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Abstract

Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation

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Background: Prostate cancer (PC) is the most common cancer in men in the UK. Radiotherapy (RT) is a recognised treatment for PC and high-dose conformal radiotherapy (CRT) is the recommended standard of care for localised or locally advanced tumours. Intensity-modulated radiotherapy (IMRT) allows better dose distributions in RT.

Objective: This report evaluates the clinical effectiveness and cost-effectiveness of IMRT for the radical treatment of PC.

Data sources: The following databases were searched: MEDLINE (1950–present), EMBASE (1980–present), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982–present), BIOSIS (1985–present), the Cochrane Database of Systematic Reviews (1991–present), the Cochrane Controlled Trials Register (1991–present), the Science Citation Index (1900–present) and the NHS Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database, Health Technology Assessment) (1991–present). MEDLINE In-Process & Other Non-Indexed Citations was searched to identify any studies not yet indexed on MEDLINE. Current research was identified through searching the UK Clinical Research Network, National Research Register archive, the Current Controlled Trials register and the Medical Research Council Clinical Trials Register. In addition, abstracts of the American Society of Clinical Oncology, the American Society for Therapeutic Radiology and Oncology, and European Society for Therapeutic Radiology and Oncology conferences were browsed.

Review methods: A systematic literature review of the clinical effectiveness and cost-effectiveness of IMRT in PC was conducted. Comparators were three-dimensional conformal radiotherapy (3DCRT) or radical prostatectomy. Outcomes sought were overall survival, biochemical [prostate-specific antigen (PSA)] relapse-free survival, toxicity and health-related quality of life (HRQoL). Fifteen electronic bibliographic databases were searched in January 2009 and updated in May 2009, and the reference lists of relevant articles were checked. Studies only published in languages other than English were excluded. An economic model was developed to examine the cost-effectiveness of IMRT in comparison to 3DCRT. Four scenarios were modelled based on the studies which reported both PSA survival and late gastrointestinal (GI) toxicity. In two scenarios equal PSA survival was assumed for IMRT and 3DCRT, the other two having greater PSA survival for the IMRT cohort. As there was very limited data on clinical outcomes, the model estimates progression to clinical failure and PC death from the surrogate outcome of PSA failure.

Results: No randomised controlled trials (RCTs) of IMRT versus 3DCRT in PC were available, but 13 non-randomised studies comparing IMRT with 3DCRT were found, of which five were available only as abstracts. One abstract reported overall survival. Biochemical relapse-free survival was not affected by treatment group, except where there was a dose difference between groups, in which case higher dose IMRT was favoured over lower dose 3DCRT. Most studies reported an advantage for IMRT in GI toxicity, attributed to increased conformality of treatment compared with 3DCRT, particularly with regard to volume of rectum treated. There was some indication that genitourinary toxicity was worse for patients treated with dose escalated IMRT, although most studies did not find a significant treatment effect. HRQoL improved for both treatment groups following radiotherapy, with any group difference resolved by 6 months after treatment. No comparative studies of IMRT versus prostatectomy were identified. No comparative studies of IMRT in PC patients with bone metastasis were identified.

Limitations: The strength of the conclusions of this review are limited by the lack of RCTs, and any comparative studies for some patient groups.
Conclusions: The comparative data of IMRT versus 3DCRT seem to support the theory that higher doses, up to 81 Gy, can improve biochemical survival for patients with localised PC, concurring with data on CRT. The data also suggest that toxicity can be reduced by increasing conformality of treatment, particularly with regard to GI toxicity, which can be more easily achieved with IMRT than 3DCRT. Whether differences in GI toxicity between IMRT and 3DCRT are sufficient for IMRT to be cost-effective is uncertain, depending on the difference in incidence of GI toxicity, its duration and the cost difference between IMRT and 3DCRT.

Contents

Glossary and list of abbreviations

Glossary

Adjuvant radiotherapy Radiotherapy supplementary to the main treatment (usually surgery, chemotherapy), given after main treatment.

Androgen deprivation A form of hormonal therapy, given to suppress or block the production or action of male sex hormones (androgens).

Chemotherapy Treatment with cytotoxic drugs that kill cancer cells, or prevent or slow their growth.

Clinical target volume Clinically defined target volume, containing tumour, unless surgically excised, and microscopic invisible tumour; to be treated with the prescribed radiation dose.

Compensators/dose compensators Method of dose modulation.

Computed tomography An X-ray technique using a scanner to take a series of images across the body.

Conformal radiotherapy Radiotherapy delivered by non-modulated beams, which can be shaped geometrically to avoid irradiating normal surrounding tissue.

Distant recurrence Recurrence of cancer at distant sites.

Dose escalation Increasing the total radiotherapy dose.

Dose–volume histogram Histogram showing the dose distribution within an outlined structure, often presented as cumulative plot-volume of organ plotted against dose.

Dosimetrist Specialist radiotherapy planning staff, also known as clinical technologist.

Forward planned intensity-modulated radiotherapy (IMRT) The planner modifies a provisional plan (based on the treatment beam arrangements that are likely to be used) until the dose distribution is improved.

Fraction A unit of radiotherapy treatment.

Fractionation Schedule of treatment sessions required for a course of radiotherapy treatment.

Gross tumour volume The gross palpable or visible/demonstrable extent and location of the malignant growth.

Gy A unit of radiation (Gray) used to measure radiation dose.

Histological grade Measure of the malignancy of a tumour.

Hypofractionated The radiotherapy dose per fraction is greater than standard care, requiring fewer total fractions to achieve the same biological equivalent dose (BED) as for standard fractionation (see Appendix 9).

Immobilisation Techniques designed to reduce patient movement during radiotherapy.

Incremental cost-effectiveness ratio (ICER) The ratio of the incremental cost of the new treatment compared with the existing treatment to the incremental effectiveness, the latter usually being expressed in quality-adjusted life-years (QALYs).

Intensity-modulated radiotherapy The beam of radiation is not uniform across the field to be irradiated, but consists of beamlets of varying intensity. Combinations of several intensity-modulated fields coming from different beam directions are used to create a highly conformal dose distribution.

Inverse planned IMRT Utilises computers, manipulating many hundreds of treatment beamlets, in order to produce highly complex treatment plans. The computer iteratively attempts to fulfil the planner's defined dose target and normal tissue constraints.

Linear accelerator Machine that generates and delivers radiation.

Locoregional recurrence Recurrence of cancer at local or regional sites, e.g. within lymph nodes.

Lymph nodes Small structures that act as filters in the lymphatic system.

Metastases/metastatic cancer Cancer which has spread to distant sites from the primary tumour.

Multileaf collimator Device attached to or inherent within to linear accelerator to allow beam modulation, uses a number of leaves to create an irregular shaped radiation beam.

Neoadjuvant Treatment given prior to surgery, chemotherapy or radiotherapy.

Overall survival Outcome measure defined as the hazard of death from any cause after a given follow-up period, or time from randomisation to death from any cause.

Planned dose inhomogeneity Planning higher doses to regions of high risk and lower doses to regions of low risk, usually termed with treatment delivered with a single treatment plan.

Planning target volume Geometrical concept defined to ensure that appropriate beam sizes and arrangements are chosen so that the prescribed dose is directed to the clinical target volume, taking into account setup and delivery errors and physiological changes such as motion and changes in tumour volume.

Progression-free survival Outcome measure defined as the hazard of disease progression or death from any cause after a given follow-up period, or time from randomisation to first of these events.

Prostatectomy Surgery to remove all of the prostate gland and some of the tissue around it, to treat prostate cancer.

Quality-adjusted life-years (QALYs) The number of life-years adjusted for population preferences for different health states. A life-year in perfect health is 1 QALY.

Quality assurance Procedures that ensure consistency of the prescription and safe delivery of prescription dose to the target volume.

Radiotherapy/radiation therapy Radiation delivered locally to affected site to kill cancer cells, or to stop cancer cells from dividing and growing.

Short Form questionnaire-36 items A health-related quality of life scale.

Staging/stage of cancer An internationally recognised system for defining a tumour in terms of its size and degree of spread through the body.

Toxicity grade A measure of the severity of adverse events, either during radiotherapy (acute) or long-term toxicity (chronic).

Wedges Method of dose modulation.

List of abbreviations

3DCRT	three-dimensional conformal radiotherapy
AE	adverse event
ASCO	American Society of Clinical Oncology
ASTRO	American Society of Therapeutic Radiology and Oncology
BED	biological equivalent dose
BPE	benign prostatic enlargement
CHHiP	Conventional or Hypofractionated High dose Intensity-modulated radiotherapy for Prostate cancer
CI	confidence interval
CRT	conformal radiotherapy
CT	computed tomographic
CTV	clinical target volume
DRE	digital rectal examination
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-PR25	European Organisation for Research and Treatment of Cancer Prostate Cancer-specific Questionnaire
EPIC	Expanded Prostate Cancer Index Composite
EQ-5D	European Quality of Life-5 Dimensions
ESTRO	European Society for Therapeutic Radiology and Oncology
GI	gastrointestinal
GP	general practitioner
GTV	gross tumour volume
GU	genitourinary
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ICRU	International Commission on Radiation Units and Measurements
IGRT	image-guided radiotherapy
IMRT	intensity-modulated radiotherapy
IPEM	Institute of Physics and Engineering in Medicine
LUTS	lower urinary tract symptoms
MAICER	maximum incremental cost-effectiveness ratio
MLC	multileaf collimator
MRC	Medical Research Council
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTC	National Cancer Institute–Common Toxicity Criteria
NICE	National Institute for Health and Clinical Excellence
NRAG	National Radiotherapy Advisory Group
PC	prostate cancer
PSA	prostate-specific antigen

PTV	planning target volume
QA	quality assurance
QALY	quality-adjusted life-year
RCR	Royal College of Radiologists
RCT	randomised controlled trial
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
SCOR	Society and College of Radiographers
SD	standard deviation
SF-36	Short Form questionnaire-36 items
SV	seminal vesicle
TNM	tumour node metastasis
TRUS	trans-rectal ultrasonography
UCLA PCI	University of California Los Angeles Prostate Cancer Index
WP	whole pelvis

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

Prostate cancer (PC) is the most common cancer in men in the UK. Radiotherapy (RT) is a recognised treatment for PC and high-dose conformal radiotherapy (CRT) is the recommended standard of care for localised or locally advanced tumours. Intensity-modulated radiotherapy (IMRT) allows better dose distributions in RT.

Objectives

This report evaluates the clinical effectiveness and cost-effectiveness of IMRT for the radical treatment of PC.

Methods

A systematic literature review of the clinical effectiveness and cost-effectiveness of IMRT in PC was conducted. Comparators were three-dimensional conformal radiotherapy (3DCRT) or radical prostatectomy. Outcomes sought were overall survival, biochemical [prostate-specific antigen (PSA)] relapse-free survival, toxicity and health-related quality of life (HRQoL). Fifteen electronic bibliographic databases were searched (including MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), MEDLINE In-Process & Other Non-Indexed Citations, etc.) in January 2009 and updated in May 2009, and the reference lists of relevant articles were checked. Studies only published in languages other than English were excluded.

An economic model was developed to examine the cost-effectiveness of IMRT in comparison to 3DCRT. Four scenarios were modelled based on the studies which reported both PSA survival and late gastrointestinal (GI) toxicity. In two scenarios equal PSA survival was assumed for IMRT and 3DCRT, the other two having greater PSA survival for the IMRT cohort. As there was very limited data on clinical outcomes, the model estimates progression to clinical failure and PC death from the surrogate outcome of PSA failure.

Results

No randomised controlled trials (RCTs) of IMRT versus 3DCRT in PC were available, but 13 non-randomised studies comparing IMRT with 3DCRT were found, of which five were only available as abstracts. One abstract reported overall survival. Biochemical relapse-free survival was not affected by treatment group, except where there was a dose difference between groups, in which case higher dose IMRT was favoured over lower dose 3DCRT. Most studies reported an advantage for IMRT in GI toxicity, attributed to increased conformality of treatment compared with 3DCRT, particularly with regard to volume of rectum treated. There was some indication that genitourinary (GU) toxicity was worse for patients treated with dose-escalated IMRT, although most studies did not find a significant treatment effect. HRQoL improved for both treatment groups following RT, with any group difference resolved by 6 months after treatment. No comparative studies of IMRT versus prostatectomy were identified. No comparative studies of IMRT in PC patients with bone metastasis were identified.

Summary of costs

The additional cost of IMRT compared with 3DCRT was estimated to be £1100, arising from additional medical, radiographer and physics staff time.

Summary of cost-effectiveness

For the scenarios with greater survival for IMRT than 3DCRT-treated patients the results are unambiguous. IMRT either dominates 3DCRT [that is results in more quality-adjusted life-years (QALYs) for lower total costs], or the incremental cost-effectiveness ratio (ICER) is relatively modest (£5000), results which are robust to variation in other key parameters.

The two scenarios where equivalent survival is assumed for IMRT and 3DCRT, and QALY differences between the two cohorts are derived solely from differences in late GI toxicity alone, show IMRT to be borderline cost-effective

depending on the difference in GI toxicity, duration of GI toxicity and the cost difference between IMRT and 3DCRT. At baseline parameter values the scenario with a difference in late GI toxicity of 5% (scenario 1) gave an ICER of £104,000, but scenario 2 with a difference in GI toxicity of 15% gave an ICER of £31,000. The probabilistic analysis of the latter scenario showed that only with a maximum incremental cost-effectiveness ratio (MAICER) of ≥ £30,000 was it probable that IMRT was more cost-effective than 3DCRT. These results are highly sensitive to two very uncertain parameters: the incremental cost of IMRT and the duration of late GI toxicity. Variation of these parameters within plausible bounds can reduce the ICER of IMRT in comparison to 3DCRT to below a threshold of £20,000, or equally push it clearly beyond a threshold of £30,000. The scenarios modelled were all based on studies where both PSA survival and toxicity were reported. To put the values of incidence of late GI toxicity from the modelled studies in context the results of other studies included in the review were considered. These suggest model scenario 2 is more representative of the literature than scenario 1.

For RT to the whole pelvis (usually only considered for men with a > 15% risk of pelvic lymph node involvement) IMRT may be more cost-effective than for treatment of the prostate (and seminal vesicles) alone. A previous report published by Sanguineti *et al.* (Sanguineti G, Cavey ML, Endres EJ, Franzone P, Barra S, Parker BC, *et al*. Does treatment of the pelvic nodes with IMRT increase late rectal toxicity over conformal prostate only radiotherapy to 76 Gy? *Strahlenther Onkol* 2006;**182**:543–9) reports a difference of 15% in late GI toxicity at only two years, despite the IMRT group receiving whole pelvis RT in comparison to treatment of the prostate only in the comparator (3DCRT) group.

Discussion

A comprehensive, systematic literature review was undertaken, but the strength of the conclusions of this review are limited by the lack of RCTs, and any comparative studies for some patient groups. The comparative data of IMRT versus 3DCRT seem to support the theory that higher doses, up to 81 Gy, can improve biochemical survival for patients with localised PC, concurring with data on CRT. The data also suggest that toxicity can be reduced by increasing conformality of treatment, particularly with regard to GI toxicity, which can be more easily achieved with IMRT than 3DCRT. Whether differences in GI toxicity between IMRT and 3DCRT are sufficient for IMRT to be cost-effective is uncertain, depending on the difference in incidence of GI toxicity, its duration and the cost difference between IMRT and 3DCRT.

Conclusions

Implications for service provision

Clinical advice suggests that most RT centres already possess the equipment required to deliver IMRT, but that lack of available staff such as medical physicists hinders implementation. 3DCRT may be safely delivered at the currently recommended total dose of 74 Gy, and there is no evidence that PSA survival is improved by giving IMRT at the same dose as 3DCRT. However, there is evidence that IMRT reduces toxicity, in particular late GI toxicity. The magnitude of the difference is uncertain, which, together with uncertainties in other variables such as the difference in cost between IMRT and 3DCRT, in turn makes the cost-effectiveness of IMRT in comparison to 3DCRT uncertain. If a difference in late GI toxicity of 15% is assumed the probability of IMRT being more cost-effective than 3DCRT is only true for a MAICER of ≥ £30,000.

Chapter 1
Background

Description of health problem

Prostate cancer (PC) is the most common cancer in men in England and Wales and constitutes approximately 25% of the new diagnoses of malignant cancer in men in England and Wales.[1] The incidence appears to be rising.[1] It is also considered to be the most common malignant disease in males in Western Europe and North America.[2] The focus of this systematic review will be to address the question 'what is the clinical and cost-effectiveness of intensity-modulated radiotherapy (IMRT) for the radical treatment of PC compared with three-dimensional radiotherapy (3DCRT) and radical prostatectomy?'.

Aetiology, pathology and prognosis

The specific causes of PC remain unknown.[2] Hsing and Chokkalingam provided a comprehensive review of PC epidemiology[3] and reported that the risk of developing PC was related to: age, genetics, and family history of PC. It was reported that putative risk factors include: obesity, hormones, smoking, dietary factors, physical inactivity, occupation, vasectomy, genetic susceptibility, and sexual factors have also been implicated.

Localised PC (confined within the prostatic capsule) is usually asymptomatic in the early stage.[4] However, with regard to locally advanced PC it is because it is frequently asymptomatic in the early stage that it often presents at a more advanced stage. Lower urinary tract symptoms (LUTS) of frequency, urgency, hesitancy, terminal dribbling and/or overactive bladder can be related to benign prostatic enlargement (BPE) alone, but can also present in early PC and in locally advanced PC cases.[5] The LUTS often present in a similar way to symptoms of benign prostatic hyperplasia within locally advanced PC.[5] However, by the time PC itself causes LUTS, it may have reached an advanced and incurable stage.[4] Garrick suggests that a new onset of impotence should also be recognised.[6] PC frequently develops into bone metastases which causes pain. An abnormal or rising prostate-specific antigen (PSA) level is the most common indication of PC in the UK health-care system. In the UK, a diagnosis of PC is typically prompted by urological symptoms and biochemical information (particularly PSA).[7] Collin *et al.* conclude in a case-control study nested within the UK population-based Prostate testing for cancer and Treatment (ProtecT) study, that a history of LUTS before PSA testing marginally improves the prediction of an individual's risk of PC.[8] The PSA test and other ways to measure PC are described in more detail in Subgroups of patients with PC for whom radiotherapy (RT) may be indicated.

Prostate cancer is no longer seen as solely an indolent disease that rarely results in mortality for PC patients.[9] Johansson *et al.* examined the natural course of early localised PC in a consecutive sample of 223 initially untreated patients observed over 21 years and found that although most PCs diagnosed at an early stage have an indolent course, local tumour progression and aggressive metastatic disease may develop in the long term.[9] The findings support early radical treatment notably among patients with an estimated life expectancy exceeding 15 years.[9] Furthermore, as men's life expectancy increases, the effect of untreated PC may need to be re-evaluated. A recent study by Widmark *et al.*[10] showed that in patients with locally advanced or high-risk localised PC, addition of local RT to endocrine treatment halved the 10-year PC-specific mortality (23.9% in the endocrine alone group and 11.9% in the endocrine plus RT group), and substantially decreased overall mortality with fully acceptable risk of side-effects compared with endocrine treatment alone. In the light of these data endocrine treatment plus RT may be regarded as the new standard.[10]

Ongoing research may clarify how best to treat men with PC. With regard to early PC, the ProtecT randomised controlled trial (RCT) aims to evaluate the clinical effectiveness, cost-effectiveness and acceptability of active monitoring, radical prostatectomy and radical conformal radiotherapy (CRT) for men with localised PC.[8] In addition, the ProSTART study, a pilot study for an international phase III randomised parallel

group trial in patients with favourable risk PC (as defined as clinical stage T1b, T1c, T2a or T2b at time of diagnosis), is comparing active surveillance therapy against radical treatment (prostatectomy or RT).[11] With regard to more advanced PC, the Medical Research Council (MRC) PR07 study,[12] is investigating the role of RT in locally advanced PC. In this trial, men with locally advanced non-metastatic PC are randomised between hormone therapy alone and hormone therapy plus RT. However, it is noted that if the subjects are allocated RT [given to the prostate and pelvis (or prostate alone if necessary)] in doses up to 69 Gy this is below the usual IMRT dose level.[12]

Incidence and prevalence

The incidence of PC in the UK, in common with many other countries, has been rising.[13] In 2006, there were 35,515 new cases of PC diagnosed in the UK.[14] Despite the large increase in incidence, the mortality rate has been relatively stable.[14]

Prostate cancer frequently progresses slowly and men with less aggressive disease rarely die of their cancer, but this is not the case for those men with the most aggressive tumours (poorly differentiated).[2] *Table 1* shows the percentage of men in whom PC was detected at autopsy in the USA.[4,15] Burford *et al.* reported that 93% of PC deaths occur in the 65 and over age group.[4] By the age of 80 years, approximately 80% of men will have some cancer cells in their prostate. *Table 1* indicates that prevalence of PC increases with age, but is not insignificant at younger ages.[4,15]

However, the extent of age-adjusted PC incidence rates varies considerably throughout the world. Between 1996 and 2006 the age-standardised (to the world standard population) rate in the UK increased by nearly 38%.[16] The lifetime risk of PC diagnosis has been estimated at 10%.[14] Further statistics concerning the incidence rates of PC in the UK during 2006 are reported in *Table 2*. The majority of cases are in England; however, in terms of the crude rate per 100,000 population, Wales has the highest rate and Scotland has the lowest rate.

Prostate cancer risk is strongly related to age; very few diagnosed cases are registered in men under 50 years and three-quarters of cases occur in men over 65 years. The largest number of cases is diagnosed in those aged 70–74 years.[14] *Figure 1* reports the age-specific incidence rates for PC in the UK during 2006.

Impact of health problem

Prostate cancer is a major health problem and is a significant burden to patients and the NHS in England and Wales.[13] Sutcliffe *et al.*[2] reported that PC is a primary reason for consultation with general practitioners (GPs) among men with cancer. It has been estimated that PC in England and Wales costs the health service at least £45M per year.[17] This is likely to be increased

TABLE 1 *Percentage of men with prostate cancer at autopsy in the USA[4,15]*

Age (years)	20–29	30–39	40–49	50–59	60–69	70–79
Percentage of men in whom PC was detected at autopsy	8	28	39	53	66	80

TABLE 2 *Number of new cases and rates of prostate cancer in the UK during 2006[14]*

	England	**Wales**	**Scotland**	**Northern Ireland**	**UK**
Cases					
Male	30,024	2164	2,506	821	35,515
Crude rate per 100,000 population					
Male	120.5	149.8	101.5	96.2	119.6
Age-standardised rate (European) per 100,000 population					
Male	98.1	108.2	81.6	92.1	97.1
95% CI	97.0 to 99.2	103.7 to 112.8	78.4 to 84.8	85.8 to 98.4	96.1 to 98.1

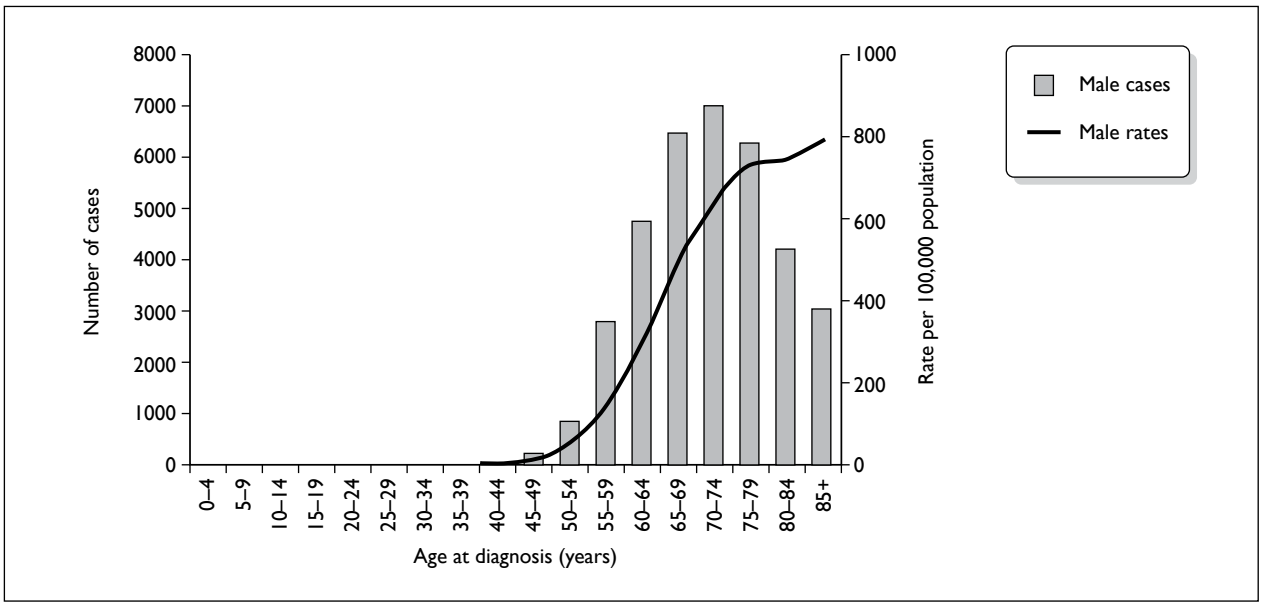

FIGURE 1 *Numbers of new cases and age-specific incidence rates of male prostate cancer in the UK during 2006.*[14]

by the burden of disease from bone metastasis (and prolonged palliative care) and this has repercussions in terms of cost to society, decreased quality of life and decreased survival.[17] In addition there is a significant patient burden of stress and anxiety, sexual function, urinary function, bowel function[18] and potential loss of earnings.

Subgroups of patients with prostate cancer for whom radiotherapy may be indicated

Several patient subgroups exist where RT may be used:

- primary radical treatment of localised cancers
- primary radical treatment of locally advanced cancers (prostate or whole pelvis)
- adjuvant RT treatment for high risk radical prostatectomy patients (prostate or whole pelvis)
- salvage treatment (prostate or whole pelvis)
- palliation of bone metastases.

The latest National Institute for Health and Clinical Excellence (NICE) clinical guideline 2008[1] states that several factors have been shown to predict the risk of recurrence after treatment of localised PC. These include the Gleason score, the serum PSA level, and the clinical T stage [according to the tumour node metastasis (TNM) staging system]. *Table 3* provides a fuller description of the TNM staging system. These predictive factors have been used to classify localised PC into recurrence risk groups, specifically:

- low-risk: PSA < 10 ng/ml and Gleason score ≤ 6 and clinical stage T1–T2a
- intermediate-risk: PSA 10–20 ng/ml or Gleason score 7 or clinical stage T2b–T2c
- high-risk: PSA > 20 ng/ml or Gleason score 8–10 or clinical stage T3–T4.[1]

Adjuvant and salvage radiotherapy

Adjuvant RT is an additional treatment given to patients with PC after localised therapy, such as surgery, which 'assists' the primary treatment. Adjuvant RT may be offered to some patients in the UK, but until recently was not standard treatment. The NICE PC guideline[1] advised that immediate post-operative RT after radical prostatectomy is not routinely recommended, even in men with margin-positive disease, other than in the context of a clinical trial. However, recent trial data appears to supersede the NICE guideline. Cozzarini *et al.*[19] conducted a phase I to II trial with 50 patients; they found excellent acute and early late toxicity outcomes of a moderately hypofractionated regimen with post-operative early adjuvant RT delivered by helical tomotherapy, which is a form of adaptive IMRT technology. In addition, Wiegel *et al.*[20] examined 192 men assigned to a wait-and-see policy compared with 193 men assigned to immediate post-operative RT. These authors examined the primary end point

of biochemical progression-free survival. Wiegel *et al.* concluded that adjuvant RT for T3 PC patients with postoperatively undetectable PSA significantly reduces the risk of biochemical progression; however, further follow-up is needed to assess the effect on metastases-free and overall survival. Further recent evidence by Thompson *et al.*[21] from the South West Oncology Group supports that adjuvant RT after radical prostatectomy for men with PC graded as T3N0M0 using the TNM classification system significantly reduces the risk of metastasis and increases survival.

Salvage RT is performed after surgery to help eliminate any remaining cancerous cells in patients with biochemical relapse. Salvage treatment in the form of radical RT treatment to the prostatic bed should be offered to patients after radical prostatectomy treatment if they have PSA failure, but there is no evidence of metastases. It is uncertain whether adjuvant hormonal therapy should also be given.

Whole pelvis radiotherapy

The role of whole pelvis RT (to include the treatment of pelvic lymph nodes) for primary or salvage treatment is controversial. The treatment may result in an increased risk of adverse effects and these patients have a relatively poor long-term survival (< 10 years). However, the use of IMRT could potentially reduce the toxic effects of treatment due to a more focused delivery of RT. The 2008 PC guideline[1] recommends that treatment to the prostate alone is currently the standard approach to radical RT for PC in the UK. In common with other cancer sites (e.g. breast), there may be a benefit from treating regional lymph nodes as well. However NICE also recommends that clinical oncologists should consider pelvic RT in men with locally advanced PC who have a > 15% risk of pelvic lymph node involvement, who are to receive neoadjuvant hormonal therapy and radical RT.

Measurement of disease

Several methods of measurement of PC currently exist. The following section presents the most common measurement methods (which are predictive parameters of disease) seen in studies of IMRT.

Gleason grading system

The initial diagnosis of PC requires confirmation and is performed via histological examination of prostate tissue from trans-rectal ultrasonography (TRUS) biopsy samples.[4] A TRUS biopsy involves taking 10–12 cores of prostatic tissue through the rectum under ultrasound guidance and the result reveals the level of tumour differentiation.[4] The predominant histological system for tumour differentiation is the Gleason grading system via analysing the most common tumour patterns. Each tumour pattern is assigned a grade (1 to 5) and these grades are combined to produce the Gleason score of 2–10.[4] Burford *et al.*[4] indicate that the lower the score, the more well differentiated the tumour, the less likely the tumour is to progress and the better the prognosis. Tumours can be classified into low grade (≤6), intermediate grade (= 7) and high grade (8–10). Berney *et al.*[22] reassigned Gleason grades to 1789 localised PC patients in the UK between 1991 and 1996 and found that there was significant reassignment in the Gleason score with increases of Gleason score across a wide spectrum of patients (the same data were reclassified as far as it is possible to determine). A drift in Gleason score over the past decade has also been reported by Veldeman *et al.*[23] This relates to the observation that PCs are now commonly graded higher than in previous decades due to diagnostic improvements, resulting in a greater percentage of higher-grade PCs.

TNM staging system and ABCD system

Developed in France in the 1940s by Pierre Denoix, the TNM classification has become the accepted basis of cancer staging[24] and has undergone several revisions. *Table 3* shows the 2002 version (Sixth Edition),[25] as, where stated, the studies included in this review use either the 1992 or 2002 version. However, a later version (Seventh Edition) was published in 2009.[25] In Europe, the TNM staging system has been most commonly used to establish how far the disease has progressed.[26] The letter T refers to the size of the primary tumour, N describes the extent of lymph node involvement and M refers to the presence or absence of metastases.[27] T1 and T2 are considered to be localised PC and both T3 and T4 are often referred to as locally advanced disease. However, some studies include patients classified as stages T1, T2 and T3 in the study of localised PC.[28,29] There are two key changes to the 2002 TNM classification system compared with the older versions, these being: (1) subdivision of the T2 disease into three clinical substages, and (2) recommendation that the Gleason scoring system is used for grading.[2]

The clinical stage is based on information obtained before surgery to remove the tumour and can

be limited since the information is obtained by making indirect assessment of the tumour while it is still in the patient.[2] Pathologic staging provides additional information from the microscopic examination of the tumour[2] and provides a direct examination of the tumour and its spread.

TABLE 3 *Tumour node metastasis staging system (2002)*[25]

Primary tumour, clinical (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically unapparent tumour not palpable or visible by imaging
T1a	Tumour incidental histologic finding in ≤ 5% of tissue resected
T1b	Tumour incidental histologic finding in > 5% of tissue resected
T1c	Tumour identified by needle biopsy (because of elevated PSA level); tumours found in one or both lobes by needle biopsy but not palpable or reliably visible by imaging
T2	Tumour confined within prostate
T2a	Tumour involving less than or equal to half a lobe
T2b	Tumour involving more than half a lobe but not more than one lobe
T2c	Tumour involving both lobes
T3	Tumour extending through the prostatic capsule; no invasion into the prostatic apex or into, but not beyond, the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invading seminal vesicle(s)
T4	Tumour fixed to or invading adjacent structures other than seminal vesicles (e.g. bladder neck, external sphincter, rectum, levator muscles, pelvic wall)
Primary tumour, pathological (PT)	
PT2	Organ-confined
PT2a	Tumour involves one half of one lobe, but not both lobes
PT2b	Tumour involves more than one half of one lobe, but not both lobes
PT2c	Tumour involves both lobes
PT3	Extraprostatic extension
PT3a	Extraprostatic extension
PT3b	Seminal vesicle invasion
PT4	Invasion of bladder, rectum
Regional lymph nodes (N)	
NX	Regional lymph nodes (cannot be assessed)
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node or nodes
Distant metastasis (M)	
PM1c	More than one site of metastasis present
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

continued

TABLE 3 *Tumour node metastasis staging system (2002)[25] (continued)*

Stage grouping				
Stage I	T1a	NO	MO	G1 (Gleason Score 2–4)
Stage II	T1a	NO	MO	G2, 3–4(Gleason Score 5–10)
	T1b	NO	MO	Any G
	T1c	NO	MO	Any G
	T1	NO	MO	Any G
	T2	NO	MO	Any G
Stage III	T3	NO	MO	Any G
Stage IV	T4	NO	MO	Any G
	Any T	N1	MO	Any G
	Any T	Any N	M1	Any G

A second staging method called the ABCD (modified Whitmore-Jewett) system is often used in the USA. It has been indicated that a weakness of the ABCD system is its inability to characterise regional lymph nodes (N+) or distant metastases (M+) relative to the category of the lesion and that N+ or M+ lesions are categorised as stage.[30] *Table 4* shows the ABCD grading system.

Table 5 is cited as Jewett[31] within Sutcliffe.[2] *Table 5* shows a comparison between the TNM classification and the Whitmore-Jewett system which was presented in Selley *et al*.[30]

Serum prostate-specific antigen level

A further method for measuring and assisting the diagnosis of PC and assessing the risk of disease burden is the PSA level. PSA is a glycoprotein, almost exclusively produced by the epithelium of the prostate gland, responsible for liquefying semen and allowing sperm to swim freely.[4,13] Burford *et al.* report that due to an alteration in the architecture of the prostate in conditions such as prostatitis and BPE as well as PC, PSA leaks out, leading to increased levels in the bloodstream.[4] Collin *et al.* describe the test's limited sensitivity and specificity which may lead to false reassurance or false alarm followed by invasive investigations.[8] The PSA test remains an imperfect predictor of PC, but remains a useful tool that is widely used in clinical practice.[32] However, until a more superior diagnostic blood test becomes widely available, screening for PC will continue to comprise PSA testing in conjunction with digital rectal examination (DRE) and fine-core biopsies of the prostate when indicated by an abnormal PSA and/or DRE.[33] Rosario *et al.*[34] (the ProtecT trial) indicate that the exact level at which to recommend biopsy is controversial and may start as low as 2.5 ng/ml; however, they conclude that following an initial PSA of 3.0–19.99 ng/ml in men aged 50–70 years, a repeat PSA within 7 weeks allows more accurate risk prediction that may assist in the decision-making as to whether or not to proceed with prostate biopsy.

Risk of recurrence

The latest NICE clinical guideline 2008[1] discusses predictive factors which have been used to classify localised PC into recurrence risk groups specifically:

- low-risk PSA < 10 ng/ml and Gleason score ≤6 and clinical stage T1–T2a
- intermediate-risk PSA 10–20 ng/ml or Gleason score 7 or clinical stage T2b–T2c
- high-risk PSA > 20 ng/ml or Gleason score 8–10 or clinical stage T3–T4.

The above risk categories closely resemble the recurrence risk groups of PC for clinically localised PC stated by the National Comprehensive Cancer Network (NCCN) in their *Clinical Practice Guidelines in Oncology*.[35] All NCCN recurrence risk groups are presented below:

- Clinically localised:
  - low-risk PSA < 10 ng/ml and Gleason score 2–6 and clinical stage T1–T2a
  - intermediate-risk PSA 10–20 ng/ml or Gleason score 7 or clinical stage T2b–T2c
  - high-risk PSA > 20 ng/ml or Gleason score 8–10 or clinical stage T3a
- locally advanced:
  - very high risk T3b–T4

TABLE 4 *ABCD grading system*[31]

Stage A
Very early and without symptoms; cancer cells confined to the prostate
A1 Well differentiated and slightly abnormal cancer cells
A2 Moderately or poorly differentiated and abnormal cancer cells in several locations within the prostate

Stage B
Confined to the prostate, but palpable (detectable by DRE) and/or detectable by elevated PSA
B0 Confined to the prostate, non-palpable; PSA elevated
B1 Single cancerous nodule in one lobe of the prostate
B2 Extensive, involvement in one or both prostate lobes

Stage C
Cancer cells found outside the prostate capsule (membrane covering the prostate); spread confined to surrounding tissues and/or seminal vesicles
C1 Extends outside the prostate capsule
C2 Bladder or urethral obstruction

Stage D
Metastasis (spread) to regional lymph nodes, or to distant bones, organs (e.g. liver, lungs), and/or other tissues
D0 Metastatic, clinically localised, and showing elevated blood prostatic acid phosphatase levels
D1 Regional lymph nodes involved
D2 Distant lymph nodes, bones, or organs involve
D3 Metastatic disease after treatment

TABLE 5 *Comparison of TNM and Whitmore-Jewett classifications for staging prostate cancer adapted from Selley* et al.[30]

TNM classification	Whitmore-Jewett
T1	A
T1,T2	A1
T2,T3	A2
T2	B
T2a,T2b	B1
T2c	B2
T3	C
T3a,T3b	C1
T3c	C2
M1 and N1	D

- metastatic:
  - any T, N1
  - any T, any N, M1
  - patients with multiple adverse factors may be shifted into the next highest risk group.[35]

Key measurement systems for adverse events

The most common measurement systems of adverse events (AE) is published by the Radiation Therapy Oncology Group (RTOG) based in Philadelphia, PA, USA. The RTOG is a national clinical cooperative group funded by the National Cancer Institute (NCI) since 1968 to increase the survival and improve the quality of life of patients diagnosed with cancer.[36] The RTOG grades are embedded within the system of AE measurement called the NCI–Common Toxicity Criteria, often abbreviated to NCI-CTC. The AEs are graded from 0 to 4 for many different types of cancer.[37] However, from January 2009 the Cancer Therapy Evaluation Program at the NCI recommends the use of the Active Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). The RTOG grades range from 1 to 5, grade 1 meaning a mild AE to grade 5 meaning death; the CTCAE lists many disorders such as gastrointestinal (GI) disorders and then lists subcategories such as rectal haemorrhage together with the definitions of grades 1–5.

Neoadjuvant/adjuvant hormone therapy

Studies also differentiate between patients who have, or have not, received adjuvant hormone treatment at baseline. As PC is driven in part by male sex hormones, the use of hormonal treatment to reduce the level of circulating male hormones is a potentially very useful method of treating all stages of this disease.[38] This technique is also sometimes called androgen deprivation or suppression. Neoadjuvant hormone therapy in the management of PC translates into administering hormone treatment before the primary therapy to assist in reducing tumour burden. Reviews suggest that adjuvant hormone therapy combined with either prostatectomy or RT can improve disease-free survival in patients with local or locally advanced PC.[38,39] Significant local control may be achieved when given prior to prostatectomy or RT, which may improve the patient's quality of life. Neoadjuvant hormone therapy is associated with significant clinical benefit when given with RT and improves pathological outcome prior to prostatectomy, but is of minimal value prior to radical prostatectomy.[40] Neoadjuvant hormones also have an important role in reducing tumour volume and therefore potentially reducing dose to the rectum and hence toxicity.

Key health-related quality of life measures

Health-related quality of life (HRQoL) is also measured in relation to PC patients receiving IMRT. HRQoL may play a crucial role in determining treatment modality as it is likely that patients with localised PC will live for a long time.[41] However, despite improvement in survival, many survivors are at risk of post-treatment psychological and physical sequelae which may reduce their quality of life.[42] HRQoL measures for PC in relation to IMRT include the following: Lips *et al.*[43] used the RAND-36 generic health survey, a cancer-specific QoL measure by the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire [QLQ-C30(+3)] and the Prostate Tumour-Specific Questionnaire by the EORTC PC module(QLC-PR25). Lips *et al.* found that IMRT and accurate position verification seem to provide a possibility to increase the radiation dose for PC without deterioration in HRQoL. In addition, within PC the well validated Medical Outcomes Survey Short Form questionnaire-36 items (SF-36) has been used to measure physical and mental components of HRQoL and the 20-item University of California Los Angeles Prostate Cancer Index (UCLA PCI) has been used to measure treatment-specific function and bother (bowel, urinary, sexual). Higher scores represented better function for both SF-36 and the PCI.[42]

Definitions of biochemical failure

As an alternative to the clinical measurement of disease-free survival (local disease recurrence, or the development of metastatic disease, or both), PSA testing has largely replaced clinical failure as a measure of treatment efficacy as it is easier to perform on a routine basis than serial bone scans and computed tomographic (CT) scans.[44] The PSA level has been used as a surrogate endpoint in trials of PC. The American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Panel[44] state that 'biochemical' failure has come to be widely used in the absence of clinical or histopathology evidence of local persistence or recurrence or demonstrable distant metastasis. An ASTRO consensus panel in 1996 agreed on four guidelines:

1. Biochemical failure is not justification *per se* to initiate additional treatment. It is not equivalent to clinical failure; it is, however, an appropriate early end point for clinical trials.
2. Three consecutive increases in PSA is a reasonable definition of biochemical failure after RT. For clinical trials, the date of failure should be the midpoint between post-irradiation nadir PSA and the first of the three consecutive rises.
3. No definition of PSA failure has as yet been shown to be a surrogate for clinical progression or survival.
4. Nadir PSA is a strong prognostic factor.[44]

However, these guidelines have been criticised as this definition was not linked to clinical progression or survival; it performed poorly in patients undergoing hormonal therapy, and backdating biased the Kaplan–Meier estimates of event-free survival.[45] Consequently, as reported in Roach *et al.*[45] a second consensus panel convened in 2005 and revised the ASTRO definition. The panel recommended:[45]

1. A rise by 2 ng/ml or more above the nadir PSA be considered the standard definition for biochemical failure after external beam RT with or without hormonal therapy.
2. The date of failure be determined 'at call' (not backdated). They recommended that investigators be allowed to use the ASTRO consensus definition after external beam RT alone (no hormonal therapy) with strict

adherence to guidelines as to 'adequate follow-up'. To avoid the artefacts resulting from short follow-up, the reported date of control should be listed as 2 years short of the median follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited.

Retaining a strict version of the ASTRO definition would allow comparisons with a large existing body of literature.[45] The current review reports, where available and appropriate, the definition of biochemical failure, as used in the studies to allow full comparison.

Kupelian *et al.*[46] reported that the length of the natural history of localised PC makes the relationship between the biochemical failure and overall survival difficult to establish for patients diagnosed in the PSA era and that biochemical failure after definitive RT for localised PC is not associated with increased mortality within the first 10 years after initial therapy, although a trend toward worse outcome was observed at 10 years. With longer follow-up from initial therapy, significant differences may be observed at 15 or 20 years after therapy and may assist our full understanding of the impact of biochemical failure on overall survival.[46]

Current service provision

Management of disease

For men with disease localised to the prostate, the 2008 NICE PC guidelines recommend active surveillance as the first choice of treatment for low-risk localised disease.[1] Radical treatment, that is either external beam CRT or prostatectomy, is recommended for those with intermediate risk localised disease.[1] Other treatment options for localised disease are watchful waiting or brachytherapy (internal seed RT).[1] RT is also offered to patients with locally advanced disease (tumours which have spread no further than the pelvic region).[1] There are other treatment options for PC, not recommended in the UK except as part of research, such as the radical treatment options cryotherapy or high-intensity focused ultrasound, and the non-radical treatment option hormone therapy alone.[1]

Radiotherapy, including 3DCRT and IMRT, stops cancer cells from dividing and growing, thus slowing tumour growth. 3DCRT is a form of external beam RT that allows better targeting of RT than two-dimensional or conventional RT, by using three-dimensional imaging to define the target volume and critical organs at risk (OAR), computerised 3D planning utilising multiple beams to conform to the 3D shape of the tumour and maximally avoid the OAR.[47] NICE recommends that patients receiving radical external beam RT for localised PC should be given a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction.[1] Whole pelvis radiation may be considered in men with locally advanced PC who have more than 15% risk of pelvic lymph node involvement, {by Roach formula $\frac{2}{3}$ PSA + [(GS−6) × 10]}, who are to receive neoadjuvant hormonal therapy and radical RT.[1]

Patients receiving RT may also be treated with neoadjuvant and/or adjuvant hormone therapy. NICE recommends adjuvant hormonal therapy for a minimum of 2 years in men receiving radical RT for localised PC who have a Gleason score of 8 or more.[1] Adjuvant chemotherapy is not usual UK practice. Chemotherapy may be given in metastatic, hormone-refractory disease.[1]

Toxicity can cause side effects during or immediately after RT treatment (acute effects) or many months or years after completion of treatment (late effects). Degree of toxicity can be related to irradiated dose volumes for organs at risk. In PC, acute effects include genitourinary (GU) symptoms (frequency, urgency, urinary retention, bladder spasms, urinary incontinence, haematuria, dysuria) and GI symptoms (proctitis, rectal or perirectal pain, rectal bleeding, diarrhoea).[23,48,49] Late effects include similar urinary symptoms, sexual dysfunction and GI symptoms; these late effects may permanently affect quality of life.[23] Management of side effects may include referral to specialist gastroenterology or urology services.[1]

Current service cost

The costing report[50] that accompanied the recent NICE guideline for PC[1] reported the costs of RT for PC. The cost of an RT fraction was assumed to be £135, from the National Tariff price 2008–9 (inflated by the national average market forces factor) for 'complex teletherapy with imaging'. The authors estimated the number of fractions provided for radical RT of PC to be 117,000 per year, based on activity data from the RT equipment survey 2007. From these figures the estimated 2008 cost was calculated as £15.8M.[50]

The 2008 PC guideline[1] recommended that men having external beam RT for localised PC should have a total dose of at least 74 Gy to the prostate at no more than 2 Gy per fraction. Thus the total number of fractions required is 37. In the costing report it was estimated that an additional 43,000 fractions were required to meet this recommendation, based on an analysis of Radiotherapy Episode Statistics data from 24 centres in the UK for the period 2000–5. The additional cost is £5.8M. Thus the total cost of radical RT, once the national guideline is implemented is estimated to be £21.6M (£15.8M + £5.8M).[50]

These figures, however, appear to omit the costs of planning RT. These costs are reported in the *NHS reference costs 2007–8*.[51] Those shown in *Table 6* are for an outpatient service, which is the most common mode.

The reported costs are not entirely consistent, with some more complex planning procedures apparently costing less than simpler ones. However they indicate that RT planning for radical RT for PC costs at least £200 per patient.

It should be noted, however, that the national guideline also recommended the option of active surveillance of low-risk localised PCs.[1] If more men choose this option the demand for radical RT may be reduced, although this recommendation is controversial. Such a reduction was not quantified in the national costing report, although a 10% reduction in radical prostatectomy was estimated.[50]

Variation in services and/or uncertainty about best practice

The needs assessment report,[52] that accompanied the recent NICE guideline for PC,[1] shows RT data for PC (2003–4) for a sample of five NHS Trusts in the South West government office region. The total dose and number of fractions per course is reported, showing clear differences between the Trusts. For example, in two of the five Trusts no courses of RT were given with a total dose of 40 Gy or more, whereas in one Trust 47% of courses were at a dose of 40 Gy or more.

Relevant national guidelines, including National Service Frameworks

The 2008 NICE PC guidelines give detailed recommendations for the management of PC, and cover a range of treatments including external beam CRT.[1] External beam CRT may be given to men with intermediate risk localised disease or with locally advanced disease.[1] NICE recommends that patients should be given a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction.[1] Whole pelvis radiation may be considered for men with locally advanced PC who have more than 15% risk of pelvic lymph node involvement and who are to receive neoadjuvant hormonal therapy and radical RT.[1]

The Royal College of Radiologists (RCR), the Institute of Physics and Engineering in Medicine (IPEM), The Society and College of Radiographers (SCOR) and The National Radiotherapy Advisory Group (NRAG) recommend the use

TABLE 6 NHS reference costs 2007–8 *for RT planning*

HRG code	Description	Activity	National average unit cost
SC01Z	Define volume for SXR, DXR, electron or megavoltage RT without imaging and with simple calculation	11,595	£121
SC02Z	Define volume for simple RT with imaging (simulator, CT scanner, etc.) but with simple calculation and without dosimetry	21,644	£219
SC03Z	Define volume for simple RT with imaging and dosimetry	17,601	£388
SC04Z	Define volume for multiple phases of complex RT with imaging and dosimetry	37,500	£209
SC05Z	Define volume for RT with imaging, dosimetry and technical support, e.g. mould room	18,554	£317
SC06Z	Define volume for RT with imaging and IMRT dosimetry or equivalent	18,530	£194

DXR, deep energy photons; HRG, Health Resource Group; SXR, superficial energy photons.

of magnetic resonance imaging (MRI) for imaging the tumour.[53,54] To reduce the random and systematiceffects of organ motion, patient interventional techniques such as drugs are used to stimulate bowel emptying to stabilise the rectal volume; alternatively rectal balloons have been suggested, although these are not in widespread use.[54] NRAG suggest image-guided RT (IGRT) may be useful in tumours that have unpredictable daily movement, and explain that changing RT across time is a technology called four-dimensional adaptive RT.[54] RCR, in a 2002 policy statement on conformal RT, recommend effective patient immobilisation techniques are used as these can reduce random and systematic errors.[53]

The RCR, IPEM and SCOR[53] recommend specialised training for all staff involved in planning RT, and suggest close collaboration between a skills mix of staff groups, which may include clinical radiologists, clinical oncologists, RT physicists, planning radiographers, therapy radiographers, dosimetrists and clinical technologists. They also recommended that IMRT should be developed and introduced across the UK with research in the form of controlled studies.[53]

The International Commission on Radiation Units and Measurements (ICRU) have produced guidelines on prescribing, recording and reporting RT. They indicate that the method used for delineation of gross tumour volume (GTV), that is gross palpable or demonstrable extent and location of the malignant growth, should be detailed. Around the GTV, ICRU describe two safety margins. The clinical target volume (CTV) takes into account subclinical malignant involvement. The planning target volume (PTV) compensates for the variations in size, shape, and position of the CTV, and for uncertainties in patient–beam positioning.[55,56]

Description of technology under assessment

Summary of intervention

Concepts of IMRT were developed by Brahme[57] and Webb[58] and is a technological advance leading on from 3DCRT. The principle behind IMRT is the use of intensity-modulated beams, which are defined as beams that deliver more than two intensity levels for a single beam direction and a single source position in space.[23] Both 3DCRT and IMRT deliver beams that are geometrically shaped, but IMRT also modulates the intensities of constituent beams.[53]

Increasing the dose of RT can increase the effectiveness in terms of biochemical relapse-free survival. There is evidence from RCTs that dose escalation to 74–79 Gy provides superior biochemical relapse-free survival compared with lower doses of approximately 64–70 Gy.[59–63] There are no convincing data supporting superior biochemical outcomes at radiation doses above 81 Gy.[64] A meta-analysis of studies comparing doses of conformal RT showed an advantage for high-dose RT over lower dose RT for biochemical failure, but not for overall survival, nor for PC specific survival.[65]

However, increased dose can increase toxicity, as has been shown in RCTs of dose escalation.[66,67] Doses upward of 78–80 Gy are difficult to achieve when using 3DCRT, due to the unacceptable risk of side effects.[68] The benefit of IMRT is largely related to the avoidance of side effects of radiation. IMRT can sculpt the radiation to the target area of the PC more precisely than 3DCRT, by allowing further conformation to the PTV compared with 3DCRT, so toxicity to the surrounding normal tissues (bladder, rectum, urethral bulb and small bowel) may be reduced, or could allow dose escalation.[54] Unlike 3DCRT or earlier forms of RT, IMRT can deliver non-uniform RT, producing concave shapes that spare critical structures that surround or push into the tumour.[47,53] IMRT allows delivery of complex dose distributions.[54] RCTs of IMRT in breast cancer, and head and neck cancer, compared with two-dimensional conformal radiotherapy or conventional RT, have shown reduced side effects or improved quality of life.[69–73]

Planning of therapy identifies a PTV which incorporates the tumour, sites of suspected microscopic malignancy, and an extended volume to take into account uncertainty in the position of the target, and set-up and delivery uncertainties.[54] There are two different methods of planning: inverse or forward. Inverse-planned IMRT utilises software algorithms, manipulating many hundreds of treatment beamlets, in order to produce highly complex treatment plans which would be beyond the scope of a treatment planner. The computer iteratively attempts to achieve the planner's defined dose target and normal tissue constraints. This complex planning process is time consuming and requires considerable quality assurance (QA) per patient. There are inherent constraints still applied to inverse planned IMRT, such as

number of beams, and advances are occurring to overcome this, such as rotational therapy. Forward-planned IMRT involves the planner modifying a provisional plan, based on the treatment beam arrangements that are likely to be used, until the dose distribution is improved. Planning studies have shown that IMRT improves upon 3DCRT with respect to conformality to, and dose homogeneity within, the target.[64]

Radiotherapy is delivered by linear accelerators, and IMRT methods of delivery comprise static compensators, step and shoot by multiple static field multileaf collimator (MLC), dynamic MLC or sliding window technique, tomotherapy, scanned photon beams, or moving attenuating bar.[53]

Quality assurance is an important component of IMRT. QA consists of ensuring that the treatment plan is correctly delivered. It involves verifying that the linear accelerator is optimally set up by making direct measurements. IMRT QA can be individualised by patient or adopted as a standardised departmental QA procedure.

Radiotherapy may be given to patients with low- or intermediate-risk localised disease who are not undergoing surgery (prostatectomy), or patients with locally advanced disease.[1] Patients are usually treated on an outpatient basis, once a day, 5 days a week, over 6 or 7 weeks.[74] For localised PC, the recommended minimum dose is 74 Gy to the prostate at no more than 2 Gy per fraction.[1] Follow-up is required for assessing disease status and management of toxicity.[1] A range of personnel is required including clinical radiologists, clinical oncologists, RT physicists, planning radiographers, therapy radiographers, dosimetrists and clinical technologists.[53]

Current usage in the NHS

The use of IMRT has been growing in the UK over the last few years. A survey of UK RT departments in 2003 identified nine of the total of 66 (14%) departments routinely offering IMRT.[75] Of these, six were using IMRT for PC. A survey in 2007 found 46% of centres using IMRT.[76] However, only 27% were using IMRT for the routine management of patients. Of the centres that were not using IMRT, 38% were planning to implement it in the next year. If their plans were realised this would mean that two-thirds of RT centres were now able to provide IMRT, although not necessarily in the routine management of patients.

The same 2007 survey[76] indicated that 8% of centres routinely used IGRT, and a further 13% used it in research studies. A quarter of departments were planning on introducing it in the next year, potentially meaning 42% of centres now have some capacity for IGRT. PC was the most common tumour for the use of IGRT.

Anticipated costs associated with intervention

No published costs for the provision of IMRT in the UK were identified. International studies which report costs of IMRT and 3DCRT for the treatment of PC are shown in *Table 7*.

The estimates from Europe and the USA are very different. The relatively generous reimbursement of IMRT in comparison to 3DCRT by Medicare in the USA has been commented on by other authors.[47] Note the cost difference between IMRT and 3DCRT reported by Marchal[77] arose almost entirely from differences in equipment and maintenance costs, assuming only 30 patients are treated a year, and therefore are likely also to represent an overestimate of current UK costs.

TABLE 7 *Published costs of IMRT and 3DCRT for prostate cancer*

Study	Cost year	Costs included	Cost source	Currency	IMRT cost	3DCRT cost	Additional cost IMRT
Marchal *et al.* 2001[77]	2002	RT (staff, capital and maintenance costs)	Prospective study	€	4911	2357	2554
Konski *et al.* 2006[78]	2004	RT	Billing units with expected Medicare reimbursement	US$	38,000	9900	28,100
Pearson *et al.* 2007[64]	2005	RT	Medicare reimbursement 2005 (constituent codes as Konski 2006)	US$	42,450	10,900	31,550

St. Bartholemew's Hospital, London, UK, had developed costs for IMRT and 3DCRT, initially for ear, nose and throat cancers. These were adapted for PC by removing items not relevant to PC (such as dental care), and amending others (e.g. planning time, frequency of treatment review, number of fractions). The time required for delivery of each fraction was assumed to be the same as for head and neck. The costs for IMRT and 3DCRT are shown in *Table 8* (Nuala Close, St. Bartholomew's Hospital, London, UK, 2009, personal communication). Tasks included within the radiographer category are simulator set-up and verification, CT scan, image referencing, and pre-treatment data input and checks. Physics time includes treatment planning and verification, as well as QA. The treatment times assumed per fraction are 18.0 minutes for 3DCRT and 20.6 minutes for IMRT, representing a 14.4% increase for IMRT. The absolute difference in time between IMRT and 3DCRT of 2.6 minutes is similar to that reported by Van de Werf *et al.*[79] of 2.8 minutes for a mixture of prostate, and head and neck cancer patients, although Van der Werf *et al.* reported lower treatment times per fraction for both IMRT and 3DCRT, so the difference of 2.8 minutes represents a 27% increase in treatment time for IMRT. Miles *et al.*[80] also report shorter treatment times, with a median of 12 minutes for a fraction of IMRT for PC patients, but reports times between 15 and 28 minutes from other published studies. No comparative data for 3DCRT is reported. For incremental cost-effectiveness it is only the additional time taken for IMRT that is important, and in this regard the information from St. Bartholomew's Hospital is consistent with Van de Werf *et al.*[79]

The category 'equipment support' comprises an allocation of capital costs for the linacs and the building used to house them, as well as maintenance costs. The calculation assumes two linacs will deliver a total of 24,000 fractions per year for 10 years.

The costs are based on the current fractionation schedule for both 3DCRT and IMRT, which is 37 fractions. Both 3DCRT and IMRT may be delivered with hypofractionated schedules (fewer fractions delivering the same biologically equivalent dose), but the potential reduction in toxicity from IMRT compared to 3DCRT may mean that hypofractionation may be more viable for IMRT than for 3DCRT. The Conventional or Hypofractionated High dose Intensity modulated radiotherapy for Prostate cancer (CHHiP) study, which is currently in progress, is studying the effects of hypofractionated IMRT on PSA survival and toxicity. Hypofractionated regimes are likely to cost less as fewer sessions are required to deliver the RT, and therefore may affect the cost difference between IMRT and 3DCRT.

TABLE 8 *Costs of IMRT and 3DCRT for prostate cancer 2008*

Cost item		Cost IMRT	Cost 3DCRT	Difference
Pay				
	Medical	£219.13	£141.61	£77.52
	Radiographers	£1709.00	£1409.16	£299.84
	Physics	£960.00	£474.57	£485.43
	Admin	£327.78	£327.78	£0.00
	Support	£16.49	£16.49	£0.00
	Total pay	**£3232.40**	**£2369.61**	**£862.79**
Non pay				
	Drugs	£25.00	£25.00	£0.00
	Consumables	£91.90	£91.90	£0.00
	Equipment support	£705.26	£705.26	£0.00
	Diagnostics	£500.00	£500.00	£0.00
	Total non pay	**£1322.16**	**£1322.16**	**£0.00**
Total direct costs		**£4554.56**	**£3691.77**	**£862.79**
Indirect costs (overheads 30%)		£1366.37	£1107.53	£258.84
Total cost of treatment		**£5920.93**	**£4799.31**	**£1121.62**

The full assumptions on which the costs shown in *Table 8* are based are shown in Appendix 6.

Note both clinical experience and evidence from the literature for head and neck cancers indicate that the time taken to deliver IMRT varies considerably according to the experience of a unit in providing the treatment. Bonastre *et al*.[81] studied resource use and costs for the provision of IMRT for head and neck cancer patients across nine centres in France. The mean treatment cost per patient at experienced centres was €6332 compared to €14,192 at centres initiating IMRT treatment. This demonstrates that the introduction of IMRT is likely to cause short-term staff and machine capacity issues.

The costs shown in *Table 8* and used in the economic analysis are from an institution which is at a relatively early stage of IMRT implementation. The difference in treatment time between IMRT and 3DCRT assumed is consistent with that reported in the literature, but the study does not report the experience of the institution with IMRT.[82] It is possible that the cost differential between IMRT and 3DCRT will be less at institutions with more experience of IMRT. The difference in treatment time assumed contributes only £157 (or 14%) to the total difference in cost assumed between IMRT and 3DCRT and so is not critical in the cost comparison.

Chapter 2

Definition of the decision problem

Decision problem

This assessment report addressed the question 'What is the clinical and cost-effectiveness of intensity-modulated radiotherapy for the radical treatment of prostate cancer?'.

Intervention

The included intervention was IMRT. This included systems that either do or do not combine the ability to simultaneously image (IGRT). IMRT using either forward planning or inverse planning was included.

Population including subgroups

Adult men with PC for whom RT is appropriate.

Subgroups principally included localised PC and locally advanced PC.

Relevant comparators

Current standard therapy: 3DCRT or radical prostatectomy.

Outcomes

Outcomes sought were survival (overall and disease-specific), progression-free survival [clinical or biochemical (PSA) relapse free], adverse effects of treatment and HRQoL.

Overall aims and objectives of assessment

The review addressed the following issues:

1. To evaluate the clinical effectiveness of IMRT in terms of overall or progression-free survival [clinical and biochemical (PSA) relapse free] compared with 3DCRT (current standard therapy).
2. To evaluate the side effect profile of IMRT compared with 3DCRT (current standard therapy).
3. To estimate the incremental cost-effectiveness of IMRT compared with 3DCRT (current standard therapy).

The review did not attempt to address IMRT in comparison with other radical treatment options such as internal seed RT (brachytherapy, cryotherapy, etc.) or the non-radical treatment options watchful waiting, active monitoring, or hormone therapy alone.

Although sought, no data were available directly comparing IMRT with prostatectomy. No data were available to compare post-operative 3DCRT with post-operative IMRT. No data were available to evaluate IMRT in patients with bone metastasis.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Search strategy

A comprehensive search was undertaken to systematically identify clinical effectiveness and cost-effectiveness literature concerning IMRT in men with PC. The search strategy comprised the following main elements: searching of electronic databases; contact with experts in the field; and scrutiny of bibliographies of retrieved papers.

The following databases were searched: MEDLINE (1950–present), EMBASE (1980–present), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982–present), BIOSIS (1985–present), the Cochrane Database of Systematic Reviews (CDSR) (1991–present), the Cochrane Controlled Trials Register (CCTR) (1991–present), the Science Citation Index (1900–present) and the NHS Centre for Reviews and Dissemination databases [Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (EED), Health Technology Assessment (HTA)] (1991–present). MEDLINE In-Process & Other Non-Indexed Citations was searched to identify any studies not yet indexed on MEDLINE. Current research was identified through searching the UK Clinical Research Network, National Research Register archive, the Current Controlled Trials register and the MRC Clinical Trials Register. In addition, abstracts of the American Society of Clinical Oncology (ASCO), ASTRO and European Society for Therapeutic Radiology and Oncology (ESTRO) conferences were browsed. Systematic reviews which incorporated evidence relating to the inclusion criteria were hand-searched in order to identify any further clinical trials. Searches were not restricted by date or publication type. Studies only published in languages other than English were excluded. The MEDLINE search strategy for randomised clinical trials is presented in Appendix 1. Searches targeted the comparators of 3DCRT and radical prostatectomy as well as 11 other comparators to capture potential data meeting the inclusion criteria hidden within other studies. Case-control and cohort studies were also sought.

All searches were conducted in January 2009 and were updated for recent publications in May 2009.

Inclusion and exclusion criteria

Study design

According to the accepted hierarchy of evidence, RCTs and meta-analyses from systematic reviews were searched initially, as they provide the most authoritative forms of evidence. As no relevant RCTs were identified, other comparative studies were included. Systematic reviews were not included in the analysis but were used to identify relevant comparative studies.

Intervention

Intensity-modulated radiotherapy with systems that either do or do not combine the ability to simultaneously image (IGRT), whether delivered using forward planning or inverse planning.

Comparators

Three-dimensional conformal radiotherapy or radical prostatectomy.

Population

The population comprised men with PC for whom radical RT was appropriate. Data were considered separately for localised PC and locally advanced PC, where available.

Outcomes

Outcomes sought were survival (overall and disease-specific), progression-free survival [clinical or biochemical (PSA) relapse free], adverse effects of treatment and HRQoL.

Exclusion criteria

Studies only published in languages other than English were excluded. Other less common treatment options such as internal seed RT (brachytherapy, cryotherapy, etc.) and non-radical treatment options such as watchful waiting, active monitoring and hormone therapy alone were outside the scope of the assessment. Studies which focused solely on planning, organ motion, proton therapy, positioning, localisation, verification, contouring, target volume definition, alignment methods, gene therapy, optimisation, dose–volume

histogram and dosimetric analysis were also excluded unless data meeting the inclusion criteria were also available.

Based on the above inclusion/exclusion criteria, study selection was made by one reviewer, with involvement of a second reviewer when necessary.

Data abstraction strategy

Data were extracted with no blinding to authors or journal. Data were extracted by one reviewer using a standardised form. Data extraction forms are available in Appendix 2.

Critical appraisal strategy

As no RCTs were found, the quality of studies was assessed according to accepted criteria for randomised and non-randomised studies by Downs and Black[83] which was adapted for the purposes of this review. The Downs and Black checklist is a structured checklist originally comprising of 27 items. Checklist items relate to the appropriateness and adequate description of the hypotheses, study design, intervention, main outcomes and methods of analysis. The checklist demonstrated good inter-rater reliability, although further development and testing of the tool was recommended.[83] After minimal adaptation the checklist comprised of 29 items with the addition of items regarding study group comparison, data collection methods and treatment group comparison. The item regarding power calculation was removed. Additional guidance regarding multivariate analysis to examine group differences was added to item 21. The answers are recorded as 'yes/no' for items 1–13 (also 'partial' for item 7) and 'yes/no/unable to determine' for items 14–30 in accordance with the original paper.[83] The evaluation of quality was conducted according to the checklist guidance for cohort and non-randomised studies.[83] One reviewer rated the quality of studies using the adapted Downs and Black checklist. The purpose of quality assessment was to provide a narrative summary of trial quality which can be found in Quality of included studies. The quality assessment checklist for the eight studies can be seen in Appendix 3. The quality assessment checklist for the five included abstracts can also be seen later in Appendix 3. The response 'unable to determine' was used throughout the checklist in Appendix 3.

Methods of data synthesis

Pre-specified outcomes were tabulated and discussed within a descriptive synthesis. Meta-analysis was precluded due to heterogeneity, mainly in the intervention and comparator treatments given. Treatments differed in PTV, dose constraints, dose delivered, fractionation and patient positioning. There were also differences between studies in population, length of follow-up and definitions of outcome measures.

Results

Quantity and quality of research available

Number of studies identified

A flow chart describing the process of identifying relevant literature can be found in *Figure 2*. Following the removal of duplicates our searches identified 1060 potentially relevant papers. A total of 896 papers not meeting our inclusion criteria were removed at title sift, leaving a total of 164 papers to be screened at abstract sifting stage. Of these, eight studies and five abstracts (in total 13 studies described in 27 publications) were concerned with IMRT compared with 3DCRT and no studies were identified comparing IMRT with radical prostatectomy.

Number and type of studies excluded

In total 83 publications were excluded from those retrieved and inspected. A list of the 83 excluded papers at full paper sift with reasons for specific exclusions are provided in Appendix 5.

Number and type of studies included

There were eight studies meeting inclusion criteria for this review that were published in peer-reviewed journals, six of which were of localised PC, and two on locally advanced PC (see Included studies). In addition, five conference abstracts were considered to meet the inclusion criteria, but are considered separately as localisation of cancer is unclear, as abstracts necessarily provide less information about the studies (see Included conference abstracts).

Included studies

There were eight included comparative studies published as full reports in peer-reviewed journals: Kupelian;[28,84–87] Sanguineti *et al.*;[88] Shu *et al.*;[29] Vora *et al.*;[89,90] Yoshimura *et al.*;[41] Zelefsky;[91–99] Ashman *et al.*[100] (this was part of the Zelefsky study, but is classified here as a different study as it has distinct treatment and population characteristics, suggesting that the patients do not overlap with those from the other Zelefsky publications); and Lips *et al.*[43]

The population for six included studies was patients with localised PC.[28,29,41,88,89,91] For two included studies the population was patients with locally advanced PC.[43,100]

Four of the studies were retrospective patient records studies.[28,29,88,89] Three studies were prospective comparisons of case series,[41,43,91] and one study[100] retrospectively selected patients from one of these prospective studies.[91] Two of the studies compared contemporary series of patients from the same hospital,[28,29] four used historical controls from the same centre,[43,89,91,100] one study used both contemporary and historical controls from the same centre,[41] while the other used historical controls from a different hospital.[88]

Four studies had a primary outcome measure of toxicity,[29,88,91,100] while for two studies the primary outcome was biochemical relapse-free survival,[28,89] and for two studies the primary outcome was HRQoL.[41,43] None of the studies reported overall survival.

Five of the studies were set in the USA,[28,29,89,91,100] one was set in both Italy and the USA,[88] one was set in Japan[41] and one was set in the Netherlands.[43] None of the studies were set in the UK, but patients and treatments in the studies were of relevance to UK practice. There was some difference from UK practice in the Ashman *et al.*[100] study in that some (30%) patients were given chemotherapy, and in the Lips *et al.*[43] study for which some (26%) of the 3DCRT group were given hyperthermia treatment (see Appendix 2).

For most studies, patients were assessed at 3 to 6 month intervals,[28,29,88,91,100] with one study setting patient assessments at 6 to 12 month intervals.[89] The two studies with primary outcome HRQoL set data collection for 12 months[41] or 6 months[43] after RT.

Two relevant systematic reviews of IMRT for PC were identified: Pearson *et al.*;[64] and Mast *et al.*[101,102] In addition two relevant systematic reviews of IMRT, which included PC, were identified via web searches: Van den Steen *et al.*;[47] and Veldeman *et al.*[23] These were searched for relevant comparative studies. No meta-analyses were presented in these reviews.

Study details for the included comparative studies are shown in *Table 9*.

Within studies, treatment groups differed in more than just IMRT versus 3DCRT. Dose was higher in the IMRT group than the 3DCRT group for the studies of Vora *et al.*,[89] Yoshimura *et al.*,[41] Zelefsky *et al.*,[91] Ashman *et al.*[100] and Lips *et al.*[43] Dose was similar between treatment groups for the studies of Kupelian *et al.*[28] (doses between two

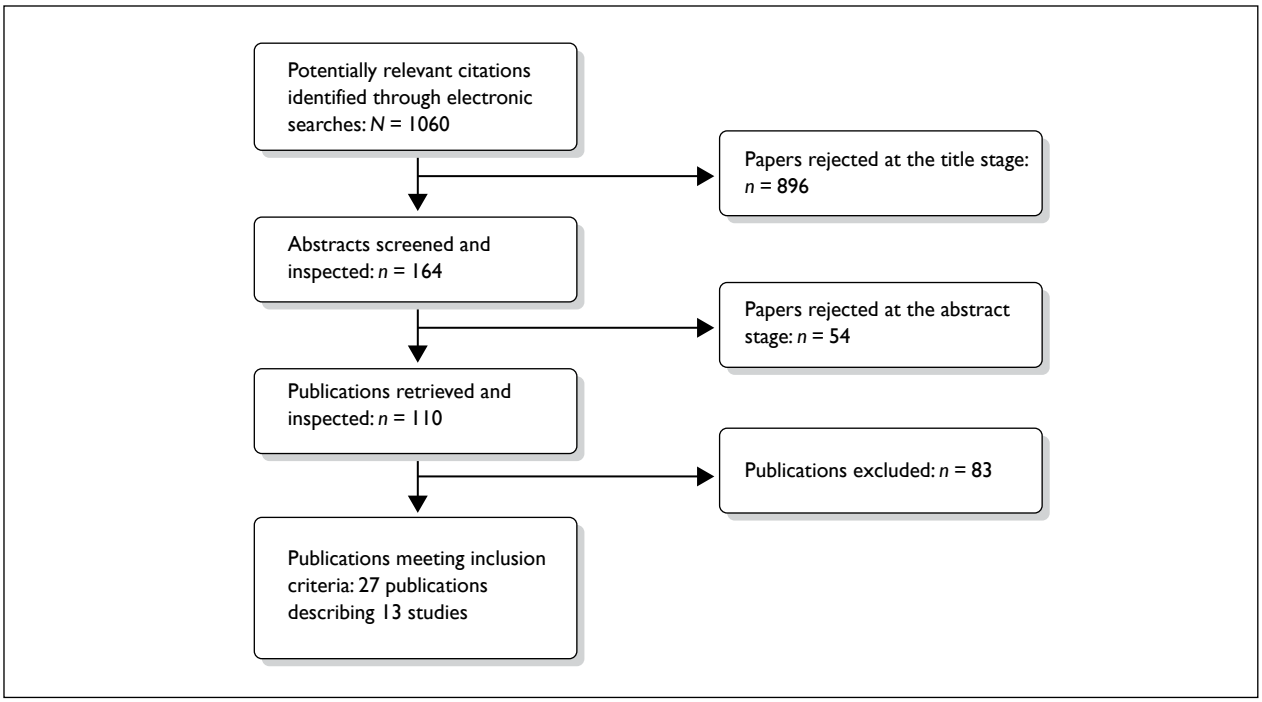

FIGURE 2 *QUOROM (quality of reporting of meta-analyses) flow chart of study selection for the review of clinical effectiveness.*

groups were reported as equivalent, 70 Gy in 28 fractions vs 78 Gy in 39 fractions), Sanguineti *et al.*[88] and Shu *et al.*[29] In the Sanguineti *et al.*[88] study, treatments differed in that IMRT involved treating the whole pelvis, whereas 3DCRT was restricted to the prostate. There was higher proportion of the IMRT group that had the whole pelvis treated than in the 3DCRT group of the Shu *et al.*[29] study. In the Lips *et al.*[43] study there was more accurate positioning of the prostate for IMRT than 3DCRT. Yoshimura *et al.*[41] and Zelefsky *et al.*[91] had two comparator groups with different doses of 3DCRT (see Appendix 2). Some studies had longer follow-up for IMRT than 3DCRT (see Appendix 2).

Between studies treatments differed in terms of PTV, dose, dose constraints, fractionation and patient positioning. More details about RT are in Appendix 2.

Included conference abstracts

Five conference abstracts of comparative studies of IMRT versus 3DCRT in PC were identified (*Table 10*). Three abstracts were from the same single centre study from the USA, Kirichenko *et al.*,[105] Sharma *et al.*,[106] and Morgan *et al.*,[107] which compared a case series of IMRT with a historical case series of 3DCRT. One of these three abstracts described a subset of patients treated with hormonal therapy,[106] and one described a subset of patients with intermediate to high risk disease.[107] One abstract,[108] also available as a poster,[109] was from a single centre in Germany which evaluated contemporary IMRT and 3DCRT patients in a matched pair analysis. One abstract[110] from a single centre in the USA studied IMRT versus 3DCRT, with both treatments utilising adaptive image guided RT. None of the abstracts specified whether the population was localised or locally advanced PC.

Quality of included studies

Quality assessment was undertaken for the eight studies which were fully reported using an adapted Downs and Black checklist[83] according to the guidance within the checklist on non-randomised studies. A summary of the quality of the eight studies can be seen in Appendix 3. A table is presented in Appendix 3 for relevant quality headings in the Downs and Black checklist (reporting, internal validity, external validity-bias and external validity-confounding). A narrative summary of the key aspects of the Downs and Black checklist follows.

Reporting

All studies clearly reported an aim or hypothesis. Seven out of eight studies clearly described the main outcomes. Seven studies clearly described patient characteristics, but Ashman *et al.*[100] did not present population characteristics per group. Seven out of eight studies did not have similar study groups on the basis of population characteristics, but one study did have groups with similar population characteristics.[91] One study[88] did not have the same data collection methods owing to the treatments being delivered in different countries, whereas the other seven studies appeared to have the same data collection methods per group. All eight studies clearly described the interventions. Four studies did not clearly describe potential confounders, two studies did clearly describe confounders[88,91] and two studies partially described confounders.[43,84] Six studies did not have similar treatment groups displaying differences in treatment years and areas to be irradiated, one study had aspects which were similar but the treatment groups were not identical, and one study[91] had similar treatment groups. Findings were clearly reported in six studies, but two studies[41,100] did not clearly report their findings. Ashman *et al.*[100] reported incorrect numbers of patients with grade 2 GU events (of 11 patients with GU events, Ashman *et al.*[100] state that eight were treated with 3DCRT and four patients were treated with IMRT which is clearly incorrect). Related papers by Ashman *et al.* were not available to clarify this point. Estimates of random variability were present in all but one study.[29] Seven studies fully addressed adverse events but one study did not[88] but focused on late rectal toxicity. Loss to follow-up was not described in seven studies and was unable to be determined in one study.[43] All eight studies reported actual probability values.

External validity

It was not possible to determine from the reporting whether or not those subjects who did participate were representative of the entire population from which they were recruited, although this may be presumed. Seven studies had a location/setting which was representative of the treatment that the majority of patients receive as far as this was possible to determine and for one study it was not possible to determine this aspect.[84]

Internal validity-bias

The eight studies were not single- or double-blinded trials and all showed clarity regarding data dredging if this occurred. Five studies adjusted for

TABLE 9 *Summary of included published studies*

		Intervention IMRT		Comparator 3DCRT				
Study	**Population**	**Whole pelvis or prostate only**	**Approximate dose**	**Whole pelvis or prostate only**	**Approximate dose**	**Number of patients**	**Outcomes**	**Follow-up**
Kupelian *et al.*[84] 2002 USA	Localised PC	Prostate only or prostate and SVs	70 Gy (hypo-fractionated)	Prostate only or prostate and SVs	78 Gy	282	Biochemical relapse-free survival Toxicity	Median 25 months
Sanguineti *et al.*[88] 2006 USA/Italy	Localised PC	Whole pelvis	76 Gy	Prostate only	76 Gy	113	Toxicity	Mean 25.9 months
Shu *et al.*[29] 2001 USA	Localised PC	Prostate only (28% patients), whole pelvis (72%)	85 Gy	Prostate only (96% patients), whole pelvis (4%)	84 Gy	44	Toxicity	Median 23.1 months
Vora *et al.*[89] 2007 USA	Localised PC	Prostate and SVs	75.6 Gy	Prostate and SVs	68.4 Gy	416	Biochemical relapse-free survival Toxicity	Median 60 months
Yoshimura *et al.*[41] 2007 Japan	Localised PC	Prostate only or prostate and SVs	76.5 Gy	Prostate only or prostate and SVs	70 or 73.5 Gy	144	HRQoL	12 months
Zelefsky *et al.*[91] 2008 USA	Localised PC	Prostate and SVs[97]	81 Gy	Prostate and SVs[96]	75.6 Gy or 66–70.2 Gy	1571	Toxicity	Median 96 months
Ashman *et al.*[100] 2005 USA	Locally advanced PC	Whole pelvis	81 Gy	whole pelvis	75.6 Gy	27	Toxicity	Median 30 months
Lips *et al.*[43] 2007 The Netherlands	Locally advanced PC	Prostate and SVs[103]	76 Gy	Prostate and SVs[104]	70 Gy	170	HRQoL	6 months

SVs, seminal vesicles.

TABLE 10 *Summary of included conference abstracts*

	Intervention IMRT		Comparator 3DCRT				
Study	**Whole pelvis or prostate only**	**Approximate dose**	**Whole pelvis or prostate only**	**Approximate dose**	**Number of patients**	**Follow-up**	**Outcome(s)**
Kirichenko *et al.*[105] 2006 USA	Prostate only, or prostate and PNs	Prescription dose 74–78 Gy, 95% PTV received 100% dose	Prostate only, or whole pelvis	Median peripheral CTV dose 72 Gy (range 70–79 Gy) prescribed to 95% isodose line	Total 1417; IMRT 489; 3DCRT 928	Median IMRT 29.9 months; 3DCRT 63.3 months	Toxicity
Sharma *et al.*[106] 2007 USA	NR (presume same as Kirichenko *et al.*)[105]	Mean 76 Gy (74–76)	NR (presume same as Kirichenko *et al.*)[105]	Mean 76 Gy (73–80)	Total 293; IMRT 123; 3DCRT 170	Median IMRT 41 months; 3DCRT 62 months	Toxicity
Morgan *et al.*[107] 2007 USA	NR (presume same as Kirichenko *et al.*)[105]	Median 81 Gy (range 77–85)	NR (presume same as Kirichenko *et al.*)[105]	Median 80 Gy (range 76–82)	Total 376; IMRT 188; 3DCRT 188	Median 35 months	Toxicity, biochemical failure, distant metastasis, cause specific mortality
Boehmer *et al.*[108] 2006 Germany	NR	79.7 Gy (78–82), simultaneous integrated boost 2 Gy	NR	72.2 Gy (70.2–73.8)	Total 187; IMRT 96; 3DCRT 91	Median 20 months	Toxicity
Martinez *et al.*[110] 2007 USA	Prostate only or prostate and SVs (60%)	Adaptive image-guided, median isocentre dose 79.7 Gy	Prostate only or prostate and SVs (51%)	Adaptive image-guided, median isocentre dose 79.7 Gy	Total 728; IMRT 172; 3DCRT 556	Median IMRT 2.2 years; 3DCRT 4.3 years	Toxicity

PNs, pelvic nodes; NR, not reported; SVs, seminal vesicles.

different follow-up lengths, two studies did not,[89,91] and it was not possible to determine this item in one study. All eight studies used appropriate statistical testing. It was not possible to determine if compliance with the intervention(s) were reliable for all eight studies. All eight studies described valid and reliable outcome measure(s).

Internal validity-confounding

Seven studies individually used comparison groups selected from the same institution, apart from one study which had comparison groups from two separate institutions.[88] Only two studies[29,91] sampled in the same time period for each group, and the other six studies sampled during different treatment periods/years per group. Kupelian *et al.* (2005)[111] suggests that independent of tumour stage, radiation dose, failure definition and follow-up parameters, the year in which RT is performed is an independent predictor of outcomes. Three studies are worst affected as they have historical controls in the previous decade[29,88,89] and these studies may overestimate biochemical control in the IMRT group.[23] None of the comparative studies were randomised, so concealment of randomisation was not an issue. Three studies made adequate adjustment for confounders[84,88,91] but five studies did not. It was not possible to determine if the studies accounted for losses of patients to follow-up.

Overall most of the information from all the eight studies has a medium- to high-risk of bias; sufficient to affect the interpretation of results (i.e. weakens confidence in the results). Therefore, the results should be interpreted with caution.

Quality of included conference abstracts

Quality assessment was undertaken for all five[105–108,110] included conference abstracts using the adapted Downs and Black checklist.[83] A summary of the quality of the five abstracts can be seen later in Appendix 4. A table is presented in Appendix 4 for key quality headings in the Downs and Black checklist (reporting, internal validity, external validity-bias, external validity-confounding) with regard to the five abstracts. However, it was not possible to perform a full quality assessment using the Downs and Black checklist[83] as the information within the abstracts was necessarily limited. None of the studies were identified as having later been published in full.

Within the limits of the abstract reporting level, it was not possible to determine the main outcomes or patient characteristics clearly for all five abstracts. However, the limited findings were largely clear; an attempt to cover the key adverse events was made, but losses to follow-up were not described in all five abstracts. Two abstracts[105,110] were marginally more clearly reported than the other abstracts. It was not possible to determine the items regarding external validity for all five abstracts. It was largely not possible to determine items regarding internal validity-bias for all five abstracts; with the exception of two studies[106,107] which mentioned that adjustment was made for different lengths of follow-up, one abstract[108] gave information about a reliable and valid outcome measure and two abstracts[105,107] indicated appropriate statistical testing. With regard to internal validity, only one abstract[108] sampled within the same time period for both groups, otherwise it was not possible to determine many of the items for the five abstracts.

Assessment of effectiveness

None of the studies reported overall survival or clinically measured disease-free survival. One conference abstract[107] reported, at 4 years, no significant difference between treatment groups in distant metastasis (from $n = 88$ in both groups, those developing distant metastasis IMRT 4%, 3DCRT 3%, $p = 0.36$), or in cause-specific mortality (IMRT 1%, 3DCRT 0%, $p = 0.32$).[107]

Biochemical relapse-free survival

The Kupelian *et al.*[84] study used the ASTRO consensus definition[44] of biochemical failure, that is three consecutive rising PSA levels after reaching a nadir, and calculated the time to failure as midway between time of nadir and first PSA rise. No significant difference between treatment groups was found ($p = 0.084$) (*Table 11*). When the Kupelian *et al.* study applied a stricter definition of biochemical relapse-free survival, that is reaching and maintaining a follow-up PSA level at less than or equal to 0.5 ng/ml, there remained no significant difference between treatment groups ($p = 0.24$). By multivariate Cox proportional hazards analysis, taking into account age, race, stage, pre-treatment PSA, biopsy Gleason score and neoadjuvant androgen deprivation, treatment group showed a non-significant trend favouring IMRT ($p = 0.058$).

The Kupelian *et al.* study[85] reported 5-year biochemical survival data for the IMRT group only ($n = 100$) at median 5.5 years follow-up. The five-year biochemical relapse-free survival using the ASTRO consensus definition was 85% [95% confidence interval (CI) 78 to 93%], and using their stricter definition was 88% (95% CI 82 to 95%). Survival data by risk groups were 97% for low-risk disease, 88% for intermediate risk, and 70% for high-risk disease. Using an expanded comparison group treated with 3DCRT ($n = 310$, median follow-up 71 months) 5-year biochemical relapse-free survival using the ASTRO consensus definition was 78%. A later report of this study,[86] when 770 IMRT patients had been recruited with a median follow-up of 45 months, reported that the 5-year biochemical relapse-free survival using the ASTRO consensus definition was 82% (95% CI 79 to 85%).

The Vora *et al.* study[89] using the ASTRO consensus definition, found a significant difference between treatment groups ($p < 0.0001$) by either univariate or multivariate analysis (*Table 11*). Multivariate Cox proportional hazards analysis took into account stage, perineural invasion, PSA, Gleason score, hormonal therapy and percentage positive biopsies in addition to treatment group, and found all factors except hormonal therapy and percentage positive biopsies were significantly associated with biochemical failure. The Vora *et al.* study also used the ASTRO Phoenix definition[45] rise in PSA level of 2 ng/ml or more above the nadir with no backdating. There was a significant difference between treatment groups by either univariate ($p < 0.0326$) or multivariate analysis ($p < 0.0359$).

The Vora *et al.* study[89] investigated biochemical survival by the NCCN defined risk group, that is risk group decided by PSA ≤ 10 ng/ml, stage T1–T2, Gleason score ≤6; if patient meets all three criteria they are considered to have low-risk disease, an increase in one indicator translates as intermediate

TABLE 11 *Biochemical relapse-free survival*

Study	Follow-up	Definition of failure	Number of patients IMRT	Number of patients 3DCRT	Survival IMRT%	Survival 3DCRT%	Comparison
Kupelian *et al.*[84]	30 months	ASTRO consensus	166	116	94 (95% CI 91 to 98)	88 (95% CI 82 to 94)	$p = 0.084$
Kupelian *et al.* [84]	30 months	PSA level reaching and maintaining 0.5 ng/mL or over	166	116	87% (95% CI 81 to 93)	80% (95% CI 72 to 88)	$p = 0.24$
Vora *et al.*[89]	36 months	ASTRO consensus	145	271	95.2	71.1	
Vora *et al.*[89]	36 months	ASTRO Phoenix	145	271	93.8	89.8	
Vora *et al.*[89]	60 months	ASTRO consensus	145	271	74.1	60.4	$p < 0.0001$
Vora *et al.*[89]	60 months	ASTRO Phoenix	145	271	84.6	74.4	$p < 0.0326$

risk, and an increase in two or three indicators is classed as high risk.[91] Using the ASTRO consensus definition, Vora *et al.* found 5-year survival for IMRT patients was 87.5% for low-risk patients, 72.6% for intermediate risk, and 60.2% for high-risk patients. For 3DCRT the survival data by risk group were 76.2%, 50.1%, and 35.0% respectively. IMRT significantly improved biochemical survival for intermediate- ($p < 0.0001$) and high-risk ($p = 0.0188$) patients, but for low-risk patients there was no significant difference between treatment groups ($p = 0.181$).

The Zelefsky study does not report comparative data, but reports data from IMRT patients using the ASTRO consensus definition. There was no dose effect on PSA relapse-free survival for IMRT dose of 81 Gy or 86.4 Gy.[92] There was no difference in results according to whether or not patients had neoadjuvant androgen deprivation.[92] For IMRT patients aged ≤60 years, a dose < 75.6 Gy was the most important predictor of biochemical relapse in younger patients.[94] The 3-year actuarial PSA relapse-free survival rates by NCCN defined risk group: low risk ($n = 275$) 92%, intermediate ($n = 322$) 86%, and high ($n = 175$) 81%.[92] The 8-year actuarial PSA relapse-free survival rates by risk group for IMRT patients were for low risk ($n = 203$) 85%, intermediate ($n = 255$) 76%, and high ($n = 103$) 69%.

The Morgan *et al.*[107] abstract reported biochemical failure using the ASTRO Phoenix definition in patients with intermediate to high-risk PC. At 4 years there was no significant difference between treatment groups, with a biochemical failure rate of 18% for the IMRT group (PSA survival 82%), and 19% (PSA survival 81%) for the 3DCRT group ($p = 0.675$).

For the studies Kupelian *et al.*[28] and Vora *et al.*[89] that reported comparative statistics, Kupelian *et al.*[28] did not report a difference between treatment groups, whereas Vora *et al.*[89] found a significant biochemical survival advantage for IMRT. The different results cannot be explained by definition of biochemical failure, as both studies used the ASTRO consensus definition. Across the two studies at 30 or 36 months, biochemical survival data appear similar for IMRT groups (see *Table 8*); however, for the 3DCRT groups Vora *et al.*[89] reported lower survival than Kupelian *et al.*[28] This might be explained by dose. The 3DCRT dose in the Vora *et al.*[89] study was lower than in the Kupelian *et al.*[28] study. The Vora *et al.*[89] study had a lower dose in 3DCRT than in the IMRT group, and the Kupelian *et al.*[28] study had an equivalent dose between treatment groups. The Morgan *et al.*[107] abstract, which did not find a treatment group difference in biochemical failure, had similar dose for both treatment groups. The 3DCRT dose in the Vora *et al.*[89] study was lower than in other studies, and was approximately 68.4 Gy. There is evidence from RCTs that in CRT 68 Gy leads to lower biochemical survival than for CRT at 78 Gy.[59] The lack of dose effect on PSA relapse-free survival for IMRT dose of 81 Gy or 86.4 Gy in the Zelefsky study[92] is consistent with the lack of evidence of benefit for increasing dose of 3DCRT above 81 Gy.[64]

It is unlikely that the difference between Kupelian *et al.*[28] and Vora *et al.*[89] study results could be explained by risk group. Although the Vora *et al.*[89] study found that low-risk disease did not benefit

significantly from IMRT over 3DCRT, they found intermediate and high-risk patients did differ significantly between treatment groups, and the Kupelian *et al.*[28] study had 70% high-risk tumours. It is unlikely that the difference between study results could be explained by their difference in hormonal therapy between treatment groups, as neither study found an association between hormonal therapy and biochemical survival, Kupelian *et al.*[28] ($p = 0.66$) and Vora *et al.*[89] ($p = 0.08$), which agrees with the Zelefsky *et al.*[91] study. However, the focus of this review was not hormonal therapy, and these limited data are not presented as conclusive evidence on the effect of hormonal therapy.

Toxicity

For defining AEs, five of the studies (Kupelian *et al.*,[28] Sanguineti *et al.*,[88] Shu *et al.*,[29] Vora *et al.*,[89] Ashman *et al.*[100]) used RTOG and the other study (Zelefsky *et al.*[91]) used NCICTC for AEs.

Among all studies, there are no mentions of treatment-related deaths, with the possible exception of one patient from the Kupelian *et al.*[28] study. However, although one patient treated with IMRT died in this study it was unclear if the death could be attributed to treatment-related late rectal toxicity or if it was due to the patient's underlying medical condition.

None of the studies report secondary malignancies, probably because the follow-up durations were not long enough. It may be that follow-up in excess of 10 years, and a larger sample size, would be needed to detect group differences in secondary malignancies.[64] There is a lack of comparative data on sexual dysfunction as an AE, but sexual function is measured as part of HRQoL.

The studies concentrate on GI and GU AEs. These are considered separately for acute and late effects.

Acute gastrointestinal toxicity

Kupelian *et al.*[84] and Zelefsky *et al.*[91] found a significant advantage for IMRT over 3DCRT (*Table 12*). Vora *et al.*[89] did not find a significant difference between treatment groups.

By univariate analysis, the Shu *et al.* study found an advantage for 3DCRT.[29] However, this might be attributed to the lower proportion of 3DCRT patients treated with whole pelvis (WP) radiation. As well as treatment group effect, the Shu *et al.* study found that WP radiation was significantly correlated with the incidence of acute GI toxicity ($p = 0.001$).[29] In the IMRT group, 9 (69%) of 13 patients receiving pelvic irradiation had acute GI toxicity versus 2 (40%) of 5 patients not receiving pelvic irradiation (both cases were grade 1). The Zelefsky *et al.* study[91] did not find any demonstrable influence of age, radiation dose or hormonal therapy on incidence of acute rectal symptoms. For patients treated with IMRT, Zelefsky found no difference in GI toxicity between doses 86.4 Gy and 81 Gy.[92]

TABLE 12 *Acute gastrointestinal toxicity in localised prostate cancer*

Study	Follow-up/ definition	Definition	Number of patients IMRT	Number of patients 3DCRT	Acute GI toxicity IMRT	Acute GI toxicity 3DCRT	Comparison
Kupelian *et al.*[84]	Acute	RTOG rectal toxicity scores	166	116	Score 0 30%, score 1 55%, and score 2 15%	Score 0 12%, score 1 70%, and score 2 18%	$p = 0.002$
Shu *et al.*[29]	Within 6 months	RTOG grades 1–3	18	26	NR	NR	$p = 0.003$ higher in IMRT group
Vora *et al.*[89]	Acute	RTOG grade	145	271	Grade 0 16%, grade 1 34%, grade 2 49%, grade 3 1%	Grade 0 27%, grade 1 20%, grade 2 54%, grade 3 0%	$p = 0.83$
Zelefsky *et al.*[91]	During or within 3 months	NCI-CTC	472	358	3%	1%	$p = 0.04$

NR, not reported.

Across studies, toxicity grades were generally low. Only one (IMRT) patient in the Shu *et al.* study developed grade 3 toxicity.[29] In the Vora *et al.* study no grade 4 or 5 toxicity was found.[89]

The only study looking at toxicity specifically in locally advanced PC, Ashman *et al.* (*Table 13*), found no grade 3 or higher acute GI toxicities developed in any of the patients; however, the sample size was small.[100] As five of the six patients in the 3DCRT group who had grade 2 diarrhoea were additionally treated with chemotherapy, it is difficult to attribute the results to treatment difference between groups.

Three of the studies[106,107,110] published as conference abstracts favoured IMRT for acute GI toxicity. The Sharma *et al.* abstract[106] on hormonally treated PC patients found significantly [hazard ratio (HR) = 4.39, $p = 0.003$] lower acute GI toxicity in the IMRT group than in the 3DCRT group. The Morgan *et al.* abstract[107] on patients with intermediate- to high-risk PC found significantly less ($p = 0.015$) grade 2 or higher acute GI toxicity in the IMRT group (4%) than the 3DCRT group (10%). The Martinez *et al.* abstract[110] on adaptive IGRT found a significantly ($p < 0.01$) lower rate of grade 2 or higher rectal pain or tenesmus in the IMRT group (5%) than the 3DCRT group (19%).

The Kirichenko *et al.* abstract[105] did not report a treatment group difference in acute toxicity, but did find that patients with WP treatment involving lymph nodes were more likely to have acute toxicity than patients with smaller treatment fields (HR = 2.1, $p < 0.0001$).

The Boehmer *et al.* abstract[108] found no treatment group differences were found for rectal pain, bleeding, urgency or incontinence. However, they did report significantly ($p = 0.002$) more proctitis (common toxicity criteria) in the IMRT group than in the 3DCRT group. Most toxicities were grade 1.[109] Unlike the Shu *et al.* study,[29] the treatment group difference does not appear to be explained by difference between WP or prostate only radiation. There was a higher dose in the IMRT group, but this was also the case for the Vora *et al.*[89] and Zelefsky *et al.*[91] studies which did not show the same pattern of treatment group effect.

Acute GU toxicity

There was no significant treatment group effect for acute GU toxicity in the Kupelian *et al.*,[85] Shu *et al.*,[29] or Vora *et al.*[89] studies, although in the Vora *et al.* study there was a trend for IMRT to have higher acute GU toxicity (*Table 14*). The Zelefsky *et al.* study results significantly favoured 3DCRT ($p = 0.001$).[91] Zelefsky attributes this to the urethral dose not being constrained in the IMRT group.[92] For patients treated with IMRT, Zelefsky found a non-significant trend for higher toxicity at 86.4 Gy than for 81 Gy.[92]

The Shu *et al.* study found that WP radiation correlated with the incidence of acute GU toxicity ($p = 0.021$).[29]

Toxicity was generally low grade; in the Shu *et al.* study no patients developed grade 3 toxicity,[29] and in the Vora *et al.* study no grade 4 or 5 toxicity was found.

The Ashman *et al.* study of locally advanced PC had slightly higher incidence of acute GU toxicity in the IMRT group than the 3DCRT group [7 or 8 (reporting unclear in publication) out of 13 patients, vs 3 or 4 out of 14 patients]; however, this was based on a small sample size.[100]

Three of the conference abstracts[106–108] on PC did not find treatment group effects. The Sharma *et al.* abstract[106] on hormonally treated PC patients found no significant treatment group difference in acute GU toxicity. They did find that hormonal treatment of 6 months or longer duration was associated with increased acute GU toxicity ($p = 0.045$). The authors gave no explanation for

TABLE 13 *Acute gastrointestinal toxicity in locally advanced prostate cancer*

Study	Follow-up/ definition	Definition	Number of patients IMRT	Number of patients 3DCRT	Acute GI toxicity IMRT	Acute GI toxicity 3DCRT
Ashman *et al.*[100]	During or within 3 months of treatment	RTOG grade 2 diarrhoea	13	14	0%	43% ($n = 6$)
Ashman *et al.*[100]	During or within 3 months of treatment	RTOG grade 2 proctitis	13	14	7% ($n = 1$)	36% ($n = 5$)

TABLE 14 *Acute GU toxicity in localised prostate cancer*

Study	Follow-up	Definition	Number of patients IMRT	Number of patients 3DCRT	Acute GU toxicity IMRT	Acute GU toxicity 3DCRT	Comparison
Kupelian *et al.*[84]	Acute	Urinary toxicity RTOG scores	166	116	Score 0 15%, score 1 62%, score 2 22%, score 3 1%	Score 0 19%, score 1 63%, score 2 17%, score 3 1%	$p = 0.64$
Shu *et al.*[29]	Within 6 months	RTOG grade 1–2	18	26	NR	NR	$p = 0.535$
Vora *et al.*[89]	Acute	RTOG grade	145	271	Grade 0 28%, grade 1 23%, grade 2 46%, grade 3 5%	Grade 0 38%, grade 1 21%, grade 2 40%, grade 3 1%	$p = 0.094$
Zelefsky *et al.*[91]	During or within 3 months of treatment	NCI-CTC grade 1 or higher GU symptoms	472	358	37%	22%	$p = 0.001$

NR, not reported.

this, and no definitive conclusions about duration are drawn from one small study. The Morgan *et al.* abstract[107] on patients with intermediate to high risk PC did not find a treatment group difference ($p = 0.116$) grade 2 or higher acute GU toxicity between the IMRT (10%) and 3DCRT (5%) groups. The Boehmer *et al.* abstract[108] did not find any treatment group difference for acute GU toxicity.

The Martinez *et al.* abstract[110] on adaptive IGRT found a significantly ($p = 0.03$) lower rate of grade 2 or higher urinary retention in the IMRT group (2%) than the 3DCRT group (7%). Other acute GU symptoms are not mentioned. This pattern of results is unlike the other studies, and cannot be explained by dose as treatment groups had equivalent doses. This study did differ from the others in that IGRT was used.

Late GI toxicity

The Zelefsky *et al.* study[91] favoured IMRT in terms of late GI toxicity (*Table 15*), as did the Kupelian *et al.* study[84] when considering only grade 3 toxicity. The Shu *et al.* study[29] did not find significant treatment effects. The Vora *et al.* study[89] did not find significant treatment effect despite the higher dose in the IMRT group. In the Sanguineti *et al.* study, the difference between groups was non-significant by univariate analysis (*Table 15*), but multivariate analysis significantly favoured IMRT, with adjusted HR = 0.1 (95% CI 0.0 to 0.06) $p = 0.01$.[88] The analysis adjusted for dose to most anterior and posterior rectal points along the central axis, age, race, hypertension, diabetes, vascular comorbidity, GI comorbidity, any other comorbidity, transurethral resection of prostate, androgen deprivation, acute toxicity and T-stage.

Sanguineti *et al.* dosimetric comparison found that although IMRT had higher average dose to anterior rectum, the percentage of rectum receiving a given dose was significantly ($p < 0.05$) lower with IMRT than the 3DCRT group. Sanguineti *et al.* reported that for 22% of 3DCRT patients, and 0% IMRT patients, treatment failed to meet dose–volume constraints.[88] A multivariate analysis of AEs from the Kupelian *et al.*[28] study found the only factor that significantly predicted grade 2–3 late rectal toxicity was the volume of rectum receiving the prescription dose ($p = 0.006$). Zelefsky *et al.*[91] found a higher incidence of late GI toxicity in those patients who experienced acute GI toxicity ($p < 0.0001$).

For patients with locally advanced PC, Ashman *et al.*[100] reported that none of the patients developed grade 3 or higher toxicity. Both patients with grade 2 late rectal bleeding were in the 3DCRT group, but sample size was too small to draw conclusions about significance. The two patients who got

TABLE 15 *Late GI toxicity in localised prostate cancer*

Study	Follow-up	Definition	Number of patients IMRT	Number of patients 3DCRT	Late GI toxicity IMRT	Late GI toxicity 3DCRT	Comparison
Kupelian *et al.*[84]	30 months	Actuarial combined grade 2 and 3 late rectal toxicity	166	116	5%	12%	$p = 0.24$
Kupelian *et al.* [84]	30 months	Grade 3 late rectal toxicity	166	116	2%	8%	$p = 0.059$
Sanguineti *et al.* [88]	Complications developing >90 days after treatment and those starting prior to and persisting for >90 days after completion of treatment, 2 years follow-up	Estimated cumulative incidence grade 2 rectal toxicity	45	68	6% ± 4%	21.2% ± 6%	HR (unadjusted) = 0.2, 95% CI 0.1 to 1.1; $p = 0.06$
Shu *et al.* [29]	Minimum 10 months	RTOG grade 1–3	18	26	NR	NR	$p = 0.163$
Vora *et al.* [89]	60 months	RTOG grade	145	271	Grade 0 56%, grade 1 20%, grade 2 23%, grade 3 1%	Grade 0 57%, grade 1 26%, grade 2 14%, grade 3 2%	$p = 0.24$
Zelefsky *et al.* [91]	10 years	NCI-CTC grade 2 or higher	472	358	5%	13%	$p < 0.001$

NR, not reported.

grade 2 rectal bleeding (*Table 16*) did not receive chemotherapy.

Four[105–107,110] of the five[105–108,110] conference abstracts favoured IMRT in terms of late GI toxicity. The Kirichenko *et al.* abstract[105] found a significantly (univariate $p = 0.009$, multivariate HR = 0.6, $p = 0.0499$) lower rate of late grade 2 or higher GI toxicity in the IMRT group (6.2%) at 3-year follow-up compared with the 3DRCT group (10.4%). In addition, treatment to the WP or lymph nodes was associated with higher late GI toxicity (HR, $p = 0.003$). The Sharma *et al.* abstract[106] on hormonally treated PC patients found significantly lower (HR = 2.45, $p = 0.02$) late grade 2 or higher GI toxicity in the IMRT group (9%) than in the 3DCRT group (22%), based on 5-year estimates. The Morgan *et al.* abstract[107] on patients with intermediate to high-risk PC found a non-significant trend for less ($p = 0.061$) grade 2 or higher late GI toxicity in the IMRT group (4%) than the 3DCRT group (9%) at 4 years. The Martinez *et al.* abstract[110] on adaptive IGRT found a significantly ($p < 0.01$) lower rate of late grade 2 or 3 rectal bleeding in the IMRT group (4%) than the 3DCRT group (16%). There was no treatment group difference for late grade 2 or 3 rectal pain, tenesmus or diarrhoea. Median time to rectal bleeding was 11 months for IMRT and 12 months for 3DCRT.

The Boehmer *et al.* abstract[108] did not find any treatment group difference ($p = 0.23$) for late GI toxicity. This was despite acute GI toxicity results showing more proctitis in the IMRT group than in the 3DCRT group.

TABLE 16 *Late GI toxicity in locally advanced prostate cancer*

Study	Follow-up/definition	Definition	Number of patients IMRT	Number of patients 3DCRT	Late GI toxicity IMRT	Late GI toxicity 3DCRT
Ashman *et al.* [100]	More than 3 months after treatment (minimum follow-up 10 months)	RTOG grade 2 rectal bleeding	12	13	0%	15% ($n = 2$)

Late GU toxicity

The Zelefsky *et al.*[91] and Shu *et al.*[31] studies favoured 3DCRT for late GU toxicity (*Table 17*). There was no significant treatment effect in the Vora *et al.*[89] study, and the Kupelian *et al.*[84] study reported they had too few events to determine significance. Shu *et al.* found late GU toxicity was related to maximal tumour dose ($p = 0.019$), and WP radiation ($p = 0.016$).[29] Both Shu *et al.*[29] and Zelefsky *et al.*[91] found a higher incidence of late GU toxicity in those patients who had experienced acute GU toxicity ($p = 0.025$ and $p < 0.001$ respectively).

For locally advanced PC, Ashman *et al.* found none of the 12 IMRT patients, but four of 13 3DCRT patients with late GU toxicities (*Table 18*).[100] All of the patients with late GU toxicity were treated with chemotherapy as well as 3DCRT, making it difficult to attribute the group difference to type of RT delivered.

Three[105,107,108] conference abstracts reported no treatment group effect on late GU toxicity. The Kirichenko *et al.* abstract[105] did not find a significant treatment group difference in late GU toxicity, although there was a trend (univariate $p = 0.06$, multivariate $p = 0.11$) for more toxicity in the IMRT group (8.4%) than the 3DCRT group (5.7%) at 3 years. The Morgan *et al.* abstract[107] on patients with intermediate to high risk PC did not find a treatment group difference ($p = 0.661$) grade 2 or higher late GU toxicity between the IMRT (2%) and 3DCRT (1%) groups. The Boehmer *et al.* abstract[108] did not find any treatment group difference ($p = 0.42$) for late GU toxicity.

The Martinez *et al.* abstract[110] on adaptive IGRT found no treatment group difference for late grade 2 or 3 frequency, urgency, haematuria or urethral stricture. However, they did report a significantly ($p < 0.05$) lower rate of late grade 2 or 3 urinary retention in the IMRT group (0.5%) than the 3DCRT group (3%). This pattern of results is unlike the other studies, and cannot be explained by dose as treatment groups had equivalent doses.

Health-related quality of life

Yoshimura *et al.*[41] assessed HRQoL in localised PC at three time points; before RT, immediately after RT, and 12 months after RT ended. On the eight domains in SF-36 there were no significant differences between treatment groups. There were also no significant differences across the three time points. On the UCLA PCI there were no significant differences between groups. Although there was a significant interaction between group and time point on the sexual function domain ($p < 0.05$), this was seemingly due to difference between groups at baseline. There was a non-significantly higher pre-RT sexual function score in the low-dose 3DCRT group, than in the other two groups. The low-dose 3DCRT group deteriorated between pre-RT and immediately post-RT then improved at 12 months, whereas the IMRT and high-dose 3DCRT groups improved between pre-RT and immediately post-RT as well as improving between immediately post-RT and 12 months. All three groups improved significantly between pre-RT and 12 months, though this was greater in the IMRT and high-dose 3DCRT groups ($p < 0.001$) than the low-dose 3DCRT group ($p < 0.01$). For all groups there was significant deterioration ($p < 0.05$) in urinary bother, bowel function and bowel bother domains during RT, but these were restored at 12 months.

Lips *et al.*[43] assessed HRQoL in locally advanced PC at three time points; before treatment, 1 month after treatment, and 6 months after treatment. Considering the time points baseline and 1 month post-RT, for six of the 29 items there was a significant interaction between treatment group and time, with the 3DCRT group showing more deterioration than the IMRT group. These items were RAND-36 (RAND-36 item health survey, that uses the same items as SF-36 but with different scoring) social functioning ($p = 0.006$), pain ($p = 0.01$) and change in health ($p < 0.0001$); EORTC QLQ-C30(+3) physical functioning ($p = 0.006$) and role functioning ($p = 0.006$); EORTC QLQ-PR25 urinary symptoms/function ($p < 0.0001$). For baseline and 6 months post-RT,

TABLE 17 *Late GU toxicity in localised prostate cancer*

Study	Follow-up	Definition	Number of patients IMRT	Number of patients 3DCRT	Late GU toxicity IMRT	Late GU toxicity 3DCRT	Comparison
Kupelian *et al.*[84]	30 months	RTOG urinary toxicity	166	116	Grade 2 $n=2$, grade 3 $n=0$	Grade 2 $n=2$, Grade 3 $n=0$	NA
Shu[29]	Minimum 10 months	RTOG grade 1–3	18	26	NR	NR	$p=0.025$
Vora[89]	60 months	RTOG grade	145	271	Grade 0 45%, grade 1 27%, grade 2 23%, grade 3 6%	Grade 0 66%, grade 1 13%, grade 2 17%, grade 3 5%	$p=0.33$
Zelefsky[91]	10 years	NCICTC grade 2 or higher	472	358	20%	12%	$p=0.01$

TABLE 18 *Late GU toxicity in locally advanced prostate cancer*

Study	Follow-up/definition	Definition	Number of patients IMRT	Number of patients 3DCRT	Late GU toxicity IMRT	Late GU toxicity 3DCRT
Ashman[100]	More than 3 months after treatment (minimum follow-up 10 months)	RTOG grade 1–3	12	13	0%	31% ($n=4$)

there were no significant differences between groups on any of the items measured. For the other 23 items there were no significant differences between groups and no significant interaction between treatment group and time. These included items relating to emotional, cognitive, social and sexual functioning, and GI symptoms.

Kupelian *et al.*[84] assessed HRQoL in localised PC, but only after treatment, no baseline data were reported. Two years after treatment 77 patients (IMRT $n=38$, 3DCRT $n=39$) completed the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. The groups did not differ in urinary ($p=0.85$), bowel ($p=0.12$) or hormonal ($p=0.38$) scores, but the IMRT group scored better on the sexual summary score ($p=0.003$). There was no difference between treatment groups on the SF-12, either on physical ($p=0.11$) or mental ($p=0.81$) QoL scores.

Discussion

No comparative studies of IMRT versus prostatectomy were identified. No RCTs were available of IMRT versus 3DCRT in PC. Eight studies[29,41,43,84,88,89,91,100] comparing IMRT and 3DCRT were found that were published in full, and an additional five studies[105–108,110] published as conference abstracts only were identified. None of the studies investigated overall survival. Comparative evidence on biochemical relapse-free survival was available from two studies[84,89] published in full and one abstract.[107] Toxicity data were available from six studies[29,84,88,89,91,100] published in full and five abstracts.[105–108,110] Comparative evidence on HRQoL with baseline and follow-up data were available from two studies[41,43] published in full. Of the studies published in full, six were studies of clinically localised PC,[29,41,84,88,89,91] and two of locally advanced PC.[43,100] The five conference abstracts[105–108,110] did not specify whether patients had localised or locally advanced PC. The only study reporting toxicity data for locally advanced PC had a sample size of only 27, precluding significance testing.[100]

With regard to overall quality of the eight studies included in the review,[29,41,43,84,88,89,91,100] the studies displayed weaknesses which included differences

between the treatment and comparator groups on population differences. Two studies involved populations which had higher biopsy Gleason scores in the IMRT group compared with one study which had higher biopsy Gleason scores in the 3DCRT group. Two studies had higher clinical T stages in the 3DCRT group and one study had higher PSA scores in the IMRT group. One study had higher numbers of patients with androgen deprivation therapy in the IMRT group compared with one study which had higher numbers of patients with androgen deprivation therapy in the 3DCRT group. The direction of bias differs between the studies on these population characteristics making it difficult to assess the impact on the treatment effect of the IMRT group. Some studies adjusted for such differences with multivariate analysis, but not all studies did. Overall the disease severity of the IMRT group patients may be higher than in the 3DCRT group patients, which may indicate that the results are biased against IMRT.[23]

Half of the studies used historical controls and many of the studies sampled different treatment years per group. With regard to the latter point, many of the studies were conducted within the last decade. However, the studies with historical controls in the previous decade and thus most affected were Vora *et al.*,[89] Sanguineti *et al.*[88] and Shu *et al.*[29] so their results may be potentially biased.[23] Studies had longer follow-up periods for the 3DCRT groups compared with the IMRT groups, as the 3DCRT groups tended to be the historical controls being sampled first. This may have introduced potential bias towards more toxicity, although in some studies the IMRT follow-up may have been long enough to capture late toxicity.

There were differences in the details of oncological management between studies and within studies including the use of hormonal therapy (which may affect PSA control, overall survival, acute toxicity, late toxicity and HRQoL). One might assume that use of this therapy suggests more advanced disease, but it might easily just represent change in standard practice. It is unlikely that the difference between study results could be explained by differences in hormonal therapy between treatment groups, as two studies did not find an association between hormonal therapy and biochemical survival,[84,89] which also agrees with the Zelefsky *et al.* study.[91]

There were differences between studies use of pelvic nodal RT (which may also affect PSA control, overall survival, acute toxicity, late toxicity and HRQoL) and regarding the use of dose-escalated RT (which may also affect PSA control, overall survival, acute toxicity, late toxicity and HRQoL). The use of dose escalation may indicate a change in standard practice, but it might also represent more advanced disease.

There were inter- and intra-study differences with regard to the definition of biochemical failure; however, studies such as Vora *et al.*[89] presented treatment group data for both the ASTRO consensus and the ASTRO Phoenix definition of biochemical failure, therefore limiting potential bias.

The reliability of results presented in abstract form may be questionable. Abstracts may present preliminary results of an ongoing study and may differ from those eventually published in full.[2,112]

For biochemical relapse-free survival, two studies did not report a difference between treatment groups. One study found a significant biochemical survival advantage for IMRT. This difference between studies is probably explained by dose. The study finding an advantage for IMRT had higher dose than in the 3DCRT group, unlike the other studies that had equivalent doses between treatment groups.

Most of the studies reported an advantage for IMRT in acute and late GI toxicity, either in reducing toxicity or producing similar toxicity to lower dose 3DCRT. GI toxicity was associated with larger treatment field, as WP versus prostate only, or as volume of rectum treated. Late GI toxicity was associated with acute GI toxicity.

Most of the studies found no treatment group effect for acute and late GU toxicity, although one study favoured 3DCRT. Adaptive IGRT favoured IMRT for GU toxicity, however this was only from one study abstract,[110] and so does not allow firm conclusions to be drawn. Acute GU toxicity was found to be associated with WP radiation or hormonal treatment of 6 months or longer duration, although this may be due to baseline differences in symptoms, with higher risk disease patients being prescribed these treatments. Late GU toxicity was associated with acute GU toxicity.

In localised PC, for both IMRT and 3DCRT there was a decrease in HRQoL during treatment, but this was restored by 12 months after RT. For patients treated with higher dose RT (IMRT or 3DCRT), HRQoL improved to a greater extent than for lower dose RT. In locally advanced PC, there was no treatment group difference by 6 months after treatment, although 1 month after RT the 3DCRT group showed more deterioration in pain, functioning and urinary symptoms. It may be that follow-up was not long enough in these studies to provide meaningful HRQoL data 'as late adverse effects frequently do not manifest until after two years of treatment completion'.[62]

Although studies had methodological flaws, taken together they seem to support the theory that higher dose up to 81 Gy can improve biochemical survival, and that restricting treatment field, particularly with regard to constraining volume of rectal wall receiving prescription dose, can lessen toxicity.

Chapter 4

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

A systematic literature search was undertaken for previous economic studies of IMRT for PC. An example search strategy for MEDLINE is shown in Appendix 8. A total of 587 studies were identified. Of these, three report a cost–utility analysis[78,113,114] and two report costs of IMRT compared with 3DCRT.[77,115] A further search for grey literature in the CRD databases (DARE, NHS EED and HTA) identified 15 records. One study[64] had a full report available in the English language and had relevant economic content. Pearson *et al.* is a review of IMRT for PC including a cost–utility study comparing IMRT with 3DCRT.[64]

Cost–utility studies

The results of the four cost–utility studies are summarised in *Table 19*. Of the three Konski studies,[64,78,114] the latest[78] is the most complete report so this was used for the quality assessment (see Appendix 7). It appears that the same model was used for all studies, although the first report (2004)[113] is an abstract only, so it is not clear. The varying results reported in the different Konski studies may be principally due to the differing time horizons of the models. The 2006 study[78] reports the incremental cost-effectiveness ratio (ICER) varying from US$57,794 at 5 years to US$28,132 at 15 years.[78] A limitation of the Konski studies are that key parameters (such as disease progression and utility values for patients following RT) are not based on a review of the literature. Data are taken from different studies for IMRT and 3DCRT, so their comparability is questionable. Utility values were taken from studies which used different methods of measurement. Reasons for the choice of data sources were not explained.

Pearson *et al.*[64] reports a very different ICER (US$706,000) to Konski *et al.* (US$40,100)[78] for IMRT compared with 3DCRT. The unit treatment costs in Pearson *et al.*[64] are based on the resource use items used by Konski *et al*. The key difference between the ICER estimates lies in different assumptions regarding the effectiveness of IMRT compared with 3DCRT. After reviewing the evidence, Pearson *et al.* concluded that there was no evidence of difference in progression-free survival or survival. The difference in quality-adjusted life-years (QALYs) in the model arises solely from a difference in rectal toxicity, with a median duration of 1 year.[64] Konski *et al*., however, based on one case series for each of IMRT and 3DCRT, assumes a 14% difference in progression-free survival between the two treatments at 5 years, and also a relatively large difference in utility following the two treatments (0.09), which endures until patients progress. Actual differences in toxic effects are not considered. This compares with the difference in utility between those with best and worst urinary and bowel function of 0.1 reported by Shimizu *et al.*[116] (see Utility values). Thus the difference in utility post-IMRT and 3DCRT used by Konski *et al.* is tantamount to assuming no IMRT patients and all 3DCRT patients suffer from late toxic GI effects until disease progression, i.e. for several years. Although data is limited, the results of Zelefsky *et al.*[91] suggests that, for the majority of men, such effects are limited to 2–3 years. Thus there appears to be bias in the assumptions made by Konski, favouring IMRT.[78]

The Pearson *et al.* model is clearly limited as it only considers adverse effects of RT, and not survival.[64] As well as the previously discussed data limitations of the Konski *et al.*[78] model, the assumption that PSA failure is synonymous with the start of hormone treatment is likely to lead to the costs of PSA failure being exaggerated in a UK setting, where hormone therapy is normally commenced only after symptomatic disease progression, proven metastases or a PSA doubling time of less than 3 months.[1] The Konski *et al.*[78] model also does not explicitly include the costs and effects on HRQoL of toxic effects of treatment. A new economic model was therefore developed, as described in Methods. The modelled disease states are the same as those used by Konski *et al*.,[78] but with the addition of a state for PSA failure (prior to hormone therapy) and also late toxic effects.

TABLE 19 *Cost-effectiveness studies of IMRT compared with 3DCRT*

Study	Patient group	Time horizon (years)	Cost year	IMRT cost US$(£)[a]	3DCRT cost US$(£)[a]	IMRT QALYs	3DCRT QALYs	ICER US$(£)[a]
Konski *et al.* 2004[113]	Age 70 years, intermediate risk	15	Not reported	$52,170 (£32,606)	$27,357 (£17,098)	7.62	6.65	$25,580 (£15,988)
Konski *et al.* 2005[114]	Age 70 years, intermediate risk	10	2004	$33,837 (£21,148)	$21,377 (£13,361)	6.29	5.52	$16,182 (£10,114)
Konski *et al.* 2006[78]	Age 70 years, intermediate risk	NR	2004	$47,931 (£29,957)	$21,865 (£13,666)	6.27	5.52	$40,101 (£25,063)
Pearson *et al.* 2007[64]	Age 69 years, low to intermediate risk (Stage T1/2, PSA ≤ 20, any Gleason)	Lifetime	2005	$42,450[b] (£26,531)	$10,900[b] (£6813)	NR	NR	$706,000 (£441,000)

NR, not reported.
a Assuming an exchange rate of US$1.6 to £1.
b Costs of treatment only.

Cost studies

Remonnay *et al.*[115] and Marchal *et al.*[77] report costs of IMRT in a prospective comparative (non-randomised) study of the costs of IMRT and 3DCRT in France. The data from Remonnay *et al.* is likely to be a subset of that used in the analysis of Marchal *et al.*, is reported in abstract only, and is not specific to PC. In both studies the time taken by medical personnel (physicists, physicians, dosimetrists and radiotherapists) to give either IMRT or 3DCRT to patients with PC or head and neck cancer is reported. Capital and maintenance costs for equipment were also included. Remonnay *et al.* only reports the difference in cost between IMRT and 3DCRT, which was €1780, assuming 30 patients a year, or €1172 if 60 patients are treated per year (2002–3).

Marchal *et al.* reports an average cost of €2357 per patient for 3DCRT for PC, compared to €4911 for IMRT, a difference of €2554 (2002). Although an additional 335 minutes of staff time was required on average for IMRT, mainly for preparation and quality control, this costs only an additional €36. The additional time relates to routine use of IMRT, after a run-in period. The total number of patients treated with IMRT was 86, of which 48 had PC. The number of patients in the training and routine phase are not specified. The greatest difference in cost arose from equipment and maintenance costs, which were an additional €2706 per patient, assuming 30 patients are treated per year (note this is greater than the overall difference in costs as there was a small cost saving for IMRT in the use of consumables).[77]

Independent economic assessment

Methods

Model structure

A discrete event simulation model was developed in SIMUL8® for patients undergoing radical treatment for PC with either IMRT or 3DCRT. There were no data to model other patient groups. All studies that reported clinical effectiveness did so in terms of PSA failure. The PSA failure hazard was not constant with time (i.e. not exponentially distributed), and the literature indicated that the hazards of clinical failure or death from the time of PSA failure is also not necessarily constant with time, which would make a Markov model formulation complex.

In a discrete event simulation individual patients are followed, with the time of events (such as transition to another state) sampled from a relevant statistical distribution. The simulation time-clock moves immediately to the time of the next event. This contrasts with a state transition model that uses fixed time cycles which is less efficient in periods of no state change, and requires numerous states when patient history affects future transition rates. The time to PSA failure was sampled for each patient and compared

with the expected time of all-cause death, taken from life tables. If the expected time of death from other causes was less than the time to PSA failure, then the patient died from other causes, without experiencing PSA progression. Similarly time to clinical progression and PC death are sampled and compared to time to death from other causes, to determine whether the patient dies of other causes or progresses through to more advanced PC disease states. Note the distributions from time from PSA failure to clinical failure and time from PSA failure to PC death were sampled independently, so there is a possibility of patients dying of PC without incurring the costs associated with the more advanced disease states, but they do incur terminal care costs. Distributions for the incidence and timing of late adverse events following RT were also sampled. The model has a lifetime perspective.

Ten thousand individual patients were simulated for each model run. This number was chosen as the mean results had clearly stabilised with this number of patients.

The model structure is shown in *Figure 3*.

Patients with localised PC enter the model at the time of treatment (IMRT or 3DCRT). At some time later they may experience PSA failure, then clinical failure and death from PC. Due to the distributions for time from PSA failure to clinical failure and PSA failure and PC death some patients may progress directly from PSA failure to PC death. Death from other causes and late AEs of treatment may occur in any state (with the obvious exception of death). A fixed loss in QALYs is attributed to a patient suffering a late AE at the time that the AE occurs. Acute toxicity is not included, as being by definition of short duration, it has a negligible effect on QALYs, especially as the difference in rates of grade 2 or more adverse effects between IMRT and 3D are small (see Chapter 3, Toxicity).

It is assumed that patients with clinical failure are on hormone therapy and hormone-refractory patients have a course of chemotherapy, as well as palliative care.

Model outputs:
The primary model outputs are:

- total costs for each treatment (IMRT/3DCRT)
- total QALYs for each treatment (IMRT/3DCRT).

From the above the ICERs were calculated for each scenario.

Other model outputs include the proportion of patients who progress to each PC disease state and death from other causes. The perspective of the analysis is England and Wales 2008–9.

Model scenarios

The rationale for IMRT is that higher doses of RT may be given, with the intention of improving PSA survival (and hence disease-specific survival), while limiting additional radiation toxicity to organs close to the prostate. Ideally different scenarios would be modelled with varying doses of IMRT and 3DCRT to investigate the relationship between survival, late toxic effects of RT and treatment costs.

The clinical studies included in the review varied as to whether the IMRT and 3DCRT cohorts received similar total doses of radiation, or

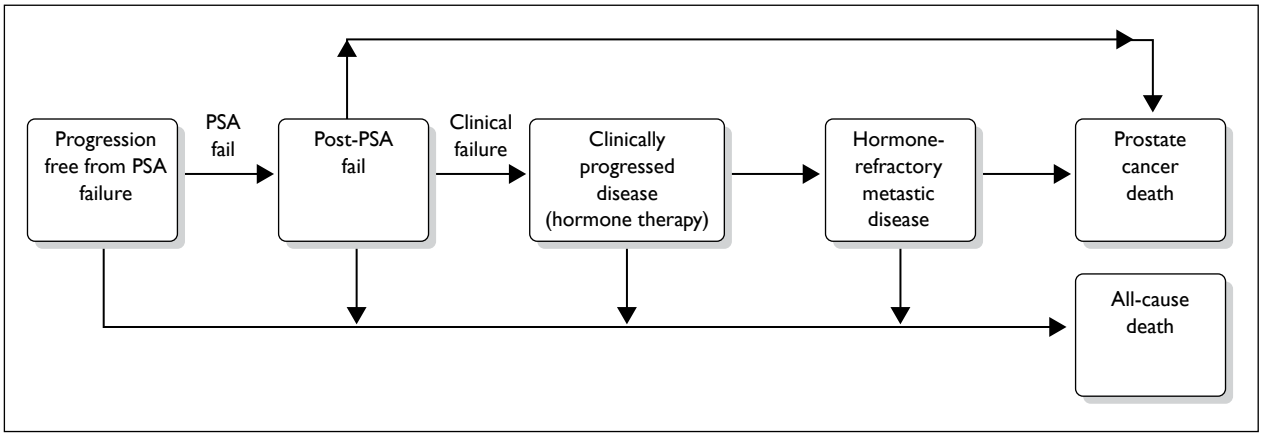

FIGURE 3 *Diagram of model structure.*

whether the dose in the IMRT cohort was higher. In some studies 3DCRT was given at relatively high total doses (≥ 80 Gy).[29,107,110] However, there is considerable heterogeneity between studies in patient disease states, adjuvant hormone therapy and RT techniques. Appendix 9 shows for the included studies a summary of PSA survival and toxicity for IMRT and 3DCRT ordered by RT dose. It can be seen that the results are too heterogeneous for dose effects to be apparent. Thus the studies are too heterogenous both for meta-analysis and to attempt to identify variation in effects by dose.

There is evidence from RCTs of dose escalation for 3DCRT that show that PSA survival improves with increasing dose.[59–62] A recent meta-regression shows the relationship to be linear across a range of doses between 64 Gy and 79.2 Gy, with a 1.8% increase in biochemical control at 5 years for each 1 Gy increase in total RT dose.[65] The results of these studies are relevant to IMRT. There is also evidence from 3DCRT studies of variation in toxicity with increasing dose. An RCT of dose escalation of 3DCRT from 64 Gy to 74 Gy showed an increase in late grade 2+ GI toxicity of 9% at 5 years.[62] The results of a meta-regression of cohort studies show that the incidence of late GI toxicity of grade 2 or more increases by 12% to 16% when the RT dose is increased from 70 Gy to 80 Gy.[117] However, the toxicity results of the 3DCRT studies are not applicable to IMRT as IMRT allows the radiation to be sculpted to the target area of the PC more precisely than 3DCRT, thus reducing toxicity to the surrounding normal tissues at similar doses. Thus there is no data on the effects of dose escalation on adverse effects for IMRT.

The effect of dose escalation on late GI toxicity for IMRT might be ascertained indirectly using the results of an analysis of the correlation of rectal toxicity with the volume of the rectum receiving different RT doses.[118] For example, for every 5% increase in rectal volume receiving 30 Gy the odds ratio of grade 2 rectal bleeding was 1.14 ($p = 0.006$), and for every 5% increase in dose of 70 Gy the similar odds ratio was 1.41 ($p = 0.001$). To use these results to compare toxic effects between IMRT and 3DCRT or for dose escalation of IMRT would require a review of dosimetric studies, which is beyond the scope of this review.

Given the limitations described it was deemed most appropriate to treat each study as a different scenario. Only three included studies reported PSA survival,[84,89,107] of which one is reported in abstract only.[107] Patients in all of these studies had localised PC and were treated with radiation to the prostate and seminal vesicles (SVs) only. In two studies where similar radiation doses were given to IMRT and 3DCRT patients there was no statistically significant difference in PSA survival,[84,107] although Kupelian *et al.*[85] did report an absolute difference of 7% at 5 years. In both studies relatively high doses of RT were given. Note that although the 3DCRT patients in the Kupelian *et al.*[84,85] study received 78 Gy compared to 70 Gy for IMRT the doses are considered *biologically* equivalent as the IMRT was given in fractions of 2.5 Gy (hypofractionated) compared to the more usual schedule of 2 Gy fractions for 3DCRT. In comparison to the total doses reported by other studies both arms in Kupelian *et al.*[84,85] may be considered to have received RT doses equivalent to 78 Gy. See Appendix 10 for details of the estimation of biologically equivalent doses. Morgan *et al.* reports a median dose of 80 Gy and 81 Gy for 3DCRT and IMRT respectively.[107]

The model scenarios are thus as follows:

1. Morgan *et al.*[107] IMRT and 3D high dose (80/81 Gy) – no PSA survival difference.
2. Kupelian *et al.*[84,85] IMRT and 3D high dose (78 Gy) – no PSA survival difference.
3. Kupelian *et al.*[85] IMRT and 3D high dose (78 Gy) – PSA survival difference as reported.
4. Vora *et al.*[89] IMRT 75.6 Gy, 3DCRT 68 Gy – PSA survival difference.

Note the total RT dose given to 3DCRT patients in the Vora *et al.*[89] study is low compared to the current NICE guideline recommendation of at least 74 Gy. The scenario will illustrate however how cost-effective IMRT may be in comparison to 3DCRT if higher doses may be given with IMRT than for 3DCRT.

A baseline age of 70 years is used, the approximate age at which PC incidence peaks. A sensitivity analysis was run on each of the four scenarios with age at 60 and 80 years,

Model distributions

Disease progression: overview

None of the studies included in the clinical effectiveness review report time to progression to the clinical outcomes of clinical progression or PC death. They do, however, report time to PSA failure. In order to estimate the effect of IMRT on clinical outcomes it is therefore necessary to estimate the time from PSA failure to clinical

disease occurrence and also to PC death. Death from other causes also needs to be considered. Thus the disease progression model requires three distributions:

- [A] time from treatment (IMRT/3DCRT) to PSA failure
- [B] time from PSA failure to clinical failure
- [C] time from PSA failure to PC death.

The method used to estimate these distributions are described in the following paragraphs.

A Effectiveness of IMRT and 3DCRT: time from treatment (IMRT/3DCRT) to PSA failure

Three studies included in the effectiveness review report time to PSA failure, all showing either a survival or time to failure curve.[84,89,107] The published graphs were scanned and imported into TECHDIG software so that points could be read more efficiently and accurately off the curves. Weibull distributions were then fitted to the data points obtained. Particular issues in fitting curves to the data are discussed for each of the studies below. The two-parameter Weibull distribution was used with shape parameter γ, and scale parameter λ.The form used is shown below, and the Weibull parameters used and resulting mean PSA survival are shown in *Table 20*.

The survivor function is:

$$S(t) = \exp(-\lambda t^{\gamma})$$

The mean of a Weibull (γ,λ) distribution is:

$$\left(\frac{1}{\lambda}\right)^{1/\gamma} \Gamma\left(1+\frac{1}{\gamma}\right)$$

where Γ(*x*) is the gamma function.

***Morgan* et al.[107]**

The Morgan *et al.* study is reported in abstract only, but a small figure was published showing actuarial time to PSA failure. At 4 years there was only 1% difference in failure rates between the IMRT and 3DCRT cohorts, which was statistically non-significant. The two failure curves cross, and are in effect indistinguishable from each other. Points were read from both lines and the results averaged at each time point to give a single curve for both IMRT and 3DCRT. The resulting survival curve is shown in *Figure 4*, together with the fitted Weibull curve.

***Kupelian* et al.[84,85]**

The length of follow-up in the Kupelian *et al.*[84] study is relatively short: median 21 and 32 months respectively for IMRT and 3DCRT. The number of patients with PSA failure was small in both cohorts, so the PSA survival curves are relatively flat. Curves fitted to this data reflected this, and gave implausibly long mean survival. Some PSA survival curves in other studies, for example Vora *et al.*[89] (see below) are also relatively flat (low rate of PSA failure) in the first few months, with the rate of failure increasing with time, suggesting that the length of follow-up in the Kupelian *et al.*[84] study is insufficiently long to base projections beyond the

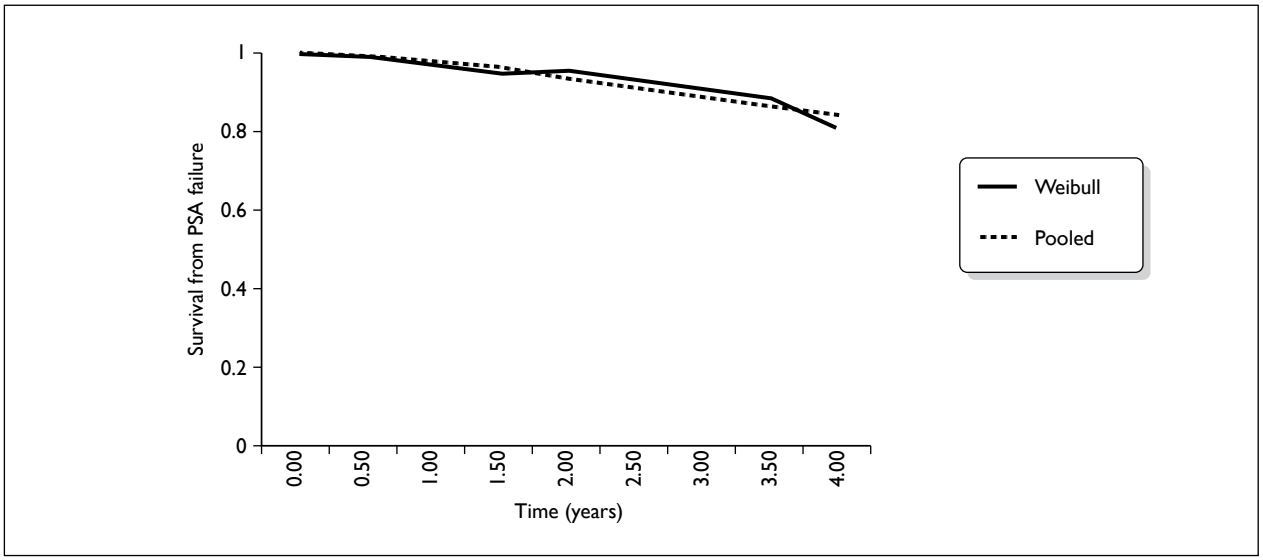

FIGURE 4 *Actual and fitted PSA survival curves: data from Morgan* et al.[107] *IMRT/3DCRT.*

duration of the study. A later publication[85] shows more mature data, albeit for a smaller cohort, but only shows a PSA survival curve for the IMRT group. The study reports an absolute difference in PSA survival of 7% at 5 years, but this was not statistically significant. The IMRT PSA survival curve was used for both 3DCRT and IMRT in the scenario which assumes no difference in PSA survival between the two treatment methods (*Figure 5*).

A second scenario was modelled to reflect the difference in survival reported in the study, although it was statistically non-significant. For this scenario the Weibull 3DCRT shape parameter was assumed to be the same as for the IMRT curve, with the scale parameter adjusted to reflect the proportional difference in survival (85% IMRT, 78% 3DCRT) reported by Kupelian *et al.*[85] [i.e. (78/85)×(shape parameter IMRT)].

Vora* et al.*[89]

The Weibull curves were fitted from 20 months onwards for both IMRT and 3DCRT curves to give a better fit to the later data, as the plot of ln(−ln(survival)) with ln(time) was not linear in the first few months. The plots of the original data and

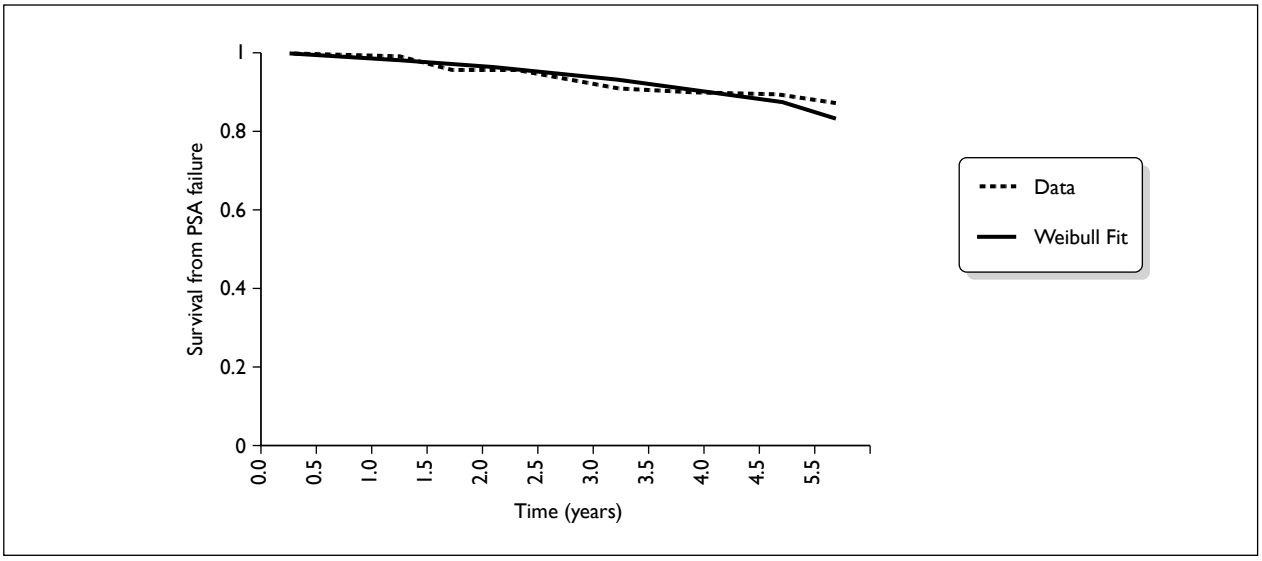

FIGURE 5 *Actual and fitted PSA survival curves: data from Kupelian* et al.[85] *IMRT.*

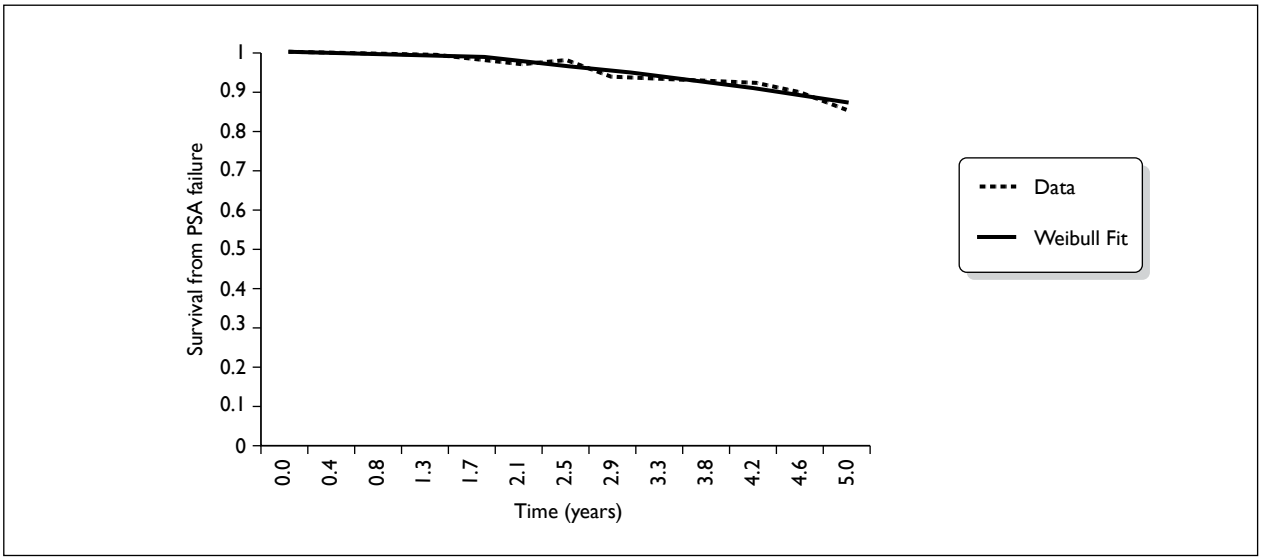

FIGURE 6 *Actual and fitted PSA survival curves: data from Vora* et al.[89] *IMRT.*

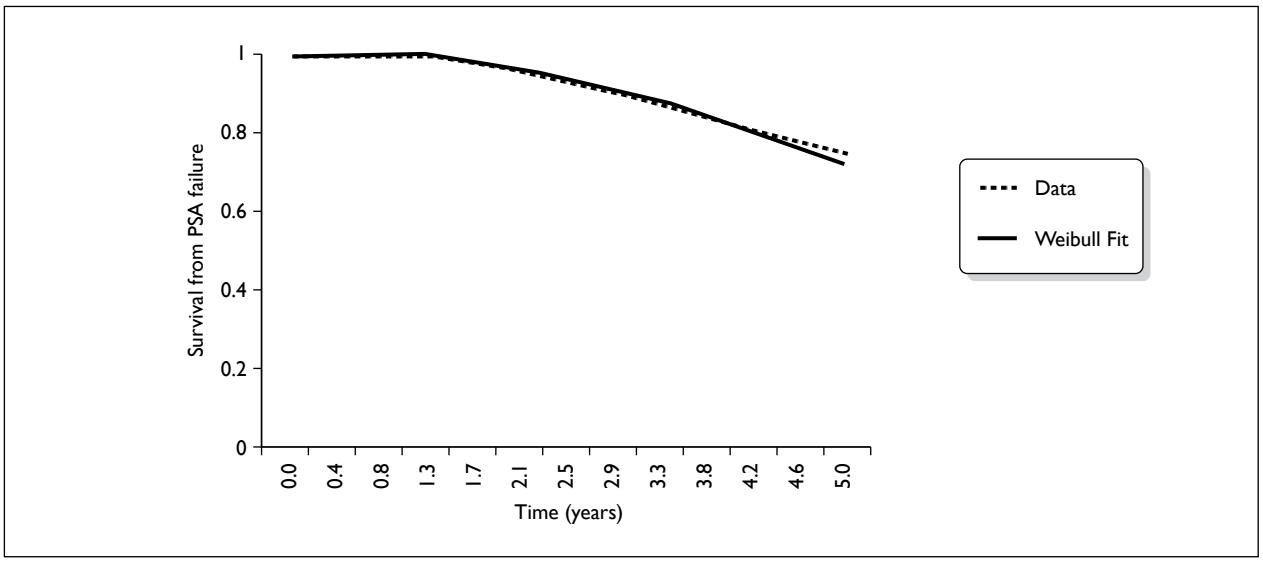

FIGURE 7 *Actual and fitted PSA survival curves: data from Vora* et al.*[89] 3DCRT.*

TABLE 20 *Summary of Weibull parameters and estimated mean survival for different scenarios*

Study	Group	Scale	Shape	Mean survival to PSA fail (years)
Vora *et al.* 2007[89]	IMRT	0.0082	1.755	13.7
	3DCRT	0.0064	2.437	7.1
Kupelian *et al.* 2002/2005[84,85]	IMRT	0.0171	1.370	17.8
	3DCRT	0.0239	1.370	14.0
Morgan *et al.* 2007[107]	IMRT/3DCRT	0.0227	1.463	12.0

fitted curves are shown in *Figures 6* and *7* for IMRT and 3DCRT respectively.

B/C Time from PSA failure to clinical failure/prostate cancer death

In 2005 a Consensus conference, jointly sponsored by ASTRO and RTOG, was held to consider evidence for a revised definition of PSA failure. At the conference several researchers presented data showing the association between varying definitions of PSA failure and clinical outcomes. This evidence is summarised in a paper by Roach *et al.*[45] As well as potentially relevant references in Roach *et al.* a MEDLINE search was undertaken on the names of the researchers named in the Roach *et al.* study. By this means one study by Kestin *et al.*[119] was identified which showed survival data from PSA failure to clinical failure and PC death, using relevant definitions of PSA failure. Relevant definitions were defined as either the ASTRO consensus or Phoenix definitions, or other definitions from which outcomes could be inferred for these.

Kestin *et al.*[119] explored the association of various biochemical failure definitions with clinical outcomes, including clinical failure and PC death. The analysis is based on 727 men at a single institution in the USA with clinically localised (T1–T3, N0, M0) PC treated with radical external-beam RT alone (no hormone therapy prior to clinical failure) between 1987 and 1997, and with at least five post-RT PSA measurements. Thus the data is a good match to the population being considered in the model, although the dates of the collection period might lead to slight underestimation of current PC survival as more recent treatments for advanced PC such as docetaxel chemotherapy would be expected to affect this.[120]

Summary results relevant to the model are shown in *Table 21*. It can be seen that the actual results

required (rates of clinical failure and PC death with time) are not reported for the ASTRO Phoenix definition of PSA failure (a rise ≥2 ng/ml above nadir PSA). However, they are reported for similar definitions: a rise of ≥1ng/ml above nadir PSA and a rise of ≥3ng/ml above nadir PSA.

The rates of clinical failure and PC death at 10 years after RT for all three definitions (a rise ≥1, 2 or 3 ng/ml above nadir PSA) are shown in *Table 22*. It appears that the relationship is linear, with the results for a rise ≥2 ng/ml above nadir PSA midway between those for 1 and 3 ng/ml. It therefore is reasonable to assume that the rate of clinical failure or PC death can be estimated as the mid-points for those for 1 and 3 ng/ml. These estimated values are shown in *Table 21*.

Weibull curves were fitted to these data points. The data and fitted curves for clinical survival and PC death from the time of PSA failure (ASTRO Phoenix) are shown in *Figures 8* and *9* respectively.

The fitted Weibull curves result in mean estimated time from PSA failure to clinical failure and PC death of 3.1 and 7.8 years respectively.

It was originally anticipated that clinical outcomes following PSA failure as defined by both ASTRO consensus and Phoenix PSA definitions would be required as Kupelian *et al.*[84] reported PSA fail with the former definition. In fact, the results of Kupelian *et al.*[84] proved to be unusable as the data was insufficiently mature, and those of Kupelian *et al.*[85] were used in their place, which were reported using the ASTRO Phoenix definition. This had the advantage that all scenarios are equivalent in this respect.

Other clinical parameters

These include duration of hormone-refractory disease, time to all-cause death and adverse effects of treatment.

Duration of hormone-refractory disease

It is assumed that the time with hormone-refractory disease is independent of the time from clinical failure to death from PC. The time in this state was taken from a review of the treatment of hormone-refractory metastatic PC with docetaxel.[120] Median survival from the TAX327 trial was 18.9 months. By fitting a Weibull distribution to the data Collins *et al*. estimated the mean survival time to be 22.4 months or 1.9 years.[120] Thus in the model it is assumed that a patient has hormone-refractory metastatic PC for the final 22 months prior to PC death.

Time from treatment to all-cause death

Mean survival death from all causes for the different age scenarios modelled was taken from UK National Statistics.[121] It was assumed that all patients survived to this time unless they had previously died from PC.

Adverse effects of treatment

The only adverse effect of treatment operationalised in the model is late GI toxicity.

TABLE 21 *Rates of clinical failure and PC death after biochemical failure (from date of failure)*

	Rates of clinical failure (%) with time (years)			Rates of PC death (%) with time (years)		
Definition **Years**	**0.5**	**2**	**5**	**0.5**	**2**	**5**
Rise of ≥ 1 ng/ml above nadir PSA	11	31	70	0.3	4	24
Rise of ≥ 3 ng/ml above nadir PSA	23	54	96	1.1	9	38
Estimated ASTRO Phoenix (rise of ≥ 2ng/ml above nadir PSA) – see text	17	43	83	0.7	6.5	31

TABLE 22 *Ten-year clinical failure and PC death from time of RT for various definitions of PSA failure*

Definition	Clinical failure (%)	PC death (%)
Rise of ≥ 1 ng/ml above nadir PSA	64	40
Rise of ≥ 2 ng/ml above nadir PSA (ASTRO Phoenix)	73	45
Rise of ≥ 3 ng/ml above nadir PSA	82	50

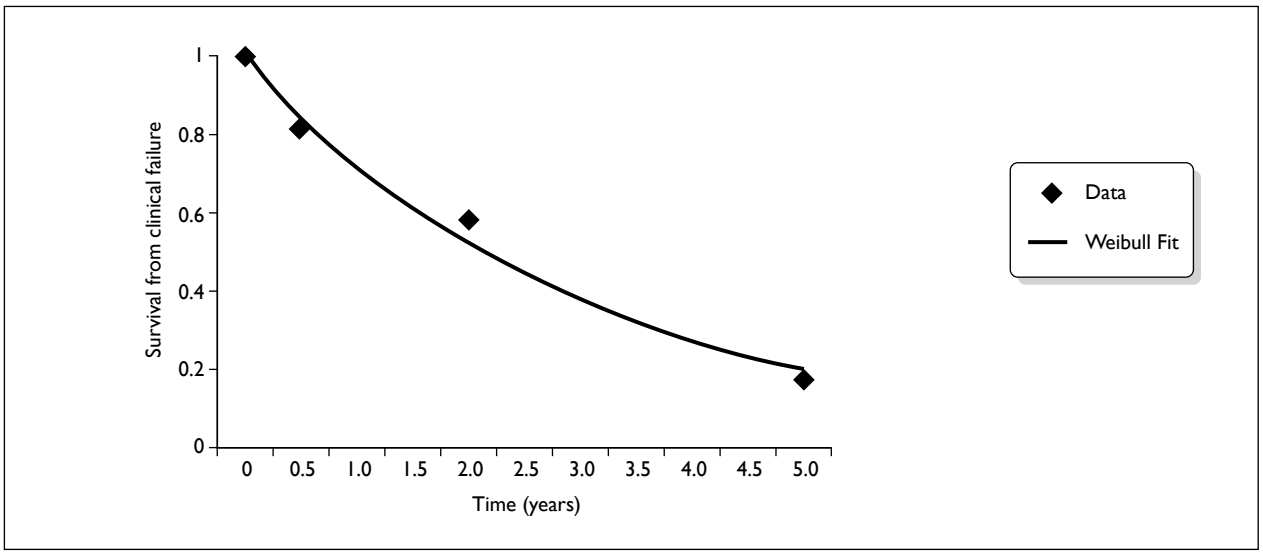

FIGURE 8 *Clinical survival from the time of PSA failure (ASTRO Phoenix).*

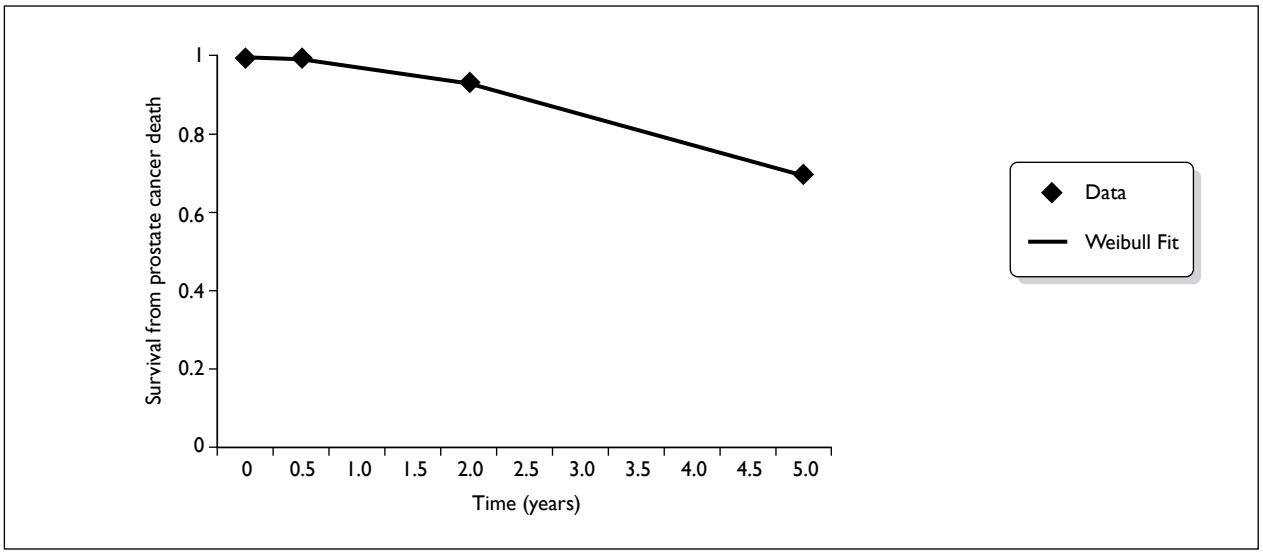

FIGURE 9 *PC survival from the time of PSA failure (ASTRO Phoenix).*

Most studies did not find a difference in GU toxicity between IMRT and 3DCRT (see Toxicity). None of the included studies report changes in sexual function following RT, and therefore it is unknown if there is any difference between the treatment modes.

Studies which showed actuarial curves for late GI toxicity indicate that incident cases with time could be approximated by a straight line, starting at 6 months after RT, and plateauing (no further incident cases) by 5 years. The data used in the model are derived from the clinical effectiveness studies, and the values shown in *Table 23*. Only grade 2 and 3 effects are considered. Grade 1 effects were seldom reported in the clinical effectiveness studies (see *Tables 15, 17*) as they are of limited clinical significance, and thus unlikely to have important economic consequences either.

Note that Kupelian *et al.*[85] only reports adverse effects of treatment for IMRT patients. In order to estimate their incidence for 3DCRT at 5 years the ratio of late GI toxicity for IMRT at 5 years[85] to that at 2.5 years[84] was applied to that for 3DCRT at 2.5 years.[84]

TABLE 23 *Incidence of late GI toxicity with time in modelled studies*

Study	Start of late GI toxic effects (years)		Finish time at which no further incidence of late GI toxic effects		Proportion of patients affected		Comment
	IMRT	3D	IMRT	3D	IMRT	3D	
Vora *et al.* 2007[89]	0.5	0.5	5	5	0.24	0.16	Not actuarial
Kupelian *et al.* 2002/2005[84,85]	0.5	0.5	5	5	0.11	0.264	Estimated – see text
Morgan *et al.* 2007[107]	0.5	0.5	3.5	3.5	0.04	0.09	

Note it has been assumed that the two different AE reporting systems (RTOG, NCI-CTC) are equivalent for GI incidence.

Duration of gastrointestinal toxicity

Only one included clinical effectiveness study[91] reports the duration for GU and GI toxicity. For GI it is reported that 91% of cases were resolved, with a median time to resolution of 26 months. An estimate was made of the lower bound of mean duration assuming:

- 91% of patients have a mean duration of 26 months
- the remaining 9% unresolved have a mean duration estimated as the difference in median follow-up time and median time to incidence, giving 79 months (median time to development 17 months and median follow-up 96 months – difference 79 months).

This results in an overall estimate of 2.6 months. As this is likely to be an underestimate, with some patients' symptoms unresolved at the end of follow-up, the number was rounded up to 36 months (3 years). Evidence from a 3DCRT dose escalation trial also shows a proportion of patients whose late GI toxicity symptoms take several months to resolve.[62] The RT01 trial showed prevalence of late GI toxicity peaking at 18 months after RT, then declining, with prevalence at 5 years approximately 30–40% of the peak value (estimated from curve). Sensitivity analysis of the duration of late toxicity was undertaken, with values of 2.5 and 4 years.

Utility values

For cost-effectiveness analysis the value of health effects are measured in terms of QALYs. QALYs are calculated by weighting life-years with utility values, to reflect patients' HRQoL. There are different methods of determining utility values. The recommended tool for use in the NICE methods guide is the European Quality of Life-5 Dimensions (EQ-5D),[122] a measure based on public preferences.

In order to identify utility values for the patient states in the model a systematic search of the following databases was undertaken: MEDLINE, EMBASE, CDSR, DARE, CCTR, HTA and NHS EED. An example search strategy is shown in Appendix 11.

A total of 101 unique references were identified. Of these 40 were selected on title and abstract for potential inclusion as reporting utility values (ascertained by any method). An iterative method of study selection was planned to identify the best evidence on utility values:

1. values obtained using the EQ-5D
2. values obtained using other public preference-based weights of patient HRQoL scores (e.g. the Health Utilities Index)
3. other studies.

Four studies report EQ-5D utilities for PC.[116,123–125] Of these, two report utilities for states relevant to the model.[116,125] The results of Korfage *et al.* are of interest only in terms of a global comparison as utility values are reported for all patients who had primary treatment of RT.[123] Pickard *et al.* was excluded as only a single utility value for PC patients of undefined disease status is reported.[124] As EQ-5D utility values were identified for all model states, utility studies using alternative measurement methods were not considered.

The key characteristics of the three studies reporting relevant EQ-5D PC utilities are shown in *Table 24*, and their results in *Table 25*.

It is assumed that following RT for localised PC men not suffering adverse effects of treatment

TABLE 24 *Studies reporting EQ-5D utility values for prostate cancer*

Study	Country	Subjects	Mean age (years)	*n*
Korfage *et al.* 2005[123]	The Netherlands	Localised PC RT (or radical prostatectomy), prior to treatment and to 52 months post-treatment	RT patients 68	RT 187
Shimizu *et al.* 2008[116]	Japan	Patients receiving RP, RT, brachytherapy, WW, or combination for localised PC, and patients with hormone-refractory PC	NR	323
Sullivan *et al.* 2007[125]	Europe, North America and Australia	Symptomatic metastatic cancer	72	280

NR, not reported; RP, radical prostatectomy; WW, watchful waiting

TABLE 25 *Summary results of EQ-5D studies*

Study	Patient group	Utility score	Comments
Korfage *et al.* 2005[123]	RT		Decrease with age was probably the result of ageing
	Pre-treatment	0.81	
	After 6 months	0.83	
	After 12 months	0.82	
	After 52 months	0.76	
Shimizu *et al.* 2008[116]	Sexual function: EPIC score		Apparently some double measurement of urinary symptoms, although both measures (urinary function, LUTS) significant in multivariate analysis of predictors of score, as was bowel and hormone function. Sexual function not significant
	16–85 (best)	0.93	
	0 (worst)	0.90	
	Urinary function: EPIC score		
	100 (best)	0.94	
	11–74 (worst)	0.84	
	Bowel problem: EPIC score		
	100 (best)	0.94	
	0–80 (worst)	0.84	
	Hormonal function: EPIC score		
	100 (best)	0.93	
	35–80 (worst)	0.84	
	LUTS: IPSS		
	EPIC score		
	0–7 (best)	0.93	
	20–35 (worst)	0.83	
Sullivan *et al.* 2007[125]	Symptomatic metastatic hormone-refractory cancer	0.635	

have the same mean utility as similarly aged men. Ara and Brazier show how utility values vary with age in UK adults.[126] For men aged 60, 70 and 80 years their mean utility was 0.850, 0.813 and 0.771 respectively. These values were used for the baseline utility values in the first year of the model for the different age scenarios. These values were also assumed to apply to patients who had PSA failure, but not clinical progression. The baseline utility values for men were assumed to decline with age as the men progress through time in the model according to the Ara and Brazier formula.[126]

The utility values reported by Shimizu *et al.*[116] (see *Table 25*) are higher in general than those reported by Ara and Brazier,[126] even for men suffering adverse effects of RT. They may be from a younger population of PC patients (age not reported), and they are not UK values. In order to estimate the utility of men suffering adverse effects of treatment in a UK population the ratio of utility values for full function and poor function was applied to the unaffected[126] utility value. This resulting utility values for men aged 70 years are shown in *Table 26*.

For example, for men who progress to clinical failure, who are assumed to be on hormone treatment, their utility is calculated as the ratio of utility score worst hormone function to utility score best hormone function (from Shimizu *et al.*[116]), applied to the Ara and Brazier[126] age-related utility. Thus for a man aged 70 years with clinical failure their utility is $(0.84/0.93) \times 0.813 = 0.734$.

Similarly an adjustment to age-related utility was calculated for hormone-refractory cancer from the utility value reported by Sullivan *et al.*[125] for men of mean aged 72 years as a ratio of the mean utility for men aged 72 years which is 0.805.[126]

Resource use/costs

All unit costs used, together with their source, are shown in Appendix 12. Most costs were sourced from *NHS reference costs 2007–8*,[51] Unit costs of health and social care[127] and the *British National Formulary*.[128] Where costs were not 2008–9 they were inflated by the Hospital and Community Health Sector (HCHS) inflation index.[127]

Cost of IMRT/3DCRT

The costs reported in Description of technology under assessment, show an additional cost of £1122 for IMRT compared to 3DCRT. As the objective of the analysis is to determine incremental cost-effectiveness it is sufficient to assume zero cost for 3DCRT and £1122 for IMRT.

Monitoring of patients post-RT (pre-PSA fail)

Initial monitoring of patients for the acute effects of RT is assumed the same for both IMRT and 3DCRT and is included in the costs of treatment shown in *Table 8*. The NICE guideline[1] indicates that patients should have two PSA tests a year for the first 2 years following RT. These normally take place at the oncology centre. It is assumed that this cost is the same for both IMRT and 3DCRT patients as very few patients progress in this time, and is therefore not included in the model.

There is some variation in practice in subsequent monitoring. Some patients may continue to be monitored by an oncology centre up to twice a year. The costs shown below, and used in the model, are based on the recommendation in the NICE guideline that after the first 2 years patients may be monitored by their GP, with one PSA test per year.[1] The costs are shown in *Table 27*.

Monitoring of patients post-PSA failure

It is assumed that these patients are monitored as hospital outpatients, with the cost of the PSA tests absorbed into the cost of the outpatient

TABLE 26 *Utility values used in the model, men aged 70 years*

State	Utility value	Source
Post-RT, no AE	0.813	Ara and Brazier[126]
Post-RT, GI toxicity (bowel problem)	0.727	Ara and Brazier,[126] Shimizu *et al.*[116] (see text)
Clinical failure (on hormone treatment)	0.734	Ara and Brazier,[126] Shimizu *et al.*[116] (see text)
Hormone-refractory cancer	0.641	Ara and Brazier,[126] Sullivan *et al.*[125] (see text)

TABLE 27 *Annual cost of patient monitoring from 2 years post-RT*

Item	Cost 2008–9	Number/year	Annual cost
PSA test	£10.19	1	£10.19
GP attendance	£36.97	1	£36.97
Total	–	–	**£47.16**

consultations. They have a CT scan and bone scan every 2 years. The costs are shown in *Table 28*.

Monitoring of patients post-clinical failure

It is assumed that these patients are on hormone therapy. While patients may go through a sequence of different hormone treatment strategies it has been assumed for simplicity that these patients are treated with the gonadorelin analogue goserelin, by injection every 3 months. The annual resources and costs for treating patients on hormone therapy are shown in *Table 29*.

Hormone refractory/metastatic

The costs of treatment of hormone-refractory metastatic cancer are taken from an analysis of the cost-effectiveness of docetaxel chemotherapy in these patients in comparison to other therapies.[120] Docetaxel with prednisolone is the only chemotherapy regime licensed for use in hormone-refractory PC.[129] While not all men will receive chemotherapy, the majority do, and the costs are likely to be a reasonable representation of the costs of care in the final months of life.

In the economic analysis by Collins *et al.*,[120] as well as the costs of chemotherapy costs of palliative and terminal care were included, all based on resource use in the TAX327 trial. The total cost of care in 2003–4 (with mean survival 1.9 years) was £15,833, including a cost for terminal care of £3528. These costs, inflated by the HCHS inflation index[127] to 2008–9 costs, gives an annual cost of care of £7385 and a terminal care cost of £4007. The latter is implemented in the model at PC death.

Cost of treating late gastrointestinal toxicity

It has been assumed that all patients with grade 2 and 3 toxicities will be monitored in a hospital outpatient setting, with the frequency depending on severity (see *Table 30*). There is no standard treatment for late GI toxicity. Most are likely to be investigated with flexible sigmoidoscopy, and possibly biopsy. The majority will be treated with low-cost items such as laxatives, the cost of which have not been considered. Some patients with more severe cases may need procedures such as laser treatment.

The average monitoring and treatment costs for the treatment of all late GI toxic effects has been calculated by estimating the proportion of patients with grade 3 toxic effects. *Table 31* shows the data available from the included studies. The weighted proportion of grade 3 toxic effects of all grade 2 and 3 effects is 26%, as shown in *Table 31*.

All costs and QALYs are discounted at 3.5% per year.[122]

Sensitivity analysis

A key parameter in the analysis is the cost difference between IMRT and 3DCRT. The costs were obtained from a single institution only, and therefore subject to some uncertainty as to their

TABLE 28 *Annual cost of patient monitoring patients who have experienced PSA failure*

Item	Cost 2008–9	Number/year	Annual cost
Oncology outpatient	£88.33	6	£529.96
CT scan (one area)	£112.98	0.5	£56.49
Bone scan	£168.44	0.5	£84.22
Total			**£670.67**

TABLE 29 *Treatment costs for patients on hormone therapy*

Item	Cost 2008–9	Number/year	Annual cost
Nurse (GP practice)	£10.27	4	£41.08
Goserelin (Zoladex LA) 10.8-mg syringe	£267.48	4	£1069.92
Oncology outpatient	£88.33	2	£176.65
Dexa scan	£72.92	0.5	£36.46
Total			**£1324.12**

TABLE 30 *The costs of treating late gastrointestinal toxic effects of RT treatment*

Annual monitoring cost	**Cost 2008–9**	**Number/year**	**Annual cost**
Grade 2			
Oncology outpatient	£88	3	£265
Grade 3			
Oncology outpatient	£88	6	£530
Mean cost (based on 26% grade 3)			**£335**
Treatment costs per patient	**Cost 2008–9**	**Number/patient**	**Total cost**
Grade 2			
Flexible sigmoidoscopy ± colonoscopy, biopsy	£497	1	£497
Laser therapy	£1201	0.25	£300
Enemas (2/day for 2 weeks, community nurse)	£26	28	£728
Grade 3			
Flexible sigmoidoscopy ± colonoscopy, biopsy	£497	2	£993
Laser therapy	£1201	2	£2403
Blood transfusion	£462	1	£462
Mean cost (based on 26% grade 3)			**£2139**

TABLE 31 *Proportion of patients with grade 2 or 3 adverse effects who have grade 3 effects*

Study	**Treatment group**	**Number of patients**	**Proportion grade 3**
Kupelian *et al.* 2002[84]	IMRT	166	0.40
	3DCRT	116	0.67
Vora *et al.* 2007[89]	IMRT	145	0.04
	3DCRT	271	0.13
Total		**698**	**0.26**

generalisability. A one-way sensitivity analysis was undertaken on this key parameter.

The mean duration of late GI toxicity is also an important parameter in some scenarios, where the difference in QALYs between IMRT and 3DCRT depends only on the difference between incidence of late GI toxicity. For these scenarios (one and two) a sensitivity analysis was undertaken, varying the baseline value of 3 years to 2.5 and 4 years.

The effect of the age of men at the time of treatment on the results was tested by running the model with starting ages of 60 and 80 years.

A probabilistic sensitivity analysis was undertaken. The purpose of a probabilistic sensitivity analysis is to show the effect of the uncertainty in individual model parameters on the uncertainty in the model results. In a probabilistic sensitivity analysis, rather than using the expected value of variables, values are sampled from a distribution. The distributions used for each parameter are shown in Appendix 13. For each scenario (e.g. Morgan *et al.*[107] IMRT) 1000 model runs were made, as this was assumed to adequately reflect the joint uncertainty between parameters within the model.

Results

Baseline scenarios

Table 32 shows the estimated total life-years and proportions of patients who progress to more advanced stages of PC disease for men aged

TABLE 32 *Modelled clinical results for men aged 70 years*

Scenario number	Scenario	Total life-years	Discounted life-years	PSA failure	Clinical failure	Hormone-refractory metastatic disease	PC death
1	Morgan *et al.* 2007[107] IMRT/3DCRT	11.3	8.9	56%	40%	26%	29%
2	Kupelian *et al.* 2002/2005[84,85] IRMT/3DCRT (equal survival scenario)	11.8	9.2	42%	29%	19%	21%
3	Kupelian *et al.* 2002/2005[84,85] IRMT	11.8	9.2	42%	29%	19%	21%
	Kupelian *et al.* 2002/2005[84,85] 3D	11.4	8.9	53%	37%	26%	28%
4	Vora *et al.* 2007[89] IMRT	11.8	9.2	49%	34%	22%	24%
	Vora *et al.* 2007[89] 3D	10.5	8.4	76%	55%	38%	42%

TABLE 33 *Total costs, QALYS and ICERs for IMRT and 3DCRT scenarios for men aged 70 years*

Scenario number	Scenario	Total discounted costs	Total discounted QALYs	Additional cost IMRT	QALY gain IMRT	Incremental cost/QALY of IMRT
1	Morgan *et al.* 2007[107] IMRT	£6173	6.802	£989	0.010	£104,066
	Morgan *et al.* 2007[107] 3DCRT	£5184	6.792			
2	Kupelian *et al.* 2002/2005[84,85] IMRT	£4946	7.070	£732	0.023	£31,162
	Kupelian *et al.* 2002/2005[84,85] 3DCRT (survival equal to IMRT)	£4214	7.046			
3	Kupelian *et al.* 2002/2005[84,85] IMRT	£4946	7.070	£40	0.087	£5295
	Kupelian *et al.* 2002/2005[84,85] 3DCRT	£4486	6.983			
4	Vora *et al.* 2007[89] IMRT	£5687	7.015	–£1802	0.613	Dominates
	Vora *et al.* 2007[89] 3DCRT	£7489	6.402			

70 years, for the four modelled scenarios. There is some variation between the scenarios in the proportion of men estimated to die from PC: 42% for Vora *et al.*[89] (3DCRT) and 21% for Kupelian *et al.*[84,85] (IMRT). This reflects differences in the study results themselves.

The total discounted costs and QALYs for each scenario for men aged 70 years is shown in *Table 33*, as well as the resulting ICER. In scenario 1, based on Morgan *et al.*,[107] IMRT is not cost-effective judged by the maximum NICE threshold of an ICER of £30,000.[122] In this scenario equal doses of RT were given to both IMRT and 3DCRT patients, resulting in the same PSA progression rates for both cohorts. The incidence of late GI toxicity was low in both cohorts compared to other studies (IMRT 4%, 3DCRT 9%), but the difference yields the small 0.01 difference in QALYs (see *Table 33*) between IMRT and 3DCRT.

In scenario 2, based on Kupelian *et al.*,[84,85] survival is also assumed to be the same for the IMRT and 3DCRT groups, but the estimated difference in

late GI toxicity was 15%, giving a total difference in QALYs between the two groups of 0.023. Although IMRT treatment itself is assumed to cost £1122 more than 3DCRT, the additional costs of treating a greater proportion of 3DCRT patients for late GI toxicity reduces the additional total cost of IMRT to £732. The ICER falls at the upper NICE threshold of £30,000. Between £20,000 and £30,000 NICE takes into consideration other factors such as the strength of evidence.[1] In scenario 4 (Vora *et al.*[89]), where a difference between IMRT and 3DCRT in mean survival to PSA failure of 6.6 years has been assumed, IMRT is actually cost-saving, owing to the reduced costs of treating advanced PC. There is also a much greater QALY gain for IMRT compared to 3DCRT, due to the increased survival for IMRT. Thus IMRT yields greater QALYs at lower cost than 3DCRT and is therefore said to dominate 3DCRT.

For scenario 3, where a smaller difference between IMRT and 3DCRT in mean survival to PSA failure of 3.8 years has been assumed, the ICER is small but positive, at £5300.

Sensitivity analyses

Age of men at the time of treatment with RT

Clearly the age of men at the time of RT has an effect on the proportion of men estimated to die of PC as older men are more likely to die of other causes before their PC progresses. *Table 34* illustrates the effect for scenario 2 (Kupelian *et al.*,[84,85] equal survival for IMRT and 3DCRT).

TABLE 34 *Proportion of men who have clinical disease progression and die of PC according to age at time of RT (Kupelian* et al.,*[84,85] equal survival for IMRT and 3DCRT)*

Age (years)	Clinical progression	PC death
60	45%	41%
70	29%	21%
80	23%	7%

Table 35 shows the variation in ICER with age. It shows that although there is some variation in the

TABLE 35 *Variation in ICER with age*

Scenario number	Scenario	Age at RT (years)		
		60	70	80
1	Morgan *et al.* 2007[107]	£92,788	£104,066	£133,832
2	Kupelian *et al.* 2002/2005[84,85] (equal survival IMRT/3DCRT)	£31,181	£31,162	£38,211
3	Kupelian *et al.* 2002/2005[84,85] (greater survival IMRT)	£1762	£5295	£16,914
4	Vora *et al.* 2007[89]	Dominates	Dominates	Dominates

TABLE 36 *Sensitivity analysis on the additional costs of IMRT compared to 3DCRT*

Scenario number	Scenario	Additional cost IMRT compared to 3DCRT				
		Baseline –40%	Baseline –20% (£900)	Baseline (£1120)	Baseline +20% (£1350)	Baseline +40% (£1570)
1	Morgan *et al.* 2007[107]	£56,832	£80,449	£104,066	£127,683	£151,301
2	Kupelian *et al.* 2002/2005[84,85] (equal survival IMRT/3DCRT)	£12,063	£21,612	£31,162	£40,711	£50,260
3	Kupelian *et al.* 2002/2005[84,85] (greater survival IMRT)	£125	£2710	£5295	£5295	£10,464
4	Vora *et al.* 2007[89]	Dominates	Dominates	Dominates	Dominates	Dominates

ICER by age, the conclusions are unaffected by the age group modelled. The ICER is generally lower for younger men, as they have more years to benefit.

Relative cost of IMRT compared to 3DCRT

The costs of IMRT and 3DCRT were obtained from a single institution. The relative cost of IMRT compared to 3DCRT may vary according to the equipment used for planning and delivery of RT, and experience of staff with the different techniques. The results of a sensitivity analysis on the additional costs of IMRT compared to 3DCRT are shown in *Table 36*. The cost difference was varied by plus and minus 20% and 40% of the baseline value at £1122.

Although the ICERs vary quite considerably with the variation in mean cost difference between IMRT and 3DCRT explored in *Table 36*, in fact the results of the sensitivity analysis show that only scenario 2 is sensitive to the variation. In the first scenario (Morgan *et al.*[107]), where late GI toxicity is low in both cohorts and there is no survival difference the ICER remains above the maximum NICE threshold of £30,000. In scenario 4 IMRT dominates 3DCRT (is less costly and more effective) even if the mean additional cost of IMRT was 40% more (a cost difference of £1570) than the baseline estimate. In scenario 3 the ICER remains well within the £20,000 threshold for the modelled cost differentials. For scenario 2, however, the additional cost of IMRT over 3DCRT is critical to cost-effectiveness. If the baseline additional cost is overestimated the ICER for IMRT in comparison to 3DCRT falls within a threshold of £20,000, but if the additional cost is greater than the baseline (cost difference greater than £1350) it falls beyond the maximum threshold of acceptability to NICE of £30,000.

Duration of late GI toxicity

The duration of late GI toxicity was reported in just one study.[91] Given the variability between studies in other parameters, there is considerable uncertainty around the estimate of 3 years which was used in the model. For scenarios 3 and 4 (Kupelian *et al.*[84,85] – survival difference, Vora *et al.*[89]) the duration of toxicity is not important, as the far greater difference in QALYs arises principally from the difference in survival. For scenarios 1 and 2 (Morgan *et al.*,[107] Kupelian *et al.*[84,85] – equal survival), where no survival difference is assumed between the IMRT and 3DCRT cohorts, the ICERs are sensitive to this parameter, as shown in *Table 37*.

However, it is only for scenario 2 (equal survival IMRT and 3D, 15% difference in late GI toxicity) that the duration of late GI toxicity is critical to cost-effectiveness.

Probabilistic sensitivity analysis

The mean cost per QALY calculated from a probabilistic sensitivity analysis is preferable to an answer from a deterministic analysis as it explicitly incorporates the uncertainty surrounding each parameter and can take non-linearities and interacting parameters into account. It is of particular use when events which are associated with high costs and high utility losses but occur with low probability exist within the model or skewed distributions such as Weibull are used.[122,130]

In fact the results of the probabilistic sensitivity analysis are similar to the results of the deterministic analysis. For scenario 1 (Morgan *et al.*[107]), the expected value of ICER is £104,000 in the deterministic analysis and £120,000 in the stochastic. For this scenario, with no survival difference and little difference in GI toxicity, there is only a 29% probability of IMRT being

TABLE 37 *Variation in ICER by mean duration of late GI toxicity*

Scenario number	Scenario	Mean duration late GI toxicity		
		2.5 years	3 years (baseline)	4 years
1	Morgan *et al.* 2007[107]	£131,231	£104,066	£73,107
2	Kupelian *et al.* 2002/2005[84,85] (equal survival IMRT/3DCRT)	£42,138	£31,162	£19,842
3	Kupelian *et al.* 2002/2005[84,85] (greater survival IMRT)	£5929	£5295	£4244
4	Vora *et al.* 2007[89]	Dominates	Dominates	Dominates

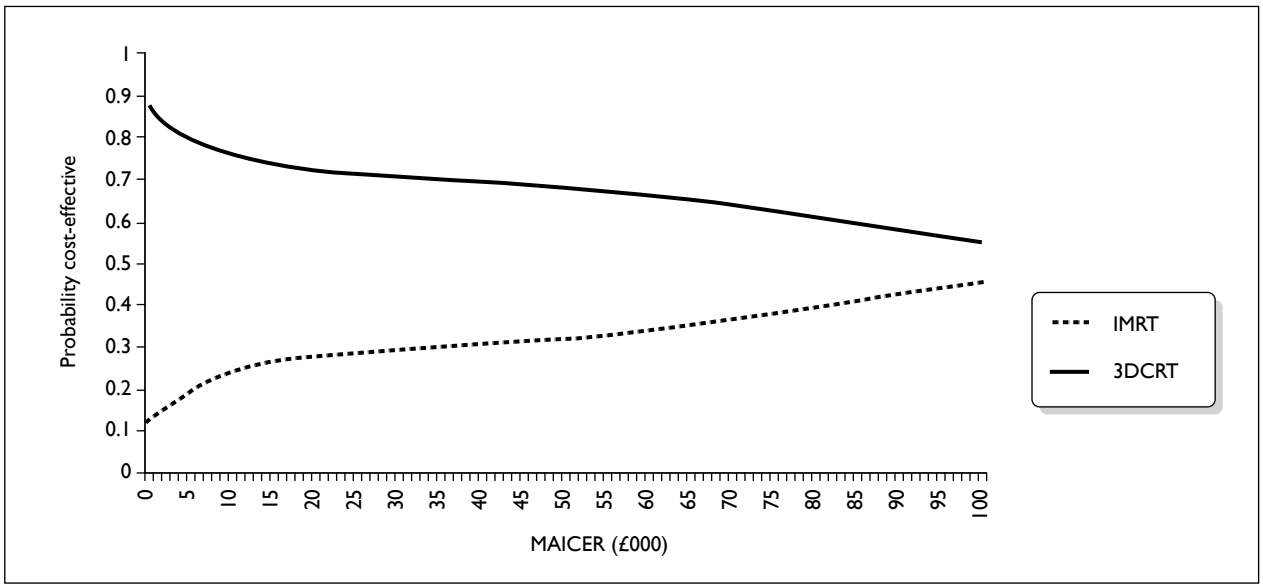

FIGURE 10 *Cost-effectiveness acceptability curve scenario 1 (Morgan* et al.*[107]).*

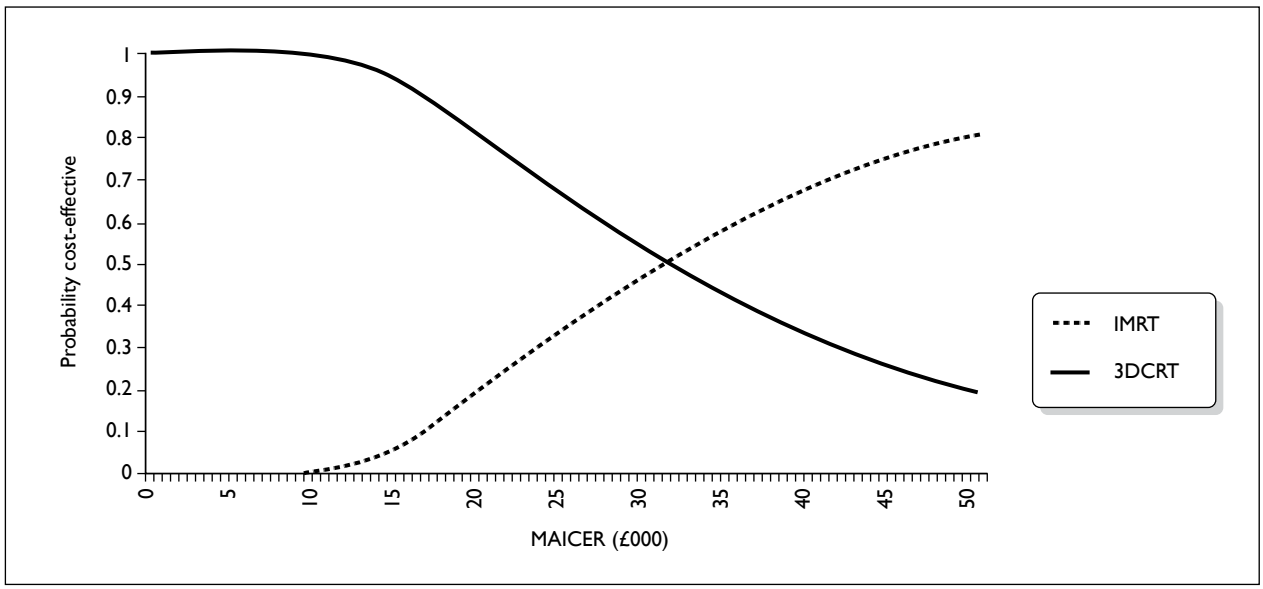

FIGURE 11 *Cost-effectiveness acceptability curve scenario 2 (Kupelian* et al.*[84,85] – equal survival IMRT/3DCRT).*

cost-effective in comparison with 3DCRT with a maximum incremental cost-effectiveness ratio (MAICER) of £30,000 (see *Figure 10*). Even with a MAICER of £100,000 there is less than 50% probability of IMRT being cost-effective in comparison with 3DCRT.

Given the similarity of the stochastic and deterministic analyses the stochastic analysis was not run for all scenarios. For scenario 2 (Kupelian *et al.*[84,85] – equal survival IMRT/3DCRT) it is of particular interest as IMRT is borderline cost-effective according to NICE thresholds.

The expected value for the ICER of IMRT in comparison to 3DCRT for the probabilistic analysis is £34,781, in comparison to £31,162 from the deterministic analysis. At a MAICER of £20,000 there is only a 20% probability that IMRT is cost-effective, but this rises to 48% for a MAICER of £30,000, as shown in the cost-effectiveness acceptability curve (*Figure 11*).

Discussion

A limitation of all economic studies comparing IMRT with 3DCRT, including this one, is the

limited clinical data comparing the two treatment modes. There are no RCTs and the comparative studies have weaknesses such as differences between the patient groups. Only three studies (all localised cancer) were identified which reported PSA survival (Morgan *et al.*,[107] Kupelian *et al.*,[84] and Vora *et al.*[89]). Of the three studies, one was reported as an abstract only, and this was the only study to report survival (Morgan[107]).

Based on these three studies four scenarios were modelled. The heterogeneity of the clinical studies is reflected in the results of economic analysis, which, depending on the scenario modelled, range from IMRT dominating 3DCRT (i.e. is both more effective and less costly) to having an ICER of £104,000.

The additional cost of IMRT compared to 3DCRT is relatively modest at £1120, so for scenarios where it is assumed that IMRT can improve freedom from PSA failure and hence survival (likely by dose escalation), IMRT is cost-effective, a result which is robust to variation in other key parameters. The baseline scenarios where equivalent survival is assumed for IMRT and 3DCRT, and QALY differences between the two cohorts are derived from differences in GI toxicity alone, show IMRT to be borderline cost-effective depending on the difference in late GI toxicity, duration of GI toxicity and the cost difference between IMRT and 3DCRT.

At baseline parameter values the scenario with a difference in late GI toxicity of 5% (Morgan *et al.*[107] – scenario 1) gave an ICER of £104,000, but scenario 2 (Kupelian *et al.*[84,85] – equal survival) with a difference in GI toxicity of 15% gave an ICER of £31,000. The probabilistic analysis of the latter scenario showed that only with a MAICER of £30,000 or more was it probable that IMRT was cost-effective in comparison to 3DCRT. This is at the upper NICE threshold, where other factors such as the strength of evidence are taken into consideration. The results for this scenario are very sensitive to the incremental cost of IMRT in comparison to 3DCRT, as well as the mean duration of late GI toxicity, both very uncertain parameters. If the incremental cost of IMRT is £860, or around 20% less than the baseline value used, the ICER falls to £20,000. Similarly if the mean duration of late GI toxicity is 4 years rather than 3 years the ICER falls to £20,000. Of course, if these parameters are varied in the opposite direction the ICER of IMRT in comparison with 3DCRT increases, and then clearly falls beyond a threshold of £30,000.

The scenarios modelled were all based on studies where both PSA survival and toxicity were reported. To put the values of incidence of late GI toxicity from the modelled studies in context the results of other studies were considered. Of those where the same RT dose was given to both IMRT and 3DCRT patients with localised cancers (Martinez *et al.*,[110] Sharma *et al.*[106]), both report a 13% difference in late GI toxicity at 5 years. Sanguineti *et al.*[88] reports a difference of 15% at 2 years, despite the IMRT group receiving WP RT in comparison to treatment of the prostate only in the comparator group. Both the Martinez *et al.*[110] and Sharma *et al.*[106] studies are reported in abstract only, but, with Sanguineti *et al.*,[88] suggest model scenario 2 (Kupelian *et al.*[84,85] – equal survival) is more representative than scenario 1 (Morgan *et al.*,[107] also reported in abstract only). Reduced toxicity from IMRT in comparison to 3DCRT may be greater in patients requiring WP RT, making it more cost-effective than for treatment of the prostate and seminal vesicles alone.

Previous economic analyses of IMRT in comparison with 3DCRT have shown very different results. Pearson *et al.*[64] assumed no difference in survival, and so in common with some scenarios modelled in this study (1 and 2), relies only on differences in GI toxicity to yield QALY differences between IMRT and 3DCRT treated patients. He reports an ICER of US$706,000. This is considerably greater than the results of our analysis, but the cost differential between IMRT and 3DCRT in the Pearson *et al.* analysis was estimated to be US$31,500 (approximately £19,000),[64] very different from our estimate of £1120.

Konski *et al.*[131] found IMRT to be cost-effective in comparison to 3DCRT, despite a cost differential almost as great as that of Pearson *et al.*[64] However, a large difference between IMRT and 3DCRT in PSA survival at 5 years was assumed (16%), derived from PSA survival in two different cohort studies. The greatest PSA survival difference reported in the studies included in this review was 14% (ASTRO consensus definition), but this was reduced to 11% when PSA failure was defined by the ASTRO Phoenix definition.[89] Konski *et al.* also assumed a long-term higher utility for all IMRT patients compared to those who had had 3DCRT, independent of adverse effects of treatment, the utility values used being derived from two separate studies using different methods of determining utility values.[131]

Chapter 5

Assessment of factors relevant to the NHS and other parties

Factors relevant to the NHS

Both IMRT and 3DCRT require a range of trained staff, including therapeutic radiographers, nurses, RT physics staff and clinical oncologists.[132] Both require equipment including a linear accelerator to deliver radiation. Changes in skills mix would be needed for widespread implementation of IMRT, such as IMRT planning and QA requiring more treatment planning, oncologist and medical physics support.[53,54] There is currently a shortage of RT physicists, which means that greater use of IMRT is likely to have implications on the provision of other services, at least in the short term. The Royal College of Radiologists is developing an e-learning programme to support the training of clinical oncologists to further enhance the UKs ability to deliver IMRT to a uniform high standard. Image-guided IMRT takes more staff time.[54] Enhanced immobilisation may be needed in IMRT for precise patient positioning.[53] Verification of IMRT delivery (QA) is time consuming.[54] The National Radiotherapy Advisory Group suggest that although new techniques increase time taken for planning and delivery, processes will become more efficient with practice.[54] IMRT requires extra equipment, such as a multi-leaf collimator able to be driven in at least 'step-and-shoot' mode; a 3D planning system capable of importing at least CT data and preferably MRI data; tools to experimentally validate dosimetry and methods to verify the patient position; and inverse planning requires computer software.[53,54] This equipment, though, is now standard. IGRT requires imaging equipment which is attached to the linear accelerator.[54] If toxicity can be reduced, this may reduce the burden on gastroenterology and urology services.

Factors relevant to other parties

Intensity-modulated RT may involve a small increase in treatment time of a few minutes per fraction, especially in centres new to delivering IMRT, potentially affecting carers as well as patients. However the additional time is negligible in relation to the total time required for travel to the centre and the treatment itself. Current research into hypofractionated schedules (delivering fewer fractions at higher dose) of both 3DCRT and
IMRT may potentially lead to patients having to attend the treatment centre less often for their course of RT.

Chapter 6
Discussion

Statement of principal findings

No RCTs were identified, only comparative studies, and all of these compared treatment with IMRT to 3DCRT for localised or locally advanced PC. There were no studies comparing IMRT with radical prostatectomy, and there were no comparative studies for adjuvant RT for high-risk radical prostatectomy patients, salvage treatment, or palliation of bone metastases. One study, reported in abstract form only, reports disease specific survival[107] and only three (of which one is reported in abstract only[107]) report biochemical survival,[46,89,107] all for the treatment of localised cancers.

The only study included in this review to show a statistically significant difference in biochemical survival between IMRT and 3DCRT gave a higher dose (75.6 Gy) of IMRT than 3DCRT (68.4 Gy).[89] The theory that dose, rather than RT technique, explains survival difference is supported by a published meta-analysis of 3DCRT dose escalation studies, which shows improved biochemical survival with increasing RT doses up to 79.2 Gy.[65]

Although studies had methodological flaws, taken together they seem to support the theory that restricting treatment field, particularly with regard to constraining volume of rectal wall receiving prescription dose, can lessen toxicity. This can be more easily achieved with IMRT than 3DCRT. Again, more systematic evidence is available from analysis of 3DCRT RCT data.[118] Some studies have given 3DCRT at doses > 80 Gy, with reported late GI toxicity rates similar to those reported at lower doses.[107,110] However, these studies are reported in abstract only, so the strength of their conclusions is uncertain, and other variations in technique (such as planning, imaging, margins treated) may account for the limitation of toxic effects. The effect of these other variables on survival and costs are unknown.

Two previous economic studies (one reported in different forms in three papers) of IMRT in comparison with 3DCRT for the treatment of localised PCs were identified.[64,113,114,131] One study,[78] which found IMRT to be cost-effective, is flawed by the biased use of data to populate the economic model. The other, which reported an ICER of over £400,000 for IMRT compared to 3DCRT, is limited in scope as it only considers toxicity.[64] Both studies are from the USA and report a much greater difference in RT costs for IMRT compared to 3DCRT (over £16,000) than was identified in this study (£1100), so the results are unlikely to be applicable to the UK. A difference between the US costs and those for the UK is that the costs from the USA actually reflect reimbursement, and therefore do not necessarily represent real cost differences in the provision of the different therapy modes.

An economic model was developed to examine the cost-effectiveness of IMRT in comparison to 3DCRT. Four scenarios were modelled based on the three studies which reported both PSA survival and late GI toxicity.[84,85,89,107] In two scenarios equal survival was assumed for IMRT and 3DCRT, the other two having greater survival for the IMRT cohort. For the latter scenarios, with greater survival for IMRT than 3DCRT-treated patients the results are unambiguous. IMRT either dominates 3DCRT (that is results in more QALYs for lower total costs), or the ICER is relatively modest (£5000), results which are robust to variation in other key parameters.

The two scenarios where equivalent survival is assumed for IMRT and 3DCRT, and QALY differences between the two cohorts are derived solely from differences in late GI toxicity alone, show IMRT to be borderline cost-effective depending on the difference in GI toxicity, duration of GI toxicity and the cost difference between IMRT and 3DCRT. At baseline parameter values the scenario with a difference in late GI toxicity of 5% (scenario 1) gave an ICER of £104,000, but scenario 2 with a difference in GI toxicity of 15% gave an ICER of £31,000. The probabilistic analysis of the latter scenario showed that only with a MAICER of £30,000 or more was it probable that IMRT was more cost-effective than 3DCRT. These results are highly sensitive to two very uncertain parameters: the incremental cost of IMRT and the duration of late

GI toxicity. Variation of these parameters within plausible bounds can reduce the ICER of IMRT in comparison to 3DCRT to below a threshold of £20,000, or equally push it clearly beyond a threshold of £30,000. The scenarios modelled were all based on studies where both PSA survival and toxicity were reported. To put the values of incidence of late GI toxicity from the modelled studies in context the results of other studies included in the review were considered. These suggest model scenario 2 is more representative of the literature than scenario 1.

For RT to the WP (usually only considered for men with a greater than 15% risk of pelvic lymph node involvement)[1] IMRT may be more cost-effective than for treatment of the prostate (and seminal vesicles) alone. Sanguineti *et al.*[88] reports a difference of 15% in late GI toxicity at only 2 years, despite the IMRT group receiving WP RT in comparison to treatment of the prostate only in the comparator (3DCRT) group.

Strengths and limitations of the assessment

The strengths of the assessment were that the literature search was comprehensive and the included studies were of relevance to UK practice in terms of populations and treatments. Populations from US studies may have earlier stage disease than UK populations due to the USA practice of screening. It is unclear if this would limit generalisability of results to UK populations. Limitations of the assessment were that there was a lack of data comparing IMRT with prostatectomy, data for patients with bone metastasis, data comparing post-operative IMRT with post-operative 3DCRT, and overall survival (OS) data or clinically measured disease-free survival data were lacking. Only one abstract was identified on image guided RT.[110] Furthermore, available data were not from RCTs and we do not know if there were relevant trials that were not published in English; however, methodology studies have indicated that language restrictions do not often influence the results of systematic reviews of conventional medicines.[133–135]

The economic model developed is based on a systematic review of the literature and is more comprehensive in its scope than previous models. The strength of the conclusions of the economic analysis is, however, necessarily constrained by the limitations of the clinical effectiveness data, discussed above. As there was very limited data on clinical outcomes, the model estimates progression to clinical failure and PC death from the surrogate outcome of PSA failure. The limitations of the marker as a surrogate for long-term therapeutic benefit have been discussed in the literature.[136]

Uncertainties

Radiotherapy treatment involves a series of processes including planning, imaging, outlining, as well as treatment itself. All of these may vary, introducing heterogeneity to comparisons both between and within some studies. There is a lack of OS data, and although it is plausible that more focused radiation at higher dose would increase survival, this depends on the target being correctly identified to include all cancer, and treatment planned and delivered accordingly. This requires highly trained and skilled staff. Given that biochemical survival is not a perfect predictor of OS, long-term OS data are needed to be sure that IMRT is effective. Costs of IMRT and 3DCRT were obtained only from a single institution, which is at a relatively early stage of IMRT implementation. The difference in treatment time between IMRT and 3DCRT assumed is consistent with that reported in the literature, but the study does not report the experience of the institution with IMRT.[82] It is possible that the cost differential between IMRT and 3DCRT will be less at institutions with more experience of IMRT. The utility values were taken from a study of Japanese men, so their applicability to UK men is unknown.

Chapter 7
Conclusions

Implications for service provision

Clinical advice suggests that most RT centres already possess the equipment required to deliver IMRT, but that lack of available staff such as medical physicists hinders implementation.[76] 3DCRT may be safely delivered at the currently recommended total dose of 74 Gy,[1] and there is no evidence that PSA survival is improved by giving IMRT at the same dose as 3DCRT. However, there is evidence that IMRT reduces toxicity, in particular late GI toxicity. The magnitude of the difference is uncertain, which, together with uncertainties in other variables such as the difference in cost between IMRT and 3DCRT, in turn makes the cost-effectiveness of IMRT in comparison to 3DCRT uncertain. If a difference in late GI toxicity of 15% is assumed the probability of IMRT being more cost-effective than 3DCRT is true for MAICERs of ≥£25,000.

Suggested research priorities

No RCTs comparing IMRT with 3DCRT were identified. There is clearly a need for such studies for the question of the clinical effectiveness and cost-effectiveness of IMRT in comparison to 3DCRT to be answered. However, given the degree of adoption of IMRT into clinical practice, it may be difficult to instigate RCTs comparing IMRT with 3DCRT. Studies are required both for radiation to the prostate alone and WP radiation.

Dose escalation studies for 3DCRT have shown how PSA survival and adverse effects vary with dose, and similar studies are required for IMRT. Stratification by risk group should be considered, as those at highest risk of progression may benefit differentially from those at low risk.

Further evolution of RT technology has led to IGRT. Randomised studies with IMRT and 3DCRT should be instigated before the technology becomes widely adopted.

Fractionation regime was not considered within this review, but there is ongoing uncertainty as to the optimum. The CHHiP study is addressing this issue in IMRT.[137]

Studies require adequate follow-up (at least 5 years) to capture late AEs, and should include HRQoL, ideally including the EQ-5D. Studies should report the evolution of AEs with time. Ideally studies would also report PC survival as PSA recurrence is limited as a predictor of this, but these require even longer follow-up. Long follow-up (at least 10 years) and large studies are likely to be required to detect group differences in secondary malignancies.[64] Whether secondary malignancies are an issue might be addressed through registry studies.

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About ScHARR

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Contribution of authors

S Hummel led the project. S Hummel and P Hemingway wrote the study protocol. S Hummel and MD Stevenson were responsible for the economic analysis, EL Simpson and P Hemingway conducted the clinical review. A Rees carried out the literature searches.

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Appendix 1

Literature search strategies

Search strategy for MEDLINE

1. Radiotherapy, Intensity-Modulated/
2. intensity modulated radiotherap*.tw.
3. intensity-modulated radiotherap*.tw.
4. intensity modulated radiation therap*.tw.
5. intensity-modulated radiation therap*.tw.
6. imrt.tw. (2343)
7. image guided radiotherap*.tw. (185)
8. igrt.tw.
9. dose compensation.tw.
10. electronic compensation.tw.
11. e compensation.tw.
12. forward planning.tw.
13. inverse planning.tw.
14. field in field.tw.
15. physical compensation.tw.
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. Randomized controlled trials as Topic/
18. Randomized controlled trial/
19. Random allocation/
20. Double blind method/
21. Single blind method/
22. Clinical trial/
23. exp Clinical Trials as Topic/
24. 16 or 17 or 18 or 19 or 20 or 21 or 22
25. clinic$adj trial$1).tw.
26. ((singl$or doubl$or treb$or tripl$) adj (blind$3 or mask$3)).tw.
27. Placebos/
28. Placebo$.tw.
29. Randomly allocated.tw.
30. (allocated adj2 random).tw.
31. 25 or 26 or 27 or 28 or 29 or 30
32. 24 or 31
33. prostatic neoplasms/
34. (prostat$adj5 (cancer$or carcin$or tumor$or tumour$or neoplasm$)).tw.
35. ((carcinoma or neoplasia or neoplasm$or adencarcinoma or cancer$or tumor$or tumour$or malignan$) adj3 prostat$).tw.
36. 33 or 34 or 35
37. 16 and 32 and 36

Appendix 2

Data abstraction tables

Study details

Study	Sample size			Study design	Setting
	Total	Intervention group (IMRT)	Control group (3DCRT)		
Kupelian[84]	282	166 (later report of study[86] has 770 IMRT but no comparator)	116 (later report of study[85] has 310 3DCRT, compared with 100 IMRT patients)	Retrospective patient records study, two contemporary case series IMRT and 3DCRT, with post hoc QoL questionnaire	Single centre USA (Cleveland Clinic Foundation, OH, USA)
Sanguineti[88]	113	45	68	Retrospective patient records study, comparison of IMRT with 3DCRT historical controls from a different hospital	Two centres, 1 IMRT (University of Texas Medical Branch, TX, USA), 1 3DCRT (National Institute of Cancer Research, Genoa, Italy)
Shu[29]	44	18	26	Retrospective patient records study, two contemporary case series, IMRT and 3DCRT, data from departmental charts or by direct patient interviews	Single centre USA (University of California, CA, USA)
Vora[89]	416	145	271	Retrospective patient records study, comparison of IMRT with 3DCRT historical controls from same centre	Single centre USA (Mayo Clinic, Scottsdale, AZ, USA)
Yoshimura[41]	144	60	84 (of which 46 dose 70.2 Gy; 38 dose 73.5 Gy)	Prospective comparison of case series, IMRT with contemporary case series of higher dose 3DCRT, and historical case series of lower dose 3DCRT	Single centre Japan (Kyoto University Graduate School of Medicine, Kyoto, Japan)
Zelefsky[91]	1571	741	830 (of which 472 at 75.6 Gy dose; 358 at 66–70.2 Gy dose)	Prospective[96] case series, dose escalation with successive case series receiving higher doses	Single centre USA (Memorial Sloan Kettering Cancer Center, New York, NY, USA)
Ashman[100]	27	13	14	Subset of patients from Zelefsky *et al.* study,[91] retrospectively identified patient records, comparison of IMRT with 3DCRT historical controls from same centre	Single centre USA (Memorial Sloan Kettering Cancer Center, New York, NY, USA)
Lips[43]	170	92	78	Prospective comparison of case series, comparison of IMRT with 3DCRT historical controls from same centre	Single centre The Netherlands (University Medical Center, Utrecht, the Netherlands)

Study details

Study	Indication	Length of follow-up	Start date	Finish date
Kupelian[84]	Localised PC	Median follow-up for all cases was 25 months (range 3–42). IMRT median follow-up 21 months (range 3–31). 3DCRT 32 months (range 3–42)	IMRT October 1998; 3DCRT January 1998	1999
Sanguineti[88]	Localised PC	Mean (SD) follow up IMRT 26.6 months(SD 7.9); 3DCRT 23.9 months (SD 8.9) (overall 25.9 SD 8.4 months)	IMRT 2002; 3DCRT 1995	IMRT 2004; 3DCRT 1999
Shu[29]	Localised PC	Overall median 23.1 months (range 10.0 to 84.7). IMRT median follow-up 18.7 months. 3DCRT 30.1 months	1992	1998
Vora[89]	Localised PC	Overall median 5 years (range 3–10 years). IMRT 48.1 months (range 36–68 months). 3DCRT 62.3 months (36–121 months)	IMRT 2000; 3DCRT 1993	IMRT 2005; 3DCRT 2000
Yoshimura[41]	Localised PC	Data collected at 12 months follow-up for all patients	IMRT or 3DCRT 73.5 Gy 2003; 3DCRT 70 Gy 2000	IMRT or 3DCRT 73.5 Gy 2004; 3DCRT 70 Gy 2003
Zelefsky[91]	Localised PC	Overall median 8 years (range 5–18). IMRT median 6.5 years. 3DCRT median 10 years	IMRT 1995;[97] 3DCRT 70.2 Gy 1988; 75.6 Gy 1991; 81 Gy 1992[96]	IMRT 2000; 3DCRT 70.2 Gy 1992; 75.6 Gy 2000; 81 Gy 2000[96]
Ashman[100]	Locally advanced PC	Overall median 30 months (range 3–87 months)	IMRT 2000; 3DCRT 1996	IMRT 2004; 3DCRT 1999
Lips[43]	Locally advanced PC	Data collected at 6 months follow-up for all patients	IMRT 2003; 3DCRT 1997	IMRT 2004; 3DCRT 2001

DOI: 10.3310/hta14470

Population

Study	Inclusion criteria	Baseline characteristics			
		Stage of cancer (% each group)	Grade of cancer (Gleason score)	Initial PSA	Age (years)
Kupelian[84]	Inclusion: localised PC Exclusion: neoadjuvant or adjuvant androgen deprivation for a period of more than 6 months or had no follow-up PSA levels available	T1–T2a IMRT 87%, 3DCRT 67%; T2b–T2c IMRT 10%, 3DCRT 22%; T3 IMRT 4%, 3DCRT 11%	Biopsy Gleason score ≤ 6 IMRT 56%, 3DCRT 39%; Gleason score ≥ 7 IMRT 44%, 3DCRT 61%	Pretreatment PSA ≤ 4 ng/ml IMRT 4%, 3DRCT 3%; > 4 to 10 ng/ml IMRT 54%, 3DRCT 51%; > 10 to 20 ng/ml IMRT 26%, 3DRCT 28%; > 20 ng/ml IMRT 17%, 3DRCT 18%	Median (both groups) 68
Sanguineti[88]	Localised PC. IMRT 15% or more risk of nodal involvement according to Roach formula, exclude patients whose PTV included reduced margins around the prostate. 3DCRT exclude if treated with 70 Gy and/or including seminal vesicles	T-stage T1a–b 3DCRT 1.5% IMRT 4.4%; T1c 3DCRT 14.7% IMRT 46.7%; T2a–b 3DCRT 61.8% IMRT 22.2%; T3a–b 3DCRT 22.1% IMRT 22.2%; T4 3DCRT 0.0% IMRT 4.4% significant difference between groups < 0.01	Gleason Score 2–6 3DCRT 58.8% IMRT 6.7%; Gleason Score 7 3DCRT 33.8% IMRT 44.4%; Gleason Score 8–10 3DCRT 5.9% IMRT 48.9%; Gleason Score Unknown 3DCRT 1.5% IMRT 0.0% significant difference between groups < 0.01	NR	3DCRT mean 70.7 (SD 5.8); IMRT mean 66.9 (SD 7.9)
Shu[29]	Clinically localised PC patients treated with external beam RT for PC, maximal dose (D_{max}) of at least 82 Gy. All pathology slides were reviewed at UCSF for confirmation of diagnosis	T-stage T1 IMRT 11%, 3DCRT 15%; T2 IMRT 56%, 3DCRT 65%; T3 IMRT 33%, 3DCRT 19%. AJCC stage II IMRT 67%, 3DCRT 81%; AJCC stage III IMRT 33%, 3DCRT 19%	Gleason score (pathology slides were reviewed) ≤ 6 IMRT 22%, 3DCRT 65%; Gleason score 7 IMRT 44%, 3DCRT 23%; Gleason score ≥ 8 IMRT 33%, 3DCRT 12%	Median (range) IMRT 12.0 (4.4 to 39.5), 3DCRT 9.8 (2.9 to 62.8)	Median IMRT 70 (range 50 to 79); 3DCRT 69 (range 53 to 76)
Vora[89]	Clinically localised PC	T-stage T1 IMRT 36%, 3DCRT 16%; T2 IMRT 61%, 3DCRT 75%; T3 IMRT 2%, 3DCRT 10%	Gleason score IMRT median 7 (range 2–9); 3DCRT median 6 (range 2–10)	PSA ng/ml IMRT median 6.8 (range 0.8 to 56.8); 3DCRT median 8 (range 0.9 to 197.4)	NR
Yoshimura[41]	Clinically localised PC	T-stage T1 IMRT 10%, 3DCRT 26%; T2 IMRT 15%, 3DCRT 31%; T3 IMRT 75%, 3DCRT 43%	Gleason score ≤ 6 IMRT 17%, 3DCRT 29%; Gleason score 7 IMRT 52%, 3DCRT 33%; Gleason score ≥ 8 IMRT 23%, 3DCRT 33%	Mean PSA ng/ml IMRT 35.0 (SD 26.4); 3DCRT high dose 30.9 (SD 56.6); 3DCRT low dose 34.2 (SD 53.8)	Mean IMRT 71.6 (SD 4.9) 3DCRT high dose 72.6 (SD 7.2); 3DCRT low dose 70.7 (SD 6.5)
Zelefsky[91]	Clinically localised stage T1–T3 PC	NR (all T1–T3 as inclusion criterion) reports NCCN risk group across both groups: low risk 22%; intermediate 42%; high 36%	NR	NR	Median (both groups) 69 (range 46 to 86)

		Baseline characteristics			
Study	**Inclusion criteria**	**Stage of cancer (% each group)**	**Grade of cancer (Gleason score)**	**Initial PSA**	**Age (years)**
Ashman[100]	Patients with PC treated with WPRT using conformal techniques. All patients had pelvic node involvement as determined by imaging ($n = 14$) or biopsy ($n = 13$)	Across both groups T1c 19% T2 26% T3 41% T4 15%	Across both groups Gleason score 6 4% score 7 37% score 8 33% score 9 26%	Across both groups Median 26.0 ng/ml (range 4.5 to 207)	Across both groups median 62 (range 42 to 80)
Lips[43]	Patients with locally advanced PC	T-stage T1 IMRT 13%, 3DCRT 5.1%; T2 IMRT 5.4%, 3DCRT 16.7%; T3 IMRT 81.5%, 3DCRT 76.9%; T4 IMRT 0%, 3DCRT 1.3%	Tumour grade G1 IMRT 12%, 3DCRT 12.8%; G2 IMRT 67.4%, 3DCRT 69.2%; G3 IMRT 20.7%, 3DCRT 17.9%	Mean PSA ng/ml IMRT 19 (range 2 to 90); 3DCRT 28 (range 0.2 to 400)	Mean (range) IMRT 67 (49 to 79); 3DCRT 67 (47 to 78)

AJCC, American Joint Committee on Cancer; NR, not reported; UCSF, University of California, San Francisco; WPRT, whole pelvis radiotherapy.

Treatment details IMRT

	IMRT	
Study	**Treatment details**	**System**
Kupelian[84]	A nominal dose of 70 Gy delivered at 2.5 Gy/fraction in 28 fractions during 5.5 weeks. The dose constraints used during inverse planning set the goal of the target volume at 70 Gy (range 65–78). The limits used for the bladder were up to 30% to receive more than 55 Gy, with the maximal level at 74 Gy; and for the rectum, up to 30% to receive more than 50 Gy, with the maximal level at 74 Gy. Radiation was delivered with 10 MV photon beams using a dynamic multileaf collimator Inverse planned. The field segments were created. The specific method of treatment delivery was the sliding window or dynamic delivery of field segments. A five-field beam arrangement was chosen: one anterior, two lateral, and two anterior oblique beams. One of the lateral fields was occasionally annulled because of the presence of a prosthetic hip. Patients were set up on the table with minimal immobilisation in the supine position. Daily localisation for treatment was performed using the BAT transabdominal ultrasound system RT to prostate only for low-risk cases, prostate and SVs for high-risk cases	Planned – Corvus treatment-planning computer BAT transabdominal ultrasound system Radiation delivered by Varian 2100-CD
Sanguineti[88]	Immobilisation alpha cradle, planning CT 0.3/0.5 cm cuts, prostate apex uretrography 41 (91.1%), CT 0 (0.0%), MRI 4 (8.8%), margins for prostate PTV or PN/SV PTV (cm) 1.0 (all directions), mean (SD) prostate volume (cm^3) 51.0 (17.4), mean (SD) prostate PTV volume (cm^3) 199.5 (45.6), mean (SD) rectal volume (cm^3) 67.5 (21.9) 0.13, mean (SD) dose to posterior rectum (Gy) 35.3 (8.6), mean (SD) dose to anterior rectum (Gy) 74.8 (1.4). Planning process combined two phases, a boost to the prostate and a pelvic treatment The initial boost delivers 16 Gy over eight fractions and it is followed by a 6 MV X-ray eight-field coplanar inverse planning IMRT technique delivering an additional 60 Gy over 30 fractions to the prostate (76 Gy total) and 54 Gy over 30 fractions to the SVs and PNs. The main reason to deliver the boost upfront is to allow more time for QA of the IMRT plan Inverse planned. Field sizes were determined by the inverse planning system, but were initially set to allow exposure of the sum of all PTVs plus an additional margin of 1.5 cm	Pinnacle (Philips Medical Systems, Madison, WI, USA) treatment-planning system
Shu[29]	All patients received a maximal dose within the target volume (D_{max}) of 82 Gy or more. IMRT treatments were either forward planned, using UM-PLAN with seven beam positions and two to three segments per position, or inverse planned, using Corvus (Nomos Corporation, Sewickley, PA, USA) with seven beam positions and multiple segments per position. For the IMRT plans, two target volumes were used. One target represented the entire prostate gland, and the other represented the DIL defined by MRI/MRSI. The DIL was treated at a higher dose per fraction concurrently with the entire prostate. Treatment duration (days) median 65 range 57–79, no. treatment fractions median 41 range 40–45, D_{max} (cGy) median 8530 range 8203–9672, minimal prostate dose (cGy) median 7380 range 7200–7560, whole pelvis treated: yes 13 (72%) no 5 (28%) Inverse planned, with seven beam positions and multiple segments per position Forward planned, using UM-PLAN with seven beam positions and 2–3 segments per position	Planned – inverse planning by Corvus (Nomos Corporation, Sewickley, PA, USA) forward planning with UM-PLAN software (University of Michigan, Ann Arbor, MI, USA)
Vora[89]	Five-field IMRT with 10 MV photons, prostate and SVs in PTV with a 6–10 mm margin. 5040 cGy 0 SVs, median dose 7560 cGy to prostate (range 7020–7740 cGy). Daily localisation for treatment was performed using transabdominal ultrasound. Dose–volume restrictions were used in treatment planning: no more than 40% bladder and rectal volume could receive more than 65 Gy; no more than 30% bladder and rectal volume could receive more than 70 Gy; no more than 10% bladder and rectal volume could receive more than 75 Gy; no more than 1.8 cm^3 bladder and rectal volume could receive 81 Gy; full thickness of femur should not receive >50 Gy	NR
Yoshimura[41]	IMRT 76.5 Gy dose, five-field dynamic MLC technique, target prostate or prostate and SVs. Inverse treatment planning. Dose–volume constraints for PTV, rectal wall, bladder wall and bowels based on dose–volume histogram – no more than 1% rectal wall volume more than prescription dose, no more than 25% rectal wall volume more than 70 Gy, no more than 35% rectal wall volume more than 60 Gy, no more than 60% rectal wall volume more than 40 Gy; no more than 60% bladder wall volume more than 40 Gy, no more than 35% bladder wall volume more than 70 Gy	Planning Helios system (Varian Medical System)

	IMRT	
Study	**Treatment details**	**System**
Zelefsky[91]	IMRT (81 Gy) with 15 MV X-rays in daily fractions of 1.8 Gy. Some patients received 86.4 Gy[99] The PTV was derived from simulation CT scans and included the entire prostate and SV plus a 10 mm safety margin, except at the prostate–rectum interface where a 6 mm margin was used to decrease the risk of rectal toxicity. Treated in prone position with thermoplastic body cast for immobilisation. The prescribed dose represented the minimum dose to the PTV, but portions of the target volume received up to 7% higher doses. Patients treated to 81 Gy received a separate multifield plan for the last 9 Gy which blocked the rectum in each field. Dose–volume histograms were used to assure that no more than 30% of the rectal wall and/or 50% of bladder wall received a maximum dose of 75.6 Gy. Beam intensity profiles were delivered by dynamic multi-leaf collimation using the sliding window technique.[95] QA before and during treatment by the MSKCC record and verify computer	MSKCC planning system[97]
Ashman[100]	PTVs for prostate and bilateral pelvic lymph nodes were contoured separately. The prostate PTV was derived from simulation CT scans and included the entire prostate and SVs plus a 1 cm safety margin, except at the prostate–rectum interface where a 6 mm margin was used to decrease the risk of rectal toxicity. Bilateral obturator, internal iliac, and external iliac nodal regions contoured with approximately 1 cm margin. Pelvic IMRT plans used five coplanar beam angles approx equally spaced around the patient. Total dose typically 81 Gy ($n = 12$), for $n = 1$ 75.6 Gy. 15 MV photons with 1.8 daily fractions. Treated in prone position with thermoplastic body cast for immobilisation. Dose–volume histograms were used to assure that no more than 30% of the rectal wall and/or 50% of bladder wall received a maximum dose of 75.6 Gy	MSKCC planning system
Lips[43]	Dose escalation to prostate, delineated on CT, 76 Gy in 35 fractions of 2.17 Gy with MLC and 10 MV photons, transrectally implanted gold markers used for daily position verification	NR

MLC, multi-leaf collimator; MSKCC, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; SVs, seminal vesicles.

Treatment details 3DCRT

	3DCRT	
Study	**Treatment**	**System**
Kupelian[84]	A 10-field arrangement: the initial four fields delivering 42 Gy, followed by a six-field boost delivering 36 Gy. The total dose was 78 Gy delivered at 2 Gy/fraction. The dose was prescribed to an isodose line covering the prostate (mean isodose line 97%). The margins were 1 cm posteriorly and 1.5 cm in all other dimensions from the edge of the prostate or prostate/SV (gross target volume) to the edge of the block. The patients were aligned to skin marks with lasers in a supine position with the feet taped (no additional immobilisation devices). No daily localisation methods were performed for the 3DCRT cases RT to prostate only for low-risk cases, prostate and SVs for high-risk cases	NR
Sanguineti[88]	Patient position supine, immobilisation thermoplastic, rectum empty, bladder empty, simulation to localise isocentre, planning CT 0.5/1 cm cuts, prostate apex uretrography 0 (0.0%), CT 58 (85.3%), MRI 10 (14.7%), margins for prostate PTV superior/inferior (cm) 1.3, anterior/lateral (cm) 1.3, posterior (cm) 0.8, margins for PN/SV PTV (cm) NR, mean (SD) prostate volume (cm^3) 50.9 (17.0), mean (SD) prostate PTV volume (cm^3) 191.7 (45.8), mean (SD) rectal volume (cm^3) 59.9 (19.6), mean (SD) dose to posterior rectum (Gy) 28.2 (10.0), mean (SD) dose to anterior rectum (Gy) 74.0 (1.6), 3DCRT setup included three isocentric coplanar photon (15 MV) fields (0°, 110°, 250°; 3F-0°, 110°, 250°), with 76 Gy prescribed to the isocentre (ICRU point). A dose distribution at central axis and at least at six to ten off-axis slices in order to optimise beam weights, no wedges used	Dose distribution was obtained with Plato (Nucletron, Veenendaal, the Netherlands)

	3DCRT	
Study	**Treatment**	**System**
Shu[29]	All patients received a maximal dose within the target volume (D_{max}) of 82 Gy or more. For 3DCRT, the minimum prescription dose to the entire prostate was 72 to 79.2 Gy with the prescription isodose ranging from 90% to 100%. This resulted in a region of the target volume receiving at least 82 Gy. Treatment duration (days) median 63 range 57–77 no. treatment fractions median 44 range 37–44 D_{max} (cGy) median 8448 range 8200–8732 minimal prostate dose (cGy) median 7920 range 7200–7920 whole pelvis treated yes 1 (4%) no 25 (96%)	UM-PLAN software (University of Michigan, Ann Arbor, MI, USA)
Vora[89]	3DCRT with a four-field box approach. prostate and SVs with 1–2cm margin from PTV to block edge. photon of 10 MV, 180–200 cGy/dy. SVs approx 4500 cGy, prostate median dose 6840 cGy (range 6600–7100 cGy)	NR
Yoshimura[41]	3DCRT old (years 2000–3) protocol: 70 Gy dose, delivered as 46 Gy in 23 fractions, four-field box with MLC, followed by 24 Gy in 12 fractions, dynamic arc conformal technique, target prostate or prostate and SVs, leaf margins 7 or 15 mm according to local stage 3DCRT new protocol (years 2003–4): 73 Gy dose, target prostate or prostate and SVs, two lateral dynamic arcs with 100 degree rotation, dynamic conformal fitting of MLCs to PTV, 3 mm margins from edge of PTV to tips of MLCs. Dose volume constraints for PTV, rectal wall, bladder wall and bowels based on dose-volume histogram – no more than 1% rectal wall volume more than prescription dose, no more than 25% rectal wall volume more than 70 Gy, no more than 35% rectal wall volume more than 60 Gy, no more than 60% rectal wall volume more than 40 Gy; no more than 60% bladder wall volume more than 40 Gy, no more than 35% bladder wall volume more than 70 Gy	NR
Zelefsky[91]	The prostate PTV was derived from simulation CT scans and included the entire prostate and SV plus a 1 cm safety margin, except at the prostate–rectum interface where a 6 mm margin was used to decrease the risk of rectal toxicity. Treated in prone position with thermoplastic body cast for immobilisation. Dose–volume histograms were used to assure that no more than 30% of the rectal wall and/or 50% of bladder wall received a maximum dose of 75.6 Gy[96]	Memorial Sloan-Kettering Cancer Center (New York, NY, USA) planning system
Ashman[100]	PTVs for prostate and bilateral pelvic lymph nodes were contoured separately. The PTV was derived from simulation CT scans and included the entire prostate and SV plus a 1 cm safety margin, except at the prostate–rectum interface where a 6 mm margin was used to decrease the risk of rectal toxicity. Bilateral obturator, internal iliac, and external iliac nodal regions contoured with approx 1 cm margin. Four-field box WP plans were used. Total dose typically 75.6 Gy (n = 13), for n = 1 64.8 Gy. 15 MV photons with 1.8 daily fractions. Treated in prone position with thermoplastic body cast for immobilisation. Dose–volume histograms were used to assure that no more than 30% of the rectal wall and/or 50% of bladder wall received a maximum dose of 75.6 Gy[96]	Memorial Sloan-Kettering Cancer Center (New York, NY, USA) planning system
Lips[43]	3DCRT external beam technique, dose of 70 Gy delivered at 2 Gy fractions, 5 fractions per week. conformal three-field isocentric technique using 6 and 18 MV photons and MLC, position verification by visualising bony anatomy using electronic portal imaging devices (possible variation of position of prostate relative to bony anatomy)	NR

MLC, multi-leaf collimator; SV(s), seminal vesicle(s).

Other treatment

Study	Neoadjuvant/adjuvant hormonal therapy	Surgery	Chemotherapy/other
Kupelian[84]	Adjuvant androgen deprivation IMRT 60%, 3DCRT 72% (hormonal therapy given to high risk patients)	Prior surgery (TURP) IMRT 3%, 3DCRT 5%	NR
Sanguineti[88]	Androgen deprivation none 3DCRT 32.4% IMRT 35.6%; neoadjuvant + concomitant 3DCRT 20.6% IMRT 6.7%; neoadjuvant + concomitant + adjuvant 3DCRT 47.1% IMRT 57.8%	Prior surgery (TURP) TURP No 3DCRT 89.7% IMRT 82.2%; Yes 3DCRT 10.3% IMRT 17.8%	NR
Shu[29]	Overall 35/44 patients had hormonal therapy	NR	NR
Vora[89]	High-risk patients PSA > 20 ng/ml or Gleason score 8–10 received long course of androgen deprivation therapy (2–3 years), IMRT 30.3%; 3DCRT 17.6%	NR	NR
Yoshimura[41]	All but two patients neoadjuvant hormonal therapy	NR	NR
Zelefsky[91]	Androgen deprivation therapy overall yes 678 (43%), no 893 (57%) neoadjuvant. No post radiation ADT	NR	None before PSA relapse
Ashman[100]	All patients neoadjuvant and concurrent complete androgen blockade	NR	30% (8/27) patients had chemotherapy, seven in the 3DCRT group, and one IMRT
Lips[43]	Hormonal treatment IMRT 26%; 3DCRT 12%	NR	Hyperthermia treatment IMRT 0%; 3DCRT 26%

ADT, androgen deprivation treatment; NR, not reported; TURP, transurethral resection of the prostate.

Additional study results reported

Study	Results
Kupelian[84]	Kupelian 2005[85] considering each treatment group separately, multivariate analysis found no association between hormonal therapy and biochemical relapse-free survival, but that pretreatment PSA and Gleason score were significant predictors of biochemical relapse-free survival A later report of this study[86] when the IMRT group had 770 patients with a median follow-up of 45 months, reported less acute GI toxicity ($p < 0.001$) in patients treated at a later period as there had been a change in treatment planning to reduce the volume of rectum receiving the prescription dose of 70 Gy. One patient died but it was unclear if this was a treatment-related death due to late rectal toxicity or the patient's underlying medical condition[86]
Vora[89]	Vora ASTRO Phoenix definition, when investigating risk groups, 5-year survival for IMRT patients was 91.5% for low-risk patients, 79.0% for intermediate risk, and 90.6% for high-risk patients. For 3DCRT the survival data by risk group were 89.3%, 68.0%, and 48.8% respectively. IMRT significantly improved biochemical survival for intermediate ($p = 0.0092$) and high risk ($p = 0.0078$) patients, but for low-risk patients there was no significant difference between treatment groups ($p = 0.9166$)

Study	Results
Zelefsky[91]	Higher incidence of late GI toxicity in those patients who experienced acute GI toxicity (42%) than those that didn't (9%) ($p < 0.0001$). Median time to development of late GI grade 2 or higher toxicities 17 months (range 4–102 months). Median time to development of late GU toxicity 30 months. GU toxicity took longer to develop, but was of shorter duration than GI toxicity. Across both treatment groups, of patients with late GI toxicity, 91% had resolution of symptoms, median time to resolution 26 months. Across both treatment groups, of patients with late GU toxicity, 81% had resolution of symptoms, median time to resolution 7 months. Higher incidence of late GU toxicity in those patients who experienced acute GU toxicity (35%) than those that did not (12%) ($p < 0.001$). Within the 3DCRT group, dose difference in late GI toxicity at 10 years, for dose 70.2 Gy 7% developed grade 2 or higher GI toxicity, for dose 75.6 Gy 18%. IMRT at 81 Gy had 5% GI toxicity
	Zelefsky 2003,[94] 740 patients, 96 of whom were 60 years or younger, 644 older than 60 years. Examined effect of radiation dose on biochemical disease-free survival in patients aged 60 years or younger. For younger patients given IMRT, 5-year PSA relapse-free survival rates were 96% for patients with favourable prognosis, 87% for intermediate, and 50% for patients with unfavourable prognosis. A 5-year PSA relapse-free survival for dose < 66 Gy was 0% for dose 68.4–72 Gy was 47%, and for dose 75.6 Gy was 75% ($p < 0.001$). Dose < 75.6 Gy was the most important predictor of biochemical relapse in younger patients. Gleason score > 7 was also a predictor. Biochemical survival rates at 5 years 82% in younger men, 79% for older men, at 7 years 79% and 78% respectively ($p = 0.48$). For intermediate or unfavourable risk patients there was a significant benefit of dose ≥ 75.6 Gy ($p = 0.003$). Non-significant for favourable risk patients, though lack of significance may be due to small number of patients
	From a sample of 2047 patients with median follow-up 6.6 years,[98] for low and intermediate-risk groups IMRT dose levels of ≥ 81 Gy did not further improve biochemical outcomes compared with 3DCRT 75.6 Gy. For high-risk patients 5-year PSA relapse-free survival outcomes for dose 86.4, 81, 75.6, and 70.2 Gy or less were 71%, 66%, 61%, and 40%, respectively; dose was only significant by univariate analysis, with multivariate analysis showing non-significant effect of dose, but significant neoadjuvant ADT ($p = 001$; HR, 0.623) – note that patients selected to receive neoadjuvant ADT were significantly more likely to receive higher radiation doses ($p < 0.0001$).[98] From a sample of 2047 patients with median follow-up 6.6 years from the Zelefsky study,[98] distant metastases-free survival was affected by dose in intermediate ($p = 0.04$) and high risk ($p = 0.01$) patients, but not low-risk patients. Dose was not a significant predictor of cause-specific mortality[98]
	Zelefsky 2002,[92] no comparator data, IMRT data only, measure of sexual function, 52% of the 540 patients who were potent before IMRT remained potent at 2 years follow-up
	Data for IMRT 86.4 Gy,[99] with no comparator data, high-dose IMRT in 478 patients, median follow-up 53 months, $n = 37$ (8%) acute grade 2 GI toxicity. $n = 105$ (22%) acute grade 2 GU toxicity, 3 (0.6%) grade 3 GU toxicity. $n = 16$ (3%) late grade 2 GI toxicity. $n = 2$ (<1%) late grade 3 GI toxicity. $n = 60$ (13%) late grade 2 GU toxicity. $n = 12$ (<3%) late grade 3 GU toxicity. A 5-year actuarial PSA relapse-free survival according to the ASTRO Phoenix definition was 98%, 85% and 70% for the low, intermediate, and high-risk NCCN prognostic groups[99]
Lips[43]	Toxicity (CTC measurement) – only one patient in the study (from the IMRT group) developed grade 3 acute toxicity – a urinary tract infection. None of the other patients developed acute toxicity above grade 2
	Considering the time points baseline and 1 month post-RT, for six of the 29 items there was a significant interaction between treatment group and time, with the 3DCRT group showing more deterioration than the IMRT group. These items were RAND-36 social functioning ($p = 0.006$), pain ($p = 0.01$) and change in health ($p < 0.0001$); EORTC QLQ-C30(+3) physical functioning ($p = 0.006$) and role functioning ($p = 0.006$); EORTC QLQ-PR25 urinary symptoms/function ($p < 0.0001$). For baseline and 6 months post-RT, there were no significant differences between groups on any of the items measured. For the other 23 items there were no significant differences between groups and no significant interaction between treatment group and time. These items were RAND-36 physical functioning, physical role restriction, emotional role restriction, mental health, vitality, general health; EORTC QLQ-C30(+3) emotional functioning, cognitive functioning, social functioning, global health/quality of life, fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties; EORTC QLQ-PR25 bowel symptoms/function, treatment-related symptoms, sexual functioning
	Both groups showed clinically significant deterioration in RAND-36 physical role restriction at 1 month and EORTC QLQ-PR25 sexual activity at 1 and 6 months post-RT, and a clinically significant improvement in RAND-36 emotional role restriction at 6 months post-RT
	Considering each treatment group separately, there were changes deemed clinically significant (change in score of 10 or more points), for IMRT which had improvement in change in health at 1 month and 6 months, for 3DCRT there were deteriorations in pain, role functioning and urinary symptoms/function at 1 month post-RT, but not at 6 months post-RT
	Comparing patients treated with hormonal therapy ($n = 33$) with without hormonal therapy ($n = 137$), the only differences were that patients treated with hormonal therapy had more treatment-related symptoms at 1 month, and better change in health at 6 months post-RT

Appendix 3

Quality assessment of the eight studies fully reported in peer-reviewed publications[83]

	Kupelian et al.[84]	Sanguineti et al.[88]	Shu et al.[29]	Vora et al.[89]	Yoshimura et al.[41]	Zelefsky et al.[91]	Ashman et al.[100]	Lips et al.[43]
Reporting								
Hypothesis clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Main outcomes clearly described	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Patient characteristics clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study groups similar	No	No	No	No	No	Yes	No	No
Data collection methods similar	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Interventions clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Confounders clearly described	Partially	Yes	No	No	No	Yes	No	Partially
Similar treatment groups	Partially	No	No	No	No	Yes	No	No
Findings are clear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Estimates off random variability	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
AEs	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Loss to follow up described	No	No	No	No	No	No	No	Unable to determine
Actual probability values	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
External validity								
Subjects asked to participate are representative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Subjects who did participate are representative	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Location representative	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Internal validity-bias								
Subjects blind	No	No	No	No	No	No	No	No
Assessors blind	No	No	No	No	No	No	No	No
Clarity re data dredging	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Adjusted for follow-up lengths	Yes	Yes	Yes	No	Unable to determine	No	Yes	Yes
Appropriate statistical tests	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reliable compliance	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Outcomes measures valid/reliable	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

	Kupelian et al.[84]	Sanguineti et al.[88]	Shu et al.[29]	Vora et al.[89]	Yoshimura et al.[41]	Zelefsky et al.[91]	Ashman et al.[100]	Lips et al.[43]
Internal validity-confounding								
Same population in each group	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Same time period	No	No	Yes	No	No	No	No	No
Randomised	No	No	No	No	No	No	No	No
Concealment	No	No	No	No	No	No	No	No
Confounding adjustment adequate	Yes	Yes	No	No	No	Yes	No	No
Losses of patients accounted for	Unable to determine	Unable to determine	No	No	Unable to determine	Unable to determine	No	Unable to determine

Appendix 4

Quality assessment for the five included abstracts[83]

	Kirichenko et al.[105]	Sharma et al.[106]	Morgan et al.[107]	Boehmer et al.[108]	Martinez et al.[110]
Reporting					
Hypothesis/aim clearly described	Yes	Yes	No	Yes	Yes
Main outcomes clearly described	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Patient characteristics clearly described	No	No	No	No	No
Study groups similar	Unable to determine	Unable to determine	Unable to determine	No	No
Data collection methods similar	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Interventions clearly described	Yes	Unable to determine	Unable to determine	Unable to determine	Yes
Confounders clearly described	Yes	No	No	No	No
Similar treatment groups	Yes	Unable to determine	Unable to determine	Unable to determine	Yes
Findings are clear	Yes	Yes	Yes	Yes	Yes
Estimates of random variability	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
AEs	Yes	Yes	Yes	Yes	Yes
Loss to follow-up described	No	No	No	No	No
Actual probability values	Yes	Yes	Yes	Yes	Yes
External validity					
Subjects asked to participate are representative	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Subjects who did participate are representative	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Location representative	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Internal validity-bias					
Subjects blind	No	No	No	No	No
Assessors blind	No	No	No	No	No
Clarity re data dredging	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Adjusted for follow-up lengths	Unable to determine	Yes	Yes	No	No
Appropriate statistical tests	Yes	Unable to determine	Yes	Unable to determine	Unable to determine
Reliable compliance	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Outcomes measures valid/reliable	Unable to determine	Unable to determine	Unable to determine	Yes	Unable to determine

	Kirichenko et *al.*[105]	**Sharma et *al.*[106]**	**Morgan et *al.*[107]**	**Boehmer et *al.*[108]**	**Martinez et *al.*[110]**
Internal validity-confounding					
Same population in each group	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Same time period	No	No	No	Yes	Unable to determine
Randomised	No	No	No	No	No
Concealment	No	No	No	No	No
Confounding adjustment adequate	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Losses of patients accounted for	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine

Appendix 5

Table of key excluded studies with rationale

The name of the first author, year and reason for exclusion are reported below. The table includes only studies that were examined at full-text sift and were potentially studies of interest, but were not deemed relevant or valid on closer inspection.

First author (year)	Reasons for exclusion
Adkinson (2008)[138]	No comparator group
Allison (2008)[139]	No comparator group
Amer (2003)[140]	Dosimetric study
Bernard (2008)[141]	No comparator group
Bossi (2008)[142]	Literature review
Bhatnagar (2006)[143]	No comparator group
Bui (2006)[68]	No comparator group
Buyyounouski (2007)[144]	No comparator group
Cahlon (2008)[99]	No comparator group
Catton (2002)[145]	No comparator group
Chan (2004)[146]	No comparator group
Chao (2004)[147]	No comparator group
Cheung (2008)[148]	No comparator group
Cohen (2006)[149]	No comparator data
Daly (2009)[150]	Protocol only
Dearnaley (1999)[151]	No IMRT group
Dearnaley (2007)[62]	Dose escalation, not IMRT
De Meerleer (2007)[108]	No comparator group
De Meerleer (2008)[152]	No comparator group
Djemil (2003)[153]	No comparator group
Dogan (2006)[154]	No comparator group
Dogan (2006)[155]	Planning study
Dong (2001)[156]	Planning study
Dubus (2002)[157]	Literature review
Engler (1997)[158]	Planning study
Fonteyne (2006)[159]	No comparator group
Guckenberger (2008)[160]	Not in English language
Guerrero (2004)[161]	Literature review
Hsi (2007)[162]	No comparator group
Jani (2007)[94]	Not conformal RT
Johnstone (2004)[163]	No comparator data
Lane/NIHR (2009)[164]	Ongoing study, not re IMRT
Lee (2007)[165]	Planning study
Liauw (2007)[166]	No separate data for 3DCRT
Livi (2006)[167]	Planning study
Liu (2007)[168]	Dosimetric study

First author (year)	Reasons for exclusion
Khoo (2008)[169]	Planning study
Kosakowski (2008)[170]	Not in English language
Kry (2006)[171]	Planning study
Kuczer (2008)[172]	Not in English language
Liauw (2007)[166]	Not clear if 3DCRT
Lim (2008)[173]	No comparator group
Ma (2008)[174]	No comparator group
Mahadevan (2006)[175]	No comparator group
Marchand (2008)[176]	No comparator group
McCammon (2006)[177]	No comparator group
McCloskey (2005)[178]	No meaningful comparative statistics
Melcon (2007)[179]	Positioning study
Michalski (2006)[180]	Literature review
Molla (2007)[181]	No comparator group
Namiki (2006)[182]	No separate comparator data
Perez (2000)[183]	Not IMRT
Perez (2007)[184]	No comparator group
Pollack (2003)[185]	Literature review re dose escalation
Pollack/NCI (2009)[186]	Ongoing study, no comparator data
Rembielek (2006)[187]	No comparator group
Reuther (2006)[188]	No comparator group
Ruben (2008)[189]	Dosimetric study
Sanders/MRC (2009)[190]	Ongoing study, no 3DCRT data
Sanguineti (2003)[191]	No separate comparator data
Sanguineti (2004)[192]	No separate comparator data
Scarbrough (2007)[193]	No comparator group
Singh (2007)[194]	No comparator group
Shahar (2004)[195]	No comparator data
Soete (2008)[196]	Not in English language
Su (2006)[197]	Not conformal RT
Teh (2001)[198]	No comparator group
Teh (2003)[199]	No comparator group
Teh (2007)[200]	No comparator group
Teslow (2001)[201]	Planning study
Thakkar (2005)[202]	No comparator group
Yuen (2008)[203]	Dosimetric study
Vaarkamp (2002)[204]	Letter only
Villa (2008)[205]	No comparator group
Wahab (2005)[206]	Dosimetric study
Wang (2004)[207]	Dosimetric study
Wang-Chesebro (2006)[208]	Dosimetric study
Wong (2008)[209]	No comparator data
Wu (2002)[210]	Planning study
Zelefsky (2002)[211]	Dosimetric review

Appendix 6

Resource use and cost assumptions for IMRT and 3DCRT

A personal communication with Nuala Close (St Bartholomew's Hospital, London, UK, 2009) provided resource use and cost assumptions for IMRT and 3DCRT.

Resource	Time (hours)	WTE effort	Time×WTE	Band (average)	Hourly rate (£)	Costs per patient
3DCRT						
Simulator	0.6	2	1.2	7	32.98	£39.58
CT	0.6	2	1.2	7	32.98	£39.58
Outlining	1	1	1	Consultant	75.26	£75.26
Plan	4	1	4	7	32.98	£131.92
Plan check	0.6	1	0.6	8a/b	37.75	£22.65
Simulator verification	0.6	2	1.2	7	32.98	£39.58
Image/plan approval (Dr)	0.3	1	0.3	Consultant	75.26	£22.58
Image referencing	0.3	1	0.3	7	32.98	£9.89
Pre-treatment data input and checks	1.5	1	1.5	6.5	32.98	£49.47
Treat (37 fractures)	11.1	3	33.3	6.5	32.98	£1098.23
	Total WTE effort		**44.6**			**£1528.73**
IMRT						
Simulator	0.6	2	1.2	7	32.98	£39.58
CT	0.6	2	1.2	7	32.98	£39.58
Outlining	1	1	1	Consultant	75.26	£75.26
Plan	8	1	8	8a	37.75	£301.97
QA	3	2	6	8a/b	37.75	£226.48
Plan check	2.5	1	2.5	8b	44.62	£111.55
Rad checks	2.75	1	2.75	7	32.98	£90.70
Simulator verification	0.6	2	1.2	7	32.98	£39.58
Image/plan approval (Dr)	1.33	1	1.33	Consultant	75.26	£100.09
Image referencing	0.3	1	0.3	7	32.98	£9.89
Pre-treatment data input and checks	1.5	1	1.5	6.5	32.98	£49.47
PI Review	1.5	1	1.5	7/8a	34.84	£52.25
Treat (37 fractures)	12.7	3	38.1	6.5	32.98	£1255.12
	36.4 Total WTE effort		**66.5**			**£2391.51**
Both						
Nurse assessment	0.5	1	0.5	7	32.98	£16.49
Patient information review before treatment	0.5	1	0.5	6	28.58	£14.29
Nurse on treatment review (weekly)	0.5	1	0.5	Band 7 (15 minutes per consultation)	32.98	£16.49

Resource	Time (hours)	WTE effort	Time×WTE	Band (average)	Hourly rate (£)	Costs per patient
Dr on treatment review (every 2 weeks)	0.75	1	0.75	Junior doctors (15 minutes per cons)	35.02	£26.27
Junior medical review (one visit)	0.5	1	0.5	30 minutes per patient	35.02	£17.51
Secretarial	2	1	1			£207.03
Dietic assessment and treatment (one visit)	0.5	1	0.5	7	32.98	£16.49
	41.6		5.3			
Sim/CT/planning		Per course		2 per patient		£500.00
Physics commissioning, QA		Per course				£320.00
Plus capital costs linac/vision		Per course		24,000 fractions per annum		£452.64
Plus equipment maintenance costs		Per course		Linacs/CT/ Software		£252.63
Consumables (paper, toner, etc.)						£3.40
Clerk: making up of folder, organising appointments	7.4	1	0.2	3	15.64	£115.75
Scheduling	1.5	1	1.5	8a	37.75	£56.62
In vivo dosimetry	0.5	1	0.5	6/7	29.32	£14.66
Non-chemo prescriptions				Pharmacy		£25.00
Cost of information given to patient				Printing		£2.50
Blood tests (FBC and LFT's/U&Es)				1 of each test once		£16.00
Other costs not covered above						£5.00
Referral district nursing	0.5	1	0.5	6	28.58	£14.29
Consumables						£45.00
Gowns (five per patient)						£25.00
						£2163.04

FBC, full blood count; LFT, liver function test; PI, portal image; Rad, radiation; U&Es, urea and electrolytes; WTE, whole time equivalent.

Appendix 7

Critical appraisal checklist for the economic evaluations using key components of the *British Medical Journal* checklist for economic evaluations together with the Eddy checklist on mathematical models employed in technology assessments

Authors		**Konski *et al.*[78]**
Year		2006
Modelling assessments should include:		**Yes/No**
1	A statement of the problem	Yes
2	A discussion of the need for modelling vs alternative methodologies	Yes
3	A description of the relevant factors and outcomes	Survival not clear
4	A description of the model including reasons for this type of model and a specification of the scope including time frame, perspective, comparators and setting	Timeframe unclear. Sensitivity analysis on timeframe suggests between 5 and 10 years. Perspective: Medicare
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence	Mostly. Source of utilities for some states not stated. Lack of comparative trial clinical data not discussed
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships and distributions) and the data	Yes
7	A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis	Yes
8	The results derived from applying the model for the base case	Yes
9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold	Yes
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect	Fairly well covered with sensitivity analysis
11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity	No
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results	No
13	A description of research in progress that could yield new data that could alter the results of the analysis	No

Authors		**Pearson *et al.*[64]**
Year		2007
Modelling assessments should include:		**Yes/No**
1	A statement of the problem	Yes
2	A discussion of the need for modelling vs alternative methodologies	No
3	A description of the relevant factors and outcomes	Yes
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting	Yes
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence	Yes
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships and distributions) and the data	Yes
7	A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis	Base case values. No distributions – limited sensitivity analysis
8	The results derived from applying the model for the base case	Yes
9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold	Limited sensitivity analysis (univariate and threshold)
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect	Limited
11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity	No
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results	No
13	A description of research in progress that could yield new data that could alter the results of the analysis	Yes

Appendix 8

Example search for cost and cost-effectiveness evidence (MEDLINE)

38. Economics/ (25834)
39. "costs and cost analysis"/ (37460)
40. Cost allocation/ (1864)
41. Cost-benefit analysis/ (44373)
42. Cost control/ (18019)
43. Cost savings/ (6144)
44. Cost of illness/ (10938)
45. Cost sharing/ (1430)
46. "deductibles and coinsurance"/ (1204)
47. Medical savings accounts/ (396)
48. Health care costs/ (17205)
49. Direct service costs/ (860)
50. Drug costs/ (8865)
51. Employer health costs/ (995)
52. Hospital costs/ (5709)
53. Health expenditures/ (10360)
54. Capital expenditures/ (1839)
55. Value of life/ (5057)
56. exp economics, hospital/ (15764)
57. exp economics, medical/ (12120)
58. Economics, nursing/ (3849)
59. Economics, pharmaceutical/ (1958)
60. exp "fees and charges"/ (24129)
61. exp budgets/ (9937)
62. (low adj cost).mp. (12442)
63. (high adj cost).mp. (5477)
64. (health?care adj cost$).mp. (2047)
65. (fiscal or funding or financial or finance$).tw. (51383)
66. (cost adj estimate$).mp. (955)
67. (cost adj variable).mp. (25)
68. (unit adj cost$).mp. (976)
69. (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (108532)
70. budget$.tw. (12665)
71. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).tw. (59198)
72. (fee or fees).tw. (9053)
73. (value adj2 (money or monetary)).tw. (787)
74. or/1-36 (371937)
75. Radiotherapy, Intensity-Modulated/ (896)
76. intensity modulated radiotherap*.tw. (1254)
77. intensity-modulated radiotherap*.tw. (1254)
78. intensity modulated radiation therap*.tw. (1364)
79. intensity-modulated radiation therap*.tw. (1364)
80. imrt.tw. (2402)
81. image guided radiotherap*.tw. (193)
82. igrt.tw. (123)
83. dose compensation.tw. (30)
84. electronic compensation.tw. (28)
85. e compensation.tw. (0)
86. forward planning.tw. (100)
87. inverse planning.tw. (334)
88. field in field.tw. (18)
89. physical compensation.tw. (4)
90. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 (3718)
91. prostatic neoplasms/ (63810)
92. (prostat$ adj5 (cancer$ or carcin$ or tumor$ or tumour$ or neoplasm$)).tw. (63945)
93. ((carcinoma or neoplasia or neoplasm$ or adencarcinoma or cancer$ or tumor$ or tumour$ or malignan$) adj3 prostat$).tw. (61853)
94. 54 or 55 or 56 (78190)
95. 53 and 57 and 37 (19)
96. from 58 keep 1-19 (19)

Appendix 9

Summary study survival and toxicity data by dose

	Dose		Number in cohort		PSA survival				Late GI toxicity (grades 2 and 3) (%)		
	IMRT	3DCRT	IMRT	3DCRT	Time in years (actuarial)	Measure	IMRT	3DCRT	Toxicity measure	IMRT	3DCRT
IMRT/3DCRT same dose											
Martinez[110]	80	80	172	556	5	–	–	–	NCI-CTC	5	18
Morgan[107]	80	81	188	188	4	Phoenix	82	81	RTOG	4	9
Kupelian 2005[85]	70[a]	78	100	310	5	Consensus	85	78			
						Phoenix	88	–			
Sharma[106]	76	76	123	170	5				NS	9	22
Higher dose IMRT											
Zelefsky[91]	81	76	472	358	10	–	–	–	NCI-CTC	5	18
Boehmer[108]	80	72	96	91	Not actuarial mean 1.6 years	–	–	–	NCI-CTC (not actuarial – mean 1.6 years)	10	11
Vora[89]	75.6	68	145	271	5	Consensus	74	60	RTOG (not actuarial – median 4/5 years IMRT/3D)	24	16
						Phoenix	85	74			

NS, not specified.
a 70 Gy given in 2.5 Gy fractions biologically equivalent dose to 78 Gy in 2 Gy fractions.

Appendix 10

Biological equivalent radiotherapy doses

If N is the total number of fractions of RT given in a treatment course, and d is the dose per fraction, the biological equivalent dose (BED) is calculated as:

$$\text{BED} = N \times d \times [1+d/(\alpha/ß)]$$

The α/ß ratio is a measure of the effect of radiation on different tissues. Kupelian *et al.* assumed an (α/ß) ratio of 3.[85]

For the 3DCRT group given a total dose of 78 Gy by 39 fractions of 2 Gy each the BED is:

$$\text{BED (3DCRT)} = 39 \times 2 \times [1+2/3] = 130$$

The IMRT group was given a hypofractionated regime of 28 fractions of 2.5 Gy each to give a total dose of 70 Gy.

$$\text{BED (IMRT)} = 28 \times 2.5 \times [1+2/3] = 128$$

Thus Kupelian assumed that although the IMRT group received a total dose of 70 Gy compared to a dose of 78 Gy for the 3DCRT group, the hypofractionated regime of the IMRT group meant that the BED doses of the two regimes were comparable.[58]

Appendix 11

Example search for utility values in prostate cancer (MEDLINE)

1. prostatic neplasms/
2. (prostat* adj5 (cancer* or carcinoma* or tumor* or tumour* or neoplasm*)).tw.
3. ((carcinoma* or neoplasia or neoplasm* or adenocarcinoma* or cancer* or tumor* or tumour* or malignan*) adj3 prostat*).tw.
4. 1 or 2 or 3
5. (utillity or utilities or eq5d or eq-5d or europol or qwb or hui2 or hui3 or 15d or sf-6d or sf6d or aqol).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6. 4 and 5

Appendix 12

Unit cost

Item	Cost	Year	Source	Cost 2008–9
PSA test	£6	1995–6	Chamberlain 1997[17]	£10.19
GP attendance	£36	2007–8	Curtis 2008[127]	£36.97
Oncology outpatient	£86	2007–8	National reference costs 2009[51]	£88.33
Nurse (GP practice)	£10	2007–8	Curtis 2008[127]	£10.27
CT scan (one area)	£110	2007–8	National reference costs 2009[51]	£112.98
Bone scan	£164	2007–8	National reference costs 2009[51]	£168.44
Dexa scan	£71	2007–8	National reference costs 2009[51]	£72.92
Goserelin (Zoladex LA) 10.8 mg syringe	£267	2009	*British National Formulary* March 2009[128]	£267.48
Flexible sigmoidoscopy ± colonoscopy, biopsy	£484	2007–8	National reference costs 2009[51]	£496.63
Laser therapy	£1170	2007–8	National reference costs 2009[51]	£1201.31
Enemas (community nurse)	£26	2007–8	Curtis 2008[127]	£26.70

Appendix 13

Prostate-specific antigen variable distribution parameters

Variable	Distribution	Mean	Source
Utility values			
Utility decrement late bowel toxicity	Beta (56.6, 75.0) scaled between 0 and 0.2	0.086	Mean Shimizu,[116] Ara[126] (see Utility values), uncertainty in mean ± 20%, author assumption
Utility multiplier hormone treatment	Beta (37.8, 4.1)	0.903	Mean Shimizu,[116] Ara[126] (see Utility values), uncertainty in mean ± 20%, author assumption
Difference between HT utility multiplier and hormone-refractory multiplier	Beta (61.6,100.5) scaled between 0 and 0.3	0.114	Mean Shimizu,[116] Ara[126] (see Utility values), uncertainty in mean ± 20%, author assumption
Costs			
Cost of post-RT patient monitoring	Normal (mean 47.2, SE 4.81)	47.2	Mean – see Chapter 4, Resource use/costs, uncertainty in mean ± 20%, author estimate
Cost of post-PSA fail patient monitoring	Normal (mean 670.7, SE 68.4)	671	Mean – see Chapter 4, Resource use/costs, uncertainty in mean ± 20%, author estimate
Cost on HT	Normal (mean 1324, SE 135.1)	1324	Mean – see Chapter 4, Resource use/costs, uncertainty in mean ± 20%, author estimate
Cost hormone refractory	Normal (mean 7385, SE 753.6)	7385	Mean – see Chapter 4, Resource use/costs, uncertainty in mean ± 20%, author estimate
Cost terminal care	Normal (mean 4007, SE 408.9)	4007	Mean – see Chapter 4, Resource use/costs, uncertainty in mean ± 20%, author estimate
Cost treating late GI toxicity – annual	Normal (mean 335, SE 34.2)	335	Mean – see Chapter 4, Resource use/costs, uncertainty in mean ± 20%, author estimate
Cost treating late GI toxicity – per patient	Normal (mean 2139 SE 218.3)	2139	Mean – see Chapter 4, Resource use/costs, uncertainty in mean ± 20%, author estimate
Incidence late GI toxicity			
Vora IMRT	Beta (35, 110)	0.24	Vora[89]
Vora 3DCRT	Beta (43,228)	0.16	Vora[89]
Kupelian IMRT	Beta (11,89)	0.11	Kupelian 2005[85]
Kupelian 3DCRT	Beta (14,102) scaled by 0.12/0.05	0.12	Kupelian 2002,[84] scale also Kupelian 2005[85]
Morgan IMRT	Beta (8,180)	0.04	Morgan[107]
Morgan 3DCRT	Beta (17,171)	0.09	Morgan[107]
Timing/duration			
Time start to finish GI incident tox (years) Vora	Normal (mean 4.5, SE 0.46)	4.5	Mean Vora,[89] uncertainty in mean ± 20%, author estimate
Time start to finish GI incident tox (years) Kupelian	Normal (mean 4.5, SE 0.46)	4.5	Mean Kupelian 2005,[85] uncertainty in mean ± 20%, author estimate
Time start to finish GI incident tox (years) Morgan	Normal (mean 3.5, SE 0.36)	3.5	Mean Morgan,[107] uncertainty in mean ± 20%, author estimate
Duration of late GI toxicity	Normal (mean 3.0, SE 0.31)	3	Mean derived from Zelefsky[91] (see Chapter 4, Other clinical parameters), uncertainty in mean ± 20%, author estimate

Variable	Distribution	Mean	Source
Duration hormone-refractory disease	Normal (mean 1.87, SE 0.19)	1.87	Mean Collins, uncertainty in mean ± 20%, author estimate

For all distributions, unless otherwise specified, it was assumed the uncertainty in the mean was ± 20%, i.e. one SE is approximately 10% of the mean value. For the incidence of late GI toxicity the alpha and beta parameters of the beta distribution were calculated directly from the number of patients affected (or the actuarial %) and the total number of patients. Note the Kupelian 3DCRT distribution is scaled by the incidence ratio of the incidence for (IMRT at 5 years)/(IMRT at 2.5 years) as the incidence of late GI toxicity for 3DCRT was only available at 2.5 years.

For the Weibull parameters for each of the survival curves (from PSA failure, clinical failure and PC death) Cholesky decomposition was used to provide correlated samples of the two Weibull parameters from a bivariate normal distribution.

HT, hormone therapy; SE, standard error.

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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.

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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.

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Suppl. 1
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Screening for hyperglycaemia in pregnancy: a rapid update for the National Screening Committee.
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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.
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Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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