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The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/34/01. The contractual start date was in July 2009. The draft report began editorial review in October 2009 and was accepted for publication in June 2010. 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.

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Abstract

A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence

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Background: Breast cancer (BC) accounts for one-third of all cases of cancer in women in the UK. Current strategies for the detection of BC recurrence include computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy. Positron emission tomography (PET) and, more recently, positron emission tomography/computed tomography (PET/CT) are technologies that have been shown to have increasing relevance in the detection and management of BC recurrence.
Objective: To review the accuracy of PET and PET/CT for the diagnosis of BC recurrence by assessing their value compared with current practice and compared with each other.
Data sources: MEDLINE and EMBASE were searched from inception to May 2009.
Study selection: Studies were included if investigations used PET or PET/CT to diagnose BC recurrence in patients with a history of BC and if the reference standard used to define the true disease status was histological diagnosis and/or long-term clinical follow-up. Studies were excluded if a non-standard PET or PET/CT technology was used, investigations were conducted for screening or staging of primary breast cancer, there was an inadequate or undefined reference standard, or raw data for calculation of diagnostic accuracy were not available.
Study appraisal: Quality assessment and data extraction were performed independently by two reviewers. Direct and indirect comparisons were made between PET and PET/CT and between these technologies and methods of conventional imaging, and meta-analyses were carried out. Analysis was conducted separately on patient- and lesion-based data. Subgroup analysis was conducted to investigate variation in the accuracy of PET in certain populations or contexts and sensitivity analysis was conducted to examine the reliability of the primary outcome measures.
Results: Of the 28 studies included in the review, 25 presented patient-based data and 7 presented lesion-based data for PET and 5 presented patient-based data and 1 presented patient- and lesion-based data for PET/CT; 16 studies conducted direct comparisons with 12 comparing the accuracy of PET or PET/CT with conventional diagnostic tests and 4 with MRI. For patient-based data (direct comparison) PET had significantly higher sensitivity [89%, 95% confidence interval (CI) 83% to 93% vs 79%, 95% CI 72% to 85%, relative sensitivity 1.12, 95% CI 1.04 to 1.21, $p = 0.005$] and significantly higher specificity (93%, 95% CI 83% to 97% vs 83%, 95% CI 67% to 92%, relative specificity 1.12, 95% CI 1.01 to 1.24, $p = 0.036$) compared with conventional imaging tests (CITs) – test performance

did not appear to vary according to the type of CIT tested. For patient-based data (direct comparison) PET/CT had significantly higher sensitivity compared with CT (95%, 95% CI 88% to 98% vs 80%, 95% CI 65% to 90%, relative sensitivity 1.19, 95% CI 1.03 to 1.37, $p = 0.015$), but the increase in specificity was not significant (89%, 95% CI 69% to 97% vs 77%, 95% CI 50% to 92%, relative specificity 1.15, 95% CI 0.95 to 1.41, $p = 0.157$). For patient-based data (direct comparison) PET/CT had significantly higher sensitivity compared with PET (96%, 95% CI 90% to 98% vs 85%, 95% CI 77% to 91%, relative sensitivity 1.11, 95% CI 1.03 to 1.18, $p = 0.006$), but the increase in specificity was not significant (89%, 95% CI 74% to 96% vs 82%, 95% CI 64% to 92%, relative specificity 1.08, 95% CI 0.94 to 1.20, $p = 0.267$). For patient-based data there were no significant differences in the sensitivity or specificity of PET when compared with MRI, and, in the one lesion based study, there was no significant differences in the sensitivity or specificity of PET/CT when compared with MRI.

Limitations: Studies reviewed were generally small and retrospective and this may have limited the generalisability of findings. Subgroup analysis was conducted on the whole set of studies investigating PET and was not restricted to comparative studies. Conventional imaging studies that were not compared with PET or PET/CT were excluded from the review.

Conclusions: Available evidence suggests that for the detection of BC recurrence PET, in addition to conventional imaging techniques, may generally offer improved diagnostic accuracy compared with current standard practice. However, uncertainty remains around its use as a replacement for, rather than an add-on to, existing imaging technologies. In addition, PET/CT appeared to show clear advantage over CT and PET alone for the diagnosis of BC recurrence.

Future work: Future research should include: prospective studies with patient populations clearly defined with regard to their clinical presentation; a study of diagnostic accuracy of PET/CT compared with conventional imaging techniques; a study of PET/CT compared with whole-body MRI; studies investigating the possibility of using PET/CT as a replacement for rather than an addition to CITs; and using modelling of the impact of PET/CT on patient outcomes to inform the possibility of conducting large-scale intervention trials.

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Contents

List of abbreviations

BC	breast cancer
CI	confidence interval
CITs	conventional imaging tests
CT	computed tomography
CW	conventional workup
FDG	^{18}F-fluorodeoxyglucose
FN	false-negative
FP	false-positive
HSROC	hierarchical summary receiver operating characteristic
NICE	National Institute for Health and Clinical Excellence
MRI	magnetic resonance imaging
PET	positron emission tomography
PET/CT	positron emission tomography/computed tomography
SROC	summary receiver operating characteristic
ROC	receiver operating characteristic
TN	true-negative
TP	true-positive

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

Breast cancer (BC) affects 1 in 13 women in their lifetime. Treatment options have developed significantly over the past decade and have had an impact on survival. The diagnosis of BC recurrence is important to allow appropriate treatment. Positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) are technologies that have application in the detection and management of cancer. The adoption of PET or PET/CT depends not only on their diagnostic accuracy but also on their comparative advantage over existing diagnostic approaches.

Objectives

This report covers the question of the effectiveness of PET and PET/CT for diagnosing BC recurrence and a second report (to follow) will provide economic modelling to address the question of their cost-effectiveness in this context. The aim of this review was to assess the value of PET and PET/CT, in addition to current practice, for the diagnosis of BC recurrence. The objectives were: (1) to assess the diagnostic accuracy of PET compared with conventional diagnostic strategies; (2) to assess the diagnostic accuracy of PET/CT compared with conventional diagnostic strategies; (3) to assess the diagnostic accuracy of PET and PET/CT compared with magnetic resonance imaging (MRI); (4) to compare the accuracy of PET with PET/CT; (5) to assess the overall diagnostic accuracy of PET and PET/CT; (6) to investigate the impact of PET and PET/CT on patient management; and (7) to explore possible mediators of the accuracy of PET and PET/CT.

Methods

A systematic review was conducted. A search for primary studies in MEDLINE (Ovid) and EMBASE (Ovid) was conducted with no language restrictions. Studies of PET or PET/CT in patients with history of BC and suspicion of recurrence were selected for inclusion. Studies were excluded if investigations were conducted for screening or staging of primary BC, if a non-standard PET or PET/CT technology was used, if there was an inadequate or undefined reference standard, or if raw data for calculation of diagnostic accuracy were not available. Both comparative and non-comparative studies were included.

Data extraction and quality assessment were conducted independently by two reviewers with any disagreements resolved by consensus. Direct and indirect comparisons were made between PET and PET/CT and between these technologies and methods of conventional imaging, and a meta-analysis was performed using a bivariate random effects model. Analysis was conducted separately on patient- and lesion-based data. Subgroup analysis was conducted to investigate variation in the accuracy of PET in certain populations or contexts and sensitivity analysis was conducted to examine the reliability of the primary outcome measures.

Results

Twenty-eight studies were included in the current review and, of these, 26 investigated the diagnostic accuracy of PET. Twenty-five presented patient-based data and seven presented lesion-based data for PET. Six studies investigated the accuracy of PET/CT, five presenting patient-based data and one presenting lesion-based data. Sixteen studies conducted direct comparisons and, of these, 12 compared the accuracy of PET or PET/CT with conventional diagnostic tests and four compared PET or PET/CT with an MRI technology. Quality varied between studies, and the major quality issue identified was the time delay between conventional tests and PET or PET/CT in comparative studies. The PET or PET/CT technology used was similar across the studies.

1. For patient-based data, in studies where direct comparisons were made, PET had significantly higher sensitivity [89%, 95% confidence interval (CI) 83% to 93% vs 79%, 95% CI 72% to 85%, relative sensitivity 1.12, 95% CI 1.04 to 1.21, $p = 0.005$] and significantly higher

specificity (93%, 95% CI 83% to 97% vs 83%, 95% CI 67% to 92%, relative specificity 1.12, 95% CI 1.01 to 1.24, $p = 0.036$), compared with conventional imaging tests (CITs) ($n = 10$). Test performance did not appear to vary according to the type of CIT that was compared with PET ($p = 0.500$). Indirect comparisons, where all CIT ($n = 11$) and PET ($n = 25$) studies were included, gave the same findings. For lesion-based data, no significant differences in sensitivity or specificity between PET and CIT were observed for studies making direct comparisons ($n = 3$) or for indirect comparisons for all PET ($n = 7$) and CIT ($n = 3$) studies. In the sensitivity analysis of patient data, for studies in which the time period between PET and comparator tests was clearly less than 1 month ($n = 6$), differences between PET and CIT tended to be smaller and the difference in sensitivity became non-significant.

2. For patient-based data, in all studies where direct comparisons were made ($n = 4$), the CIT used was CT. In these studies, compared with CT, PET/CT had significantly higher sensitivity (95%, 95% CI 88% to 98% vs 80%, 95% CI 65% to 90%, relative sensitivity 1.19, 95% CI 1.03 to 1.37, $p = 0.015$) but the increase in specificity was not significant (89%, 95% CI 69% to 97% vs 77%, 95% CI 50% to 92%, relative specificity 1.15, 95% CI 0.95 to 1.41, $p = 0.157$). Indirect comparisons, where all CIT ($n = 11$) and PET/CT ($n = 5$) studies were included, gave the same findings. No lesion-based data compared PET/CT with CIT. In the sensitivity analysis of patient data, for studies in which the time period between PET/CT and comparator tests was clearly less than 1 month ($n = 3$) differences between PET/CT and CT became non-significant.
3. For patient-based data, three studies compared PET with different types of MRI technology. In each of these studies, there were no significant differences in the sensitivity or specificity of PET compared with MRI. One study compared PET/CT and MRI on a lesion basis and there were no significant differences in sensitivity or specificity for PET/CT compared with MRI.
4. For patient-based data, in the analysis of studies directly comparing PET/CT and PET ($n = 4$), PET/CT had significantly higher sensitivity (96%, 95% CI 90% to 98% vs 85%, 95% CI 77% to 91%, relative sensitivity 1.11, 95% CI 1.03 to 1.18, $p = 0.006$), but the increase in specificity was not significant compared with PET (89%, 95% CI 74% to 96% vs 82%, 95% CI 64% to 92%, relative specificity 1.08, 95% CI 0.94 to 1.20, $p = 0.267$). The same pattern of results was observed for the indirect comparison of all PET/CT ($n = 5$) and PET ($n = 25$) studies. In the lesion-based analysis, indirect comparison of PET/CT ($n = 2$) and PET ($n = 7$) showed no significant differences in sensitivity or specificity between PET/CT and PET.
5. For overall diagnostic accuracy, on a patient basis, PET/CT ($n = 5$) and PET ($n = 25$) had sensitivities of 96% (95% CI 89% to 99%) and 91% (95% CI 86% to 94%) and specificities of 89% (95% CI 75% to 95%) and 86% (95% CI 79% to 91%) respectively. On a lesion basis, PET/CT ($n = 2$) and PET ($n = 7$) had sensitivities of 96% (95% CI 80% to 99%) and 89% (95% CI 78% to 95%) and specificities of 83% (95% CI 61% to 94%) and 91% (95% CI 83% to 96%), respectively. There was considerable heterogeneity in the spread of results for PET.
6. Changes in patient management in study participants ranged from 11% to 74% (median 27%). These changes included initiation and avoidance of medical treatment such as hormone therapy and chemotherapy. In the three studies where only changes in management directly due to PET or PET/CT were considered (patients were not correctly diagnosed by conventional imaging techniques), estimates ranged from 11% to 25%.
7. In subgroup analysis, the accuracy of PET did not appear to be related to the location of disease or to whether PET was conducted with or without knowledge of previous clinical history and imaging studies. Characteristics of patient populations varied in many respects and it was not possible to draw definite conclusions about patient characteristics that may have an impact on test accuracy.

Conclusions

- For detection of BC recurrence, in addition to conventional imaging techniques, PET may generally offer improved diagnostic accuracy compared with current standard practice. Uncertainty remains around its use as a replacement, rather than an add-on, to existing imaging technologies.
- PET/CT appears to show a clear advantage over CT for the diagnosis of BC recurrence. Although PET/CT may give an advantage over other CITs, its incremental value over

other tests has yet to be directly assessed in studies. Concurrent use with, rather than replacement of, other conventional tests may be appropriate.
- PET/CT appears to show a clear advantage over PET and it is likely to be preferred to PET for use in this context.
- PET and PET/CT appear to have some impact on patient management but there is currently no evidence of the effect of their use on patient outcomes.

Recommendations for future research

- Prospective studies with patient populations clearly defined with regard to their clinical presentation.
- Study of the diagnostic accuracy of PET/CT compared with conventional imaging techniques.
- Study of PET/CT compared with whole-body MRI.
- Studies investigating the possibility of using PET/CT as a replacement for, rather than an addition to, CITs.
- Using modelling of the impact of PET/CT on patient outcomes (to be published in another report) to inform the possibility of conducting large-scale intervention trials to assess impacts on long-term patient outcomes.

Implications for policy

PET/CT has largely superseded PET in current practice, and the apparent advantage of PET/CT over PET found in this review supports that move. On the basis of some of the uncertainties observed, it may be premature to make recommendations about the precise diagnostic role of PET/CT in practice. However, current recommendations for its use for diagnosing metastatic BC following equivocal findings on conventional imaging techniques appear to be justified. It appears that PET/CT may be useful as an addition to current practice for the diagnosis of BC recurrence but this should be reassessed in light of the analysis of its cost-effectiveness.

Chapter 1
Introduction

Breast cancer

One in thirteen women in the UK will develop breast cancer (BC) in their lifetime. In women, BC accounts for one-third of all cases of cancer. In the UK, from 2004–6, the incidence rate of new BC was 122 per 10,000 women.[1] Most women fortunately present with early-stage breast cancer (ESBC) and the UK NHS Breast Screening Programme currently offers screening at 50 years of age. ESBC is treated with surgery and adjuvant therapy often involving combinations of hormone therapy, chemotherapy and radiation therapy.[2] Treatment options have developed significantly over the past decade and, with early diagnosis, rates of 5-year survival are currently > 80% and have increased steadily over the past 10–20 years.[1] However, a number of women will develop metastatic disease and die of their BC.

Follow-up and treatment in the setting of recurrence

In most BC units, after treatment for the initial disease, patients are routinely followed up with clinical examination and mammography for at least 5 years,[3] specifically looking for treatable local recurrence and symptoms to suggest metastatic disease. Investigational screening for metastatic disease is not performed routinely. If symptoms suggest relapse with metastatic disease, further investigations may be conducted where there is suspicion of disease. Rates of BC recurrence have been shown to be around 20%[4,5] and recurrence may be local (in the breast), regional (lymph nodes in the ipsilateral axilla) or distant metastases (in tissues such as bone, liver, lungs and brain). Of patients with BC recurrence, one study showed that 27% had bone metastases, 27% had local recurrence, 16% had lung metastases and 13% had liver metastases.[4]

If metastatic disease is established, patients are generally not curable and treatment is aimed at palliating symptoms and improving survival if possible. Useful and sometimes lengthy clinical responses can be obtained by using hormone therapy in hormone-responsive disease and with chemotherapy, particularly with the newer agents. Taxane-based chemotherapy is considered likely to increase overall survival, time to progression and overall response in the second-line setting,[2] and Herceptin® (trastuzumab, Roche) is showing promising results in HER (human epidermal growth factor receptor)-2-positive disease. Radiotherapy, combined with appropriate analgesia, may be effective in reducing persistent localised bone pain.[2]

Existing diagnostic strategies

Women with a past history of BC may present with symptoms that may be innocent or indicate disease. There is a range of strategies that may be involved in patient diagnosis and the choice of tests used depends on the presenting symptoms. Conventional workup (CW) often includes conventional X-rays, computed tomography (CT), ultrasound, bone scintigraphy and measurement of serum tumour markers and, in a limited number of settings, magnetic resonance imaging (MRI) may be available for use.

Conventional X-rays are widely available and are routinely used for cases of suspected BC recurrence. X-rays may be particularly useful for the diagnosis of metastases in the lung and bones (chest or individual bone X-ray).[6] CT scans can be used to detect cancer in a range of tissue types (lung, bone, soft tissue, etc.).[7] Ultrasound can be used to detect liver metastases.[6] Bone scintigraphy uses radionuclides of technetium-99m-labelled disphosphonates and is used for the identification of bone metastases.[8]

Several biochemical compounds in the serum/plasma may act as indicators of the presence, risk or prognosis of cancer.[9] In patients with history of BC, elevated tumour marker levels may represent cases of tumour relapse.[9] It has been shown that increasing levels of these markers is associated with disease recurrence and may indicate the need for further investigation. MRI may be used for the detection of local BC recurrence[10] or, with imaging of the whole body, for the additional detection of

bone metastases[11] and other distant metastases.[12] However, access to MRI is limited[6] and it is not routinely used for diagnosing suspected BC recurrence.

In the setting of diagnosis of BC recurrence, CW is likely to comprise a combination of these technologies (in most cases, CW will not include MRI). Patients may undergo a variety of tests depending on their presenting symptoms and on the basis of the results of other imaging tests.

PET and PET/CT

Positron emission tomography (PET) and, more recently, positron emission tomography/computed tomography (PET/CT) are technologies that have been increasingly shown to have application in the detection and management of cancer, with the introduction of whole-body PET and PET/CT in the late 1990s. These technologies involve administration of a radioactive isotope and detection of photons produced in the process of radioactive decay and interaction with surrounding tissues.[13] In oncology, the most commonly used radionuclide is ^{18}F-fluorodeoxyglucose (FDG) which is taken up into cells in the same way as glucose. FDG accumulates in tumour tissue owing to increased glucose requirements and therefore increased glucose uptake. Also, in most tissues, FDG accumulates following uptake and phosphorylation, as, unlike glucose, it cannot enter the normal glycolytic pathway.[13] FDG is administered intravenously to patients and, following an interval of time (usually 60–90 minutes) to allow uptake, PET scans are conducted. The whole body may be imaged during a single session[14] and these technologies may be used to detect both local and metastatic tumours.

PET/CT combines information obtained from PET with data from CT scanning.[15] As these technologies provide different types of data (PET gives metabolic and CT anatomical data), their combination provides greater diagnostic information. CT data are also used for attenuation correction of PET images.[15] An attenuation map of CT can be used to estimate attenuation factors for PET and this correction can be applied to increase the accuracy of the images produced.[13]

In 2005, the Royal College of Radiologists published a strategy document detailing the provision of PET/CT instruments across the UK.[16] At that time, there were 11 fixed scanning PET/CT units installed in the UK predominantly for clinical use. Recommendations included a hub and satellite system, where central hub staff and resources would be used to maintain PET/CT scanners in more numerous satellite settings.[16] Initially, provision was to be made for one PET/CT system per 1.5 million of the population,[16] equating to ~40 machines for the current UK population.

Measurement of diagnostic accuracy

Diagnostic accuracy is usually defined as the sensitivity and specificity of a test, where sensitivity describes the ability of a test to correctly identify individuals with the disease and specificity describes the ability of a test to correctly identify individuals without the disease. The test under study is referred to as the index test and the results of this test are compared with the 'reference standard'. The reference standard is a test that is considered to show the true disease status of each individual and determines which individuals are classed as having or not having the disease. The comparison of the index test with the reference standard allows findings for each patient to be classed into one of four categories:

True-positive (TP) The index test detects disease and is in agreement with the reference standard that also detected disease.

True-negative (TN) The index test does not detect disease and is in agreement with the reference standard that also did not detect disease.

False-positive (FP) The index test detects disease but disagrees with the reference standard that did not detect disease.

False-negative (FN) The index test does not detect disease but disagrees with the reference standard that did detect disease.

Findings for TP, TN, FP and FN can be used to calculate the sensitivity and specificity of the index test, where sensitivity is the ratio of the number of people correctly identified with the disease compared with the total number of people classed with the disease [sensitivity = TP/(TP + FN)], and specificity is the ratio of the number of people correctly identified as not having the disease compared to the total number of people classed as not having the disease [specificity = TN/(TN + FP)]. As in the current review, where additional comparator tests are also being considered, these

are assessed as if they were another index test, i.e. findings for the comparator test are compared with those of the reference standard to class them as TP, TN, FP or FN.

Results from test accuracy studies may be presented on summary receiver operating planes, where each point on the graph represents the diagnostic accuracy of a test found in each particular study. Specificity is plotted on the *x*-axis and sensitivity on the *y*-axis and the results from meta-analysis of the studies are shown as summary points.

Potential modifiers of the diagnostic accuracy of PET and PET/CT

The diagnostic accuracy of PET and PET/CT are likely to vary depending on features of the patient population, technology used and design of the investigative study.

Features of the patient population, such as the nature of disease, may affect the accuracy of PET or PET/CT. For example, if lesions are small or particularly difficult to detect, sensitivity may tend to be lower. Accuracy may also depend on the location of disease, and PET and PET/CT may vary in their ability to diagnose local, regional and metastatic disease.

The methods used for PET or PET/CT investigations may be important modifiers of diagnostic accuracy. As these techniques use radioactive isotopes of glucose to indicate sites of increased metabolic activity, misdiagnosis may result from elevated blood glucose levels. It is recommended that all patients fast for at least 4–6 hours before scanning.[14] The presence of patient fasting, and exclusion of those with diabetes or impaired glucose tolerance, may be important mediators of diagnostic accuracy. The presence of attenuation correction, using CT data or another correction method, is an important predictor of diagnostic accuracy and may cause variation in the accuracy of PET or PET/CT in studies. Further aspects of technology that may affect diagnosis are features such as the length of radioisotope uptake, image acquisition time and the mode of image interpretation.

The study design may also have an impact on diagnostic accuracy. A distinction may be made between studies where assessors have knowledge of previous clinical and imaging findings and studies where assessors interpret PET or PET/CT without knowledge of these results. Where assessors have knowledge of previous findings, apparent diagnostic accuracy may be anticipated to be better than when assessors do not have knowledge of previous imaging findings. This also has implications for the applicability of study findings to clinical use. If PET or PET/CT is to be used instead of existing diagnostic imaging tests, only the results of studies in which previous imaging results are unknown may be relevant, whereas, if PET and PET/CT are to be used as technologies in addition to standard imaging procedures, studies in which assessors have knowledge of previous findings may be more applicable.

Current guidelines

Guidelines have been developed by the National Institute for Health and Clinical Excellence (NICE) for the treatment of early/locally advanced[3] and advanced[17] BC. In the early BC guidance, key recommendations for the follow-up of patients with BC include provision of designated health-care professionals, dates for review of any adjuvant therapy, surveillance with mammography and contact points for specialist care.[3] The guidance suggests that future research should involve determination of the appropriate length of follow-up and suitable methods for detecting disease recurrence.[3]

The advanced BC guidelines give advice on the treatment of advanced/metastatic disease that is generally only amenable to palliative care without curative intent. These guidelines do not specifically relate to the diagnosis of BC recurrence. However, some guidance given may be applicable. The NICE guidelines state that 'Positron emission tomography fused with computed tomography (PET-CT) should only be used to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.'[17] In other words, PET/CT would only be used for diagnosis in cases where conventional imaging techniques fail to properly diagnose the presence or absence of metastases. Although these guidelines relate to the use of PET/CT, all of the evidence reviewed to inform them are studies or systematic reviews of PET and not PET/CT. Additionally, these guidelines refer only to the diagnosis of metastatic, and not local, recurrence and the evidence base relating to the application of PET and PET/CT for the detection of recurrent BC is not clear.

Chapter 2
Rationale and objectives

This report covers the question of the effectiveness of PET and PET/CT for diagnosing BC recurrence and another report (to follow) will provide economic modelling to address the question of their cost-effectiveness in this context.

We have reviewed existing systematic reviews assessing the effectiveness of PET and PET/CT in the diagnosis of recurrent BC. The two most relevant were the Blue Cross/Blue Shield report 2001[18] and Isasi *et al.* 2005.[19] The latter provides the most up-to-date assessment of test accuracy of PET in evaluations up to 2004, but no estimation of accuracy compared with existing diagnostic strategies. However, the key outstanding issue was the amount of improvement that PET and PET/CT offer over existing diagnostic approaches and this was the focus of the current review.

The main aims of this review were to assess the incremental diagnostic accuracy of PET and PET/CT compared with existing diagnostic strategies and to compare the diagnostic accuracy of PET and PET/CT for the diagnosis of BC recurrence. The accuracy of PET and PET/CT were to be considered in addition to standard practice.

Further aims were to assess the overall test accuracy of PET and PET/CT, to assess the impact of PET and PET/CT on patient management and to investigate possible determinants of variation in the diagnostic accuracy of PET. For clarity, objectives were, in the detection of BC recurrence:

1. To assess the incremental diagnostic accuracy of PET in addition to standard practice compared with conventional imaging tests (CITs).
2. To assess the incremental diagnostic accuracy of PET/CT in addition to standard practice compared with CITs.
3. To assess the incremental diagnostic accuracy of PET and PET/CT in addition to standard practice compared with MRI.
4. To compare the diagnostic accuracy of PET and PET/CT.
5. To obtain independent estimates of the diagnostic accuracy for PET and PET/CT in addition to standard practice.
6. To examine changes in patient management owing to the use of PET and PET/CT.
7. To explore possible determinants of variation in the accuracy of PET and PET/CT.

Chapter 3
Methods

The protocol was reviewed by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (see Appendix 10) and there were no major departures from it when conducting the review.

Identifying studies

Search strategy

Searches were conducted in MEDLINE (Ovid) and EMBASE (Ovid) and strategies combined MeSH (Medical Subject Headings) and text words to define the index test (PET and PET/CT) and the population (suspected breast cancer recurrence) (see Appendix 1). No language restrictions were used and searches were carried out from inception of the databases up to May 2009.

Selection of studies

Titles/abstracts obtained from the literature search were scanned for inclusion by one reviewer. Where information given in title/abstracts suggested that the study (1) included patients with past history of breast cancer, (2) conducted PET or PET/CT scans in those patients, and (3) assessed test accuracy, full paper articles were retrieved for further assessment. Additionally, studies potentially containing information on cost-effectiveness or one or more relevant clinical outcome measures were retrieved. If there was doubt regarding inclusion from the title and abstract, the full article was obtained for clarification. Stringent inclusion/exclusion criteria were applied to full paper studies in order to obtain the final set of included studies.

Inclusion/exclusion criteria

Full paper articles were screened in relation to the following inclusion/exclusion criteria by one reviewer with reference to a second reviewer where there was any doubt about their eligibility.

Population

The patient population was to be under investigation for suspicion of BC recurrence. Patients were to have had a previous diagnosis of BC and to have completed a course of primary treatment. The initial aim of this review was to include only studies in which patients had previously been cleared of BC. However, it soon became evident that, in many studies, the exact patient group was unclear. It was often not fully clear whether patients with history of BC had subsequently been cleared or if they had known BC and were having further imaging investigations in order to diagnose metastatic disease. Exclusion of these types of studies was likely to substantially limit the scope of this review and restrict its application.

A decision was therefore made to include studies investigating the diagnosis of BC recurrence in patient groups that may have been cleared or not cleared of their original disease. All studies were to have been conducted in the context of secondary BC investigations, i.e. they did not form part of the initial BC diagnosis, BC staging or monitoring of response to primary BC treatment. Included studies were required to show evidence that investigations were distinct from primary investigations and were conducted after completion of the primary course of treatment.

Index test

Included studies were to have used PET or PET/CT to diagnose BC recurrence in patients with history of BC. The PET or PET/CT technology was required to be a dedicated machine and use a FDG tracer. Studies were excluded if coincidence gamma camera PET had been used or if other types of radioactive tracers had been used.

Reference standard

Studies were included if the reference standard used to define the true disease status was histological diagnosis (operation/biopsy) and/or long-term clinical follow-up. Studies were excluded if details of the reference standard were not given or if no suitable reference standard was used, e.g. other imaging studies conducted without follow-up.

Comparator

This review included both studies with and without comparator groups. Within-study comparisons are more robust as they effectively eliminate differences in potential modifiers of test accuracy between the two tests being compared. Indirect comparisons (comparison of independently pooled summary estimates across all studies) can also be conducted on the larger set of comparative and non-comparative studies. For studies including comparator groups, those using any diagnostic comparators were included but patients were also to have undergone PET or PET/CT and the reference standard. Studies in which PET or PET/CT and other diagnostic techniques were compared without use of a reference standard were excluded.

Outcomes

Studies giving sufficient information on the diagnosis of BC recurrence to determine the number of TP, TN, FP and FN test results were included. Recurrence could be local, regional or distant but disease was to be considered to be a consequence of the originally diagnosed breast cancer. Additional studies that contained information on the influence of PET or PET/CT on patient management or the reasons for FP and FN results were also included.

Data extraction

The number of TP, TN, FP and FN values were extracted from each study. In all studies, only data for participants who had undergone a satisfactory reference standard were extracted. In studies where there were comparator tests, where possible, only data for participants who had undergone both the index and comparator tests were selected. Information relating to patient management and location sites of FPs and FNs on PET or PET/CT scans was also extracted. Test accuracy data was extracted by two independent reviewers. Where there were differences in the retrieved data, these were discussed and a consensus of the true values was reached. Data related to patient management and sites of FPs and FNs were extracted by one reviewer. Authors of potentially included studies were contacted if relevant study data was incomplete but it appeared likely to have been obtained.

Quality assessment

Quality assessment was conducted independently by two reviewers, using relevant items from the QADAS (Quality Assessment of Diagnostic Accuracy Studies) tool,[20] and differences resolved by consensus. Quality assessment criteria for study methodology related to patient selection, use of the reference standard, blinding and external validity. Additionally, the time delay between the index and comparator tests was assessed as an aspect of study quality as this has potential to bias estimates of relative test accuracy. The technical quality of the PET or PET/CT technology was assessed with reference to procedure guidelines,[21] as used by Isasi *et al*.,[19] with particular reference to pre-scan blood glucose testing, the use of attenuation correction and the duration of FDG uptake. Quality criteria were set with the specifications outlined in *Table 1*.

Data analysis

Positron emission tomography and PET/CT were considered as independent technologies for analysis. Comparative tests considered to be conventionally used for diagnosis in this setting were grouped together for comparison with PET and PET/CT. CITs were defined as one or more of bone scintigraphy, CT, X-ray and general CW. Single comparators, e.g. CT or bone scintigraphy, were classed as CIT if they were judged to be adequate diagnostic methods in the context of the study. For example, for the diagnosis of bone metastases, bone scintigraphy was considered as CIT because, despite being a single diagnostic test, it would be appropriate in the context of diagnosing bone metastases. MRI was considered as a separate technology from CIT as, in many hospitals, it may not be part of the conventional diagnostic strategy (Professor Patricia Price, Imperial College London, 2010, personal communication). Data from studies in which PET or PET/CT were used in addition to other imaging techniques and studies in which assessors were blinded to previous imaging results were pooled in the analysis. This approach was considered conservative in light of the emphasis of the review (to assess the diagnostic accuracy of PET and PET/CT in addition to standard practice).

REVIEW MANAGER 5.0 was used to produce a methodological quality summary table and

TABLE 1 *Quality assessment criteria*

Quality item	Criteria
Representative spectrum	Patients typical of those presenting for BC recurrence?
Acceptable reference standard	Histology or follow up for >6 months?
Acceptable delay between tests	≤ 1 month between PET or PET/CT and comparator test?
Partial verification avoided	All patients received adequate reference standard?
Differential verification avoided	All patients received same reference standard regardless of results of PET or PET/CT?
Incorporation avoided	Results of PET or PET/CT were not used as part of the final diagnosis of BC?
Index test results blinded	Interpreters of PET or PET/CT were not aware of the final diagnosis of BC?
Relevant clinical information	Assessors of PET or PET/CT had information on patient histories and previous imaging studies?
Additional technology-specific criteria	
Measurement of blood glucose	Exclusion of patients with blood glucose levels ≥ 130 mg/dl?
Attenuation correction	Was attenuation correction used for PET or PET/CT scans?
Uptake >60 minutes	Were patients given doses of FDG glucose >60 minutes prior to scanning?

forest plots of sensitivity and specificity for each test from the extracted 2×2 data and to present meta-analytic results in receiver operating characteristic (ROC) space. In order to make inferences about the relative accuracy of the tests in terms of sensitivity and specificity (instead of the diagnostic odds ratio), a bivariate method, rather than the [7]hierarchical summary receiver operating characteristic (HSROC) method, as specified in the protocol, was used for statistical analysis. A meta-analysis was done for each pair-wise comparison of imaging modalities to estimate ratios of sensitivity and specificity. The bivariate random effects approach described by Reitsma *et al.*[22] was used to obtain summary estimates of sensitivity, specificity and ratios of values between tests (relative sensitivity and specificity). This approach preserves the two-dimensional nature of the data by incorporating the correlation between sensitivity and specificity. It also takes into account both within-study sampling variability in estimates of sensitivity and specificity and between-study variability in test performance through the inclusion of random effects. All models were fitted using the NLMIXED procedure in SAS based on the formulation proposed by Chu and Cole.[23]

To investigate differences in test performance according to type of CIT (CT, CW and bone scintigraphy), a second covariate was introduced into the analytical model comparing PET with CIT. To achieve convergence, this model was simplified by setting the correlation parameter equal to zero. This is equivalent to fitting two random effects logistic regression models for sensitivity and specificity separately.

Data presented on a patient and lesion basis were considered separately in the analysis. Patient-based data were used as the basis for the main analysis and for the investigation of heterogeneity. As limited patient data were available on a location-specific basis, lesion data were used to inform investigation of relative test accuracy in different sites. For patient-based data, each patient constituted the unit of analysis and, for lesion-based data, each lesion suspected of disease constituted the unit of analysis.

The primary outcomes of interest were the accuracy of PET and PET/CT compared with conventional technologies and the accuracy of PET compared with PET/CT. Using patient- and lesion-based data (where available), comparisons were made for:

- PET compared with CIT
- PET/CT compared with CIT
- PET compared with PET/CT.

Estimations of the differences in test accuracy were first made using only studies in which PET or PET/CT had been compared directly with other technologies or with each other (referred to as direct comparisons). Indirect comparisons were also made by pooling estimates for each test across all included studies before making between-test comparisons.

Sensitivity analysis

Sensitivity analysis was conducted to examine the reliability of findings for comparisons among PET, PET/CT and CIT. As the emphasis of this review was on studies directly comparing tests, sensitivity analysis was applied only to direct comparisons. Issues of quality related to individual studies, e.g. representativeness of patient spectrum, quality of the reference standard, etc., were unlikely to have affected the comparisons and these factors were therefore not included in the sensitivity analysis. However, aspects that could have differed between tests under investigation were eligible for sensitivity analysis. The area of potential concern, where conditions for different tests may have varied, was the time delay between the index (PET or PET/CT) and comparator tests and the reference standard. In the sensitivity analysis, to remove the bias associated with different time lapses between tests and the reference standard, studies were removed if PET or PET/CT investigations were not conducted within 1 month of comparator tests or if the period of time between tests was unclear.

Subgroup analysis

Subgroup analyses were conducted to investigate factors that may have been sources of heterogeneity. The limited number of direct comparison studies (10 for PET vs CIT and 4 for PET/CT vs CIT) limited subgroup analysis within this set but subgroup analysis was conducted on the larger set of studies in which PET (with or without a comparator group; $n = 25$) had been performed. Subgroup analysis was not performed for PET/CT owing to the limited amount of data available. Subgroup analysis was conducted to compare studies of:

- PET in patients with negative results for previous imaging studies versus PET in patients with positive or suspicious previous imaging results
- PET in different locations of the body
- PET for investigation of those cleared of BC versus PET for those not cleared/where disease status is unclear
- PET in addition to standard practice versus PET instead of standard practice.

Chapter 4
Results

A total of 2526 citations were retrieved from the search of the databases, of which 522 were duplicates. After title/abstract screening, a total of 185 full papers was ordered for review. Thirty-two studies were included in the final review, 28 provided quantitative data and the reasons for full paper exclusions are given in *Figure 1*.

Included studies

Twenty-eight studies were identified as containing information on diagnostic accuracy relevant to the current review. Most of these studies investigated PET ($n = 26$) and fewer assessed PET/CT ($n = 6$) (four studies investigated both PET and PET/CT). Sixteen studies were direct comparisons and 12 were non-comparative (*Table 2*). Direct comparison studies investigated the accuracy of PET or PET/CT compared with MRI ($n = 4$) or with more conventional diagnostic strategies (CW, CT and bone scintigraphy) ($n = 12$). In most studies, data were presented on a patient basis ($n = 26$). In nine studies, lesion data were presented and seven studies presented both patient and lesion data (*Table 2*). The numbers of patients for the main groups for analysis are shown in *Table 2*.

Three studies contained information on changes in patient management owing to PET or PET/CT. These were excluded from quantitative synthesis because there was no test accuracy data,[52,53] a less sophisticated PET technology[54] or an unsatisfactory reference standard,[55] but information from these studies was included in the patient management part of the review (see Chapter 4, Changes in patient management).

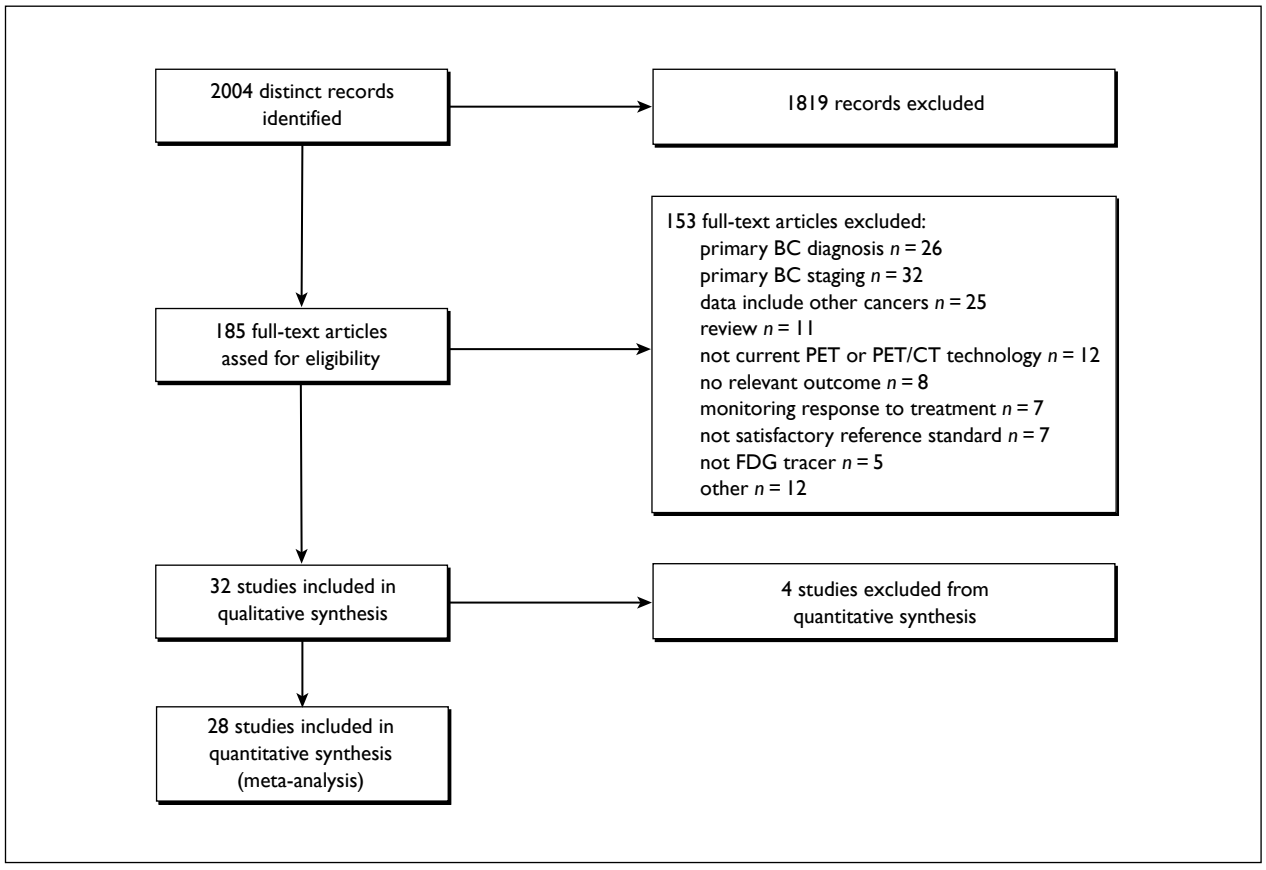

FIGURE 1 *PRISMA diagram.*

TABLE 2 *Numbers of studies and patients/lesions in the main groups for analysis*

Analysis	Number of studies[a]	Number of patients/lesions
Patient data		
PET vs CIT	10	456 patients
PET/CT vs CIT	4	167 patients
PET vs PET/CT	4	188 patients
PET	25	1379 patients
PET/CT	5	225 patients
Lesion data		
PET vs CIT	3	449 lesions (154 patients)
PET	7	690 lesions (331 patients)
PET/CT	2	443 lesions (79 patients)

a Numbers do not add up to 28 because some studies contain data for PET and PET/CT or patient and lesion data.

Population characteristics

The characteristics of patient populations in the included studies are shown in *Table 4* (comparative studies) and *Table 5* (non-comparative studies). The size of study samples ranged from 10 to 291 patients (median 45). In most cases the reference standard was a combination of histology and clinical follow-up including conventional imaging techniques.

In all studies, patients were being investigated for BC disease distinct from primary investigations. In 16 of the studies[25,30–36,38–40,42,43,46–48] it appeared that all patients had previously been cleared of BC, whereas in the remaining 12 studies,[24,26–29,37,41,44,45,49–51] investigations were for the diagnosis of metastases in patients with a diagnosis of BC or where the diagnosis of patients was unclear.

Quality of study methodology

In the assessment of study quality (*Figure 2*), approximately one-third ($n = 10$) of the studies[29–31,35,43,45–48,50] were considered to have investigated a representative spectrum of patients. In these studies, patients were selected in a consecutive series or all patients examined within a certain period of time were selected for investigation. In other studies, the method for patient selection was unclear or it appeared that the patients being investigated were not representative of those that might typically present for diagnosis of BC recurrence.

The majority of studies used an acceptable reference standard ($n = 21$) (histology or follow-up > 6 months) but in three studies in some patients follow-up was < 6 months,[28,32,41] in two studies the duration of follow-up was unclear,[34,42] and in one study changes in tumour markers were used to define the reference standard in some patients.[25]

In the majority of comparative studies, PET or PET/CT were conducted after the comparator. The time delay between PET or PET/CT and the comparator was < 1 month in 11 studies[24,27,28,30,32,33,41,44,46,48,51] but, in the rest of the comparative studies, the time delay was either not reported or appeared to be longer than 1 month.

In most studies ($n = 19$), it was reported that all patients received a reference standard (avoiding partial verification bias). However, it was often not clear whether this was a criterion for enrolment into the study, i.e. patients without reference standard data (follow-up, histology, etc.) were excluded from the study and not mentioned in the reporting of results. Studies in which exclusions for incomplete follow-up were explicit, and were therefore considered to be at risk of partial verification bias ($n = 8$),[27,28,30,34,36,44,47,48] may therefore not have been of poorer study quality but may have simply been more transparent in their reporting of study methods.

The results of PET or PET/CT may have had some influence on the mode or intensity of subsequent patient follow-up (differential verification bias).

TABLE 3 *Included studies with diagnostic accuracy data*

	Index test		Comparator		Data	
	PET	**PET/CT**	**CIT**	**MRI**	**Patient**	**Lesion**
Abe 2005[24]	✓		Bone scintigraphy		✓	✓
Aide 2007[25]	✓		–		✓	
Bender 1997[26]	✓		–	✓	✓	
Dirisamer 2010[27]	✓	✓	CT		✓	
Fueger 2005[28]	✓	✓	–		✓	
Gallowitsch 2003[29]	✓		CW		✓	✓
Goerres 2003[30]	✓		–	✓	✓	
Guillemard 2006[31]	✓		–		✓	
Hathaway 1999[32]	✓		–	✓	✓	
Haug 2007[33]	✓	✓	CT		✓	
Hubner 2000[34]	✓		CT		✓	
Kamel 2003[35]	✓		–		✓	✓
Kim 2001[36]	✓		–		✓	✓
Lin 2002[37]	✓		–		✓	✓
Liu 2002[38]	✓		–		✓	
Lonneux 2000[39]	✓		–		✓	
Moon 1998[40]	✓		–		✓	✓
Ohta 2001[41]	✓		Bone scintigraphy		✓	
Pecking 2004[42]	✓		–		✓	
Radan 2006[43]		✓	CT		✓	✓
Raileanu 2004[44]	✓		Bone scintigraphy		✓	
Santiago 2006[45]	✓		–		✓	
Schmidt 2008[46]		✓	–	✓		✓
Suarez 2002[47]	✓		–		✓	
Veit-Haibach 2007[48]	✓	✓	CT		✓	
Vranjesevic 2002[49]	✓		CW		✓	
Wolfort 2006[50]	✓		CW		✓	
Yang 2002[51]	✓		Bone scintigraphy			✓

In most studies this was thought to have been likely or uncertain. In one study,[50] follow-up was histology in all patients and therefore differential verification was not considered to have been a source of bias in this study.

Incorporation bias, the inclusion of index test results as part of the reference standard, may have played some role in most studies. Findings from PET or PET/CT may have influenced final diagnosis. However, the relative influence of PET or PET/CT findings compared with subsequent follow-up examinations may have been small and limited the size of this bias.

Blinding of the interpretation of PET or PET/CT to the results of the reference standard (index test blinding) clearly took place in nine studies.[24,25,27,28,30,35,40,48,49] In the remaining studies the presence of blinding was unclear. The interpretation of PET or PET/CT will be naturally blinded in prospective studies as the reference standard diagnosis is assigned after PET or PET/CT during follow-up. In retrospective studies, if results are those of PET or PET/CT reassessed at a later date (after the reference standard), without blinding to final patient diagnosis, there is risk of bias. In the remaining studies, it was often unclear whether (1) studies were prospective or

TABLE 4 *Characteristics of study populations for studies comparing PET and/or PET/CT with other imaging tests*

Study and date	Age (years) (range)	*n*	Data *n*[a]	Reason for investigation with PET or PET/CT	Prevalence (%)	Location of test	Reference standard
CIT comparator							
Abe 2005[24]	56 (35–81)	44	44	BC patients with suspicion of bone metastases	32	Bone	Biopsy or clinical follow-up (> 6 months)
Dirisamer 2010[27]	61 (40–84)	52	52	Restaging due to elevated tumour markers (*n* = 32), clinical deterioration (*n* = 16) or suspicious conventional imaging (*n* = 48)	81	Whole body	Histology or clinical follow-up examinations and imaging (6 months)
Gallowitsch 2003[29]	58 (range NR)	62	62	Suspected recurrence/metastases based on suspicious or inconclusive CIT or increase in tumour markers	55	Whole body	Histology and/or clinical follow-up (8–54 months, mean 24 months)
Haug 2007[33]	51 (28–73)	34	34	Suspicion of recurrence on basis of increased tumour markers (negative previous CIT)	76	Whole body	Histology and clinical/radiological follow-up > 12 months
Hubner 2000[34]	59	57	64/44[b]	Suspected BC recurrence (reason for referral not specified)	66	Whole body	Histology or clinical follow-up
Ohta 2001[41]	49 (29–79)	51	51	BC patients with suspicion of bone metastases	17	Bone	Confirmation by one or more imaging techniques on follow-up
Radan 2006[43]	60 (32–79)	46	37[c]	Suspected recurrence based on elevated serum tumour markers	54	Whole body	Pathology (23%) and imaging follow-up (mean 17.2 months, 1–42 months)
Raileanu 2004[44]	53 (range NR)	20	20	BC patients with suspicion of bone metastases	35	Bone	Clinical follow-up over 6 months
Veit-Haibach 2007[48]	56 (36–80)	44	44[d]	Suspicion of BC recurrence due to increased tumour markers (*n* = 15) or suspicious conventional imaging (*n* = 29)	43	Whole body	Histology (15 patients) and clinical follow-up (mean 15 months, 5–31 months)
Vranjesevic 2002[49]	54 (32–91)	61	61	Examined for residual or recurrent disease for: no reason (*n* = 42), increased tumour markers (*n* = 10) and/or equivocal CIT (*n* = 9)	69	Whole body	Clinical follow-up (> 6 months, mean 21 months)
Wolfort 2006[50]	NR	23	18[e]	Clinical suspicion (symptoms) of recurrence or systemic disease	70	Whole body	Clinical follow up (exam every 3 months for 3 years, then every 6 months for years 3–5)
Yang 2002[51]	38–67	48	127[f]	BC patients with suspicion of bone metastases	Lesion basis	Bone	Histology or clinical follow up > 12 months with CT, MRI or PET

Study and date	Age (years) (range)	*n*	Data *n*[a]	Reason for investigation with PET or PET/CT	Prevalence (%)	Location of test	Reference standard
MRI comparator							
Bender 1997[26]	46 (32–74)	75	75	Suspected recurrent or metastatic disease	19	Whole body	Histology (95%) or clinical follow-up
Goerres 2003[30]	57 (32–76)	49	32[g]	Suspected local/regional recurrence or contralateral BC	44	Local	Cytology/histology (17) or clinical follow-up (15) of > 12 months
Hathaway 1999[32]	58.4 (45–71)	10	7[h]	Suspicion of local-regional recurrence based on clinical signs or symptoms	86	Local	Surgical confirmation (*n* = 4) or follow-up PET studies (2–24 months)
Schmidt 2008[46]	55 (24–79)	33	263[f]	Suspicion of recurrence due to clinical examination (*n* = 9), findings on conventional imaging (*n* = 14), newly elevated tumour markers (*n* = 10)	NR	Whole body	Clinical and radiological follow up > 6 months (mean 14 months, 6–37 months)

NR, not reported.
a Data that were used for analysis.
b Sixty-four PET scans in 57 patients, only 44 had CT.
c Only 37 of 46 patients had comparative CT data available.
d In this study data for restaging were presented on a patient basis and could therefore be interpreted in terms of diagnostic accuracy: correctly up-staged patients TP, correctly down-staged patients TN, under-staged patients FN, over-staged patients FP. This interpretation gave a conservative assessment of test accuracy as correct patient diagnosis may be achieved without necessarily correct patient staging.
e Only 18 of 23 patients had results for PET, conventional imaging and the reference standard.
f Lesions.
g Only 32 of 49 patients had follow-up data and PET and MRI results.
h Excluding patients being investigated for initial staging in the setting of primary diagnosis.

TABLE 5 *Characteristics of study populations for studies not comparing PET and/or PET/CT with other imaging tests*

Study and date	Age (years) (range)	*n*	Data *n*[a]	Reason for investigation with PET or PET/CT	Prevalence (%)	Location of test	Reference standard
Aide 2007[25]	61 (42–84)	35	35	Suspected recurrence based on increased tumour marker CA 15–3. No abnormality at conventional imaging 3 months before	80	Whole body	Histology or imaging and clinical follow up over > 12 months
Fueger 2005[28]	53 (29–80)	58	58	Restaging due to elevated tumour markers, symptoms or equivocal/suspicious conventional imaging findings	57	Whole body	Biopsy, other imaging and clinical follow-up
Guillemard 2006[31]	62 (49–76)	14	14	Suspicion of recurrence based on increased tumour markers. Asymptomatic with inconclusive conventional imaging results	57	Whole body	Histology and follow-up (> 6 months)
Kamel 2003[35]	55 (30–79)	60	46/57[b]	Clinical suspicion of recurrence based on physical examination ($n = 35$) and abnormal CIT ($n = 25$)	52	Whole body	Histopathology or imaging/ clinical follow-up for 6–30 months
Kim 2001[36]	46 (28–62)	27	27	Clinical suspicion of recurrence or systemic disease based on physical examination or imaging studies	63	Whole body	Histology and clinical/ radiological follow-up for > 6 months
Lin 2002[37]	48 (35–68)	36	36	Suspected local recurrence or systemic disease	11	Local	Histology and/or biopsy or follow-up > 12 months
Liu 2002[38]	(mean NR) (38–65)	30	30	Suspected recurrence based on increased tumour marker levels, all patients negative for conventional imaging	93	Whole body	Histiology or clinical imaging follow-up > 12 months
Suarez 2002[47]	58 (35–80)	38	38	Suspicion of recurrence based on elevated tumour markers (asymptomatic and negative clinical examinations)	68	Whole body	Histology, other imaging or clinical follow-up for > 12 months
Moon 1998[40]	55 (30–80)	57	57	Clinical suspicion of recurrence based on symptoms ($n = 10$), mass lesions ($n = 10$) and increased tumour markers ($n = 13$)	51	Whole body	Follow-up imaging studies for > 6 months
Lonneux 2000[39]	57 (36–78)	39	39	Suspicion of recurrence based on increased tumour markers ($n = 34$) and clinical symptoms ($n = 5$)	85	Whole body	Follow-up (12–24 months)
Pecking 2004[42]	51 (31–79)	291	291	Suspected BC recurrence based on elevated tumour markers (without any evidence of malignancies)	92	Whole body	Conventional imaging and pathology over 2 months or follow-up at 6 and 12 months
Santiago 2006[45]	55 (34–82)	133	133	Suspicion of recurrence/metastases due to clinical suspicion ($n = 31$) equivocal conventional imaging ($n = 63$) or elevated tumour markers ($n = 15$) or staging/restaging ($n = 33$)	74	Whole body	Follow-up for > 6 months with conventional imaging

CA, cancer antigen; NR, not reported.
a Data that were used for analysis.
b Forty-six examined for loco-regional recurrence, 57 examined for metastasis.

retrospective, (2) results were for scans assessed at the time of investigation or those of reassessment at a later date, and (3) whether blinding was used if scans were being reassessed. There was therefore some uncertainty around this item of quality.

In 10 studies, PET or PET/CT were interpreted with knowledge of relevant clinical information (knowledge of previous patient history and imaging results).[26,29,36–39,43,45,50,51] In 10 studies assessors were blinded to previous relevant clinical information.[24,25,27,30,33,34,41,46,48,49] In these studies, the assessment of incremental diagnostic accuracy of PET or PET/CT in addition to standard practice was likely to be underestimated. In eight studies,[28,31,32,35,40,42,44,47] it was unclear what information was available to assessors.

	Representative spectrum?	Acceptable reference standard?	Acceptable delay between tests?[a]	Partial verification avoided?	Differential verification avoided?	Incorporation avoided?	Index test results blinded?	Relevant clinical information?	Measurement of blood glucose?	Attenuation correction?	Uptake time >60 minutes?
Abe 2005[24]	?	+	+	+	?	–	+	–	+	+	+
Aide 2007[25]	?	–		+	–	–	+	–	+	+	+
Bender 1997[26]	?	+	?	+	?	?	?	+	–	+	–
Dirisamer 2010[29]	+	+	+	–	?	?	+	–	–	?	–
Fueger 2005[28]	+	?	+	–	?	?	+	?	–	+	+
Gallowitsch 2003[29]	+	+	–	+	–	–	?	+	+	+	+
Goerres 2003[30]	+	+	+	–	–	–	+	–	–	+	–
Guillemard 2006[31]	+	+		+	?	–	?	?	+	+	+
Hathaway 1999[32]	?	–	+	+	–	–	?	?	+	+	–
Haug 2007[33]	?	+	+	+	?	–	?	–	+	+	+
Hubner 2000[34]	?	?	?	–	?	?	?	–	–	+	?
Kamel 2003[35]	+	+		+	?	–	+	?	–	+	–
Kim 2001[36]	?	+		–	?	–	?	+	–	+	+
Lin 2002[37]	?	+		+	?	–	?	+	–	–	?
Liu 2002[38]	?	+		+	?	–	?	+	–	+	–
Lonneux 2000[39]	?	+		+	?	–	?	+	–	–	+
Moon 1998[40]	?	+		+	?	–	+	?	–	–	–
Ohta 2001[41]	?	–	+	+	?	–	?	–	–	?	–
Pecking 2004[42]	–	?		+	?	–	?	?	–	+	+
Radan 2006[43]	+	+	–	+	?	–	?	+	+	+	+
Raileanu 2004[44]	–	+	+	–	?	–	?	?	–	?	+
Santiago 2006[45]	+	+		+	?	–	?	+	–	?	–
Schmidt 2008[46]	+	+	+	+	?	–	?	–	–	+	+
Suarez 2002[47]	+	+		–	?	–	?	?	+	+	+
Veit-Haibach 2007[48]	+	+	+	–	?	–	+	–	+	?	–
Vranjesevic 2002[49]	?	+	–	?	?	–	+	–	–	–	–
Wolfort 2006[50]	+	+	–	+	+	–	?	+	?	?	?
Yang 2002[51]	?	+	+	+	?	–	?	+	–	?	–

FIGURE 2 *Quality assessment of all included studies. (a) Quality item was applied to studies where diagnostic accuracy of tests was compared.*

Characteristics and quality of PET or PET/CT technology

The characteristics and quality determinants of the PET and PET/CT technologies used are given in Appendix 2. Quality findings for three specific factors, identified as particularly important aspects of technical quality, are shown in *Figure 2*. PET and PET/CT machines were considered standard in all of the included studies, but attenuation correction was only used in 19 studies. Attenuation correction was not used or not reported in the remaining nine studies.[27,37,40,41,44,45,49–51] Interpretation of scans was predominantly by visual inspection. Standardised uptake values were used for sole classification in one study[42] and, in seven studies, both visual and quantitative methods were used.[27,32,34,36,46–48] In almost all studies it was reported that patients were asked to fast at the time of PET, but in only nine studies blood glucose levels were measured before the test and used as criteria for entry into the study.[24,25,29,31–33,43,47,48] The dose of FDG ranged from 101 MBq to 740 MBq. In 18 studies dose appeared to have been adjusted on the basis of body weight, and in nine studies dose was constant.[27,29,30,33,37–39,48,51] Dose was not reported in one study.[50] Visual inspection of the three technical aspects of PET and PET/CT quality revealed no relationship between these aspects of quality and the diagnostic accuracy of PET or PET/CT.

Test accuracy results

For each of the objectives, results for patient and then lesion data are presented.

PET compared with CITs

Patient data

Ten studies investigated the diagnostic accuracy of conventional imaging techniques compared with PET on a patient basis.[24,27,29,33,34,41,44,48–50] *Figure 3* provides individual study data, *Table 6* gives pooled summary estimates, *Figure 4* gives quality scores and *Figure 5* displays the SROC plane for studies directly comparing PET with CITs. In these studies, PET had significantly higher sensitivity [89%, 95% confidence interval (CI) 83% to 93% vs 79%, 95% CI 72% to 85%, relative sensitivity 1.12, 95% CI 1.04 to 1.21, $p = 0.005$] and significantly higher specificity (93%, 95% CI 83% to 97% vs 83%, 95% CI 67% to 92%, relative specificity 1.12, 95% CI 1.01 to 1.24, $p = 0.036$) (*Table 6*). The relative accuracy of PET did not appear to vary according to the type of CIT (bone scintigraphy, CW, CT) with which it was compared ($p = 0.50$).

For all studies of PET ($n = 25$) or CIT ($n = 11$) (indirect comparison), PET had significantly higher sensitivity (91%, 95% CI 87% to 93% vs 81%, 95% CI 73% to 87%, relative sensitivity 1.12, 95%

Study	*n*		TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abe 2005[24]	44	PET	14	1	0	29	1.00 (0.77 to 1.00)	0.97 (0.83 to 1.00)
		BS	11	0	3	30	0.79 (0.49 to 0.95)	1.00 (0.88 to 1.00)
Ohta 2001[41]	51	PET	7	1	2	42	0.78 (0.40 to 0.97)	0.98 (0.88 to 1.00)
		BS	7	8	2	34	0.78 (0.40 to 0.97)	0.81 (0.66 to 0.91)
Raileanu 2004[44]	20	PET	6	0	1	13	0.86 (0.42 to 1.00)	1.00 (0.75 to 1.00)
		BS	7	3	0	10	1.00 (0.59 to 1.00)	0.77 (0.46 to 0.95)
Dirisamer 2010[27]	52	PET	34	0	8	10	0.81 (0.66 to 0.91)	1.00 (0.69 to 1.00)
		CT	28	0	14	10	0.67 (0.50 to 0.80)	1.00 (0.69 to 1.00)
Haug 2007[33]	34	PET	23	1	3	7	0.88 (0.70 to 0.98)	0.88 (0.47 to 1.00)
		CT	24	2	2	6	0.92 (0.75 to 0.99)	0.75 (0.35 to 0.97)
Hubner 2000[34]	44	PET	36	6	6	16	0.86 (0.71 to 0.95)	0.73 (0.50 to 0.89)
		CT	22	6	9	7	0.71 (0.52 to 0.86)	0.54 (0.25 to 0.81)
Veit-Haibach 2007[48]	44	PET	17	6	2	19	0.89 (0.67 to 0.99)	0.76 (0.55 to 0.91)
		CT	17	6	2	19	0.89 (0.67 to 0.99)	0.76 (0.55 to 0.91)
Gallowitsch 2003[23]	62	PET	33	5	1	23	0.97 (0.85 to 1.00)	0.82 (0.63 to 0.94)
		CW	28	13	6	15	0.82 (0.65 to 0.93)	0.54 (0.34 to 0.72)
Vranjesevic 2002[49]	61	PET	39	3	3	16	0.93 (0.81 to 0.99)	0.84 (0.60 to 0.97)
		CW	33	6	9	13	0.79 (0.63 to 0.90)	0.68 (0.43 to 0.87)
Wolfort 2006[50]	23	PET	13	0	3	7	0.81 (0.54 to 0.96)	1.00 (0.59 to 1.00)
		CW	11	0	4	7	0.73 (0.45 to 0.92)	1.00 (0.59 to 1.00)

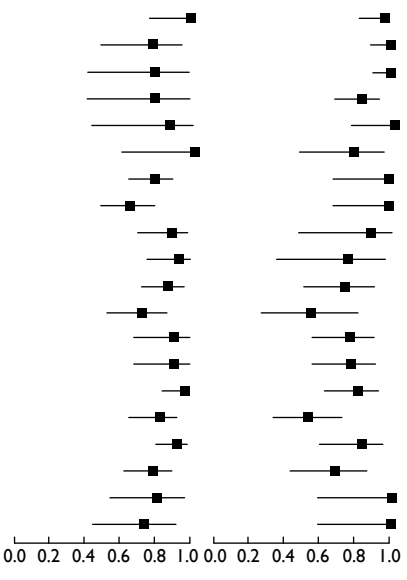

FIGURE 3 *Patient data for the diagnostic accuracy of PET and CITs in comparative studies. BS, bone scintigraphy.*

TABLE 6 *Patient data: direct and indirect comparisons of the sensitivity and specificity of PET compared with CITs*

Comparison	PET sensitivity % (95% CI)	CIT sensitivity % (95% CI)	Relative sensitivity (95% CI)	PET specificity % (95% CI)	CIT specificity % (95% CI)	Relative specificity (95% CI)
Direct PET vs CIT	89 (83 to 93) $n = 10$	79 (72 to 85) $n = 10$	1.12 (1.04 to 1.21) $p = 0.005$	93 (83 to 97)	83 (67 to 92)	1.12 (1.01 to 1.24) $p = 0.036$
Indirect PET vs CIT	91 (87 to 93) $n = 25$	81 (73 to 87) $n = 11$	1.12 (1.04 to 1.21) $p = 0.005$	86 (79 to 91)	73 (59 to 83)	1.18 (1.03 to 1.36) $p = 0.017$

CI 1.04 to 1.21, $p = 0.005$) and significantly higher specificity (86%, 95% CI 79% to 91% vs 73%, 95% CI 59% to 83%, relative specificity 1.18, 95% CI 1.03 to 1.36, $p = 0.017$) compared with CIT (*Table 6* and Appendix 3, *Figure 13*).

Sensitivity analysis

When the comparison between PET and CIT was conducted with only studies in which PET and CIT (patient data) were done within a 1-month time period ($n = 6$),[24,27,33,41,44,48] PET was no longer significantly more sensitive than CIT ($p = 0.4797$) but the significant increase in specificity remained ($p = 0.022$) (Appendix 7, *Table 11a* and *Figure 27*).

Lesion data

For lesion-based data, three studies directly compared the diagnostic accuracy of PET with CIT.[24,29,51] For these studies, there were no significant differences in sensitivity (relative sensitivity 0.93, 95% CI 0.76 to 1.13, $p = 0.447$) or specificity (relative specificity 1.29, 95% CI 0.57 to 2.90, $p = 0.540$) for PET compared with CIT (Appendix 4, *Figures 17* and *18*). In the indirect comparison of PET studies presenting lesion data ($n = 7$) with CIT studies presenting lesion data ($n = 3$), there were no significant differences in sensitivity (relative sensitivity 0.98, 95% CI 0.90 to 1.07, $p = 0.624$) or specificity (relative specificity 2.57, 95% CI 0.41 to 16.07, $p = 0.313$) for PET compared with CIT (Appendix 4, *Table 9* and *Figure 18*).

PET/CT compared with CITs

Patient data

Four studies compared the accuracy of PET/CT with CIT on a patient basis[27,33,43,48] and, in each

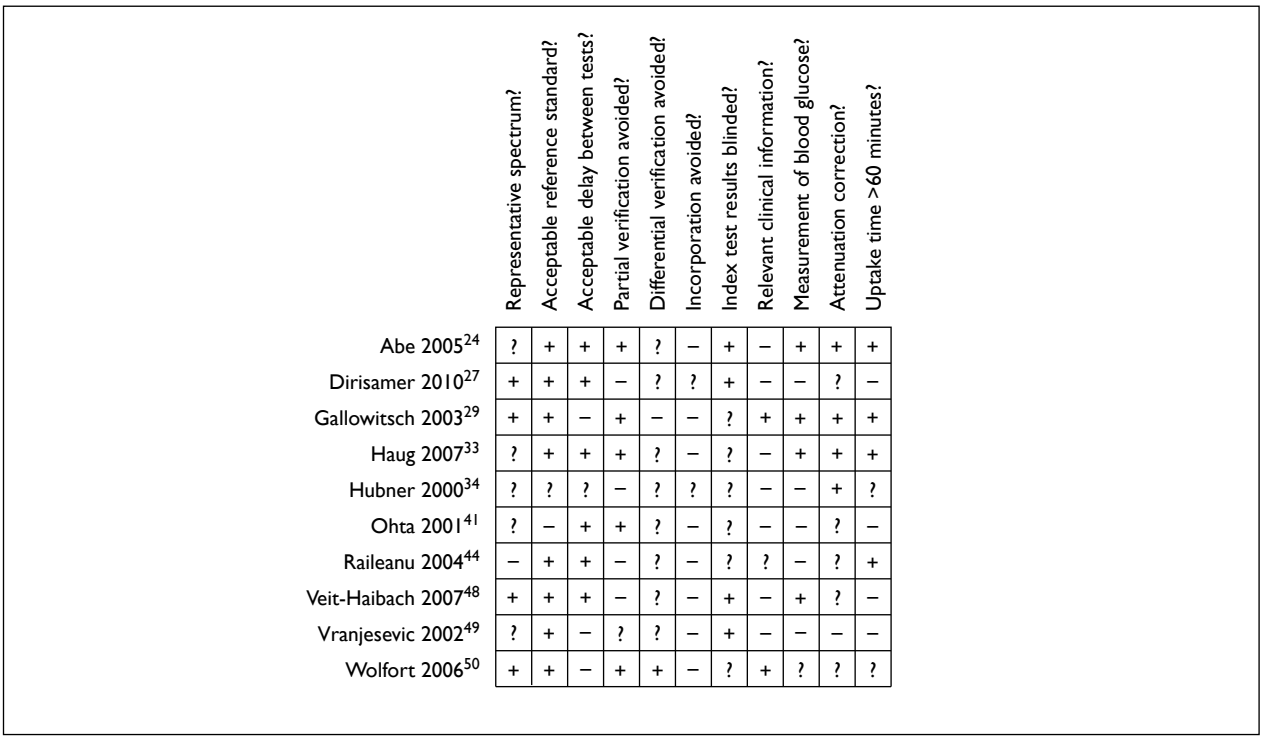

FIGURE 4 *Quality assessment for studies comparing PET with CITs.*

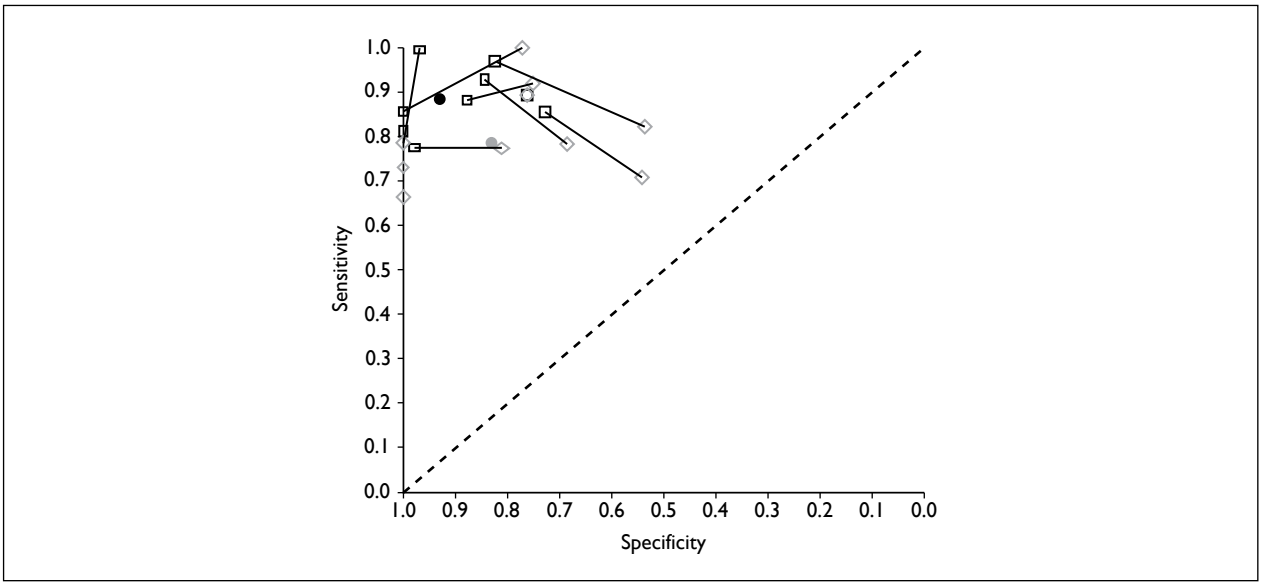

FIGURE 5 *Summary receiver operating characteristic plane for studies directly comparing the diagnostic performance of PET (□) and CITs (◊) for patients with suspected BC recurrence.*

Study	*n*		TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dirisamer 2010[27]	52	PET/CT	40	0	2	10	0.95 (0.84 to 0.99)	1.00 (0.69 to 1.00)
		CT	28	0	14	10	0.67 (0.50 to 0.80)	1.00 (0.69 to 1.00)
Haug 2007[33]	34	PET/CT	24	1	1	8	0.96 (0.80 to 1.00)	0.89 (0.52 to 1.00)
		CT	24	2	2	6	0.92 (0.75 to 0.99)	0.75 (0.35 to 0.97)
Radan 2006[43]	37	PET/CT	17	4	3	13	0.85 (0.62 to 0.97)	0.76 (0.50 to 0.93)
		CT	14	9	6	8	0.70 (0.46 to 0.88)	0.47 (0.23 to 0.72)
Veit-Haibach 2007[48]	44	PET/CT	19	4	0	21	1.00 (0.82 to 1.00)	0.84 (0.64 to 0.95)
		CT	17	6	2	19	0.89 (0.67 to 0.99)	0.76 (0.55 to 0.91)

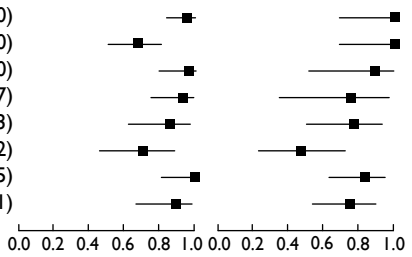

FIGURE 6 *Patient data for the diagnostic accuracy of PET/CT and CT in comparative studies.*

case, the conventional imaging technique was CT. *Figure 6* provides individual study data, *Table 7* gives pooled summary estimates, *Figure 7* gives quality scores and *Figure 8* displays the SROC plane for studies directly comparing PET/CT with CT. In these studies, in comparison with CT, PET/CT had significantly higher sensitivity (95%, 95% CI 88% to 98% vs 80%, 95% CI 65% to 90%, relative sensitivity 1.19, 95% CI 1.03 to 1.37, $n = 4$, $p = 0.015$) but the increase in specificity was not significant (89%, 95% CI 69% to 97% vs 77%, 95% CI 50% to 92%, relative specificity 1.15, 95% CI 0.95 to 1.41, $p = 0.157$) (*Table 7*). For all studies of patient-basis PET/CT ($n = 5$) and CIT ($n = 11$) in indirect comparisons, the sensitivity was significantly higher (95%, 95% CI 89% to 97% vs 78%, 95% CI 72% to 84%, relative sensitivity 1.21, 95% CI 1.11 to 1.31, $p < 0.0001$) but the increase in specificity was not significant (89%, 95% CI 76% to 96% vs 79%, 95% CI 65% to 88%, relative specificity 1.13, 95% CI 0.99 to 1.29, $p = 0.063$) (*Table 7*).

Sensitivity analysis

One study in which CT was not conducted at the same time as PET/CT was removed in the sensitivity analysis.[43] Despite the continued pattern of advantage of PET/CT over CT in the remaining studies ($n = 3$), PET/CT was no longer significantly more sensitive ($p = 0.063$) or specific ($p = 0.367$) compared with CIT (Appendix 7, *Table 11b* and *Figure 28*).

Lesion data

No studies comparing the accuracy of PET/CT with CIT presented lesion-based data.

TABLE 7 *Patient data: direct comparison of the sensitivity and specificity of PET/CT compared with CT and indirect comparison of PET/CT compared with a range of CITs*

Comparison	PET/CT sensitivity% (95% CI)	CIT sensitivity % (95% CI)	Relative sensitivity (95% CI)	PET/CT specificity % (95% CI)	CIT specificity % (95% CI)	Relative specificity (95% CI)
Direct PET/CT vs CT	95 (88 to 98), *n* = 4	80 (65 to 90), *n* = 4	1.19 (1.03 to 1.37) *p* = 0.015	89 (69 to 97)	77 (50 to 92)	1.15 (0.95 to 1.41) *p* = 0.157
Indirect PET/CT vs CIT	95 (89 to 97), *n* = 5	78 (72 to 84), *n* = 11	1.21 (1.11 to1.31) *p* < 0.0001	89 (76 to 96)	79 (65 to 88)	1.13 (0.99 to 1.29) *p* = 0.063

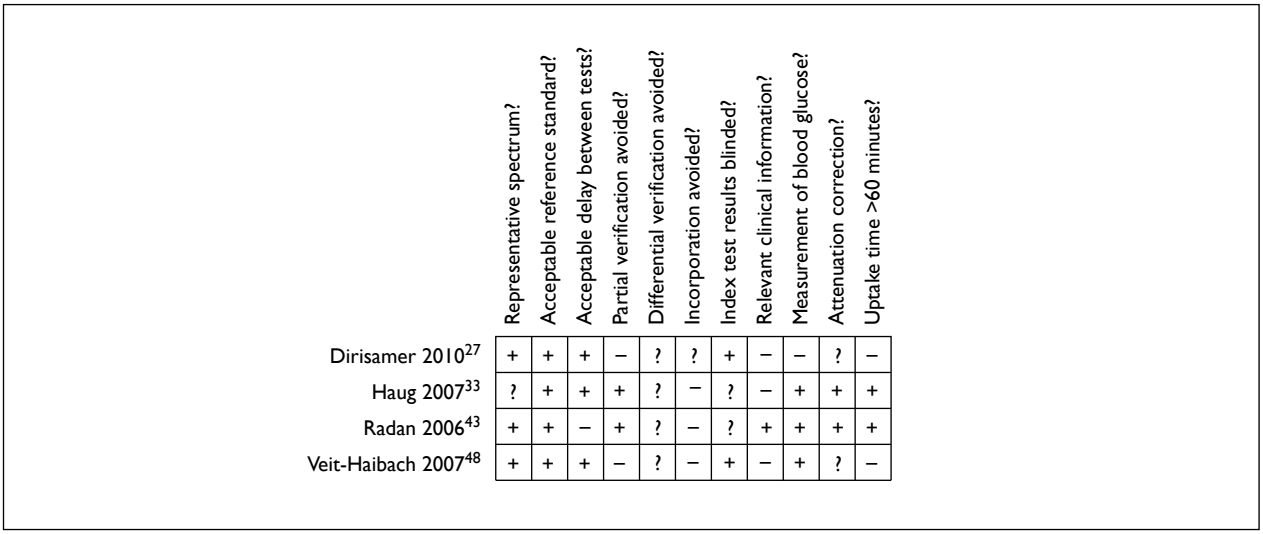

FIGURE 7 *Quality assessment of studies comparing PET/CT and CIT (CT).*

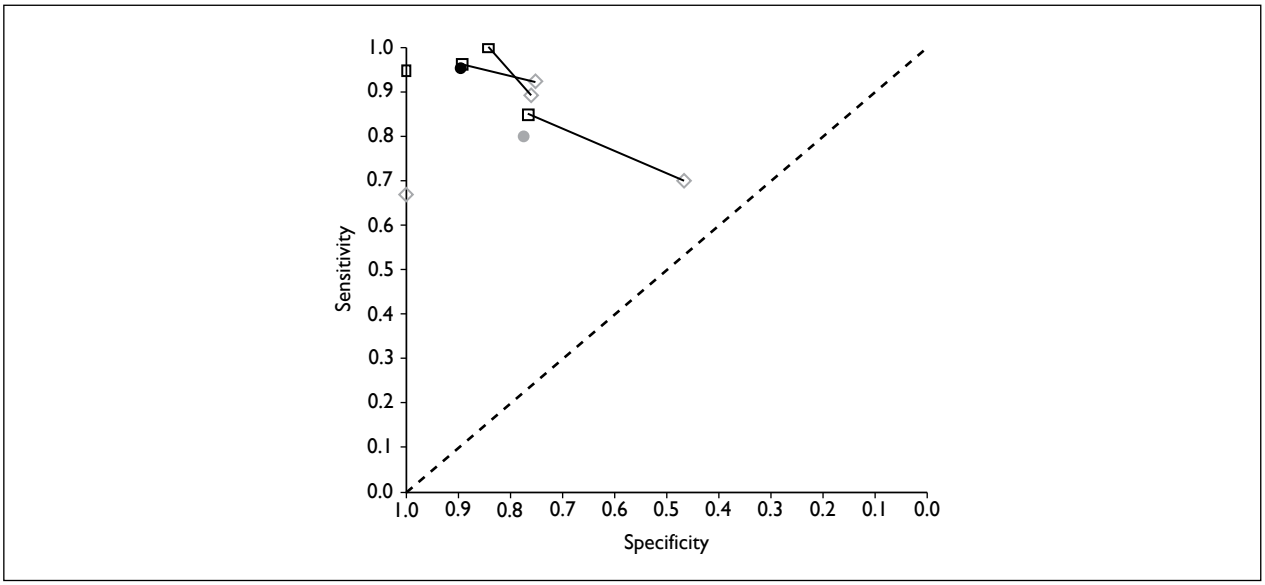

FIGURE 8 *Summary receiver operating characteristic curve for studies directly comparing the diagnostic performance of PET/CT (□) and CT (◊) for patients with suspected BC recurrence.*

PET and PET/CT compared with MRI

Patient data

Three studies investigated the diagnostic accuracy of PET and MRI on a patient basis, but the MRI technologies used in these studies were quite distinct. In one study[32] auxiliary and supraclavicular MRI was used to diagnose local recurrence. In the second study[26] whole-body MRI and/or CT was used to detect local recurrence and distant metastases, and in the third study[30] breast MRI was used for local recurrence. Results for these studies are shown in *Figure 9*. There were no significant differences in sensitivity or specificity between PET and MRI in any of these studies and, because of the differences in the MRI technologies, results from the studies were not combined.

Lesion data

One lesion-based study compared PET/CT with MRI[46] and there was no significant difference in sensitivity and specificity for PET/CT compared with MRI (Appendix 4, *Figure 19*).

PET/CT compared with PET

Patient data

Four studies compared the accuracy of PET and PET/CT on a patient basis.[27,28,33,48] *Figure 10* provides individual study data, *Table 8* gives pooled summary estimates, *Figure 11* shows quality scores and *Figure 12* displays the SROC planes for studies directly comparing PET with PET/CT. In these studies, PET/CT had significantly higher sensitivity (96%, 95% CI 90% to 98% vs 85%, 95% CI 77% to 91%, relative sensitivity 1.11, 95% CI 1.03 to 1.18, $p = 0.006$) but the increase in specificity was not significant (89%, 95% CI 74% to 96% vs 82%, 95% CI 64% to 92%, relative specificity 1.08, 95% CI 0.94 to 1.20, $p = 0.267$) compared with PET (*Table 8* and *Figure 12*). For all patient-based studies of PET/CT ($n = 5$) and PET ($n = 25$), in indirect comparisons PET/CT had significantly higher sensitivity (96%, 95% CI 91% to 98% vs 90%, 95% CI 86% to 93%, relative sensitivity 1.06, 95% CI 1.01 to 1.10, $p = 0.009$) but the increase in specificity was not significant (89%, 95% CI 77% to 95%, vs 86%, 95% CI 79% to 91%, relative specificity 1.04, 95% CI 0.95 to 1.13, $p = 0.377$) compared with PET (*Table 8* and Appendix 3, *Figure 15*).

Study	*n*		TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bender 1997[26]	64	PET	10	2	4	48	0.71 (0.42 to 0.92)	0.96 (0.86 to 1.00)
	74	MRI	13	2	1	58	0.93 (0.66 to 1.00)	0.97 (0.88 to 1.00)
Goerres 2003[30]	32	PET	11	1	3	17	0.79 (0.49 to 0.95)	0.94 (0.73 to 1.00)
		MRI	14	5	0	13	1.00 (0.77 to 1.00)	0.72 (0.47 to 0.90)
Hathaway 1999[32]	7	PET	6	0	0	1	1.00 (0.54 to 1.00)	1.00 (0.03 to 1.00)
		MRI	6	0	0	1	1.00 (0.54 to 1.00)	1.00 (0.03 to 1.00)

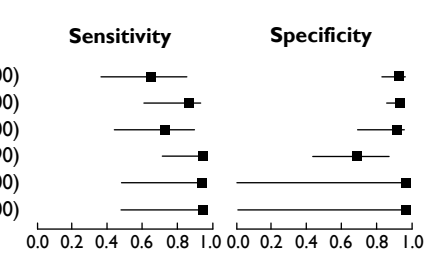

FIGURE 9 *Patient data for the diagnostic accuracy of PET and MRI in comparative studies. No studies compared the diagnostic accuracy of PET/CT with MRI on a patient basis.*

Study	*n*		TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dirisamer 2010[27]	52	PET/CT	40	0	2	10	0.95 (0.84 to 0.99)	1.00 (0.69 to 1.00)
		PET	34	0	8	10	0.81 (0.66 to 0.91)	1.00 (0.69 to 1.00)
Fueger 2005[28]	58	PET/CT	31	4	2	21	0.94 (0.80 to 0.99)	0.84 (0.64 to 0.95)
		PET	28	7	5	18	0.85 (0.68 to 0.95)	0.72 (0.51 to 0.88)
Haug 2007[33]	34	PET/CT	24	1	1	8	0.96 (0.80 to 1.00)	0.89 (0.52 to 1.00)
		PET	23	1	3	7	0.88 (0.70 to 0.98)	0.88 (0.47 to 1.00)
Veit-Haibach 2007[48]	44	PET/CT	19	4	0	21	1.00 (0.82 to 1.00)	0.84 (0.64 to 0.95)
		PET	17	6	2	19	0.89 (0.67 to 0.99)	0.76 (0.55 to 0.91)

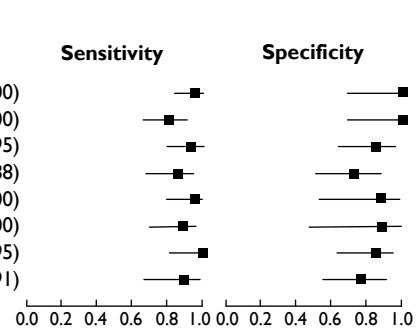

FIGURE 10 *Patient data for the diagnostic accuracy of PET and PET/CT in comparative studies.*

TABLE 8 *Patient data: direct and indirect comparisons of the relative sensitivity and specificity of PET/CT compared with PET*

Comparison	PET/CT sensitivity % (95% CI)	PET sensitivity % (95% CI)	Relative sensitivity (95% CI)	PET/CT specificity % (95% CI)	PET specificity % (95% CI)	Relative specificity (95% CI)
Direct PET/CT vs PET	96 (90 to 98), $n=4$	85 (77 to 91), $n=4$	1.11 (1.03 to 1.18) $p=0.006$	89 (74 to 96)	82 (64 to 92)	1.08 (0.94 to 1.20) $p=0.267$
Indirect PET/CT vs PET	96 (91 to 98), $n=5$	90 (86 to 93), $n=25$	1.06 (1.01 to 1.10) $p=0.009$	89 (77 to 95)	86 (79 to 91)	1.04 (0.95 to 1.13) $p=0.377$

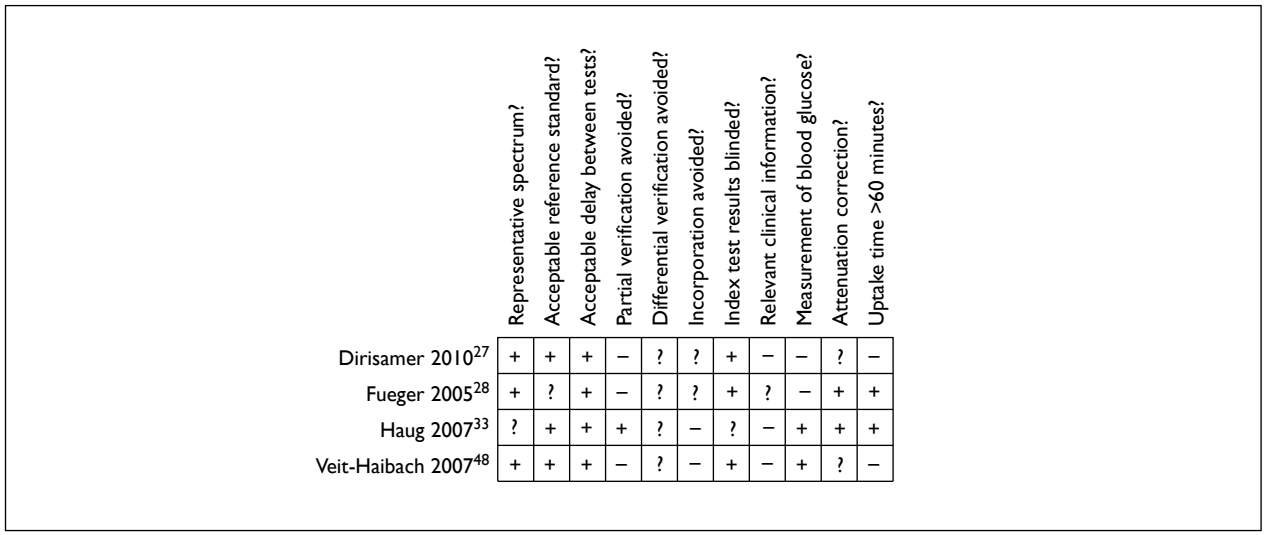

FIGURE 11 *Quality assessment of studies comparing the diagnostic accuracy of PET and PET/CT.*

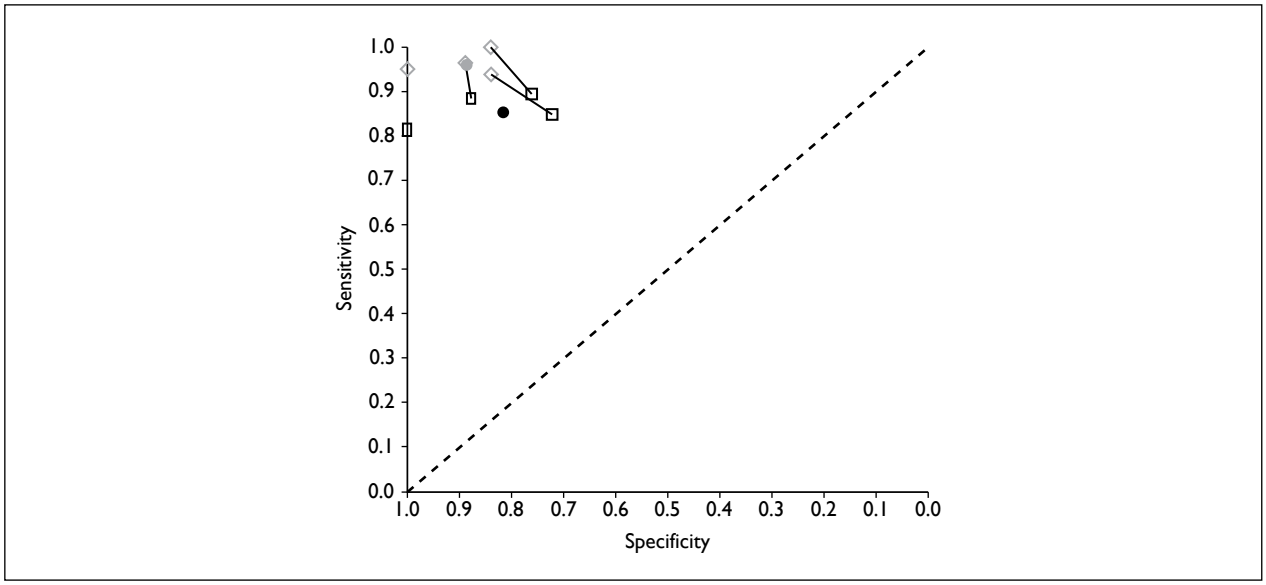

FIGURE 12 *Summary receiver operating characteristic plane for studies directly comparing the diagnostic performance of PET (□) and PET/CT (◊) for patients with suspected BC recurrence.*

Sensitivity analysis

In all studies in which PET/CT was compared with PET, tests were undertaken simultaneously and no studies were therefore removed in the sensitivity analysis.

Lesion data

No studies comparing the accuracy of PET and PET/CT presented lesion-based data.

Diagnostic accuracy of PET and PET/CT

Patient data

Patient data were presented for PET in 25 studies and for PET/CT in five studies. Sensitivity and specificity for PET were 91% (95% CI 86% to 94%) and 86% (95% CI 79% to 91%) respectively and for PET/CT were 96% (95% CI 89% to 99%) and 89% (95% CI 75% to 95%) respectively. Study data used for the calculation of overall sensitivity and specificity and figures for test accuracy findings are given in Appendix 5 (*Figures 20–23*).

Lesion data

On a lesion basis, mean sensitivity and specificity for PET ($n = 7$ studies) were 89% (95% CI 78% to 95%) and 91% (95% CI 83% to 96%). Two studies assessed the accuracy of PET/CT on a lesion basis and pooled sensitivity and specificity were 96% (95% CI 80% to 99%) and 83% (95% CI 61% to 94%) respectively (no model could be fitted to the data). Study data used for the calculation of overall sensitivity and specificity and figures for test accuracy findings are given in Appendix 5 (*Figures 24–26*).

Changes in patient management

Changes in patient management in individual studies are given in Appendix 6. Overall, the estimated numbers of patients with changes in management in studies ranged from 11% to 74% (median 27%). In the three studies where only changes in management directly owing to PET or PET/CT were considered (patients were not correctly diagnosed by conventional imaging techniques),[48,49,55] estimates tended to be lower (11–25%).

Variation in the diagnostic accuracy of PET

Further investigation of the diagnostic accuracy of PET was conducted to investigate factors that may influence test accuracy. Subgroup analysis was not conducted for PET/CT as these data were limited.

PET and location of disease

Table 12 and *Figure 29* in Appendix 8 show the relative accuracy of PET in different locations of the body with lesion-based data (limited location-specific patient-based data were available). There were no significant differences in the sensitivity or specificity of PET for the detection of local recurrence, distant metastases or disease in lymph nodes.

PET and previous imaging results

Comparisons were made between studies of PET where all patients had previously had positive or equivocal results on other imaging modalities and studies in which previous imaging had been negative in all patients (Appendix 8, *Table 13a* and *Figure 30*). Sensitivity was not significantly different in studies with negative compared with positive/equivocal previous diagnostic imaging (relative sensitivity 0.99, 95% CI 0.899 to 1.093, $p = 0.859$) but specificity was significantly lower (relative specificity 0.734, 95% CI 0.560 to 0.960, $p = 0.024$).

PET and disease status at the time of investigation

In 14 studies,[25,27,28,31–35,38–40,42,47,48] PET was exclusively used for the detection of recurrent BC in patients who had been cleared of initial disease. In the remaining 11 studies,[24,26,29,30,36,37,41,44,45,49,50] PET was used to investigate further metastases in patients with known BC or, in some studies, the disease status of the patient group was a mixture of known and unknown BC diagnosis. There was no difference in sensitivity (relative sensitivity 1.004, 95% CI 0.924 to 1.092, $p = 0.920$) but specificity was significantly lower for studies in which patients were cleared of initial disease at the time of investigation compared with studies in patients with diagnosed BC or in mixed diagnosis populations (relative specificity 0.844, 95% CI 0.734 to 0.971, $p = 0.018$) (Appendix 8, *Table 13b* and *Figure 31*).

PET and assessors knowledge of previous clinical findings

In nine studies,[24,25,27,30,33,34,41,48,49] assessors of PET were blinded to information on previous clinical examination and imaging. In eight

studies[26,29,36,37,38,39,45,50] assessors had access to previous clinical results, and in eight studies[28,31,32,35,40,42,44,47] it was unclear whether assessors had knowledge of previous findings. There was no difference in sensitivity (relative sensitivity 0.962, 95% CI 0.886 to 1.043, $p = 0.346$) or specificity (relative specificity 1.045, 95% CI 0.910 to 1.201, $p = 0.533$) between studies where assessors did not have information on previous findings compared with studies where assessors had information or where access to previous information was unclear (Appendix 8, *Table 13c*).

FP and FN PET results

The numbers of FPs and FNs for PET and PET/CT are given for studies where data was available (Appendix 9, *Tables 14* and *15*). FPs fell largely into three categories: infections and inflammation (41%), physiological muscle uptake (29%) and degenerative process/old fracture sites (10%), while the remaining 20% were assigned to other artifacts of measurement. FNs were most commonly lesions in the lymph nodes or bone.

Chapter 5
Discussion

Principal findings

PET compared with CITs

In the patient-based analysis, absolute estimates of sensitivity and specificity were around 10% higher for PET compared with CIT and differences were statistically significantly for both direct and indirect comparisons (*Table 6*). Lesion-based results were inconsistent with results for patient-based data and no significant differences were found in sensitivity or specificity for comparisons of PET with CIT (Appendix 4, *Table 9*). Lesion data are considered to be less reliable than patient data[56] and may also relate more to the ability of tests to stage, rather than diagnose, disease. There was a high degree of heterogeneity between comparative studies presenting lesion data (Appendix 4, *Figure 16*) and, for the study in which PET had very poor lesion-based sensitivity (56%),[29] patient-based data indicated a typical to high level of sensitivity (97%). Lesion-based data were not used for primary interpretation, not only owing to the small sample size and seemingly erratic nature of the data but also because of the wide recognition that patient-based data are a more true representation of the accuracy of patient diagnosis. From patient-based data, it appears that PET may give improved diagnostic accuracy compared with CIT for the diagnosis of BC recurrence, but there may be some constraints and uncertainties related to this.

In many of the included studies, sources of bias may bring some uncertainty around the apparent advantage of PET over CIT. In many of the studies comparing PET and CIT, it was unclear whether the patients selected were representative of those that might normally be examined in this context (*Figure 4*). Inclusion criteria were often not stated and it was unclear whether consecutive patients were enrolled or whether investigators selected particular individuals to take part in the study. Another aspect of quality identified as potentially important was the time delay between comparator tests and PET. Differences observed in some studies may be due partly to PET being conducted at a later time point, when disease was likely to be further developed and more detectable. In the sensitivity analysis including only studies in which PET and CIT were conducted within a 1-month time period, the difference in sensitivity between PET and CIT was reduced and became non-significant (Appendix 7, *Table 11a* and *Figure 27*), although the difference in specificity remained.

There may also be uncertainty around the magnitude of advantage of PET over different types of existing diagnostic tests. Relative accuracy may vary depending on the location of investigation and the accuracy of the particular comparative test conventionally used for diagnosis in that location. Included comparator groups classed as CIT fell into three categories: CW (a range of examination and imaging techniques), CT and bone scintigraphy. Further inspection identified that, for the three studies investigating the diagnosis of bone metastases,[24,41,44] a less consistent pattern of effect was observed, with variable advantage in sensitivity and specificity over bone scintigraphy. A recent systematic review compared the diagnostic accuracy of PET with bone scintigraphy.[57] In that review, for patient-based data, PET had similar sensitivity to bone scintigraphy (81%, 95% CI 70% to 89% and 78%, 95% CI 67% to 68%, respectively) and higher specificity but not significantly so (93%, 95% CI 84% to 97% and 79%, 95% CI 40% to 95% respectively). However, in formal statistical testing, there was no difference in the relative accuracy of PET when compared with CW, CT and bone scintigraphy ($p = 0.50$), suggesting that PET may have similar benefit when used in different contexts.

The absence of comparisons of PET with individual conventional diagnostic tests may be a limitation of this review. However, to some extent this may be counteracted by the benefit of making some estimation of the general advantage of adding PET to standard practice. The decision to combine studies of different conventional tests was made not only because of the limited number of available studies for each individual test but also so that the review might be more applicable to current practice. In practice it may be difficult to make distinctions in the use of PET for specific case presentations and there may be value in assessing whether there is likely to be a general advantage for its use for patients presenting with suspected recurrence.

It is likely that any potential advantage of PET should be considered in the context of its use in addition to, rather than instead of, existing strategies. The aim of this review was to assess comparative diagnostic accuracy in addition to standard practice but, in some of the included studies, assessors of PET were blinded to the results of previous imaging tests. This is displayed in the quality assessment as 'relevant clinical information?', i.e. were assessors blinded to previous clinical results? (*Figure 4*). In the subgroup analysis, the accuracy PET did not appear to be affected by whether assessors had knowledge of previous patient investigations (Appendix 8, *Table 13c*). Also, although the specificity of PET was lower in studies where previous imaging tests had shown negative compared with positive/equivocal findings, the level of sensitivity was similar (Appendix 8, *Table 13a*) suggesting that PET may be useful for disease diagnosis where previous imaging tests have failed. However, despite some suggestion that PET may be useful as a replacement technology, uncertainty remains around its comparative advantage in every setting and this does not warrant the recommendation of PET as a replacement to conventional imaging procedures.

Overall, PET appears to give improved diagnostic accuracy compared with CIT. However, there may be some uncertainty around these findings. There is currently insufficient evidence for the use of PET as a replacement for existing imaging technologies but, in addition to standard practice, it may give improved diagnostic accuracy compared with conventional imaging.

PET/CT compared with CITs

Positron emission tomography/computed tomography was compared with CT in four studies. PET/CT showed significantly improved sensitivity for both direct and indirect patient-based comparisons (absolute sensitivity was ~ 15% higher) but the absolute increase in specificity (~ 10%) was not statistically significant (*Table 7*). Differences were consistency shown across all of the four studies (*Figure 8*), with increases in sensitivity and specificity in each case where it could be achieved (in one study specificity was 100% for both PET/CT and CT).

In three of the four studies, patient samples appeared to be a representative spectrum of those that might be typical in clinical practice. CTs were performed as part of the PET/CT in three of the four studies but, in the other study, a separate CT was conducted earlier and the time interval before PET/CT in some of the patients was more than 1 month. After removal of this study in the sensitivity analysis, the increase in sensitivity compared with CT became non-significant (Appendix 7, *Table 11b* and *Figure 28*). However, a consistent pattern of effect was still observed for the remaining studies.

The poor availability of studies comparing the diagnostic accuracy of PET/CT with other imaging tests may to some extent limit the interpretation of findings. In comparative studies of PET/CT, the only CIT used was CT and there may be some uncertainty around the relative advantage of PET/CT over different individual CITs. In the indirect comparison, when PET/CT was compared with the range of conventional diagnostic tests (*Table 7* and Appendix 3, *Figure 14*), sensitivity was 20% higher for PET/CT than for CIT ($p < 0.0001$). However, as this analysis was not based on direct comparison studies, the finding may be interpreted with caution, and uncertainty remains around the variation in benefit of PET/CT when compared with different conventional tests.

In three of the four studies, assessors of PET/CT were blind to CT results and previous clinical findings (*Figure 7*) and it may be that, in situations where the choice of CIT is CT, PET/CT can be used as a replacement test. However, the presence of uncertainty around the comparative advantage of PET/CT over other CITs is likely to make a conservative approach more appropriate. As for PET, it may be prudent to consider PET/CT in addition to, rather than instead of, conventional diagnostic tests.

Despite the small number of available studies, the consistent improvement in test accuracy for PET/CT compared with CT provides reasonable evidence for an advantage of PET/CT over CT. PET/CT may give diagnostic advantage over other CITs but currently there is no direct evidence of the comparative advantage of PET/CT over other imaging tests.

PET and PET/CT compared with MRI

In the current review only three studies compared PET and MRI on a patient basis and, as the types of MRI technology used were different, results of these studies could not be combined. There were no significant differences in sensitivity or

specificity between PET and MRI in any of these studies and further research may be required to assess their comparative diagnostic accuracy. Only one study compared the diagnostic accuracy of PET/CT with MRI and, for this study, data were presented on a lesion basis. Sensitivity and specificity were similar for PET/CT and MRI and further patient-based studies may be important to establish the comparative accuracy of PET/CT and MRI.

PET/CT compared with PET

In this review, for all studies comparing the diagnostic accuracy of PET with PET/CT ($n = 4$), PET/CT was consistently shown to have improved sensitivity compared with PET (*Figure 12*). Differences in sensitivity were significant for both direct and indirect comparisons, but differences in specificity were not (*Table 8*). In these studies, PET/CT was used for the diagnosis of local disease and metastases in different locations and the advantage of PET/CT over PET appears to be true when considered for the detection of disease over a range of locations.

In three of the four studies, patient samples appeared to be representative of patients that might be typical in clinical practice. All studies interpreted PET images obtained during the course of conducting PET/CT and, as tests were conducted simultaneously, none needed to be removed in the sensitivity analysis.

Despite the limited number of PET/CT studies, there appears to be reasonable evidence that PET/CT gives improved sensitivity compared with PET over the whole body. If it is found to be more cost-effective, PET/CT may be considered for use instead of PET in this context.

Diagnostic accuracy of PET and PET/CT

In the current review, the sensitivity and specificity of PET are very similar to those obtained in the most recently conducted systematic review[19] (sensitivity 91% compared with 90% and specificity 86% compared with 87%), suggesting that more recent studies, not included in the previous review, have not influenced overall estimates of diagnostic accuracy. The criterion for inclusion in both of these reviews was that a dedicated PET machine was to have been used but, since the development of these types of instruments, there have been no major changes in the technology of PET (Dr Theodoros Arvanitis, University of Birmingham, 2009, personal communication). This review supports the suggestion that PET technology has reached a consistent level and confirms previous findings. No previous systematic review has attempted to meta-analyse the accuracy of PET/CT and the current review gives no indication as to whether the diagnostic accuracy of this technology has changed, or is likely to change, during its evolution.

Inspection of the individual results for PET studies (Appendix 5, *Figure 20*) shows heterogeneity in estimates of sensitivity and specificity (for some studies 95% CIs do not overlap). This was not observed with studies of PET/CT (Appendix 5, *Figure 21*) but the number of these studies was smaller. It appears likely that there are differences in the patient groups, study methods or mode of investigation in studies of PET and this may bring uncertainty around the overall estimates for test accuracy in this context.

Changes in patient management and outcome

Despite the reasonable data available to determine the diagnostic accuracy of PET and PET/CT, their impact on patient management is uncertain. Individual studies assert that these technologies do lead to changes in management, but it is difficult to determine to what extent these changes would have taken place with conventional diagnostic procedures and, more importantly, whether they resulted in changes in final patient outcome.

Some sense about impact on patient management may be gained by considering the consequences of FN and FP results, both of which appear to be reduced when comparing PET with conventional imaging and PET/CT with PET. FN results generally lead to delayed treatment, which is likely to be important where the condition is life threatening. In distantly recurring BC delaying treatments with palliative intent will make a considerable impact on quality of life over the short to medium term. For systemic treatments aiming to alter the course of metastatic disease, there are also likely to be modest gains in survival and thus FN CITs will delay these treatments. Some patients will suffer a sufficient fall in performance status by the time of diagnosis for there to be fewer appropriate treatment options available. The consequences of avoidance of FPs, which also appears to be achieved by the use of PET and PET/CT, are clearer. Avoiding unnecessary exposure

to costly and potentially harmful, occasionally life-threatening, treatment such as chemotherapy is clearly desirable and could be anticipated to bring about improvements in quality of life, if not survival. Avoiding the anxiety associated with treatment and the fact that BC has recurred adds to this. This prediction of impact on the patient assumes that there are no further steps in the diagnostic pathway beyond conventional imaging with or without PET/CT. Biopsies of possible BC recurrences following CITs are sometimes performed. In these cases, FNs can result in significant unnecessary risk and morbidity to patients. Overall, there appears to be a clear potential value for a diagnostic technique that reduces both the rate of FPs and FNs.

Of primary interest is the impact of PET and PET/CT on patient prognosis and survival. If detection of recurrence by PET or PET/CT gives patients additional quality of life or extends survival, these technologies may be important diagnostic tools. In order to directly assess the effects of PET or PET/CT on long-term outcomes, large-scale intervention studies may be required. Owing to the intensive follow-up and the large sample sizes required, these types of studies are expensive, and modelling work may be used to provide information on whether these trials are worthwhile. The construction of models relating diagnostic accuracy and features of disease progression to long-term patient outcomes would give information on the potential impact of PET and PET/CT on patient outcome. Where modelling findings suggest a potential benefit of PET or PET/CT, this may support the implementation of large-scale interventional studies to investigate long-term impacts.

Variation in the diagnostic accuracy of PET

The variation in estimates of test accuracy for PET was investigated by conducting subgroup analysis on this group of studies, but no conclusive pattern emerged to explain the variability. There was no apparent difference in the accuracy of PET in different locations of the body, although this analysis was conducted using lesion-based data (may be less reliable than patient-based data). The diagnosis of local disease may be considered more valuable than the diagnosis of disease in lymph nodes or distant metastases as surgical treatment may more realistically be employed for local recurrence. Findings suggest that the overall estimates of diagnostic accuracy for PET can be applied in the specific case of local recurrence and this may help to better predict the potential benefits from the use of PET. Data for the use of PET/CT for diagnosis in different locations were limited, and location-specific analysis could not be conducted. However, it may be anticipated that similar findings would be shown and PET/CT may have similar diagnostic accuracy for local recurrence as for metastatic disease.

PET had similar sensitivity in studies where patients had been negative on previous imaging tests compared with studies where previous findings were positive/equivocal but specificity was significantly reduced (Appendix 8, *Table 13a*). Specificity was also significantly reduced for studies in which patients were cleared of BC at the time of investigation compared with other studies (Appendix 8, *Table 13b*). Selective patient sampling by previous imaging testing in these studies may have had some impact on apparent specificity. However, it is difficult to ascertain whether these observations are due to random statistical significance of if they may be confounded by other potentially moderating factors. As numerous factors are likely to be involved in determining diagnostic accuracy of PET, it is difficult to identify specific factors responsible for the heterogeneity observed. Also, as subgroup analysis was not restricted to the group of comparative studies, it was not possible to examine whether these observations would result in a comparative difference in test accuracy between PET and CIT.

Strengths and limitations of the review

One strength of the current review was that it was likely to have included the majority of the relevant literature. This review included 14 of the 18 studies included in the most recent previous systematic review.[19] The current review was restricted to studies performed in the secondary diagnostic setting and this led to the exclusion of the other four studies.[58–61] The current report includes an additional 14 studies, not covered by the previous review and, for the first time, reviews evidence for the diagnostic accuracy of PET/CT.

A second strength of this work was the comparative nature of the review. Estimations of individual values for diagnostic accuracy may give some information on the likely benefit of these technologies. However, comparative analysis allows proper investigation of the possible advantage

of adopting PET or PET/CT over conventional diagnostic strategies.

A further strength of this review may be the use of direct comparisons. The large spread of results for test accuracy, particularly for PET, suggests that there are other important mediators of test accuracy that influence results. In indirect comparisons, where results from different studies are compared, the comparison of PET and PET/CT with CIT may be affected by many factors associated with the populations, study methods and technologies used. In direct comparisons, some of these moderating factors are avoided as index and comparator tests are conducted in the same populations and the same study methods are used.

Although direct comparisons are desirable and can eliminate between-study variability associated with indirect comparisons, methods currently recommended for meta-analysis of test accuracy studies do not exploit the paired nature of the data when all patients receive each of the two tests under evaluation as well as the reference standard. For such analyses to be possible, test accuracy data from primary studies must be presented in a suitable format, i.e. joint classification of the results of the tests, but this is rarely the case. Only six of the studies in this review presented data in this format, one comparing PET with PET/CT[28] two comparing PET with MRI,[30,32] one comparing PET with bone scintigraphy[44] and two comparing PET with CW.[49,50] Methods that combine evidence from both direct and indirect comparisons, such as the adjusted indirect comparison method and network meta-analysis techniques for comparing health-care interventions, make optimal use of all relevant data but such methods are lacking for test comparisons. Current methodology may result in a more conservative estimate of relative differences in test accuracy when analysis is restricted to direct comparisons and this may be a limitation of this review.

A limitation of this review was that subgroup analysis was conducted on the whole set of studies investigating PET ($n = 25$) and not on comparative studies for PET ($n = 10$) and PET/CT ($n = 4$). This was necessary as the number of comparative studies was limited. However, it is difficult to interpret subgroup findings because within-test analysis does not give information on the actual diagnostic advantage in different settings and patient populations. If more data were available, analysis of differences in the diagnostic accuracy of PET or PET/CT in different settings or groups relative to conventional tests may be useful to inform decision-making about specific contexts for their use.

A limitation in the interpretation of this review may be the distinction of results for direct and indirect comparisons. It should be noted that, particularly for PET/CT, studies included in the direct comparison analysis also largely constituted the studies included in the indirect comparison analysis. Because some of the study data are used in both analyses, although indirect comparisons may be taken to some extent to support comparative results, findings are not independent. Although they may be useful for corroborating findings, results for direct and indirect comparisons should not be interpreted as independent outcomes.

A further limitation of indirect comparisons in the current review is the exclusion of conventional imaging studies that were not compared with PET or PET/CT. Studies of CIT were only included in this review if they contained a comparison with PET or PET/CT, and it is unclear whether this could have had an impact on findings. In order to make true independent comparisons, an additional systematic review of all CIT studies would be necessary. However, owing to the large volume of evidence relating to each conventional diagnostic strategy, the workload involved would be sizable.

A further limitation of this review is the small size of the majority of included studies. The average (median) size of studies was 45 (10–291) and only 456 and 167 patients constituted the analysis groups for PET and PET/CT versus CIT respectively. Although sample sizes were adequate for testing statistical significance, they may, to some extent, limit the generalisability of these findings.

The short duration over which this review was conducted to some extent limited the number of included studies. As some studies appeared to have recorded the relevant information but not included it in publications, authors were contacted to request raw data for inclusion in the review. One investigator provided the relevant data[33] but, in other cases, data were not retrieved and further follow-up may have proved successful in obtaining data and increasing the information available in this review.

Chapter 6
Conclusions

- For the detection of BC recurrence, in addition to conventional imaging techniques, PET may generally offer improved diagnostic accuracy compared with current standard practice. Uncertainty remains around its use as a replacement, rather than an add-on, to existing imaging technologies.
- PET/CT appears to show a clear advantage over CT for the diagnosis of BC recurrence. Although PET/CT may give an advantage over other conventional imaging strategies, its incremental value over other tests has yet to be assessed in studies directly. Concurrent use with, rather than replacement of, other conventional tests may be appropriate.
- PET/CT appears to show a clear advantage over PET and, if found to be more cost-effective, it may be preferred to PET for use in this context.
- PET and PET/CT appear to have some impact on patient management but there is currently no evidence of the effects of their use on patient outcome.

Recommendations for future research

Future research studies should ideally be large and prospective, avoiding some sources of bias associated with retrospective studies. Studies should be comparative and, where possible, any comparator tests used should be conducted close in time to PET or PET/CT. Patient populations should be clearly defined with regard to their clinical presentation, e.g. only patients with suspected BC recurrence on the basis of previous conventional imaging findings.

- Further study of the diagnostic accuracy of PET/CT compared with specific CITs may help to assess the comparative advantage of PET/CT over different CITs.
- Further research may inform the use of PET/CT as a replacement technology. In future research, reading of scans with assessors both blinded and unblinded to previous results would allow assessment of the comparative accuracy of PET/CT as a replacement compared with an add-on technology. This may help to determine whether PET/CT may potentially be used as a replacement to tests currently used in clinical practice.
- Further research may investigate the application of MRI of the whole body compared with PET/CT in this context.
- Modelling work (to be published in another report) may be used to examine the potential impact of PET/CT on long-term patient outcomes. This work may be used to inform the implementation of large-scale intervention studies to examine the long-term impact of PET/CT.

Implications for policy

Positron emission tomography/computed tomography has largely superseded PET in current practice and the apparent advantage of PET/CT over PET found in this review supports this move. On the basis of some of the uncertainties observed, it may be premature to make recommendations about changes in the precise diagnostic role of PET/CT in current practice. However, current recommendations for its use following equivocal findings on conventional imaging techniques may be justified. It appears that PET/CT may be useful as an addition to current practice for the diagnosis of BC recurrence but this should be reassessed in light of the analysis of its cost-effectiveness.

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Contribution of authors

Mary Pennant contributed to the development of the protocol, conducted abstract and full-paper screening, data extraction and quality assessment, contributed to the interpretation of findings and was responsible for writing the report. Yemisi Takwoingi was responsible for the statistical analysis and reviewed the report. Lucy Pennant conducted the data extraction. Clare Davenport contributed to the interpretation of findings and reviewed the report. Anne Fry-Smith and Anne Eisinga devised the search strategy and Anne Fry-Smith carried out the searches. Lazaros Andronis reviewed the protocol and the report. Theo Arvanitis gave technical guidance on imaging technologies and reviewed the report. Jon Deeks gave guidance for statistical analysis and reviewed the report. Chris Hyde developed the protocol, conducted quality assessment, contributed to the interpretation of findings and reviewed the report.

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Appendix 1

MEDLINE search strategy

Database: Ovid MEDLINE 1950 to Week 2 May 2009

1. exp tomography, emission-computed/ (52882)
2. (emission adj2 comput$ adj2 tomograph$).tw. (9710)
3. (tomograph$ adj2 emission adj2 comput$).tw. (9941)
4. (radionuclide-comput$ adj2 tomograph$).tw. (19)
5. (radionuclide adj2 cat scan$).tw. (4)
6. (radionuclide adj2 ct scan$).tw. (29)
7. (scintigraph$ adj2 comput$ adj2 tomograph$).tw. (373)
8. (positron adj2 emission adj2 tomograph$).tw. (21399)
9. (pet or petct).tw. (30218)
10. or/1–9 (65938)
11. exp breast neoplasms/ (162433)
12. (breast$ adj5 (cancer$ or carcinoma$ or adenocarcinoma$ or carcinogen$ or sarcoma$ or malignan$ or tumo?r$ or neoplas$)).tw. (149035)
13. or/11–12 (191059)
14. 10 and 13 (1422)
15. (recur$ or relaps$ or metasta$ or restag$ or re-stag$).mp. (633461)
16. 14 and 15 (730)

Appendix 2
Characteristics of FDG-PET technology

Study and date	Camera	Attenuation correction	Interpretation	Image reconstruction	Positive scan definition given?	BG testing and fasting	FDG dose	Uptake time	Acquisition time
Abe 2005[24]	ECAT EXACT HR+	Y	Visual	Ordered-subset expectation maximisation (OSEM) algorithm	N	BG measured as 87–135 mg/dl, >4-hour fast	101–434 MBq	60 minutes	2 minutes
Aide 2007[25]	HR+ CTI siemens	Y	Visual	Iterative	N	BG < 120 mg/dl, fast > 6 hour	2 MBq/kg	60 minutes	7 minutes
Bender 1997[26]	ECAT EACT 927/47	Y	Visual	Filtered back projection	Y	Given BG test, don't give results, fasting	185–370 MBq	45–60 minutes	10 minutes per position
Dirisamer 2010[27]	Discovery LS	NR	Visual and SUV	Unclear	Y	BG < 150 mg/dl, fasting	370 MBq	50 minutes	4 minutes
Fueger 2005[28]	REVEAL RT PET/CT scanner	Y	Visual	Filtered backprojection for CT. Iterative algorithms (OSEM) for PET	Y	Only those <200 mg/dl included, fast >6 hours	7.77 MBq/kg	60 minutes	NR
Gallowitsch 2003[29]	ECAT ART Siemens CTI MS	Y	Visual	Iterative		BG < 130 mg/dl, fasting	200 MBq	70 minutes	9 minutes
Goerres 2003[30]	GE Advance	Y	Visual	Iterative OSEM algorithm	Y	4 hours fasting	386 MBq	45 minutes	4 minutes per field of view
Guillemard 2006[31]	Biograph PET/CT, Siemens AG	Y	Visual	NR	N	BG controlled before, >6-hour fast	300–520 MBq	60 minutes	~2 minutes
Hathaway 1999[32]	GE Advance	Y	Visual and SUV	Filtered back-projection	Y	BG >80 < 140 mg/dl, >4-hour fast	260–370 MBq	45–60 minutes	10 minutes
Haug 2007[33]	Phillips Gemini	Y	Visual and SUV	NR	Y	Tested ensure < 120 mg/dl, >6-hour fast	200 MBq	60 minutes	3 minutes
Hubner 2000[34]	ECAT/EACT 921	Y	Visual and SUV	Using 0.4 Hann filter and 1.5 zoom	Y	BG recorded but not given, 4-hour fast	185–370 MBq	NR	NR
Kamel 2003[35]	GE Advance	Y	Visual	Iterative and some standard filtered back projection	Y	4-hour fast	300–400 MBq	45 minutes	4 minutes
Kim 2001[36]	ECAT EXACT 47	Y	Visual and SUV	NR	Y	Overnight fast	370–555 MBq	60 minutes	6 minutes, 30 minutes if evidence

DOI: 10.3310/hta14500

Study and date	Camera	Attenuation correction	Interpretation	Image reconstruction	Positive scan definition given?	BG testing and fasting	FDG dose	Uptake time	Acquisition time
Lin 2002[37]	GE Advance whole body	N	Visual	Standard filtered back projection	N	4-hour fast	370 MBq	NR	30 minutes
Liu 2002[38]	CTI-Siemens ECAT HR+	Y	Visual	NR	Y	Fast > 4 hours	370 MBq	30–45 minutes	7 minutes
Lonneux 2000[39]	ECAT EXACT HR, CTI	Y, N	Visual	Filtered backprojection (no attenuation correction) or attenuation-weighted OSEM	Y	> 6-hour fast	370 MBq	60 minutes	5 minutes
Moon 1998[40]	ECAT 931 (67%) and ECAT 961	N	Visual	NR	N	No exclusions, > 6-hour fast	370–555 MBq	40 minutes	4 minutes (931) or 6 minutes (961)
Ohta 2001[41]	ECAT EXACT47	NR	Visual	NR	N	?, > 4-hour fast	260–370 MBq	45 minutes	7 minutes
Pecking 2004[42]	Discovery LS	Y	SUV	NR	Y	NR	296–407 MBq	60 minutes	20 minutes
Radan 2006[43]	Discovery LS	Y	Visual	Order subsets expectation maximisation	Y	BG < 11 mmol/l, fasting 4–6 hours	370–666 MBq	60 minutes	4 minutes
Raileanu 2004[44]	ADAC-philips	NR	Visual	NR	N	NR	2 MBq/kg	1 hour	NR
Santiago 2006[45]	GE Advance	NR	Visual	Filtered backprojection		BG < 200 mg/dl, > 6-hour fast	370–550 MBq	45–60 minutes	6 minutes
Schmidt 2008[46]	2-detector row scanner (Gemini)	Y	Visual + SUV	Row action maximum likelihood algorithm	Y	Fast > 6 hours	202–378 MBq	60 minutes	NR
Suarez 2002[47]	ADAC C-PET-250	Y	Visual and SUV	Iterative	Y	BG < 120 mg/dl, > 6-hour fast	2 MBq/kg	60 minutes	NR
Veit-Haibach 2007[48]	CT -Somatom emotion PET -ECAT HR+	Y	Visual and SUV	Iterative	Y	BG measured to ensure normal, fast 4 hours	340 MBq	1 hour	
Vranjesevic 2002[49]	ECAT EXACT or HR+	N (20% with)	Visual	Filtered backprojection	N	> 6-hour fast	370–555 MBq	45–60 minutes	
Wolfort 2006[50]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yang 2002[51]	ECAT HR+	NR	Visual	NR	Y	> 4-hour fast	370 MBq	30–45 minutes	3 minutes

BG, blood glucose; N, no; NR, not reported; SUV, standardised uptake value; Y, yes

Appendix 3

Figures for indirect comparisons of patient-based data

PET versus conventional imaging tests

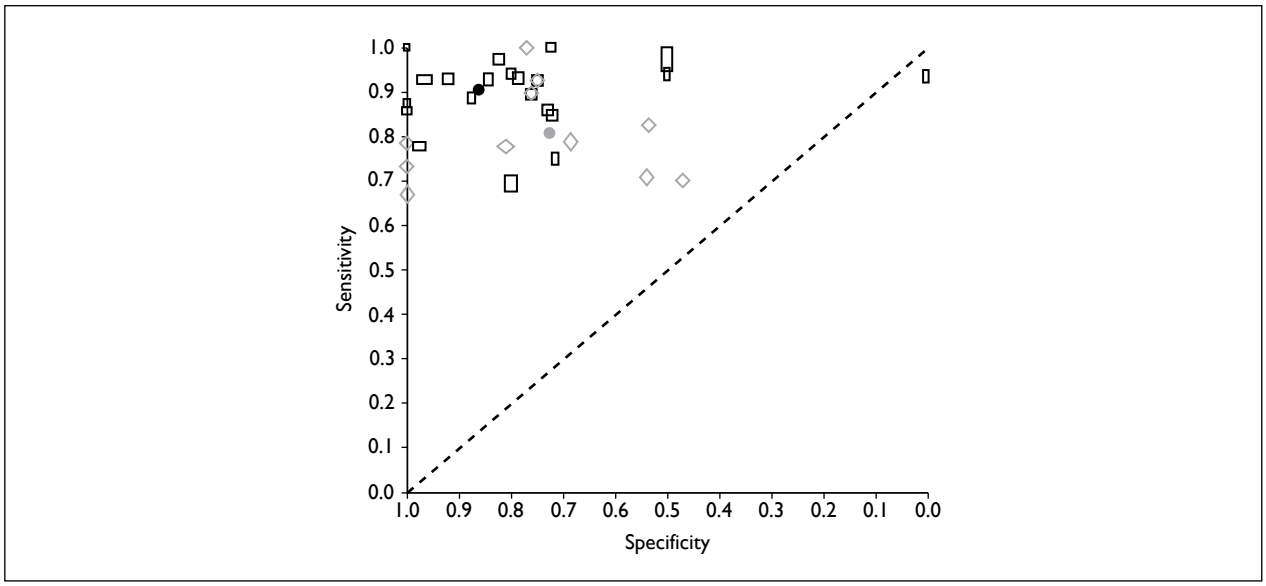

FIGURE 13 *Summary receiver operating characteristic plane for indirect comparison of the diagnostic performance of PET (□) and CIT (◊) for patients with suspected BC recurrence.*

PET/CT versus conventional imaging tests

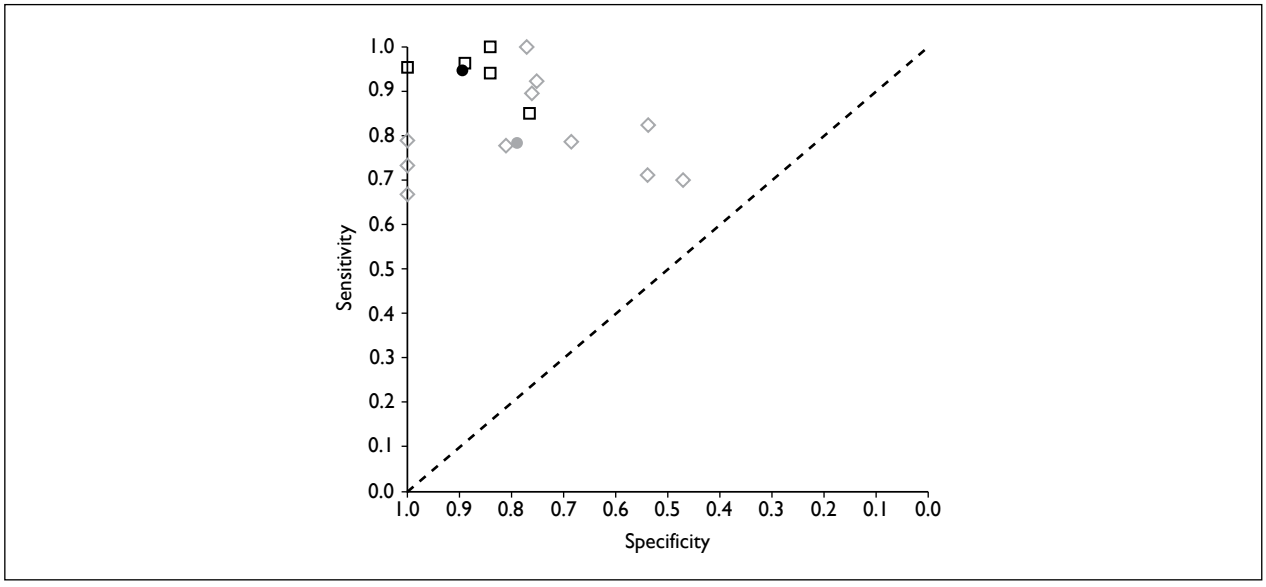

FIGURE 14 *Summary receiver operating characteristic plane for indirect comparison of the diagnostic performance of PET/CT (□) and CIT (◊) for patients with suspected BC recurrence.*

PET versus PET/CT

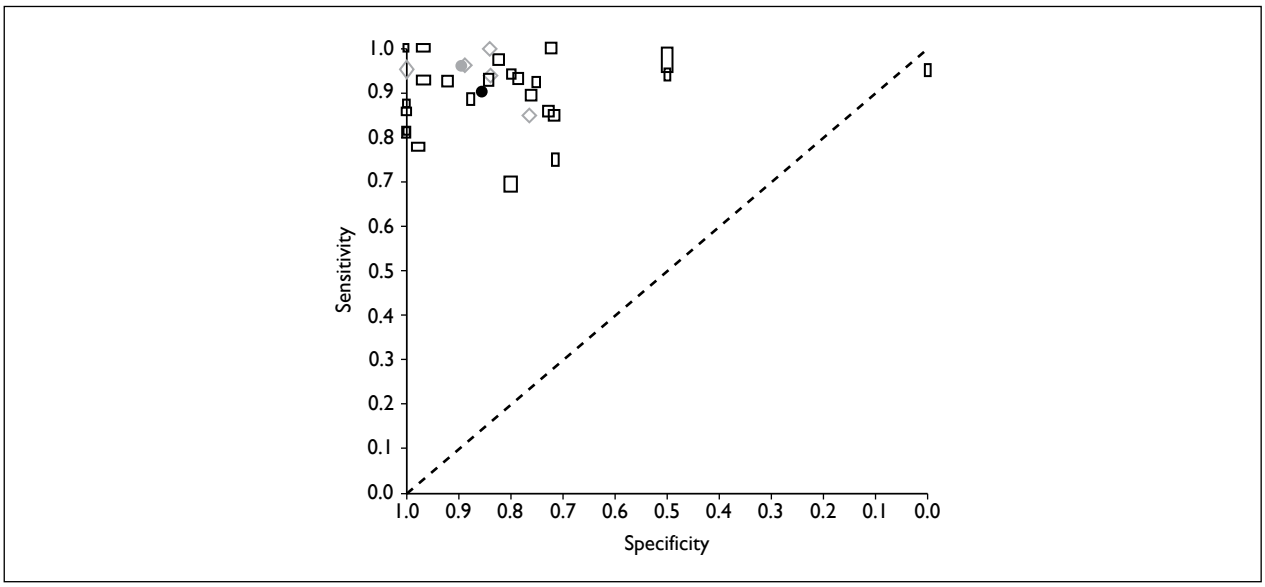

FIGURE 15 *Summary receiver operating characteristic plane for indirect comparison of the diagnostic performance of PET (□) and PET/CT (◊) for patients with suspected BC recurrence.*

Appendix 4

Comparative lesion-based data

Study	*n*	Test	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abe 2005[24]	187	PET	38	2	7	140	0.84 (0.71 to 0.94)	0.99 (0.95 to 1.00)
Abe 2005[24]		CIT	36	2	9	140	0.80 (0.65 to 0.90)	0.99 (0.95 to 1.00)
Gallowitsch 2003[29]	135	PET	61	3	47	24	0.56 (0.47 to 0.66)	0.89 (0.71 to 0.98)
Gallowitsch 2003[29]		CIT	97	7	11	20	0.90 (0.83 to 0.95)	0.74 (0.54 to 0.89)
Yang 2002[51]	127	PET	100	2	5	20	0.95 (0.89 to 0.98)	0.91 (0.71 to 0.99)
Yang 2002[51]		CIT	98	20	7	2	0.93 (0.87 to 0.97)	0.09 (0.01 to 0.29)

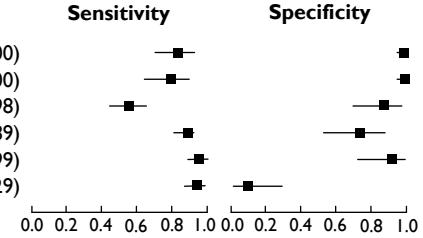

FIGURE 16 *Lesion data for the diagnostic accuracy of PET and CITs in comparative studies. Note: no studies comparing the accuracy of PET/CT and CIT presented lesion data.*

TABLE 9 *Lesion data for direct and indirect comparisons of PET compared to CITs*

Comparison	PET sensitivity % (95% CI)	CIT sensitivity % (95% CI)	Relative sensitivity (95% CI), *p*-value	PET specificity% (95% CI)	CIT specificity % (95% CI)	Relative specificity (95% CI), *p*-value
Direct PET vs CIT: lesion data	83 (56 to 95), *n* = 3	90 (84 to 94), *n* = 3	0.93 (0.76 to 1.13) *p* = 0.447	95 (87 to 98)	74 (10 to 99)	1.29 (0.57 to 2.90) *p* = 0.540
Indirect PET vs CIT: lesion data	89 (78 to 95), *n* = 7	91 (86 to 94), *n* = 3	0.98 (0.90 to 1.07) *p* = 0.624	91 (83 to 95)	35 (3 to 91)	2.57 (0.41 to 6.07) *p* = 0.313

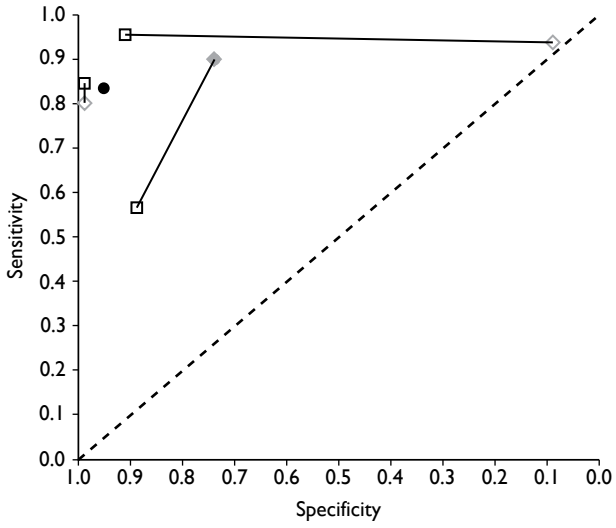

FIGURE 17 *Summary receiver operating characteristic plane for studies directly comparing the diagnostic performance of PET (□) and CITs (◊) for lesions with suspected disease.*

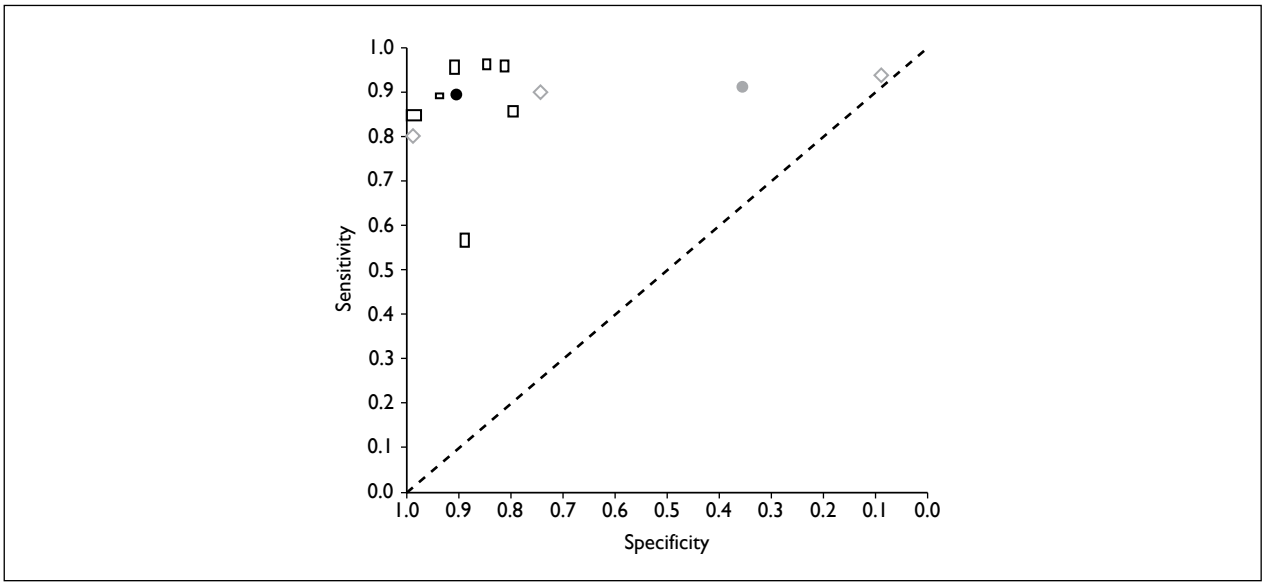

FIGURE 18 *Summary receiver operating characteristic plane for indirect comparison of the diagnostic performance of PET (□) and CITs (◊) for lesions with suspected disease.*

TABLE 10 *Lesion data for the indirect comparison of PET with PET/CT*

Comparison	PET/CT sensitivity% (95% CI)	PET sensitivity % (95% CI)	Relative sensitivity (95% CI)	PET/CT specificity% (95% CI)	PET specificity% (95% CI)	Relative specificity (95% CI)
Indirect PET/CT vs PET: lesion basis	97 (86 to 99), *n* = 2	89 (78 to 95), *n* = 7	1.1 (1.0 to 1.2) *p* = 0.137	84 (62 to 94)	91 (83 to 95)	0.9 (0.8 to 1.1) *p* = 0.414

Study	*n*	Test	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity	Specificity
Schmidt 2008[46]	263	PET/CT	170	8	16	69	0.91 (0.86 to 0.95)	0.90 (0.81 to 0.95)		
		MRI	172	11	14	66	0.92 (0.88 to 0.96)	0.86 (0.76 to 0.93)		

FIGURE 19 *Lesion data for the diagnostic accuracy of PET/CT and MRI in the comparative study of PET/CT and MRI. Note: no studies comparing the accuracy of PET and MRI presented lesion data.*

Appendix 5

Study data and figures for independent estimates of PET and PET/CT

Patient data

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abe 2005[24]	14	1	0	29	1.00 (0.77 to 1.00)	0.97 (0.83 to 1.00)
Aide 2007[25]	21	2	7	5	0.75 (0.55 to 0.89)	0.71 (0.29 to 0.96)
Bender 1997[26]	13	2	1	58	0.93 (0.66 to 1.00)	0.97 (0.88 to 1.00)
Dirisamer 2010[27]	34	0	8	10	0.81 (0.66 to 0.91)	1.00 (0.69 to 1.00)
Fueger 2005[28]	28	7	5	18	0.85 (0.68 to 0.95)	0.72 (0.51 to 0.88)
Gallowitsch 2003[29]	33	5	1	23	0.97 (0.85 to 1.00)	0.82 (0.63 to 0.94)
Goerres 2003[30]	14	5	0	13	1.00 (0.77 to 1.00)	0.72 (0.47 to 0.90)
Guillemard 2006[31]	7	0	1	6	0.88 (0.47 to 1.00)	1.00 (0.54 to 1.00)
Hathaway 1999[32]	6	0	0	1	1.00 (0.54 to 1.00)	1.00 (0.03 to 1.00)
Haug 2007[33]	23	1	3	7	0.88 (0.70 to 0.98)	0.88 (0.47 to 1.00)
Hubner 2000[34]	36	6	6	16	0.86 (0.71 to 0.95)	0.73 (0.50 to 0.89)
Kamel 2003[35]	25	2	2	23	0.93 (0.76 to 0.99)	0.92 (0.74 to 0.99)
Kim 2001[36]	16	2	1	8	0.94 (0.71 to 1.00)	0.80 (0.44 to 0.97)
Lin 2002[37]	4	1	0	31	1.00 (0.40 to 1.00)	0.97 (0.84 to 1.00)
Liu 2002[38]	27	2	1	0	0.96 (0.82 to 1.00)	0.00 (0.00 to 0.84)
Lonneux 2000[39]	31	3	2	3	0.94 (0.80 to 0.99)	0.50 (0.12 to 0.88)
Moon 1998[40]	27	6	2	22	0.93 (0.77 to 0.99)	0.79 (0.59 to 0.92)
Ohta 2001[41]	7	1	2	42	0.78 (0.40 to 0.97)	0.98 (0.88 to 1.00)
Pecking 2004[42]	260	12	7	12	0.97 (0.95 to 0.99)	0.50 (0.29 to 0.71)
Raileanu 2004[44]	6	0	1	13	0.86 (0.42 to 1.00)	1.00 (0.75 to 1.00)
Santiago 2006[45]	68	7	30	28	0.69 (0.59 to 0.78)	0.80 (0.63 to 0.92)
Suarez 2002[47]	24	3	2	9	0.92 (0.75 to 0.99)	0.75 (0.43 to 0.95)
Veit-Haibach 2007[49]	17	6	2	19	0.89 (0.67 to 0.99)	0.76 (0.55 to 0.91)
Vranjesevic 2002[50]	39	3	3	16	0.93 (0.81 to 0.99)	0.84 (0.60 to 0.97)
Wolfort 2006[51]	13	0	3	7	0.81 (0.54 to 0.96)	1.00 (0.59 to 1.00)

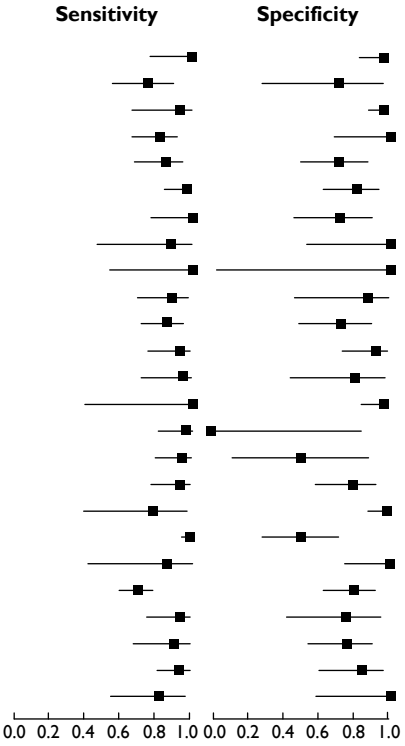

FIGURE 20 *Study data for the accuracy of PET on a patient basis.*

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dirisamer 2010[27]	40	0	2	10	0.95 (0.84 to 0.99)	1.00 (0.69 to 1.00)
Fueger 2005[28]	31	4	2	21	0.94 (0.80 to 0.99)	0.84 (0.64 to 0.95)
Haug 2007[33]	24	1	1	8	0.96 (0.80 to 1.00)	0.89 (0.52 to 1.00)
Radan 2006[43]	17	4	3	13	0.85 (0.62 to 0.97)	0.76 (0.50 to 0.93)
Veit-Haibach 2007[48]	19	4	0	21	1.00 (0.82 to 1.00)	0.84 (0.64 to 0.95)

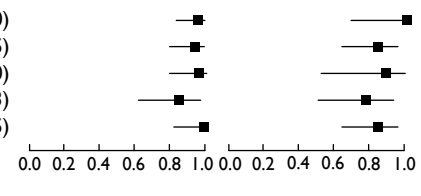

FIGURE 21 *Study data for the accuracy of PET/CT on a patient basis.*

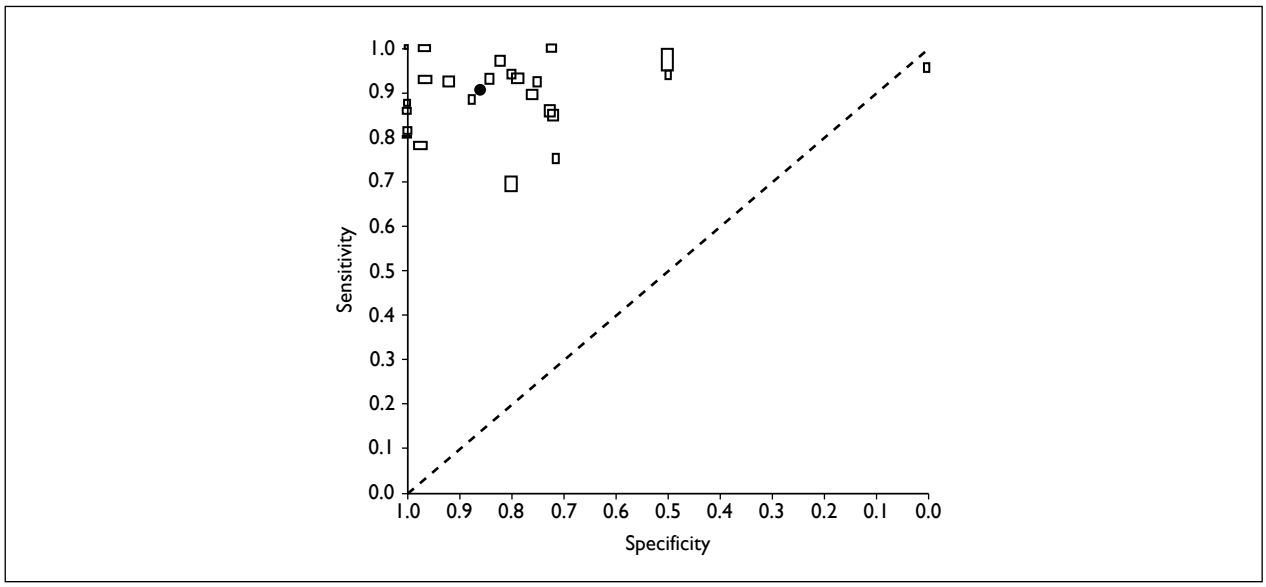

FIGURE 22 *Summary receiver operating characteristic plane for studies measuring the diagnostic performance of PET (□) for patients with suspected BC recurrence.*

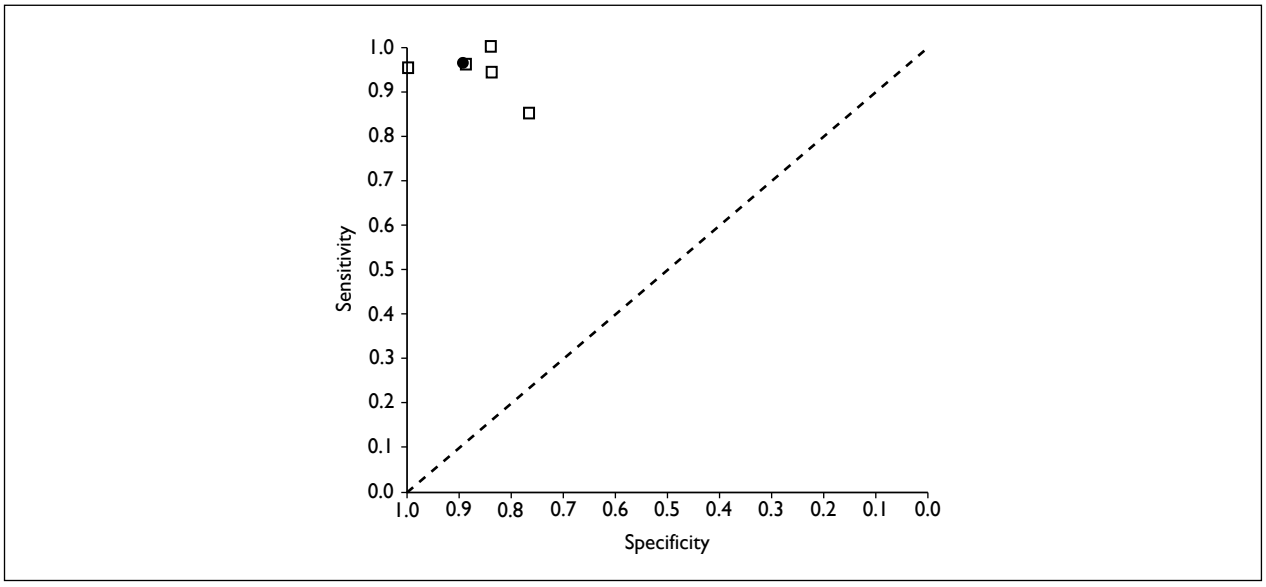

FIGURE 23 *Summary receiver operating characteristic plane for studies measuring the diagnostic performance of PET/CT (□) for patients with suspected BC recurrence.*

Lesion data

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abe 2005[24]	38	2	7	140	0.84 (0.71 to 0.94)	0.99 (0.95 to 1.00)
Gallowitsch 2003[29]	61	3	47	24	0.56 (0.47 to 0.66)	0.89 (0.71 to 0.98)
Kamel 2003[35]	43	3	2	13	0.96 (0.85 to 0.99)	0.81 (0.54 to 0.96)
Kim 2001[36]	46	2	2	11	0.96 (0.86 to 0.99)	0.85 (0.55 to 0.98)
Lin 2002[37]	8	2	1	28	0.89 (0.52 to 1.00)	0.93 (0.78 to 0.99)
Moon 1998[40]	35	8	6	31	0.85 (0.71 to 0.94)	0.79 (0.64 to 0.91)
Yang 2002[51]	100	2	5	20	0.95 (0.89 to 0.98)	0.91 (0.71 to 0.99)

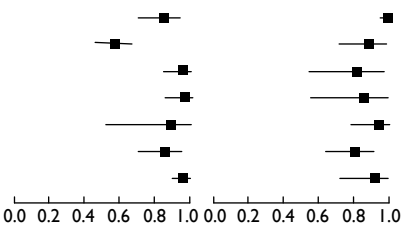

FIGURE 24 *Study data for the accuracy of PET on a lesion basis.*

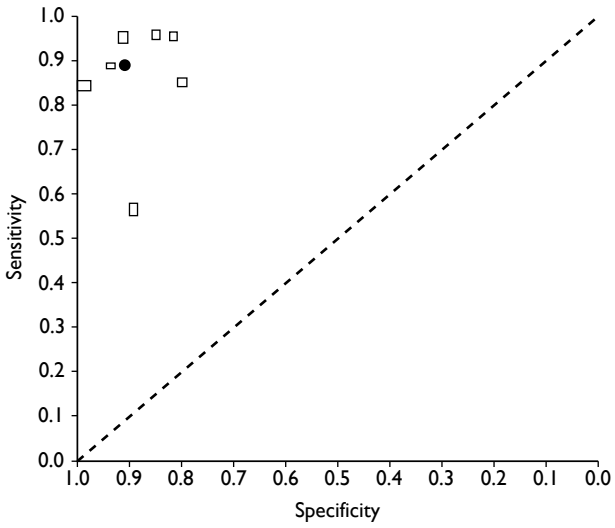

FIGURE 25 *Summary receiver operating characteristic plane for studies measuring the diagnostic performance of PET (□) for lesions with suspected disease.*

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Radan 2006[43]	151	5	2	13	0.99 [0.95 to 1.00]	0.72 [0.47 to 0.90]
Schmidt 2008[46]	179	8	16	69	0.92 [0.87 to 0.95]	0.90 [0.81 to 0.95]

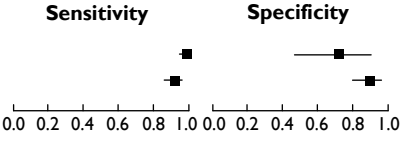

FIGURE 26 *Study data for the accuracy of PET/CT on a lesion basis.*

Appendix 6

Changes in patient management

	Additional gain	*n*	Patients with overall changes in management *n* (%)	Start/ changed medical therapy *n* (%)	Changed to surgery *n* (%)	Avoided medical treatment *n* (%)	Avoided surgery *n* (%)
Dirisamer 2010[27]	N	52	7 (13%)	3 (6%)			4 (8%)
Bělohlávek 2002[53]	N	51	31 (60%)				
Eubank 2004[55]	N	125	40 (32%)	22 (18%)	2 (2%)	2 (2%)	14 (11%)
Eubank 2004[55]	Y[a]	20	5 (25%)	4 (16%)	1 (4%)		
Gallowitsch 2003[29]	N	62	13 (21%)	6 (3%)	2 (3%)		
Grahek 2004[54]	N	75	25 (33%)	10 (13%)	5 (7%)	4 (5%)	3 (4%)
Kim 2001[36]	N	27	13 (48%)	6 (22%)		7 (26%)	
Radan 2006[43]	N	47	24 (51%)	17 (36%)	2 (4%)	1 (2%)	
Santiago 2006[45]	N	133	99 (74%)				
Veit-Haibach 2007[48]	Y[a]	44	5 (11%)				
Vranjesevic 2002[49]	Y[a]	61	10 (16%)	10 (16%)			
[b]Yap 2001[52]	N	50	29 (58%)	22 (44%)	4 (8%)		3 (6%)

N, no; Y, yes.
a In patients not correctly identified by conventional imaging.
b Half of patients referred for initial staging of BC.

Appendix 7

Sensitivity analysis

TABLE 11a *Diagnostic accuracy of PET and CIT for studies in which tests were conducted within a 1-month time period*

Comparison	PET sensitivity % (95% CI)	CIT sensitivity % (95% CI)	Relative sensitivity (95% CI), *p*-value	PET specificity % (95% CI)	CIT specificity % (95% CI)	Relative specificity (95% CI), *p*-value
Direct PET vs CIT	87 (79 to 93) *n* = 6	84 (72 to 91) *n* = 6	1.04, (0.92 to 1.15) *p* = 0.4797	96 (83 to 99)	87 (75 to 94)	1.10, (1.01 to 1.17) *p* = 0.022

TABLE 11b *Diagnostic accuracy of PET/CT and CIT for studies in which tests were conducted within a 1-month time period*

Comparison	PET/CT sensitivity % (95% CI)	CIT sensitivity % (95% CI)	Relative sensitivity (95% CI), *p*-value	PET/CT specificity % (95% CI)	CIT specificity % (95% CI)	Relative specificity (95% CI), *p*-value
Direct PET/CT vs CIT (CT)	97 (90 to 99) *n* = 3	84 (66 to 94) *n* = 3	1.13 (0.99 to 1.26), *p* = 0.063	93 (65 to 99)	86 (59 to 97)	1.07 (0.91 to 1.22) *p* = 0.367

TABLE 11c *Diagnostic accuracy of PET/CT and PET for studies in which tests were conducted within a 1-month time period*

Comparison	PET/CT sensitivity % (95% CI)	PET sensitivity % (95% CI)	Relative sensitivity (95% CI), *p*-value	PET/CT specificity % (95% CI)	PET specificity % (95% CI)	Relative specificity (95% CI), *p*-value
Direct PET/CT vs PET	96 (90 to 98) *n* = 4	85 (77 to 91) *n* = 4	1.11 (1.03 to 1.18) *p* = 0.006	89 (74 to 96)	82 (64 to 92)	1.08 (0.94 to 1.20) *p* = 0.267

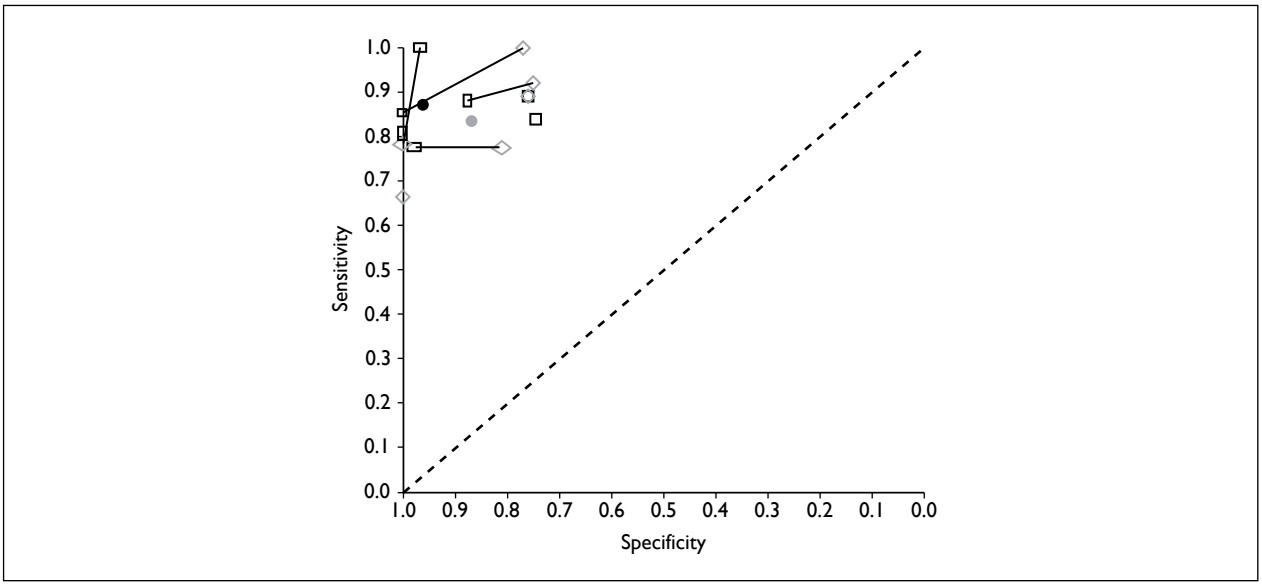

FIGURE 27 *Summary receiver operating characteristic plane for direct comparison of the diagnostic performance of PET (□) and CITs (◊) for patients with suspected BC recurrence for studies where PET and CIT were conducted within a 1-month time period.*

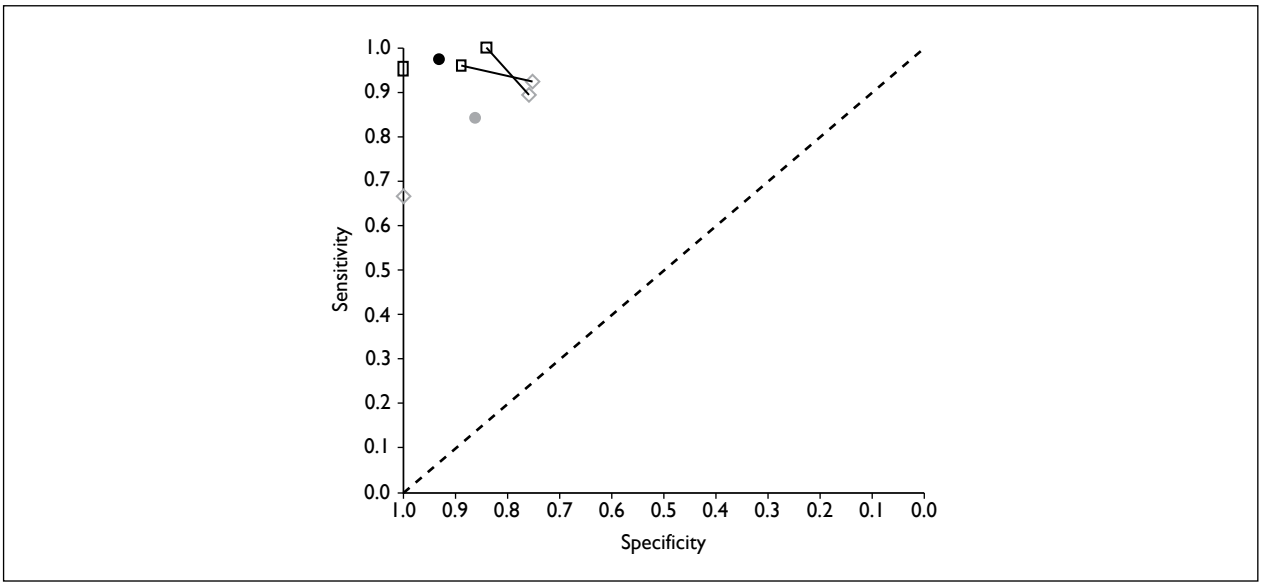

FIGURE 28 *Summary receiver operating characteristic plane for direct comparison of the diagnostic performance of PET/CT (□) and CT (◊) for patients with suspected BC recurrence for studies where PET/CT and CT were conducted within a 1-month time period.*

Appendix 8

Subgroup analysis

TABLE 12 *Indirect comparison of the diagnostic accuracy of PET for detecting lesions of disease in different locations in the body*

	Local (*n* = 4 studies)	*p*	Lymph nodes (*n* = 3 studies)	*p*	Distant metastases (*n* = 7 studies)	*p*
Relative specificity (95% CI)						
Local	–		1.01 (0.81 to 1.17)	0.936	1.02 (0.9 to 1.12)	0.744
Lymph nodes	0.99 (0.83 to 1.19)	0.936	–		0.98 (0.75 to 1.17)	0.874
Distant metastases	0.98 (0.88 to 1.10)	0.744	1.02 (0.83 to 1.25)	0.874	–	
Relative sensitivity (95% CI)						
Local	–		0.91 (0.69 to 1.09)	0.334	0.93 (0.74 to 1.09)	0.442
Lymph nodes	1.09 (0.91 to 1.31)	0.334	–		1.02 (0.89 to 1.16)	0.822
Distant metastases	1.07 (0.91 to 1.26)	0.442	0.98 (0.84 to 1.11)	0.822	–	

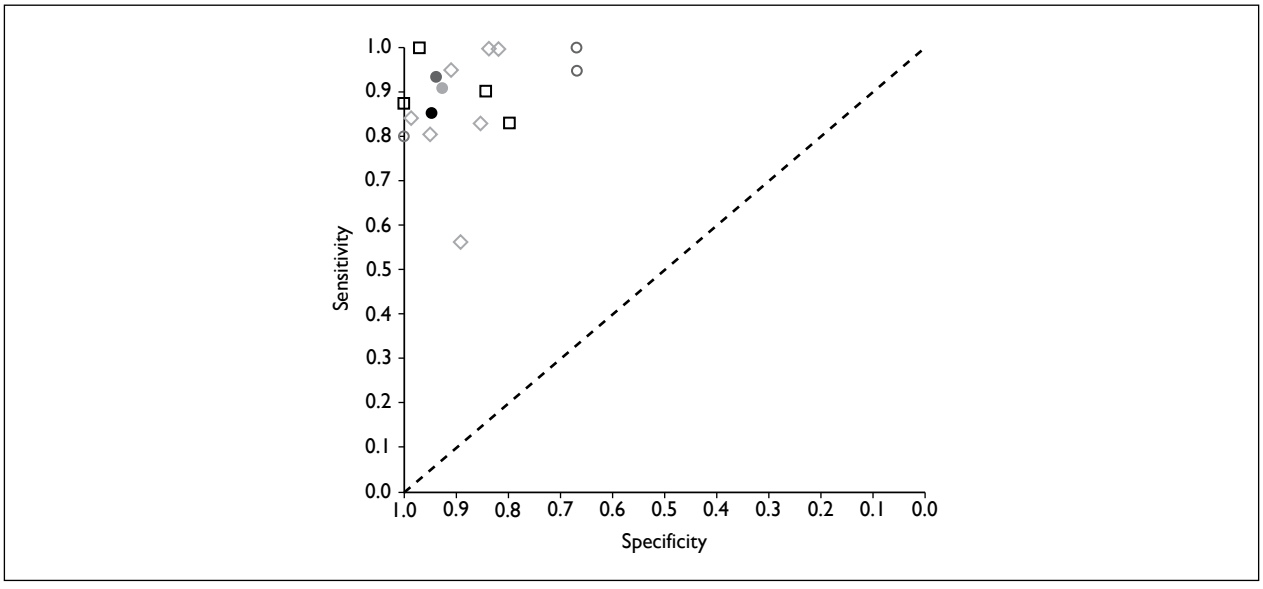

FIGURE 29 *Indirect comparison of the diagnostic accuracy of PET for the detection of local (□), lymph node (○) or distant metastatic (◊) lesions.*

Variability of PET with study characteristics

TABLE 13a *Indirect comparisons of the variability of PET with the outcome of previous imaging investigations*

	PET positive on previous imaging (*n* = 5)	PET negative on previous imaging (*n* = 5)	Relative sensitivity/ specificity	*p*
Sensitivity (95% CI)	94% (82 to 98)	93% (84 to 97)	0.99 (0.90 to 1.09)	0.859
Specificity (95% CI)	90% (77 to 96)	66% (48 to 80)	0.73 (0.56 to 0.96)	0.024

TABLE 13b *Indirect comparisons of the variability of PET with patient disease status at the time of investigation*

	PET in patients with known BC or diagnosis unclear (*n* = 11)	PET in patients cleared of BC (*n* = 14)	Relative sensitivity/ specificity	*p*
Sensitivity (95% CI)	91% (82 to 95)	91% (86 to 94)	1.00 (0.92 to 1.09)	0.920
Specificity (95% CI)	92% (85 to 95)	77% (66 to 86)	0.84 (0.73 to 0.97)	0.018

TABLE 13c *Indirect comparisons of the variability of PET with assessors knowledge of previous clinical and imaging investigations at the time of study*

	PET assessors with knowledge of previous findings/knowledge unclear (*n* = 16)	PET assessors blinded to previous findings (*n* = 9)	Relative sensitivity/ specificity	*p*
Sensitivity (95% CI)	92% (87 to 95)	88% (81 to 93)	0.96 (0.87 to 1.04)	0.346
Specificity (95% CI)	85% (75 to 91)	88% (76 to 95)	1.05 (0.91 to 1.20)	0.533

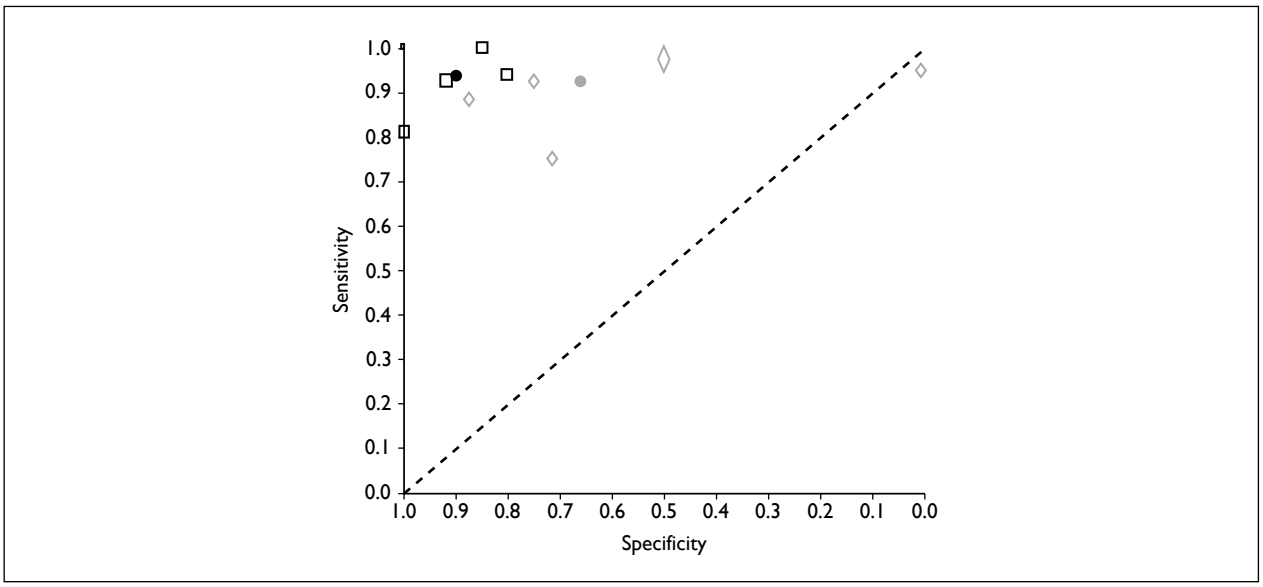

FIGURE 30 *Summary receiver operating characteristic plane for comparison of the diagnostic performance of PET in studies where all patients had been positive or equivocal (□) or negative (◊) for breast cancer recurrence in previous imaging tests.*

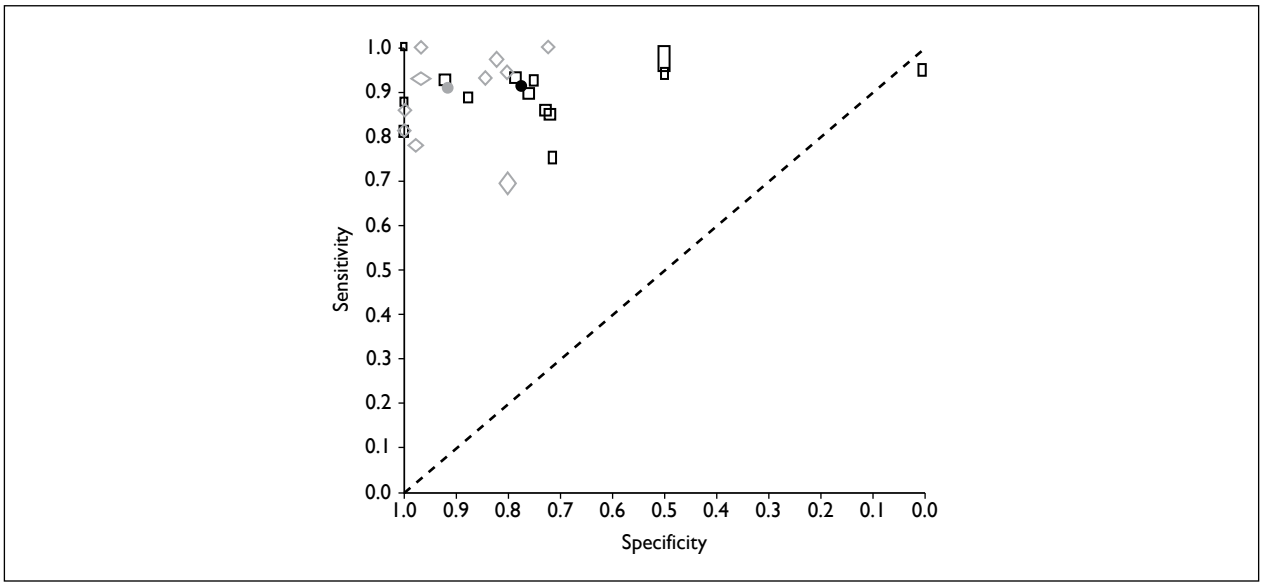

FIGURE 31 *Summary receiver operating characteristic curve for comparison of the diagnostic performance of PET in studies of patients previously cleared of BC (□) or of patients with known BC or where disease status was unclear (◊).*

Appendix 9

False-positives and false-negatives

TABLE 14 *Causes of FPs in PET and PET/CT studies*

	Infection/ inflammation	Physiological activity	Degenerative process/ old fractures	Other artefacts
Bender 1997[26]		4		2
Dirisamer 2010[27]			2	
Fueger 2005[28]	5		1	1
Gallowitsch 2003[29]	3	1	1	
Goerres 2003[30]	2	3		
Grahek 2004[54]	2	1	1	
Hubner 2000[34]	2	1		1
Kamel 2003[35]	2	1		
Kim 2001[36]		1	1	
Lin 2002[37]	4		1	
Liu 2002[38]	2			
Lonneux 2000[39]	1		1	1
Moon 1998[40]	4	5		9
Ohta 2001[41]	1			
Radan 2006[43]	2	2		
Suarez 2002[47]	1	4		1
Veit-Haibach 2007[48]	2			
Vranjesevic 2002[49]	1	1		1
	41%	29%	10%	20%

TABLE 15 *Sites of FNs in PET and PET/CT scans*

	Local/ regional	Cutaneous/ subcutaneous/ soft tissue	Peritoneal	Lymph node	Lung	Bone	Liver	Brain
Bender 1997[26]	4			1				
Dirisamer 2010[27]					4			
Gallowitsch 2003[29]							1	
Grahek 2004[54]	1	2			2	2	2	
Hubner 2000[34]		1		3	1	1		
Kamel 2003[35]	1	2						
Kim 2001[36]	1			1				
Liu 2002[38]		2		1				
Lonneux 2000[39]		1	1					
Moon 1998[40]	1					5		
Radan 2006[43]	1		1		1			
Siggelkow 2003[62]	1			5		1		
Suarez 2002[47]		1						1
Veit-Haibach 2007[48]				2		2		
Vranjesevic 2002[49]		1				2	1	
Wolfort 2006[50]		1				1		1

Appendix 10
Protocol

Positron emission tomography (PET) and PET/CT in breast cancer recurrence: draft protocol

Produced by West Midlands Health Technology Assessment Collaboration, Department of Public Health, Epidemiology & Biostatistics, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

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Date completed: June 2009

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Background

Breast cancer is a serious life-threatening disease. Treatment options have developed significantly over the past decade, and have impacted on survival. Inevitably, recurrence of breast cancer has increased and its diagnosis is important, as early appropriate treatment also has small but clear associated advantage for survival.

For women who have suffered with breast cancer, following clearance, NICE recommends continued access to a breast cancer nurse for an indefinite period of time.[1] This nurse is to provide advice, support and counselling via the telephone and, where appropriate, to arrange additional hospital appointments. Women also undergo the normal population-wide screening programme (mammography every 3 years for those aged 50–64 years[1]).

Breast cancer recurrence may be local (in the breast), regional (lymph nodes, collar bone, etc., same side of body as original cancer) or distant (in other body organs such as bone, liver, lungs and brain) and is associated with symptoms such as weight loss, abdominal pain, respiratory symptoms, bone pain and neurological signs. Women with a past history of breast cancer may present with symptoms which may be innocent or the first indication of recurrence. The nature of these symptoms will dictate the nature of the investigation but tests will often include bone scans, chest X-ray, CT scans, MRI scans and ultrasound.

PET and, more recently, PET/CT are new tools that may be used to diagnose breast cancer recurrence. These technologies trace radioactive isotopes in the body. Isotopes of glucose, most commonly fluorodeoxyglucose (FDG), are used for the detection of tumours since glucose is taken up and retained in tumour tissue, making it visible in PET images. Whether PET or PET/CT offer advantages over existing diagnostic approaches depends in the first instance on whether their diagnostic accuracy is good. However, ultimately, these need to be translated into more appropriate applications of effective treatment strategies, leading in turn to improved patient outcomes. As well as detecting recurrence, a new diagnostic tool may also be able to improve outcomes by correctly differentiating solitary recurrences from multiple metastases.

We have reviewed existing systematic reviews assessing the effectiveness of PET and PET/CT in the diagnosis of recurrent breast cancer. The two most relevant were Blue Cross/Blue Shield 2001[2] and Isasi *et al*. 2005[3]. The latter provides the most up-to-date assessment of test accuracy in evaluations up to 2004, with pooled sensitivity and specificity for PET both in the region of 90%. Although this review could be up-dated and improved on, the key outstanding issue is the amount of improvement PET and PET/CT offer over existing diagnostic approaches and this is the focus of the research proposed in this protocol.

Objectives

1. To assess the diagnostic accuracy of PET and PET/CT in the diagnosis of breast cancer recurrence.
   - The primary aim is to assess the incremental diagnostic accuracy of PET and PET/CT compared to existing diagnostic strategies.
   - If there are insufficient within-study comparisons to assess incremental diagnostic accuracy, basic test accuracy values will be reported.
2. To assess the impact of PET and PET/CT on the type of patient diagnosis, treatment and outcome.
3. To assess the cost-effectiveness of PET and PET/CT in the diagnosis and treatment of breast cancer recurrence.

A further objective, to be met by conducting an additional modelling review, is:

4. To model the effectiveness and cost-effectiveness of PET and PET/CT relative to existing diagnostic strategies in suspected breast cancer recurrence.

Population

The population to be studied are patients with a history of breast cancer but who have been cleared of having the disease and, at the time of study, have not been diagnosed with breast cancer recurrence. Breast cancer recurrence may or may not be suspected at the time of study and tests may be conducted as part of follow-up examinations or in response to presentation of symptoms suggestive of breast cancer recurrence.

Studies will be excluded if:

- Patients have confirmed breast cancer.
- Patients have never suffered from breast cancer.

- Populations include both patients with and without breast cancer but data from the two patient types cannot be differentiated.
- Populations include patients undergoing tests to diagnose primary breast cancer and breast cancer recurrence but data from the two patient types cannot be differentiated.
- Patients may have impaired glucose tolerance/diabetes or may not have been fasting at the time of PET or PET/CT scanning.

Index tests

The index tests under assessment are PET and PET/CT and these will be considered separately. They may be used in addition to standard tests, e.g. in combination with clinical examination/bone scanning, etc., and also instead of standard tests. Studies where whole body PET and PET/CT are conducted as well as studies using only breast imaging may be considered. Studies will be excluded if:

- FDG is not the radioactive tracer used.
- Planar (not tomographic) imaging is used.

Reference standard

The reference standard used to define the true disease status of patients may be histological diagnosis (operation/biopsy) or long term clinical follow-up/autopsy findings. Studies will be excluded if:

- Other diagnostic tests, e.g. CT, are used as the reference standard.
- It is not clear what reference standard has been used.

Comparator

In order to be able to directly compare the accuracy of PET and PET/CT for the detection of recurrent breast cancer with other diagnostic strategies, in the first instance, studies investigating both PET or PET/CT and another method of detection (and both compared to the same reference standard – see above), will be included. There is evidence that these types of studies exist since some are included in the review by Isasi et al. 2005. This approach is preferential as it allows direct comparison of PET or PET/CT test accuracy with the accuracy of other detection methods and it allows a more simple and direct modelling approach for the calculation of cost-effectiveness (calculated from additional test accuracy and additional test cost).

Where there are sufficient studies that use a comparator test (in addition to the reference standard), these will be used to assess the incremental diagnostic accuracy of PET and PET/CT. The tests for comparison may be existing diagnostic strategies (as defined by UK treatment guidelines) such as clinical examination, mammography, bone scan, chest x-ray, liver ultrasound and CT. Studies will be excluded if:

- No comparator tests were undertaken.
- Not all the patients have undergone both the index and comparator test.
- Index tests and comparator tests were not undertaken during the same investigation period.

If sufficient studies with comparator groups are not available then it is anticipated that the emphasis of the review will be changed to include studies with no additional comparator test (but still with a reference standard).

Target condition

The outcome to be assessed by studies is breast cancer recurrence as defined by the reference standard (see above). Recurrence may be local, regional or distant but must be considered to be a consequence of the originally diagnosed breast cancer. It is anticipated that, in the majority of studies, PET or PET/CT will have been used to detect distant recurrence. Studies will be excluded if they investigate:

- The diagnosis of primary breast cancer in previously disease-free individuals.
- Diagnosis of lymph node/distant metastases in breast cancer patients who have not been cleared of having breast cancer.
- Diagnosis of tumours that are not considered to be related to the initial breast cancer.

Study design

Studies in which subjects undergo the index test (PET or PET/CT), a comparison test (e.g. mammography) and the reference standard (histology/long-term follow-up) will be included. If there are insufficient tests with comparator groups, studies where subjects only undergo the index test and the reference standard will also be included.

All study designs assessing test accuracy will be considered for inclusion. Additionally, all study designs providing information on cost-effectiveness or relevant outcomes related to diagnosis, treatment or outcome will also be considered. Studies will be excluded if:

- Data is not available to determine test accuracy, cost-effectiveness or other relevant outcomes.
- They are not published in peer-reviewed journals
- They are case-control studies comparing test results in diseased versus non-diseased individuals.

Subgroup analysis

Subgroup analysis may be conducted to assess the differential diagnostic accuracy of PET and PET/CT in different patient groups, settings or methods of use.

PET and PET/CT may have different diagnostic accuracy depending on the mode of presentation. The primary focus for subgroup analysis may be differentiation on the basis of presentation at the time of the index test. Groups have been identified as:

- Patients undergoing a follow-up examination with no clinical symptoms of recurrence.
- Patients presenting with clinical symptoms suggestive of breast cancer recurrence, e.g. bone pain, shortness of breath, weight loss and neurological symptoms.
- Patients with a rise in tumour marker levels.
- Patients testing positive for other imaging techniques (mammography, ultrasonography, CT or bone scintigraphy)

Studies may present patient or lesion-based data, i.e. either recurrence in one patient or one lesion of recurrence in a patient can be taken as the unit of measurement. If this is the case, studies presenting patient and lesion based data will be separated in the analysis of data.

Other possible subgroup analysis

The diagnostic accuracy of PET and PET/CT may depend on the location of recurrence. It may be that studies do not differentiate between patients on the basis of recurrence location, especially where whole-body scans have been conducted. However, where possible, subgroup analysis may be conducted to assess the differential diagnostic accuracy for breast cancer recurrence in the bone, liver, lung and brain.

PET scans may be interpreted by quantitative (using standard uptake values) or qualitative (visual assessment) methods. The mode of interpretation may influence diagnostic accuracy and subgroup analysis may include comparison of PET and PET/CT diagnostic accuracy using quantitative versus qualitative methodology.

The methodological quality, e.g. presence of blinding, length of reference standard follow-up etc, of included studies may affect the apparent accuracy. Other possible subgroup analysis are to examine the diagnostic accuracy of PET and PET/CT in studies that differ for aspects of methodological quality.

Method

A systematic review of the literature will be conducted to identify studies assessing:

1. The test accuracy of PET and PET/CT. In the first instance, only studies in which PET or PET/CT are compared to existing methodologies will be included in the review. If there are insufficient studies to provide useful information, the review will be extended to include studies of PET or PET/CT without comparator groups.
2. The impact of PET and PET/CT on patient diagnosis, treatment and outcome.
3. The cost-effectiveness of PET and PET/CT.

In a separate piece of work, the results of this review will be used to devise a simple decision tree model to explore health effects and costs associated with changes in diagnostic error. A further protocol will be developed to detail methodology for this modelling review, including further targeted searches to identify best available parameters, e.g. effects of treatments, side-effects and costs.

Standard Cochrane and diagnostic test accuracy methods will be used to conduct the review. The possibility of this work being conducted as a Cochrane review will also be explored.

Search strategy

Relevant primary studies will be sought in MEDLINE (Ovid) and EMBASE (Ovid). Search strategies will be devised by combining index and text words defining the index test: PET and PET/

CT; and the population: suspected breast cancer recurrence. There will be no language restrictions and searches will be done from inception of the databases up to the current date. Details of the proposed search strategy for MEDLINE is available in the appendix.

Selection of studies

Titles/abstracts obtained from the literature search will be scanned for inclusion. Full articles will be retrieved for further assessment if the information given suggests that the study: 1) includes patients who have had breast cancer in the past, 2) conducts PET or PET/CT scans in those patients, and 3) assesses test accuracy, cost-effectiveness or one or more relevant clinical outcome measure. If there is any doubt regarding inclusion from the title and abstract, the full article will be retrieved for clarification. Full paper articles will be screened with another checklist, using inclusion/exclusion criteria as detailed in this protocol.

Quality assessment

Quality assessment will be conducted using the QADAS tool that includes criteria relating to patient selection, use of the reference standard, detail of reporting, blinding, follow-up and external validity. Since this quality assessment tool does not address issues related to the use of an additional comparator test, a small number of additional quality criteria will be added.

Data analysis

PET and PET/CT will be considered as separate technologies in data analysis. For the stated research objectives, data analysis will be undertaken as follows:

- Hierarchical methods are recommended[4] for meta-analyses of diagnostic test accuracy studies. The HSROC model[5] which takes account of both within- and between-study variation in test performance will be used to quantitatively combine data from eligible studies. The relative accuracy of PET and PET/CT compared to the comparator tests will be determined and potential sources of heterogeneity investigated using extensions of this model where possible.
- Narrative synthesis will be used to combine information from studies assessing the impact of PET or PET/CT on patient diagnosis (e.g. differentiating solitary recurrences and multiple metastases), treatment and outcome.
- Studies of the relative cost-effectiveness of PET or PET/CT versus other comparator tests will be subjected to narrative synthesis.

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4. Leeflang MMG, Deeks JJ, Gatsonis C, Bossuyt PMM and on behalf of the Cochrane Diagnostic Test Accuracy Working Group. Systematic Reviews of Diagnostic Test Accuracy. *Ann Intern Med* 2008; 889–897.

5. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* 2001;**20**:2865–84.

Appendix: MEDLINE search strategy

Database: Ovid MEDLINE 1950 to May Week 2 2009

1. exp tomography, emission-computed/ (52882)
2. (emission adj2 comput$ adj2 tomograph$).tw. (9710)
3. (tomograph$ adj2 emission adj2 comput$).tw. (9941)
4. (radionuclide-comput$ adj2 tomograph$).tw. (19)
5. (radionuclide adj2 cat scan$).tw. (4)
6. (radionuclide adj2 ct scan$).tw. (29)
7. (scintigraph$ adj2 comput$ adj2 tomograph$).tw. (373)
8. (positron adj2 emission adj2 tomograph$).tw. (21399)
9. (pet or petct).tw. (30218)
10. or/1–9 (65938)
11. exp breast neoplasms/ (162433)
12. (breast$ adj5 (cancer$ or carcinoma$ or adenocarcinoma$ or carcinogen$ or sarcoma$

or malignan$ or tumo?r$ or neoplas$)).tw. (149035)
13. or/11–12 (191059)
14. 10 and 13 (1422)
15. (recur$ or relaps$ or metasta$ or restag$ or re-stag$).mp. (633461)
16. 14 and 15 (730)

Appendix 11
Excluded studies

Reference[a]	Reason for exclusion
Al-Husaini H, Amir E, Fitzgerald B, Wright F, Dent R, Fralick J, *et al*. Prevalence of overt metastases in locally advanced breast cancer. *Clin Oncol* 2008;**20**(5):340–4	No relevant outcomes
Andrieux A, Switsers O, Chajari MH, Jacob JH, Delozier T, Gervais R, *et al*. Clinical impact of fluorine-18 fluorodeoxyglucose positron emission tomography in cancer patients. A comparative study between dedicated camera and dual-head coincidence gamma camera. *Q J Nucl Med Mol Imaging* 2006;**50**(1):68–77	No reference standard
Basu S, Mavi A, Cermik T, Houseni M, Alavi A. Implications of standardized uptake value measurements of the primary lesions in proven cases of breast carcinoma with different degree of disease burden at diagnosis: Does 2-deoxy-2-[F-18]fluoro-d-glucose-positron emission tomography predict tumor biology? *Mol Imaging Biol* 2008;**10**(1):62–6	In patients with newly diagnosed BC
Beer AJ, Niemeyer M, Carlsen J, Sarbia M, Nahrig J, Watzlowik P, *et al*. Patterns of alpha$_v$beta$_3$ expression in primary and metastatic human breast cancer as shown by ^{18}F-galacto-RGD PET. *J Nucl Med* 2008;**49**(2):255–9	Patients with primary or suspected primary BC
Bellon JR, Livingston RB, Eubank WB, Gralow JR, Ellis GK, Dunnwald LK, *et al*. Evaluation of the internal mammary lymph nodes by FDG-PET in locally advanced breast cancer (LABC). *A J Clin Oncol* 2004;**27**(4):407–10	Part of staging in initial BC diagnosis
Belohlavek O, Kantorova I. Influence of positron emission tomography (PET) on therapeutic decision at breast cancer – preliminary report. [Czech]. *Klinicka Onkologie* 2002;**15**(5);189–91	No test accuracy data (included for data on patient management)
Bos R, Van der Hoeven JJ, van der WE, van Der GP, Van Diest PJ, Comans EF, *et al*. Biologic correlates of (18)fluorodeoxyglucose uptake in human breast cancer measured by positron emission tomography. *J Clin Oncol* 2002;**20**(2):379–87	Pre-operative PET, primary setting
Brix G, Henze M, Knopp MV, Lucht R, Doll J, Junkermann H, *et al*. Comparison of pharmacokinetic MRI and ^{18}F fluorodeoxyglucose PET in the diagnosis of breast cancer: Initial experience. *Eur Radiol* 2001;**11**(10):2058–70	Diagnosis of primary BC
Buchmann I, Riedmuller K, Hoffner S, Mack U, Aulmann S, Haberkorn U, *et al*. Comparison of 99mtechnetium-pertechnetate and 123-iodide SPECT with FDG-PET in patients suspicious for breast cancer. *Cancer Biother Radiopharm* 2007;**22**(6):779–89	Primary BC diagnosis
Can N, Kapucu LO, Uner A, Unlu M. The role of 18F-FDG PET/CT in follow up of advanced stage breast cancer. [Turkish]. *Uluslararasi Hematoloji-Onkoloji Dergisi* 2008;**18**(1):9–15	No relevant outcomes
Carkaci S, Macapinlac HA, Cristofanilli M, Mawlawi O, Rohren E, Gonzalez Angulo AM, *et al*. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: Preliminary data. *J Nucl Med* 2009;**50**(2):231–8	Unclear reasons for patient referral
Chae BJ, Bae JS, Kang BJ, Kim SH, Jung SS, Song BJ. Positron emission tomography-computed tomography in the detection of axillary lymph node metastasis in patients with early stage breast cancer. *Jpn J Clin Oncol* 2009;**39**(5):284–9	For primary staging
Chin K, Finger PT, Kurli M, Tena LB, Reddy S, Chin K, *et al*. Second cancers discovered by (18) FDG PET/CT imaging for choroidal melanoma. *Optometry* 2007;**78**(8):396–401	Diagnosis of second primary tumours
Danforth DN, Jr., Aloj L, Carrasquillo JA, Bacharach SL, Chow C, Zujewski J, *et al*. The role of 18F-FDG-PET in the local/regional evaluation of women with breast cancer. *Breast Cancer Res Treat* 2002;**75**(2):135–46	For primary staging
Dehdashti F, Mortimer JE, Siegel BA, Griffeth LK, Bonasera TJ, Fusselman MJ, *et al*. Positron tomographic assessment of estrogen receptors in breast cancer: Comparison with FDG-PET and in vitro receptor assays. *J Nucl Med* 1995;**36**(10):1766–74	Incomplete reference standard, data not extractable
Dizendorf EV, Baumert BG, Von Schulthess GK, Lutolf UM, Steinert HC, Dizendorf EV, *et al*. Impact of whole-body 18F-FDG PET on staging and managing patients for radiation therapy. *J Nucl Med* 2003;**44**(1):24–9	Staging in primary setting

Reference[a]	Reason for exclusion
Dose J, Bleckmann C, Bachmann S, Bohuslavizki KH, Berger J, Jenicke L, *et al.* Comparison of fluorodeoxyglucose positron emission tomography and 'conventional diagnostic procedures' for the detection of distant metastases in breast cancer patients. *Nucl Med Commun* 2002;**23**(9):857–64	Data merged for patients in the setting of primary and secondary investigation
Eby PR, Partridge SC, White SW, Doot RK, Dunnwald LK, Schubert EK, *et al.* Metabolic and vascular features of dynamic contrast-enhanced breast magnetic resonance imaging and (15)O-water positron emission tomography blood flow in breast cancer. *Acad Radiol* 2008;**15**(10):1246–54	No relevant outcomes
Eubank WB, Mankoff D, Bhattacharya M, Gralow J, Linden H, Ellis G, *et al.* Impact of FDG PET on defining the extent of disease and on the treatment of patients with recurrent or metastatic breast cancer. *AJR Am J Roentgenol* 2004;**183**(2):479–86	Unsatisfactory reference standard (included for data on patient management)
Fuster D, Duch J, Paredes P, Velasco M, Munoz M, Santamaria G, *et al.* Preoperative staging of large primary breast cancer with [18F]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. *J Clin Oncol* 2008;**26**(29):4746–51	Pre-operative staging in primary setting
Garcia JR, Simo M, Soler M, Perez G, Lopez S, Lomena F, *et al.* Relative roles of bone scintigraphy and positron emission tomography in assessing the treatment response of bone metastases. *Eur J Nucl Med Mol Imaging* 2005;**32**(10):1243–4	Assessing response to treatment
Grahek D, Montravers F, Kerrou K, Aide N, Lotz JP, Talbot JN, *et al.* [18F]FDG in recurrent breast cancer: diagnostic performances, clinical impact and relevance of induced changes in management. *Eur J Nucl Med Mol Imaging* 2004;**31**(2):179–88	PET gamma camera used (included for data on patient management)
Heinisch M, Gallowitsch HJ, Mikosch P, Kresnik E, Kumnig G, Gomez I, *et al.* Comparison of FDG-PET and dynamic contrast-enhanced MRI in the evaluation of suggestive breast lesions. *Breast* 2003;**12**(1):17–22	Confirmation of primary diagnosis prior to surgery
Heusner TA, Kuemmel S, Umutlu L, Koeninger A, Freudenberg LS, Hauth EAM, *et al.* Breast cancer staging in a single session: Whole-body PET/CT mammography. *J Nucl Med* 2008;**49**(8):1215–1222.	PET for primary diagnosis
Hoh CK, Hawkins RA, Glaspy JA, Dahlbom M, Tse NY, Hoffman EJ, *et al.* Cancer detection with whole-body PET using 2-[18F]fluoro-2-deoxy-D-glucose. *J Comput Assist Tomogr* 1993;**17**(4):582–9	Data not separated for PETs done for primary diagnosis and recurrence
Iagaru A, Masamed R, Keesara S, Conti PS, Iagaru A, Masamed R, *et al.* Breast MRI and 18F FDG PET/CT in the management of breast cancer. *Ann Nucl Med* 2007;**21**(1):33–8	PET/CT for initial staging or post-operative assessment
Ide M. Cancer screening with FDG-PET. *Q J Nucl Med Mol Imaging* 2006;**50**(1):23–7	BC screening in asymptomatic people
Imbriaco M, Caprio MG, Limite G, Pace L, De FT, Capuano E, *et al.* Dual-time-point 18F-FDG PET/CT versus dynamic breast MRI of suspicious breast lesions. *AJR Am J Roentgenol* 2008;**191**(5):1323–30	Primary diagnosis of BC
Inoue T, Kim EE, Wallace S, Yang DJ, Wong FC, Bassa P, *et al.* Positron emission tomography using [18F]fluorotamoxifen to evaluate therapeutic responses in patients with breast cancer: preliminary study. *Cancer Biother Radiopharm* 1996;**11**(4):235–45	Unclear if patients in primary or secondary treatment setting
Inoue T, Yutani K, Taguchi T, Tamaki Y, Shiba E, Noguchi S, *et al.* Preoperative evaluation of prognosis in breast cancer patients by [(18)F]2-Deoxy-2-fluoro-D-glucose-positron emission tomography. *J Cancer Res Clin Oncol* 2004;**130**(5):273–8	Pre-operative staging
Kitajima K, Nakamoto Y, Okizuka H, Onishi Y, Senda M, Suganuma N, *et al.* Accuracy of whole-body FDG-PET/CT for detecting brain metastases from non-central nervous system tumors. *Ann Nucl Med* 2008;**22**(7):595–602	Mixed for different primary cancers
Klaeser B, Wiederkehr O, Koeberle D, Mueller A, Bubeck B, Thuerlimann B, *et al.* Therapeutic impact of 2-[fluorine-18]fluoro-2-deoxy-D-glucose positron emission tomography in the pre- and postoperative staging of patients with clinically intermediate or high-risk breast cancer. *Ann Oncol* 2007;**18**(8):1329–34	Initial staging
Kumar R, Zhuang H, Schnall M, Conant E, Damia S, Weinstein S, *et al.* FDG PET positive lymph nodes are highly predictive of metastasis in breast cancer. *Nucl Med Commun* 2006;**27**(3):231–6	Mixed population for primary diagnosis and staging

Reference[a]	Reason for exclusion
Landheer ML, Steffens MG, Klinkenbijl JH, Westenberg AH, Oyen WJ, Landheer MLEA, *et al.* Value of fluorodeoxyglucose positron emission tomography in women with breast cancer. *Br J Surg* 2005;**92**(11):1363–7	No proper reference standard, no results for TN and FNs
Mahner S, Schirrmacher S, Brenner W, Jenicke L, Habermann CR, Avril N, *et al.* Comparison between positron emission tomography using 2-[fluorine-18]fluoro-2-deoxy-D-glucose, conventional imaging and computed tomography for staging of breast cancer. *Ann Oncol* 2008;**19**(7):1249–54	Raw data not provided
Moy L, Ponzo F, Noz ME, Maguire J, Murphy-Walcott AD, Deans AE, *et al.* Improving specificity of breast MRI using prone PET and fused MRI and PET 3D volume datasets. *J Nucl Med* 2007;**48**(4):528–37	No results for PET, only for MRI/PET fused
Pecking A-P, Corone MC, Alberini JL, Bertrand KF, Pallud C, Floiras JL, *et al.* FDG-PET and detection of occult disease in oncology. [French]. *Immuno-Analyse et Biologie Specialisee* 2002;**17**(5):287–92	Coincidence PET gamma camera
Piperkova E, Raphael B, Altinyay ME, Castellon I, Libes R, Sandella N, *et al.* Impact of PET/CT in comparison with same day contrast enhanced CT in breast cancer management. *Clin Nucl Med* 2007;**32**(6):429–34	Cannot separate data for staging, restaging and evaluating therapy response
Roman CD, Martin WH, Delbeke D. Incremental value of fusion imaging with integrated PET-CT in oncology. *Clin Nucl Med* 2005;**30**(7):470–7	No proper reference standard
Rostom AY, Powe J, Kandil A, Ezzat A, Bakheet S, El-Khwsky F, *et al.* Positron emission tomography in breast cancer: A clinicopathological correlation of results. *B J Radiol* 1999;**72**: 1064–8	Mixed population with PET for primary diagnosis, staging and suspected recurrence
Schirrmeister H, Guhlmann A, Kotzerke J, Santjohanser C, Kuhn T, Kreienberg R, *et al.* Early detection and accurate description of extent of metastatic bone disease in breast cancer with fluoride ion and positron emission tomography. *J Clin Oncol* 1999;**17**(8):2381–9	F-18-PET (not FDG)
Schirrmeister H, Kuhn T, Guhlmann A, Santjohanser C, Horster T, Nussle K, *et al.* Fluorine-18 2-deoxy-2-fluoro-D-glucose PET in the preoperative staging of breast cancer: Comparison with the standard staging procedures. *Eur J Nucl Med Mol Imaging* 2001;**28**(3):351–8	Predominantly patients having PET for primary diagnosis
Schwarz-Dose J, Untch M, Tiling R, Sassen S, Mahner S, Kahlert S, *et al.* Monitoring primary systemic therapy of large and locally advanced breast cancer by using sequential positron emission tomography imaging with [18F]fluorodeoxyglucose. *J Clin Oncol* 2009;**27**(4):535–41	Measuring response to chemotherapy
Siggelkow W, Zimny M, Faridi A, Petzold K, Buell U, Rath W, *et al.* The value of positron emission tomography in the follow-up for breast cancer. *Anticancer Res* 2003;**23**(2C):1859–67	Data unclear and cannot be extracted
Smith IC, Ogston KN, Whitford P, Smith FW, Sharp P, Norton M, *et al.* Staging of the axilla in breast cancer: Accurate in vivo assessment using positron emission tomography with 2-(fluorine-18)-fluoro-2-deoxy-D- glucose. *Ann Surg* 1998;**228**(2):220–7	Staging in primary breast cancer assessment
Specht JM, Tam SL, Kurland BF, Gralow JR, Livingston RB, Linden HM, *et al.* Serial 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) to monitor treatment of bone-dominant metastatic breast cancer predicts time to progression (TTP). *Breast Cancer Res Treat* 2007;**105**(1):87–94	Referred for staging
Stecco A, Romano G, Negru M, Volpe D, Saponaro A, Costantino S, *et al.* Whole-body diffusion-weighted magnetic resonance imaging in the staging of oncological patients: Comparison with positron emission tomography computed tomography (PET-CT) in a pilot study. *Radiologia Medica* 2009;**114**(1):1–17	Mixed results for different cancers
Taira N, Ohsumi S, Takabatake D, Hara F, Aogi K, Takashima S, *et al.* Determination of indication for sentinel lymph node biopsy in clinical node-negative breast cancer using preoperative 18F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging. *Jpn J Clin Oncol* 2009;**39**(1):16–21	Primary staging for lymph node metastases
Tatsumi M, Cohade C, Mourtzikos KA, Fishman EK, Wahl RL, Tatsumi M, *et al.* Initial experience with FDG-PET/CT in the evaluation of breast cancer. *Eur J Nucl Med Mol Imaging* 2006;**33**(3):254–62	No proper reference standard, PET/CT vs CT compared
Terauchi T, Murano T, Daisaki H, Kanou D, Shoda H, Kakinuma R, *et al.* Evaluation of whole-body cancer screening using 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography: a preliminary report. *Ann Nucl Med* 2008;**22**(5):379–85	Primary screening investigations

Reference[a]	Reason for exclusion
Tran A, Pio BS, Khatibi B, Czernin J, Phelps ME, Silverman DH, *et al.* 18F-FDG PET for staging breast cancer in patients with inner-quadrant versus outer-quadrant tumors: comparison with long-term clinical outcome. *J Nucl Med* 2005;**46**(9):1455–9	PET for staging
Uematsu T, Yuen S, Yukisawa S, Aramaki T, Morimoto N, Endo M, *et al.* Comparison of FDG PET and SPECT for detection of bone metastases in breast cancer. *AJR Am J Roentgenol* 2005;**184**(4):1266–73	Patients referred for staging or restaging
Uematsu T, Kasami M, Yuen S. Comparison of FDG PET and MRI for evaluating the tumor extent of breast cancer and the impact of FDG PET on the systemic staging and prognosis of patients who are candidates for breast-conserving therapy. *Breast Cancer* 2009;**16**(2):97–104	Setting of primary BC staging
Van der Hoeven JJ, Krak NC, Hoekstra OS, Comans EF, Boom RP, Van GD, *et al.* 18F-2-fluoro-2-deoxy-d-glucose positron emission tomography in staging of locally advanced breast cancer. *J Clin Oncol* 2004;**22**(7):1253–9	Investigations in primary BC staging
Weir L, Worsley D, Bernstein V. The value of FDG positron emission tomography in the management of patients with breast cancer. *Breast* 2005;**11**(3):204–9	PET for staging or unclear reason for referral
Yap CS, Seltzer MA, Schiepers C, Gambhir SS, Rao J, Phelps ME, *et al.* Impact of whole-body 18F-FDG PET on staging and managing patients with breast cancer: the referring physician's perspective. *J Nucl Med* 2001;**42**(9):1334–7	No test accuracy data (included for data on patient management)
Zornoza G, Garcia-Velloso MJ, Sola J, Regueira FM, Pina L, Beorlegui C, *et al.* 18F-FDG PET complemented with sentinel lymph node biopsy in the detection of axillary involvement in breast cancer. *Eur J Surg Oncol* 2004;**30**(1):15–19	PET for staging

a A full list of the 185 excluded hard-copy references with reasons for exclusion can be provided on request.

Health Technology Assessment reports published to date

Volume 1, 1997

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Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

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

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A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

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Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

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Informed decision making: an annotated bibliography and systematic review.
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Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
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A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al.*

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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.*

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The debridement of chronic wounds: a systematic review.
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Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
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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.
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Volume 4, 2000

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A review by Cairns JA, van der Pol MM.

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Geriatric rehabilitation following fractures in older people: a systematic review.
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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.

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The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 5, 2001

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 6, 2002

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 7, 2003

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 8, 2004

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Volume 9, 2005

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

No. 23

A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.

By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al.*

No. 24

An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.

By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al.*

No. 25

Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.

By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al.*

No. 26

Indirect comparisons of competing interventions.

By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al.*

No. 27

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

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

No. 28

Outcomes of electrically stimulated gracilis neosphincter surgery.

By Tillin T, Chambers M, Feldman R.

No. 29

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

By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al.*

No. 30

Systematic review on urine albumin testing for early detection of diabetic complications.

By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al.*

No. 31

Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.

By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32

Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.

By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al.*

No. 33

Cost-effectiveness and safety of epidural steroids in the management of sciatica.

By Price C, Arden N, Coglan L, Rogers P.

No. 34

The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.

By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35

Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.

By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al.*

No. 36

The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.

By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37

A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.

By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al.*

No. 38

The causes and effects of socio-demographic exclusions from clinical trials.

By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al.*

No. 39

Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.

By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al.*

No. 40

A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.

By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al.*

No. 41

Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.

By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42

Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.

By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al.*

No. 43

The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.

By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44

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

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

No. 45

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

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

No. 46

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

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

No. 47

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

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

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.

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

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.

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

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.

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

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.

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

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.

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

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.

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

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.

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

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.

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

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.

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

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.

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

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.

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

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.

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

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.

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

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.

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

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.

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

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).

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

No. 14
The cost-effectiveness of screening for oral cancer in primary care.

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

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.

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

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.

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

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.

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

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.

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

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.

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

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.

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

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.

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

No. 22
Pressure relieving support surfaces: a randomised evaluation.

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

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.

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

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.

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

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.

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

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.

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

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.

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

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.

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

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.

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

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.

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

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.

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

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.

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

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.

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

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.

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

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.

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

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.

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

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.

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

No. 38
A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.

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

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.

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

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).

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

No. 41
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.

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

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.

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

No. 43
Telemedicine in dermatology: a randomised controlled trial.

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

No. 44
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.

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

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.

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

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.

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

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.

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

No. 48
Evaluation of the ventricular assist device programme in the UK.

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

No. 49
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.

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

No. 50
Amniocentesis results: investigation of anxiety. The ARIA trial.

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

Volume 11, 2007

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.

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

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.

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

No. 3
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.

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

No. 4
The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.

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

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.

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

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.

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

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.

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

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.

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

No. 9
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.

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

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.

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

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.

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

No. 12
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.

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

No. 13
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.

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

No. 14
A systematic review and economic evaluation of statins for the prevention of coronary events.

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

No. 15
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.

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

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.

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

No. 17
Screening for type 2 diabetes: literature review and economic modelling.

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

No. 18
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.

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

No. 19
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.

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

No. 20
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.

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

No. 21
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.

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

No. 22
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.

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

No. 23
Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

No. 50
Evaluation of diagnostic tests when there is no gold standard. A review of methods.

By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.

By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, *et al.*

No. 52
A review and critique of modelling in prioritising and designing screening programmes.

By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, *et al.*

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.

By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.

By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, *et al.*

No. 2
'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.

By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.

By Thornton J, Ashcroft D, O'Neill T, Elliott R, Adams J, Roberts C, *et al.*

No. 4
Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.

By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

No. 5
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.

By Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, *et al.*

No. 6
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.

By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al.*

No. 7
The use of economic evaluations in NHS decision-making: a review and empirical investigation.

By Williams I, McIver S, Moore D, Bryan S.

No. 8
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.

By Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, *et al.*

No. 9
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.

By Loveman E, Frampton GK, Clegg AJ.

No. 10
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.

By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.

By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al.*

No. 12
The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.

By Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y, *et al.*

No. 13
Stepped treatment of older adults on laxatives. The STOOL trial.

By Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, *et al.*

No. 14
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.

By Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, *et al.*

No. 15
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.

By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

No. 16
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.

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

No. 17
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.

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

No. 18
Structural neuroimaging in psychosis: a systematic review and economic evaluation.

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

No. 19
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.

By Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, *et al.*

No. 20
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years.

By Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, *et al.*

No. 21
Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.

By Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, *et al.*

No. 22
Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.

By Underwood M, Ashby D, Carnes D, Castelnuovo E, Cross P, Harding G, *et al.*

No. 23
A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.

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

No. 24
A review and critical appraisal of measures of therapist–patient interactions in mental health settings.

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

No. 25
The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.

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

No. 26
A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.

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

No. 27
A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.

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

No. 28
Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.

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

No. 29
Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.

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

No. 30
A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.

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

No. 31
The effectiveness and cost-effectivness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.

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

No. 32
Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.

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

No. 33
Performance of screening tests for child physical abuse in accident and emergency departments.

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

No. 34
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.

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

No. 35
Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.

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

No. 36
Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.

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

Volume 13, 2009

No. 1
Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.

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

No. 2
Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.

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

No. 3
Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.

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

No. 4
Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis.

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

No. 5
Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.

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

No. 6
The harmful health effects of recreational ecstasy: a systematic review of observational evidence.

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

No. 7
Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.

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

No. 8
The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports.

By Taylor RS, Elston J.

No. 9
Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial.

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

No. 10
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.

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

No. 11
Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation.

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

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

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

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

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

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

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

No. 18
The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history.
By Fortnum H, O'Neill C, Taylor R, Lenthall R, Nikolopoulos T, Lightfoot G, *et al.*

No. 19
Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study.
By Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA, *et al.*

No. 20
Systematic review of respite care in the frail elderly.
By Shaw C, McNamara R, Abrams K, Cannings-John R, Hood K, Longo M, *et al.*

No. 21
Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID).
By Tyrer P, Oliver-Africano P, Romeo R, Knapp M, Dickens S, Bouras N, *et al.*

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

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

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

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

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

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

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

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

Suppl. 1
Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal.
By Ward S, Pilgrim H, Hind D.

Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal.
By Chilcott J, Lloyd Jones M, Wilkinson A.

The use of paclitaxel in the management of early stage breast cancer.
By Griffin S, Dunn G, Palmer S, Macfarlane K, Brent S, Dyker A, *et al.*

Rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma.
By Dundar Y, Bagust A, Hounsome J, McLeod C, Boland A, Davis H, *et al.*

Bortezomib for the treatment of multiple myeloma patients.
By Green C, Bryant J, Takeda A, Cooper K, Clegg A, Smith A, *et al.*

Fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia.
By Walker S, Palmer S, Erhorn S, Brent S, Dyker A, Ferrie L, *et al.*

Erlotinib for the treatment of relapsed non-small cell lung cancer.
By McLeod C, Bagust A, Boland A, Hockenhull J, Dundar Y, Proudlove C, *et al.*

Cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck.
By Griffin S, Walker S, Sculpher M, White S, Erhorn S, Brent S, *et al.*

Infliximab for the treatment of adults with psoriasis.
By Loveman E, Turner D, Hartwell D, Cooper K, Clegg A.

No. 30
Psychological interventions for postnatal depression: cluster randomised trial and economic evaluation. The PoNDER trial.
By Morrell CJ, Warner R, Slade P, Dixon S, Walters S, Paley G, *et al.*

No. 31
The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis.
By Rogowski R, Burch J, Palmer S, Craigs C, Golder S, Woolacott N.

No. 32
Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care.

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

No. 33
A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial.

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

No. 34
Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation.

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

No. 35
Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation.

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

No. 36
Methods to identify postnatal depression in primary care: an integrated evidence synthesis and value of information analysis.

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

No. 37
A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with persistent bilateral otitis media with effusion in primary care.

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

No. 38
The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model.

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

No. 39
Rehabilitation of older patients: day hospital compared with rehabilitation at home. A randomised controlled trial.

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

No. 40
Breastfeeding promotion for infants in neonatal units: a systematic review and economic analysis.

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

No. 41
The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation.

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

No. 42
Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness.

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

No. 43
Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling.

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

No. 44
The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model.

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

Suppl. 2
Gemcitabine for the treatment of metastatic breast cancer.

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

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

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

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

By Lloyd Jones M, Holmes M.

Rituximab for the treatment of rheumatoid arthritis.

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

Omalizumab for the treatment of severe persistent allergic asthma.

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

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

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

Adalimumab for the treatment of psoriasis.

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

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

By Holmes M, Carroll C, Papaioannou D.

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

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

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

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

No. 45
Vitamin K to prevent fractures in older women: systematic review and economic evaluation.

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

No. 46
The effects of biofeedback for the treatment of essential hypertension: a systematic review.

By Greenhalgh J, Dickson R, Dundar Y.

No. 47
A randomised controlled trial of the use of aciclovir and/or prednisolone for the early treatment of Bell's palsy: the BELLS study.

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

Suppl. 3
Lapatinib for the treatment of HER2-overexpressing breast cancer.

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

Infliximab for the treatment of ulcerative colitis.

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

Rimonabant for the treatment of overweight and obese people.

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

Telbivudine for the treatment of chronic hepatitis B infection.

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

Entecavir for the treatment of chronic hepatitis B infection.

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

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

By Stevenson M, Pandor A.

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

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

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

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

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

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

Ustekinumab for the treatment of moderate to severe psoriasis.

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

No. 48

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

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

No. 49

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

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

No. 50

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

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

No. 51

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

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

No. 52

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

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

No. 53

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

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

No. 54

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

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

No. 55

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

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

No. 56

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

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

No. 57

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

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

No. 58

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

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

No. 59

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

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

No. 60

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

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

No. 61

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

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

No. 62

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

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

Volume 14, 2010

No. 1

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

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

No. 2

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

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

No. 3

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

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

No. 4

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

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

No. 5

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

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

No. 6

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

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

No. 7

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

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

No. 8
Dissemination and publication of research findings: an updated review of related biases.

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

No. 9
The effectiveness and cost-effectiveness of biomarkers for the prioritisation of patients awaiting coronary revascularisation: a systematic review and decision model.

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

No. 10
Comparison of case note review methods for evaluating quality and safety in health care.

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

No. 11
Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation.

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

No. 12
Self-monitoring of blood glucose in type 2 diabetes: systematic review.

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

No. 13
North of England and Scotland Study of Tonsillectomy and Adeno-tonsillectomy in Children (NESSTAC): a pragmatic randomised controlled trial with a parallel non-randomised preference study.

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

No. 14
Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial.

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

No. 15
A randomised controlled multicentre trial of treatments for adolescent anorexia nervosa including assessment of cost-effectiveness and patient acceptability – the TOuCAN trial.

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

No. 16
Randomised controlled trials for policy interventions: a review of reviews and meta-regression.

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

No. 17
Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review.

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

No. 18
A systematic review of outcome measures used in forensic mental health research with consensus panel opinion.

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

No. 19
The clinical effectiveness and cost-effectiveness of topotecan for small cell lung cancer: a systematic review and economic evaluation.

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

No. 20
Antenatal screening for haemoglobinopathies in primary care: a cohort study and cluster randomised trial to inform a simulation model. The Screening for Haemoglobinopathies in First Trimester (SHIFT) trial.

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

No. 21
Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis.

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

No. 22
A randomised controlled trial of cognitive behaviour therapy and motivational interviewing for people with Type 1 diabetes mellitus with persistent sub-optimal glycaemic control: A Diabetes and Psychological Therapies (ADaPT) study.

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

No. 23
A randomised controlled equivalence trial to determine the effectiveness and cost–utility of manual chest physiotherapy techniques in the management of exacerbations of chronic obstructive pulmonary disease (MATREX).

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

No. 24
A systematic review and economic evaluation of the clinical effectiveness and cost-effectiveness of aldosterone antagonists for postmyocardial infarction heart failure.

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

No. 25
Avoiding and identifying errors in health technology assessment models: qualitative study and methodological review.

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

No. 26
BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A.

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

No. 27
Weighting and valuing quality-adjusted life-years using stated preference methods: preliminary results from the Social Value of a QALY Project.

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

Suppl. 1
Cetuximab for the first-line treatment of metastatic colorectal cancer.

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

Infliximab for the treatment of acute exacerbations of ulcerative colitis.

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

Sorafenib for the treatment of advanced hepatocellular carcinoma.

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

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

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

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

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

Alitretinoin for the treatment of severe chronic hand eczema.

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

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

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

Topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix.
By Paton F, Paulden M, Saramago P, Manca A, Misso K, Palmer S, *et al.*

Trabectedin for the treatment of advanced metastatic soft tissue sarcoma.
By Simpson EL, Rafia R, Stevenson MD, Papaioannou D.

Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia.
By Edlin R, Connock M, Tubeuf S, Round J, Fry-Smith A, Hyde C, *et al.*

No. 28
The safety and effectiveness of different methods of earwax removal: a systematic review and economic evaluation.
By Clegg AJ, Loveman E, Gospodarevskaya E, Harris P, Bird A, Bryant J, *et al.*

No. 29
Systematic review of the clinical effectiveness and cost-effectiveness of rapid point-of-care tests for the detection of genital chlamydia infection in women and men.
By Hislop J, Quayyum Z, Flett G, Boachie C, Fraser C, Mowatt G.

No. 30
School-linked sexual health services for young people (SSHYP): a survey and systematic review concerning current models, effectiveness, cost-effectiveness and research opportunities.
By Owen J, Carroll C, Cooke J, Formby E, Hayter M, Hirst J, *et al.*

No. 31
Systematic review and cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared to episodic in-hospital treatment or continuous antiarrhythmic drug therapy.
By Martin Saborido C, Hockenhull J, Bagust A, Boland A, Dickson R, Todd D.

No. 32
Chemoprevention of colorectal cancer: systematic review and economic evaluation.
By Cooper K, Squires H, Carroll C, Papaioannou D, Booth A, Logan RF, *et al.*

No. 33
Cross-trimester repeated measures testing for Down's syndrome screening: an assessment.
By Wright D, Bradbury I, Malone F, D'Alton M, Summers A, Huang T, *et al.*

No. 34
Exploring the needs, concerns and behaviours of people with existing respiratory conditions in relation to the H1N1 'swine influenza' pandemic: a multicentre survey and qualitative study.
By Caress A-L, Duxbury P, Woodcock A, Luker KA, Ward D, Campbell M, *et al.*

Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant.
By Yates L, Pierce M, Stephens S, Mill AC, Spark P, Kurinczuk JJ, *et al.*

The impact of communications about swine flu (influenza A H1N1v) on public responses to the outbreak: results from 36 national telephone surveys in the UK.
By Rubin GJ, Potts HWW, Michie S.

The impact of illness and the impact of school closure on social contact patterns.
By Eames KTD, Tilston NL, White PJ, Adams E, Edmunds WJ.

Vaccine effectiveness in pandemic influenza – primary care reporting (VIPER): an observational study to assess the effectiveness of the pandemic influenza A (H1N1)v vaccine.
By Simpson CR, Ritchie LD, Robertson C, Sheikh A, McMenamin J.

Physical interventions to interrupt or reduce the spread of respiratory viruses: a Cochrane review.
By Jefferson T, Del Mar C, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, *et al.*

No. 35
Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR).
By Peek GJ, Elbourne D, Mugford M, Tiruvoipati R, Wilson A, Allen E, *et al.*

No. 36
Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation.
By Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, *et al.*

No. 37
Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin.
By Fayter D, Corbett M, Heirs M, Fox D, Eastwood A.

No. 38
Towards single embryo transfer? Modelling clinical outcomes of potential treatment choices using multiple data sources: predictive models and patient perspectives.
By Roberts SA, McGowan L, Hirst WM, Brison DR, Vail A, Lieberman BA.

No. 39
Sugammadex for the reversal of muscle relaxation in general anaesthesia: a systematic review and economic assessment.
By Chambers D, Paulden M, Paton F, Heirs M, Duffy S, Craig D, *et al.*

No. 40
Systematic review and economic modelling of the effectiveness and cost-effectiveness of non-surgical treatments for women with stress urinary incontinence.
By Imamura M, Abrams P, Bain C, Buckley B, Cardozo L, Cody J, *et al.*

No. 41
A multicentred randomised controlled trial of a primary care-based cognitive behavioural programme for low back pain. The Back Skills Training (BeST) trial.
By Lamb SE, Lall R, Hansen Z, Castelnuovo E, Withers EJ, Nichols V, *et al.*

No. 42
Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation.
By Takeda A, Cooper K, Bird A, Baxter L, Frampton GK, Gospodarevskaya E, *et al.*

No. 43
A pragmatic randomised controlled trial to compare antidepressants with a community-based psychosocial intervention for the treatment of women with postnatal depression: the RESPOND trial.
By Sharp DJ, Chew-Graham C, Tylee A, Lewis G, Howard L, Anderson I, *et al.*

No. 44
Group cognitive behavioural therapy for postnatal depression: a systematic review of clinical effectiveness, cost-effectiveness and value of information analyses.
By Stevenson MD, Scope A, Sutcliffe PA, Booth A, Slade P, Parry G, *et al.*

No. 45
Screening for hyperglycaemia in pregnancy: a rapid update for the National Screening Committee.
By Waugh N, Royle P, Clar C, Henderson R, Cummins E, Hadden D, *et al.*

No. 46
Open-label, randomised, parallel-group, multicentre study to evaluate the safety, tolerability and immunogenicity of an AS03B/oil-in-water emulsion-adjuvanted (AS03B) split-virion versus non-adjuvanted wholevirion H1N1 influenza vaccine in UK children 6 months to 12 years of age.
By Waddington CS, Andrews N, Hoschler K, Walker WT, Oeser C, Reiner A, *et al.*

Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections.
By Simonds AK, Hanak A, Chatwin M, Morrell MJ, Hall A, Parker KH, *et al.*

Evaluation of triage methods used to select patients with suspected pandemic influenza for hospital admission: cohort study.
By Goodacre S, Challen, K, Wilson R, Campbell M.

Virus shedding and environmental deposition of novel A (H1N1) pandemic influenza virus: interim findings.
By Killingley B, Greatorex J, Cauchemez S, Enstone JE, Curran M, Read R, *et al.*

Neuraminidase inhibitors for preventing and treating influenza in healthy adults: a Cochrane review.
By Jefferson T, Jones M, Doshi P, Del Mar C, Dooley L, Foxlee R.

No. 47
Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation.
By Hummel S, Simpson EL, Hemingway P, Stevenson MD, Rees A.

No. 48
Computerised decision support systems in order communication for diagnostic, screening or monitoring test ordering: systematic reviews of the effects and cost-effectiveness of systems.
By Main C, Moxham T, Wyatt JC, Kay J, Anderson R, Stein K.

No. 49
Relapse prevention in UK Stop Smoking Services: current practice, systematic reviews of effectiveness and cost-effectiveness analysis.
By Coleman T, Agboola S, Leonardi-Bee J, Taylor M, McEwen A, McNeill A.

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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.

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