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42

A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.

By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al.*

No. 43

Telemedicine in dermatology: a randomised controlled trial.

By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44

Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.

By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45

Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.

By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al.*

No. 46

Etanercept and efalizumab for the treatment of psoriasis: a systematic review.

By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al.*

No. 47

Systematic reviews of clinical decision tools for acute abdominal pain.

By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al.*

No. 48

Evaluation of the ventricular assist device programme in the UK.

By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al.*

No. 49

A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.

By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al.*

No. 50

Amniocentesis results: investigation of anxiety. The ARIA trial.

By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al.*

Volume 11, 2007

No. 1

Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.

By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al.*

No. 2

A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.

By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al.*

No. 3

A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.

By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al.*

No. 4

The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.

By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5

A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.

By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al.*

No. 6

Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.

By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al.*

No. 7

Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis.

By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8

Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.

By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al.*

No. 9

Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.

By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al.*

No. 10

Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.

By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al.*

No. 11

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.

By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12

Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.

By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13

A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.

By Wilson J, Yao GL, Raftery J, Bohlus J, Brunskill S, Sandercock J, *et al.*

No. 14

A systematic review and economic evaluation of statins for the prevention of coronary events.

By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al.*

No. 15

A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.

By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al.*

No. 16

Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.

By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17

Screening for type 2 diabetes: literature review and economic modelling.

By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al.*

No. 18

The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.

By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al.*

No. 19

The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.

By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20

A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.

By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al.*

No. 21

The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.

By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22

A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.

By Fayer D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al.*

No. 23

Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.

By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al.*

No. 24

The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.

By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al.*

No. 25

A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.

By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26

Hormonal therapies for early breast cancer: systematic review and economic evaluation.

By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wylid 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, Dünder Y, Haycox A, McLeod C, *et al.*

No. 47

The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.

By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al.*

No. 48

Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.

By Campbell MK, 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, Shephstone 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, Tumor I, Eggington E, Sutcliffe P, Ryan A.

No. 16

Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.

By Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A.

No. 17

Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.

By Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, *et al.*

No. 18

Structural neuroimaging in psychosis: a systematic review and economic evaluation.

By Albon E, Tsourapas A, Frew E, Davenport C, Oyeboode F, Bayliss S, *et al.*

No. 19

Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta₂ 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 beta₂ 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, Castelnovo E, Cross P, Harding G, *et al.*

No. 23

A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.

By George S, Pockney P, Primrose J, Smith H, Little P, Kinley H, *et al.*

No. 24

A review and critical appraisal of measures of therapist–patient interactions in mental health settings.

By Cahill J, Barkham M, Hardy G, Gilbody S, Richards D, Bower P, *et al.*

No. 25

The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.

By Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

No. 26

A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.

By de Verteuil R, Imamura M, Zhu S, Glazener C, Fraser C, Munro N, *et al.*

No. 27

A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.

By Karnon J, Czoski-Murray C, Smith K, Brand C, Chakravarthy U, Davis S, *et al.*

No. 28

Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.

By Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A.

No. 29

Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.

By Fader M, Cottenden A, Getliffe K, Gage H, Clarke-O'Neill S, Jamieson K, *et al.*

No. 30

A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.

By French B, Leathley M, Sutton C, McAdam J, Thomas L, Forster A, *et al.*

No. 31

The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.

By Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, *et al.*

No. 32

Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.

By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

No. 33

Performance of screening tests for child physical abuse in accident and emergency departments.

By Woodman J, Pitt M, Wentz R, Taylor B, Hodes D, Gilbert RE.

No. 34

Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.

By Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, *et al.*

No. 35

Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.

By Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R, *et al.*

No. 36

Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.

By Wang D, Cummins C, Bayliss S, Sandercock J, Burls A.

Volume 13, 2009**No. 1**

Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.

By McLeod C, Fleeman N, Kirkham J, Bagust A, Boland A, Chu P, *et al.*

No. 2

Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.

By Simpson EL, Stevenson MD, Rawdin A, Papaioannou D.

No. 3

Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.

By Main C, Liu Z, Welch K, Weiner G, Quentin Jones S, Stein K.

No. 4

Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis.

By McDaid C, Griffin S, Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, *et al.*

No. 5

Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.

By Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al.*

No. 6

The harmful health effects of recreational ecstasy: a systematic review of observational evidence.

By Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, *et al.*

No. 7

Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.

By Mowatt G, Houston G, Hernández R, de Verteuil R, Fraser C, Cuthbertson B, *et al.*

No. 8

The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports.

By Taylor RS, Elston J.

No. 9

Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial.

By Potter J, Mistri A, Brodie F, Chernova J, Wilson E, Jagger C, *et al.*

No. 10

Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.

By Pilgrim H, Lloyd-Jones M, Rees A.

No. 11

Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation.

By Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R, *et al*

No. 12

Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.

By Hobart J, Cano S.

No. 13

Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial.

By Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL, *et al.*, on behalf of the CAST trial group.



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, NCCHTA

Dr Andrew Cook,
Consultant Advisor, NCCHTA

Dr Peter Davidson,
Director of Science Support,
NCCHTA

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,
NCCHTA

Dr Edmund Jessop,
Medical Adviser, National
Specialist, National
Commissioning Group (NCG),
Department of Health, London

Ms Lynn Kerridge,
Chief Executive Officer,
NETSCC and NCCHTA

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,
NCCHTA

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 Statistics,
Department of Primary Health
Care, University of Oxford

Professor Ian Roberts,
Professor of Epidemiology &
Public Health, London School
of Hygiene and Tropical
Medicine

Professor Mark Sculpher,
Professor of Health Economics,
University of York

Professor Helen Smith,
Professor of Primary Care,
University of Brighton

Professor Kate Thomas,
Professor of Complementary &
Alternative Medicine Research,
University of Leeds

Professor David John
Torgerson,
Director of York Trials Unit,
University of York

Professor Hywel Williams,
Professor of Dermato-
Epidemiology, University of
Nottingham

Observers

Ms Kay Pattison,
Section Head, NHS R&D
Programmes, Research and
Development Directorate,
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 Oyeboode,
Consultant Psychiatrist
and Head of Department,
University of Birmingham

Dr Andrew Prentice,
Senior Lecturer and Consultant
Obstetrician and Gynaecologist,
The Rosie Hospital, University
of Cambridge

Dr Martin Shelly,
General Practitioner, Leeds,
and Associate Director, NHS
Clinical Governance Support
Team, Leicester

Dr Gillian Shepherd,
Director, Health and Clinical
Excellence, Merck Serono Ltd

Mrs Katrina Simister,
Assistant Director New
Medicines, National Prescribing
Centre, Liverpool

Mr David Symes,
Service User Representative

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 Levy,
Chief Executive, Motor
Neurone Disease Association,
Northampton

Professor James Lindesay,
Professor of Psychiatry for the
Elderly, University of Leicester

Professor Julian Little,
Professor of Human Genome
Epidemiology, University of
Ottawa

Professor Alistaire McGuire,
Professor of Health Economics,
London School of Economics

Professor Rajan Madhok,
Medical Director and Director
of Public Health, Directorate
of Clinical Strategy & Public
Health, North & East Yorkshire
& Northern Lincolnshire
Health Authority, York

Professor Alexander Markham,
Director, Molecular Medicine
Unit, St James's University
Hospital, Leeds

Dr Peter Moore,
Freelance Science Writer,
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.