NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Degarelix (Firmagon®) for the treatment of adult male patients with advanced hormone-dependent prostate cancer

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Executive summary

Degarelix (Firmagon®) is a gonadotrophin-releasing hormone (GnRH) antagonist, which received its marketing authorisation for Europe in April 2009.[1] Degarelix competitively and reversibly binds to the pituitary GnRH receptors, leading to a rapid reduction in the release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) and, consequently, to a rapid reduction of testosterone secretion by the testes to castrate levels.[2,3] Degarelix was accepted for the treatment of advanced hormone-dependent prostate cancer by the Scottish Medicines Consortium (SMC) in January 2011[4] and by the All Wales Medicines Strategy Group (AWMSG) in December 2012.[5]

Degarelix is available as a powder and solvent for solution for injection in vials containing 120 mg or 80 mg degarelix (as acetate). Administration is by subcutaneous injection, with a starting dose of 240 mg (two injections of 120 mg each), followed, after one month, by maintenance doses of 80 mg administered every 28 days.[2,3] The UK NHS Drug Tariff price for degarelix is £260.00 for the starting dose (2 x 120mg vials), and £129.37 per maintenance dose (1 x 80 mg vial).[6]

Degarelix is indicated for the treatment of adult male patients with advanced hormone-dependent prostate cancer.[2,3] It is the first GnRH antagonist to receive a licence for this indication in the UK. Patients receive one single continuous course of treatment with degarelix until the disease progresses to hormone-refractory prostate cancer, or until the end of life (depending on local practice).[7]

Comparator therapies for the management of advanced disease consistent with the decision problem (described in NICE final scope) include LHRH agonists, namely goserelin, leuprorelin and triptorelin, with initial co-administration of bicalutamide to counteract testosterone flare. Bicalutamide monotherapy may also be used as an alternative to LHRH agonists for a subset of patients with locally advanced disease.[8]

The key evidence to support the efficacy of degarelix derives from six randomised controlled trials (RCTs) that compared degarelix with an LHRH agonist (with and without initial anti-androgen therapy) (see Section 6.5.3).[9-38] Additional evidence is available from six randomised dose-finding trials [39-53] and seven non-randomised studies (mostly extensions of the completed RCTs).[54-71] Data from a number of post-hoc exploratory analyses pooled results of the completed Phase III/IIIb trials are also presented in this STA submission (see Section 6.9.2).[72-77]

Results of the included studies show that degarelix provides benefits over existing LHRH agonist therapy, including:

- **More rapid and improved disease control and lower risk of disease progression**:[2,3,9,10,21,74-76]
  - Degarelix achieves more rapid suppression of prostate-specific antigen (PSA) levels: median reduction at Day 28 of 82.3% versus 66.7% ($p<0.0001$) (see Section 6.5.3).[9,21]
  - Degarelix suppresses serum testosterone to castrate levels more rapidly than LHRH agonists ($p<0.0001$) (see Section 6.5.3).[2,3,9,10]

  - Degarelix is associated with a statistically lower risk of fractures (p=0.0234) joint-related signs and symptoms (p=0.0116), and urinary tract-related adverse events (p<0.0001) (see Section 6.9.2).[74-76]
- **Improved survival:**[74-76]
  - Rates of overall survival at one year are statistically higher with degarelix than with LHRH agonists (p<0.05) (see Section 6.6.1).[74-76]
- **Fewer cardiovascular events in patients with a history of cardiovascular disease**:[73,77]
  - Degarelix is associated with a statistically significant 50% lower risk of cardiovascular events – including arterial embolic and thrombotic events, haemorrhagic and ischaemic cerebrovascular conditions, myocardial infarction and other forms of ischaemic heart disease – and cardiovascular-related death[73,77] (p=0.0023)[73] (see Section 6.9.2).
- **No testosterone flare with initial treatment**:[2,3]
  - LHRH agonists are associated with a transient increase in testosterone levels – this can result in increased bone pain, spinal cord compression, pathological fracture, bladder outlet obstruction and death.[78] Concomitant therapy with an anti-androgen reduces the incidence of this 'testosterone flare' but does not completely remove the possibility of its occurrence.[79] Degarelix rapidly suppresses testosterone to castrate levels[2,3] and avoids this testosterone flare (see 'in Section 6.5.3). In addition, concomitant anti-androgen therapy is not needed with degarelix, a cost offset.

A Markov treatment-sequence model was developed in Microsoft® Excel to estimate the costs and benefits of degarelix treatment over a lifetime horizon for patients with advanced hormone-dependent prostate cancer (see Section 7.2.2). The model was designed to replicate disease progression over time by estimating outcomes over the treatment sequence typically followed by a patient with the condition (see Section 7.2.4).

Two patient groups are included in the economic evaluation. The first treatment group is the intention-to-treat (ITT) population from the CS21 and CS21A trials. This population reflects the licensed indication for the treatment of advanced hormone-dependent prostate cancer; however, the ITT population also includes some patients with localised prostate cancer, and in UK clinical practice, some of these patients would not be treated with hormonal therapy. A secondary group from the CS21 population is, therefore, also considered: patients with PSA levels >20 ng/ml. These patients are a higher-risk subgroup of the ITT population and are more reflective of the population treated with hormonal therapy in the UK (Sections 7.2.1 and 7.9).

The model successfully replicates the trial data, with predicted outcomes consistent with the wider clinical literature (see Sections 7.7.1 and 7.8). The model estimates that within the ITT population, patients treated with degarelix will remain on first-line therapy for an additional 0.37 years compared with patients treated with goserelin 10.8 mg, the most commonly-prescribed LHRH agonist in the UK. Over the patient's lifetime, treatment with degarelix results in an incremental gain of 0.58 quality-adjusted life-years (QALYs) and a cost saving of £1,541 (see Table 1 below, and

Section 7.7.6). This saving is due to the reduced costs of subsequent-line therapies and a reduced number of cardiovascular/musculoskeletal events compared with LHRH agonists.

A range of scenario analyses was undertaken in addition to deterministic and probabilistic sensitivity analysis. The results of the model were relatively insensitive to variations in the underlying assumptions, with degarelix being the cost-effective treatment option in 99.5% at a willingness-to-pay of £20,000 per QALY and in 100% at £30,000 per QALY (see Section 7.7.8).

Table 1. Base-case cost-effectiveness results

	Degarelix	**Goserelin (10.8 mg)**
Technology acquisition cost	£8,524	£3,978
Other costs	£17,571	£23,657
Total costs	£26,095	£27,636
Difference in total costs	N/A	-£1,541
LYG	9.58	9.21
LYG difference	N/A	0.37
QALYs	5.85	5.27
QALY difference	N/A	0.58
ICER	N/A	Dominating

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY(s) = quality-adjusted life year(s)

Table 2 shows the results for the PSA >20 ng/ml subgroup and indicates that treatment with degarelix is likely to be cost saving for this subgroup in the base case population.

This STA submission demonstrates that degarelix is cost-effective/dominant and offers clinicians a clinically effective and well-tolerated management strategy for patients with advanced prostate cancer.

A further point that should be considered when reviewing this submission is the level of data, and innovation provided for degarelix. In order to support this indication, six randomised controlled trials have been conducted, with long term data available to 5 years. Coupled with the predicted increase in life (0.37 years), and estimated cost savings of approximately £1,500 per patient, degarelix should be recognised for the innovation provided to both patients, and the healthcare system.

Table 2. PSA >20 ng/ml subgroup results

	Degarelix	**Goserelin (10.8 mg)**
Technology acquisition cost	£6,683	£2,927
Other costs	£21,623	£26,867
Total costs	£28,306	£29,794
Difference in total costs	N/A	–£1,489
LYG	9.22	8.78
LYG difference	N/A	0.44
QALYs	5.36	4.77
QALY difference	N/A	0.58
ICER	N/A	Dominating

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; PSA = prostate-specific antigen; QALY(s) = quality-adjusted life year(s)

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device

Name: Firmagon® (degarelix)[2,3]

Pharmacotherapeutic group: Other hormone antagonists and related agents[2,3]

ATC code: L02BX02[2,3]

1.2 What is the principal mechanism of action of the technology?

Prostate cancer is known to be androgen sensitive and, therefore, responds to treatment that removes the source of androgen – either through surgical or medical castration, or by inhibiting the action of circulating androgens.[2,3,79]

Degarelix provides a medical approach to castration. It is a selective gonadotrophin releasing-hormone (GnRH) antagonist, licensed in the UK for the treatment of advanced hormone-dependent prostate cancer, which competitively and reversibly binds to pituitary GnRH receptors, leading to a rapid reduction in the release of the gonadotrophins luteinising hormone (LH) and follicle-stimulating hormone (FSH). A decrease in LH and FSH levels results in a rapid reduction of testosterone secretion by the testes to castrate levels.[2,3]

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) granted marketing authorisation for degarelix in Europe, including the UK, on 17 February 2009.[1]

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

In line with the CHMP's requirements, Ferring has set up the necessary procedures to ensure that, before prescribing, healthcare professionals are provided with information and training on administration, gel depot formation, possible injection site reactions, and any identified and potential risks.[1,80,81]

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Degarelix is indicated for the treatment of adult male patients with advanced hormone-dependent prostate cancer.[2,3]

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

A number of post hoc exploratory analyses of individual patient-level data from the pooled results of completed Phase III/IIIb trials have been presented as posters at international conferences and are also due to be published in peer-reviewed journals within the next two to six months.[72-77] The data from these analyses are included among those presented in this NICE STA submission.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Degarelix was launched in the UK on 5 May 2009.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Degarelix has received regulatory approval in 64 countries in addition to the UK (see Table 3).

Table 3. List of countries with regulatory approval for degarelix

Asia	Europe		North America	Oceania	South America
• Bahrain • Hong Kong • India • Israel • Jordan • Kazakhstan • Kuwait • Lebanon • Oman • Philippines • Qatar • Russia • Saudi Arabia • Syria • Thailand • United Arab Emirates • Vietnam	• Austria • Belgium • Bosnia and Herzegovina • Bulgaria • Croatia • Cyprus • Czech Republic • Denmark • Estonia • Finland • France • Georgia • Germany • Greece • Hungary • Iceland • Ireland • Italy • Latvia	• Liechtenstein • Lithuania • Luxembourg • Macedonia FYR • Malta • Netherlands • Norway • Poland • Portugal • Romania • Serbia and Montenegro • Slovakia • Slovenia • Spain • Sweden • Switzerland • Ukraine • UK	• Canada • Costa Rica • Dominican Republic • Guatemala • Mexico • Trinidad and Tobago • USA	• Australia	• Argentina • Brazil • Peru

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

No health technology assessments (HTAs) of degarelix are currently ongoing in the UK.

On resubmission, on 17 January 2011, the Scottish Medicines Consortium (SMC) accepted degarelix for use within NHS Scotland for the treatment of adult male patients with advanced hormone-dependent prostate cancer, taking into account the benefits of a patient access scheme (PAS) that improves the cost-effectiveness of the drug.[4]

On resubmission, on 12 December 2012, the All Wales Medicines Strategy Group (AWMSG) issued a Final Appraisal Recommendation on degarelix, recommending it as an option for use within NHS Wales for the treatment of adult male patients with

advanced hormone-dependent prostate cancer when the approved PAS Wales is utilised.[5]

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 4. Unit costs of technology being appraised

Pharmaceutical formulation	Degarelix is available as a powder and solvent for solution for injection in: • Vials containing 120 mg degarelix (as acetate)[3] • Vials containing 80 mg degarelix (as acetate).[2] Each 120 mg pack contains: • 2 vials containing degarelix • 2 solvent-prefilled glass syringes • 2 plunger rods • 2 vial adapters • 2 needles.[3] Each 80 mg pack contains: • 1 vial containing degarelix • 1 prefilled glass syringe • 1 plunger rod • 1 vial adapter • 1 injection needle.[2]
Acquisition cost (excluding VAT)	UK NHS Drug Tariff price: • Starting dose: two 120 mg vials: £260.00[6] • Maintenance dose: one 80 mg vial: £129.37.[6]
Method of administration	Subcutaneous injection[2,3]
Doses	Starting dose of 240 mg (administered as two subcutaneous injections of 120 mg each), followed, after one month, by a monthly maintenance dose of 80 mg[2,3]
Dosing frequency	Monthly (every 28 days)[2,3]
Average length of a course of treatment	Using a cost–utility model devised to represent cost and outcomes for patients with advanced hormone-dependent prostate cancer in England and Wales, the average time spent on first-line treatment with degarelix is 5.4 years and the total time spent on treatment is 5.9 years (including time spent receiving combined androgen blockade and in anti-androgen withdrawal). Time spent on treatment is dependent on several model inputs, including PSA progression (based on data from the CS21 trial),[10] probability of treatment failure for later lines of treatment and mortality rates.

Average cost of a course of treatment	Using the cost–utility model, the estimated undiscounted cost of technology acquisition over a course of treatment (5.9 years), with degarelix as first-line therapy, is £10,075. The total cost of treatment including administration is £12,306.
Anticipated average interval between courses of treatments	Patients will receive continuous treatment with degarelix until the disease progresses to hormone-refractory prostate cancer or until the end of life, depending on local practice.[7]
Anticipated number of repeat courses of treatments	As described above, patients will only receive one continuous course of treatment with degarelix.
Dose adjustments	The therapeutic effect should be monitored by clinical parameters and PSA levels; however, degarelix is only licensed at a starting dose of 240 mg, followed by a monthly maintenance dose of 80 mg, so an increase or decrease in dose is not permitted.[2,3] Dose adjustments are not necessary in the elderly or patients with mild or moderate impairment of liver or kidney function.[2,3] Caution is warranted in patients with severe liver or kidney impairment, as degarelix has not been studied in this population.[2,3]

Key: PSA = prostate-specific antigen

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No. The tests or investigations for the selection of patients suitable for degarelix would be the same as those that are currently standard practice for patients receiving treatment for advanced hormone-dependent prostate cancer with luteinising hormone-releasing hormone (LHRH) agonists (also known as GnRH agonists).

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No. Patients treated with degarelix require no additional monitoring, other than that currently required with the administration of monthly LHRH agonists.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No additional therapies are likely to be administered at the same time as degarelix, as this drug does not induce the testosterone flare associated with LHRH agonists and so does not require the flare protection with an anti-androgen at the start of therapy that is required with LHRH-agonists.[2,3]

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Prostate cancer is a disease in which tumours develop in the prostate gland, which normally produces the liquid component of semen and, thus, forms part of the male reproductive system.[1] Primary tumours are located in the prostate gland, when the disease is considered to be localised and is designated as T1 or T2 under the TNM (tumour, node, metastasis) classification for prostate cancer.[8,82] Locally advanced prostate cancer encompasses a spectrum of disease states, including extension of the disease through the prostate capsule (T3a disease), spread to affect the seminal vesicles (T3b disease), and spread to adjacent structures including the bladder neck, external sphincter, rectum, levator muscles and pelvic wall (T4 disease).[8,82] The condition may also be described as locally advanced when it has spread to affect the regional lymph nodes (N1 disease).[82] Eventually, metastases may develop distant from the prostate gland, when the disease is described as metastatic (M1).[8,82] A full description of the TNM classifications is provided in Appendix A. In accordance with the final NICE scope for this submission, the term 'advanced' prostate cancer encompasses both locally advanced and metastatic disease.[83]

Prostate cancer is the most common cancer in men, accounting for about 25% of new diagnoses of malignant cancer in England and Wales.[8] During 2011 (the year for which the most recent published figures for England and Wales individually are available), 35,567 men in England and 2,346 in Wales were diagnosed with the condition, and the age-standardised incidence rate was 106.7 and 107.0 per 100,000, respectively.[84,85] The number of new prostate cancer registrations in 2012 was 45,410 for the UK as a whole, with an age-standardised incidence rate of 111.1 per 100,000. Data from the British Association of Urological Surgeons in 2010 on the stage of disease at presentation, where this is known, indicate that 0.6% of patients are diagnosed with Stage I disease (T1a N0 M0 well differentiated), 65.9% with Stage II disease (T1a–c N0 M0 moderately/poorly differentiated, T2 N0 M0), 21.8% with Stage III disease (T3 N0 M0), and 11.8% with Stage IV disease (T4 N0 M0, any T N1 M0, and any T any N M1).[86]

The incidence of prostate cancer increases in an approximately linear fashion with age from the age of 50 years,[8] with an estimated incidence of 1% in those older than 85 years but only 0.1% in those younger than 50 years.[87] Around 85% of cases are diagnosed in those older than 65 years,[87] and the peak in absolute numbers in England is between the ages of 65 and 74 years.[84] As prostate cancer is more common in older populations, it affects those in whom cardiovascular-related disease and osteoporosis and related fractures are also more common.[88-90] Patients with prostate cancer are, therefore, particularly susceptible to, and at risk of, these co-

morbidities and associated mortality. Indeed, cardiovascular disease has been reported to account for approximately 18–53% of deaths in patients with prostate cancer.[91-94]

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Degarelix is indicated for the treatment of adult male patients with advanced hormone-dependent prostate cancer.[2,3]

The number of patients eligible for treatment with degarelix has been estimated by first calculating the incidence for prostate cancer in 2013, as follows:

- The 2011 incidence was calculated by combining the annual incidence of prostate cancer patients in England[84] and Wales[85] for 2011.
- The annual rate of increase in incidence, which was calculated using the average percentage increase in incidence between 2009 and 2011, was applied.[84,85]

The number of patients eligible for treatment with degarelix was then calculated by multiplying this incidence for prostate cancer by the proportion of incident patients with prostate cancer who are treated with hormonal therapy without radiation or prostatectomy (39%).[95]

The estimated number of patients in the subgroup of prostate-specific antigen (PSA) levels >20 ng/ml has been estimated by multiplying the expected number of patients treated with hormonal therapy by the percentage of patients in the CS21 trial who had PSA levels >20 ng/ml (48%).

The total numbers of eligible patients from Year 1 to Year 5 (that is, 2014–18) are shown in Table 5 below.

Table 5. Eligible Population in England and Wales

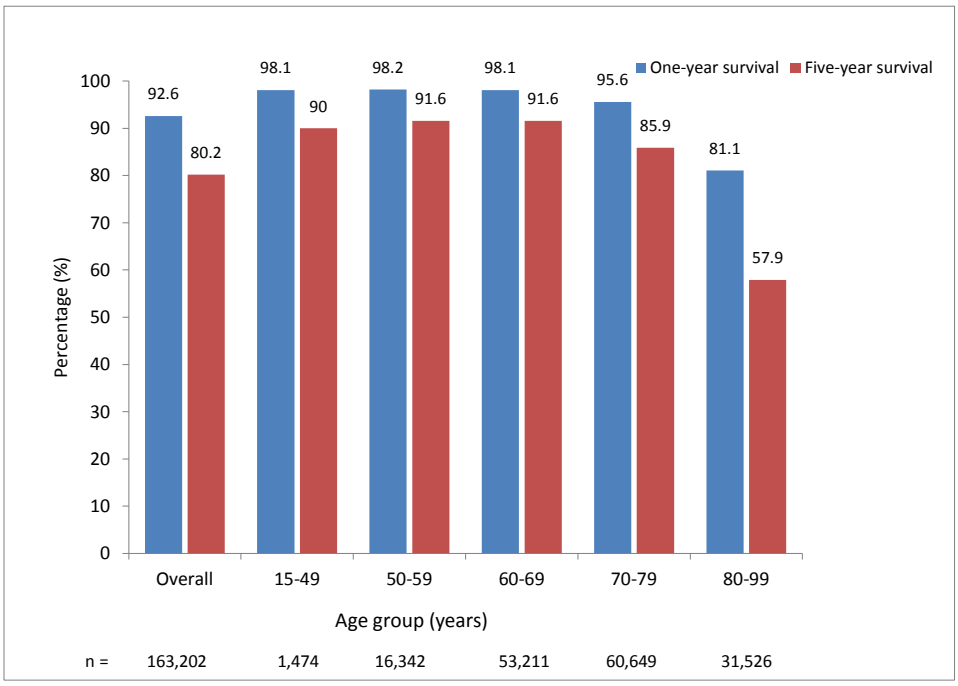
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Expected number of patients with newly diagnosed prostate cancer	39,376	39,877	40,383	40,896	41,416
Expected number treated with hormonal therapy	15,458	15,655	15,854	16,055	16,259
Expected number treated with hormonal therapy – PSA >20 ng/ml subgroup	7,425	7,519	7,615	7,712	7,810

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Prostate cancer is the second most common cause of death in men with any cancer in the UK – second only to lung cancer – with a mortality of 23.9% in England and 23.3% in Wales in 2008–10.[96] Most of the deaths are estimated to occur in patients with hormone-refractory metastatic prostate cancer.[97]

According to data from the Office for National Statistics for the period of 2006–11, 92.6% of men in England survived prostate cancer for one year and 80.2% for five years or more, with the proportions varying considerably with age (see Figure 1).[98]

Figure 1. One- and five-year survival rates for patients with prostate cancer, by age group during 2006–11[98]



2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

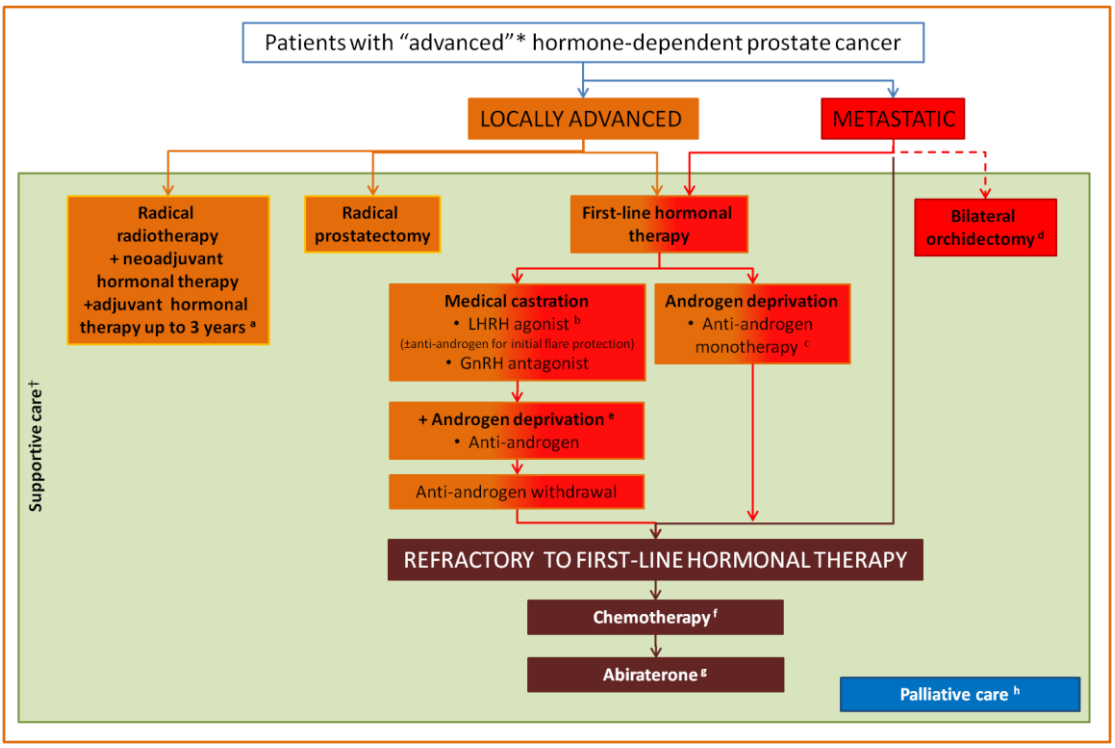
NICE CG58[8] is the most relevant guidance with respect to degarelix. This clinical guideline covers the whole population of patients with prostate cancer – from diagnosis through to palliative care – but recognises that the management of diagnosed prostate cancer varies according to the stage of disease (localised, locally advanced and metastatic), the risk of progression and the treatment response.[8,79] NICE CG58 is currently being reviewed, with the update due to be published prior to the completion of this NICE STA.

In addition to NICE CG58,[8] Ferring recognises that the European Association for Urology (EAU) guidelines published in 2012[79] also represent up-to-date and relevant guidance for the treatment of prostate cancer.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

NICE CG58 includes a recommended care pathway for patients with prostate cancer, from diagnosis through treatment options for the various stages of disease to management of hormone-refractory disease and palliative care.[8] Using information provided by this guideline, as well as UK clinicians' expert opinion, the current treatment pathway for advanced (locally advanced and metastatic) hormone-dependent prostate cancer is summarised in Figure 2,[7,8] which also illustrates where degarelix would fit into the pathway.

Figure 2. Current treatment pathway for advanced hormone-dependent prostate cancer[7,8]



* Advanced as per indication for degarelix/NICE scope.[2,3,83]

† Including specialist continence services, synthetic progestogens, prophylactic radiotherapy to prevent gynaecomastia, specialist erectile dysfunction services, decompression, bisphosphonates and strontium 89.[8]

[a] Neoadjuvant and concurrent LHRH therapy is recommended for three to six months in men receiving radical radiotherapy for locally advanced prostate cancer. Adjuvant hormonal therapy is recommended for a minimum of 2 years in men receiving radical radiotherapy for locally advanced prostate cancer who have a Gleason score of ≥8.[8]

[b] When treated with LHRH agonists, patients are initially offered concomitant therapy with an anti-androgen to counteract testosterone flare that may result from use of LHRH agonists. Anti-androgens should be started on the same day or a few days prior as the depot LHRH injection and should be continued for a short period.[79] Treatment with anti-androgens decreases the incidence of testosterone flare associated with LHRH agonists, but does not completely remove the possibility of its occurrence.[79] Based on expert opinion from UK clinicians, LHRH agonists are always initially prescribed in conjunction with an anti-androgen for flare protection.[7]

[c] Bicalutamide monotherapy is licensed for use in locally advanced disease and not for metastatic disease. [8] Bicalutamide monotherapy may be used as an alternative in patients who do not wish to risk the sexual dysfunction and/or lethargy associated with LHRH agonists.[8]

[d] Bilateral orchidectomy should be offered as an alternative to continuous LHRH agonist therapy[8] but is rarely chosen as a treatment option by patients.[7]

[e] When LHRH agonist monotherapy fails (after a short period of anti-androgen therapy to prevent tumour flare), an anti-androgen may be added as an adjuvant second-line hormonal therapy.[8]

[f] First-line chemotherapy treatment is docetaxel (with prednisone or prednisolone).[97]

[g] Abiraterone (with prednisone or prednisolone) is a second-line anti-androgen treatment option that can be used upon disease progression on or after one docetaxel-containing chemotherapy regimen.[99]

[h] Healthcare professionals should ensure that palliative care is available when needed and is not limited to the end of life. It should not be restricted to hospice care.[8]

NICE recommends that locally advanced and metastatic prostate cancer should be managed using hormonal manipulation, either with androgen withdrawal or androgen receptor blockade. Locally advanced disease may also be treated with radical radiotherapy (with or without adjunctive hormonal therapy) or radical prostatectomy.[8]

Androgen withdrawal involves the use of LHRH agonists or bilateral orchidectomy to remove the supply of endogenous hormones, while androgen receptor blockade using anti-androgen therapies reduces the effect of endogenous hormones.

- In terms of pharmacological therapy, LHRH agonists are usually the first-line approach. At the start of treatment, these are prescribed in combination with anti-androgen therapy – for example, with bicalutamide – to counteract the initial surge in testosterone levels that may result from the use of LHRH agonists. When LHRH agonist monotherapy (after a short period of anti-androgen therapy to prevent tumour flare) fails, an anti-androgen may be added as an adjuvant second-line hormonal therapy.[8]
- Bicalutamide monotherapy, which is licensed for use in locally advanced disease but not for metastatic disease, may also be used as an alternative in patients who do not wish to risk the sexual dysfunction and/or lethargy associated with LHRH agonists, although gynaecomastia and mastalgia may develop with anti-androgen therapy.[8]
- Degarelix is a selective GnRH antagonist licensed in the UK for the treatment of adult male patients with advanced hormone-dependent prostate cancer.[2,3] In accordance with the final NICE scope, the term 'advanced' encompasses both locally advanced and metastatic disease for the purpose of this STA submission.[83]
- Degarelix, therefore, provides an alternative to LHRH agonists, with the additional benefit that it does not require concomitant administration of an anti-androgen agent, as it does not induce the initial testosterone flare associated with LHRH agonists.

A patient's initial treatment options and subsequent treatment pathway will depend on the stage of their disease at presentation and diagnosis.[8] Most men currently receive hormonal therapy, in the form of an LHRH agonist with initial anti-androgen therapy for flare protection. If the cancer is locally advanced with a risk of pelvic node involvement, patients may receive hormonal therapy in combination with radiotherapy. Bilateral orchidectomy should be offered as an alternative to continuous LHRH agonist therapy, but it is rarely chosen as a treatment option by patients.[7,8]

Throughout the treatment pathway, patients may require supportive care to help them cope with symptoms and complications of the disease. Palliative care may also be needed and should not be reserved solely for those approaching the end of life.[8]

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

The lack of national guidance on the appropriate use of degarelix within the prostate cancer pathway has led to variable and inconsistent prescribing of this product at a local level. Thus, current practice is based on local-level interpretation, as opposed to a complete evidence-based approach, resulting in an inequity of patient access. The clear guidance and consensus recommendation on the use of degarelix that will

result from this STA will ensure equality of access to the product for patients treated in NHS England and NHS Wales.

2.7 Please identify the main comparator(s) and justify their selection.

In line with the specifications of the final NICE scope, the comparators to be evaluated are the LHRH agonists, goserelin, leuprorelin, triptorelin (in combination with short-term anti-androgen treatment) and bicalutamide monotherapy.

Three-monthly goserelin (10.8 mg, Zoladex®) will be used as the primary comparator in the base case scenario for the cost–utility analysis that forms part of this STA submission. Goserelin was chosen as the primary base case comparator on the advice of the clinical advisory board,[7] based on it being the LHRH agonist most commonly used in the UK for the treatment of prostate cancer (see Table 6).[100] Published evidence and results from systematic reviews indicate that none of the LHRH agonists has superior clinical efficacy over the others (see Section 6.7).

The alternative LHRH agonists, leuprorelin and triptorelin, are also compared with degarelix in the base case, but they are only included in the sensitivity analysis as scenario analyses because only the comparator price is altered between analyses.

Bicalutamide monotherapy has been included as a comparator in the final scope for this STA; however, published, randomised controlled trial (RCT) evidence comparing bicalutamide monotherapy with degarelix and/or LHRH agonists is lacking. It was, therefore, not possible to complete a robust mixed treatment comparison to compare degarelix with bicalutamide monotherapy. In addition, the licensed indications for bicalutamide monotherapy and degarelix are non-equivalent; degarelix is indicated in adult male patients with advanced hormone-dependent prostate cancer,[2,3] which includes a spectrum of disease states (locally advanced and metastatic disease), whereas bicalutamide monotherapy is indicated in a smaller patient population that includes only those with locally advanced, non-metastatic prostate cancer.[101] Bicalutamide monotherapy could, therefore, not be evaluated within the cost-effectiveness section of this STA submission.

Table 6. Volume (pack sales) of comparator treatments in England and Wales 2011–12[100]

Treatment	Total units	Percentage
Goserelin 10.8 mg (Zoladex®) (three-monthly formulation)	172,341	39.70
Goserelin 3.6 mg (Zoladex®) [a] (one-monthly formulation)	76,011	17.51
Leuprorelin 11.25 mg (Prostap®) [a] (three-monthly formulation)	105,414	24.28
Leuprorelin 3.75 mg (Prostap®) [a] (one-monthly formulation)	41,988	9.67
Triptorelin 11.25 mg (Decapeptyl® SR) [a] (three-monthly formulation)	21,749	5.01
Triptorelin 3 mg (Decapeptyl® SR) [a] (one-monthly formulation)	8,883	2.05
Triptorelin 22.5 mg (Decapeptyl® SR) (six-monthly formulation)	653	0.15
Triptorelin 3.75 mg (Gonapeptyl Depot®) [b] (one-monthly formulation)	3,706	0.85

[a] Treatment dose is used in additional indications outside advanced prostate cancer

[b] Gonapeptyl Depot will not be included in the cost–utility sensitivity analysis, as it is more expensive for the equivalent dose frequency (one-monthly formulation) and is used less frequently in clinical practice (indicated by IMS data) than 3 mg Decapeptyl SR.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Androgen withdrawal commonly causes hot flushes, loss of sexual drive and weight gain.[8] Men receiving this treatment may also become lethargic, describing loss of drive and energy.[8] In the long term, bone mineral density may decrease, leading to an increased risk of pathological fractures.[8] Lipid alterations commonly develop within three months of treatment initiation.[79] Insulin sensitivity decreases and fasting plasma insulin levels (a marker of insulin resistance) may increase.[79] These parameters also coincide with an increased risk of metabolic syndrome – including, and in addition to, diabetes, cardiovascular disease and myocardial infarction – in patients taking androgen deprivation therapy.[79] The side-effects of long-term androgen deprivation therapy can, thus, not only have a detrimental effect on quality of life but also contribute to an increased risk of health concerns associated with ageing.[79] Men starting androgen withdrawal therapy should be encouraged to make lifestyle changes, including regular resistance exercise – which reduces fatigue, improves quality of life and can impact on bone mineral density – smoking cessation, reduced alcohol consumption and normalisation of body mass index.[8,79]

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Treatment with degarelix is initiated in secondary care, with a urologist or oncologist providing the diagnosis of a patient's condition and determining the treatment and monitoring options (such as a bone scan). Thus, the 240 mg initiation dose (administered as two subcutaneous injections of 120 mg each into the abdominal area) is administered in secondary care. Subsequent maintenance doses (administered as a monthly subcutaneous injection of 80 mg into the abdominal area) would typically be administered in primary care by a practice/district nurse. A patient's general health and necessary monitoring tests (for example, serum PSA levels) would be managed by their GP in primary care, with any relevant information being passed onto secondary care professionals (for example, via a shared care protocol).

Table 7 lists the resources that may be utilised, according to local practice and individual patient needs, for all lines of therapy.[6,102-104]

Table 7. Resource use for patients[6]

Resource	Value
Resource use for first-line treatments taken monthly (including degarelix)	
First-line treatment	1 per cycle
Nurse appointment for administration of treatment	1 each cycle after initiation
Urology outpatient consultant appointment and PSA test	1 on initiation of treatment and 1 every 6 months subsequently
Bone scans	1 on initiation of treatment
CT scans	1 on initiation of treatment
Bicalutamide (only when treated with an LHRH agonist)	28 × 50 mg tablets in first cycle
Resource use for first-line treatments taken once every three months	
First-line treatment	1 every 3 cycles
Nurse appointment for administration of treatment	1 every 3 months each cycle after initiation
Urology outpatient consultant appointment and PSA test	1 on initiation of treatment and 1 every 6 months subsequently
Bone scans	1 on initiation of treatment
CT scans	1 on initiation of treatment
Bicalutamide (only when treated with an LHRH agonist)	28 × 50 mg tablets in first cycle
Resource use for anti-androgen addition	
First-line treatment	As previously
Nurse appointment for administration of treatment	As for first-line treatment
Urology outpatient consultant appointment	1 on initiation of treatment and 1 every

and PSA test	3 months thereafter
Bone scans	1 on initiation of treatment
CT scans	1 on initiation of treatment
Bicalutamide	28 × 150 mg tablets each cycle
Resource use for anti-androgen withdrawal patients	
First-line treatment	As previously
Nurse appointment for administration of treatment	As for first-line treatment
Urology outpatient consultant appointment and PSA test	1 on initiation of treatment and 1 every 3 months thereafter
Bone scans	1 on initiation of treatment
CT scans	1 on initiation of treatment
Resource use for patients receiving first-line chemotherapy	
Bone scan, CT scan and MRI scan	1 on initiation of treatment and 1 on treatment end
Blood test	1 on initiation
Oncology outpatient consultant appointment	1 on initiation of treatment and 1 every chemotherapy administration thereafter
Frequency of docetaxel administration	Every 3 weeks (average total of 7.3 sessions per patient are assumed)
Number of 80 mg vials required per docetaxel administration	2.25 per session
Number of 2 mg dexamethasone tablets required per docetaxel administration	12 per session
Number of 5 mg dexamethasone tablets required per docetaxel administration	2 per day
Re*source use for patients receiving abiraterone*	
Bone scan, CT scan and MRI scan	1 on initiation of treatment and 1 on treatment end plus 1 every 6 weeks for 5% of patients
Blood test	1 on initiation and one every 6 weeks thereafter
Oncology outpatient consultant appointment	1 every 2 weeks for 3 months and monthly thereafter
Abiraterone	112 × 250 mg tablets per cycle
Prednisolone	56 × 5 mg tablets per cycle

Key: LHRH = luteinising hormone-releasing hormone

2.10 Does the technology require additional infrastructure to be put in place?

Additional infrastructure will not be required.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

  Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

It is unlikely that this appraisal will cause any of the three situations described above.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Degarelix delivers innovation in a variety of ways, and can be considered a 'step change' in therapy from the current standard of care, LHRH agonists.

- More rapid and improved disease control compared with LHRH agonists:[21,74-76]
  - Degarelix achieves more rapid suppression of PSA levels than LHRH agonists: median reduction at Day 28 of 82.3% with degarelix and 66.7% with LHRH agonist treatment (p<0.0001) (see 'PSA data from trial CS21' in Section 6.5.3).[9,21]
  - Degarelix suppresses serum testosterone to castrate levels (≤0.5 ng/ml) more rapidly than LHRH agonists (p<0.0001) (see 'Testosterone response' in Section 6.5.3).[9,10]
  - Degarelix is associated with statistically lower risks of fractures (p=0.0234), joint-related signs and symptoms (p=0.0116), and urinary tract-related adverse events (p<0.0001) than LHRH agonists (see 'Disease-related AE analysis of individual patient data' in Section 6.9.2).[74-76]
- Lower risk of disease progression compared with LHRH agonists:
  - In patients in whom PSA progression occurs, including those at high risk of progression (PSA >20 ng/ml), the time to progression is statistically longer with degarelix than with LHRH agonists (p=0.04) (see Section 6.5.3).[21]
  - Suppression of serum levels of alkaline phosphatase (a marker of metastatic disease[20]) is significantly greater with degarelix than with LHRH agonists (p=0.0383) (see Section 6.5.3).[75,76]

Implications for patients and the NHS

- Patients treated with degarelix will experience fewer signs and symptoms of disease.
- Patients treated with degarelix will experience delayed signs and symptoms of disease.
- Degarelix will keep patients on first-line hormonal therapy for longer, which is more cost-effective and associated with better health-related quality of life than subsequent treatment stages (see Section 7.4).

- Improved survival compared with LHRH agonists:
  - Rates of overall survival at one year are statistically higher with degarelix than with LHRH agonists (p=0.025) (see 'Overall survival' in Section 6.6.1).[9,11,13,15,17]
- Degarelix is associated with fewer cardiovascular events than LHRH agonists:
  - Cardiovascular morbidity and mortality are common among the older age groups in which prostate cancer is most prevalent,[88,90] and LHRH agonists are reported to be associated with an increased risk of certain cardiovascular diseases (myocardial infarction, sudden cardiac death, and stroke).[105]

- In patients with a history of cardiovascular disease, degarelix is associated with a statistically significant 50% lower risk of cardiovascular events – including arterial embolic and thrombotic events, haemorrhagic and ischaemic cerebrovascular conditions, myocardial infarction and other forms of ischaemic heart disease – and cardiovascular-related death compared with LHRH agonists (p=0.0023) (see 'CVD AE analysis of individual patient data' in Section 6.9.2).[73]

Implications for patients and the NHS

- Degarelix offers an effective and alternative hormonal therapy for the treatment of patients with prostate cancer that is associated with a 50% lower risk of cardiovascular events.

- No testosterone flare with initial treatment:
  - LHRH agonists are associated with a transient increase in testosterone levels that can result in increased bone pain, spinal cord compression, pathological fracture, bladder outlet obstruction and death[78] before chronic administration suppresses testicular steroid secretion. Concomitant therapy with an anti-androgen reduces the incidence of this 'testosterone flare' but does not completely remove the possibility of its occurrence.[79]
  - By acting directly to block GnRH receptors, degarelix avoids the testosterone flare associated with LHRH agonists,[2,3] rapidly suppressing testosterone to castrate levels without an increase in the first two weeks of treatment (see 'Testosterone response' in Section 6.5.3); thus, concomitant anti-androgen therapy is not needed with degarelix.

Implications for patients and the NHS

- Patients do not need to take an anti-androgen in addition to degarelix.
- Degarelix is particularly useful for patients with impending or actual spinal cord compression, impending or actual urinary outflow obstruction, and bony metastases associated with intractable pain.
- Degarelix is particularly useful for patients in whom anti-androgen therapy is contraindicated; for example, those with abnormal liver function.
- Degarelix will save the NHS money as a result of reduced healthcare utilisation, with an estimated saving of £931,788 over five years (see Section 8).

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

All relevant health-related benefits associated with degarelix therapy will be included in the QALY calculation. These take the form of increased QALYs, due to longer survival and better quality of life, and cost savings.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Not applicable.

5 Statement of the decision problem in the UK

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key that the information in the evidence submission will address.

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Adults with advanced hormone-dependent prostate cancer (locally advanced or metastatic, including biochemical relapse) in whom orchidectomy is not preferred.	Same as identified in the scope	N/A – The decision problem aligns with the final scope.
Intervention	Degarelix	Same as identified in the scope	N/A –The decision problem aligns with the final scope.
Comparator(s)	• Gonadotrophin-releasing hormone agonists in combination with short-term anti-androgen treatment including: ○ Goserelin ○ Leuprorelin ○ Triptorelin • Bicalutamide	• Gonadotrophin-releasing hormone agonists in combination with short-term anti-androgen treatment including: ○ Goserelin ○ Leuprorelin ○ Triptorelin	Goserelin has been chosen as the comparator in the base case scenario. Reasons for this choice are explained in Section 2.7. Bicalutamide monotherapy is included in the scope, but published RCT evidence comparing bicalutamide with degarelix is lacking, and the licensed indications for bicalutamide monotherapy and degarelix are non-equivalent. Bicalutamide will, therefore, not be evaluated within the cost-effectiveness section.

Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Testosterone response • Prostate-specific antigen (PSA) response • Time to PSA progression • PSA progression-free survival • Adverse effects of treatment • Health-related quality of life.	• Same as identified in the scope	N/A – The decision problem aligns with the final scope.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost-effectiveness of treatments will be expressed in terms of incremental cost per quality-adjusted life-year. The time-horizon of the cost-effectiveness analysis will be 20 years. Costs are considered from an NHS and Personal Social Services perspective.	N/A – Stipulations of the reference case have been adhered to.

Subgroups to be considered	If evidence allows, the following subgroups will be considered: • High-risk patients with PSA >20 ng/ml • Patients with spinal metastases with impending or actual spinal cord compression • Patients with high tumour volume with impending or actual urinary outflow obstruction • Patients with bony metastases associated with intractable pain • Patients for whom standard anti-androgen treatment is contraindicated • Patients at risk of evolving cardiovascular comorbidity.	The outcome measures to be considered include: • High-risk patients with PSA >20 ng/ml • Patients with pre-existing cardiovascular disease	The subgroups to be considered are those for which a sufficiently large number of patients was included in randomised clinical trials and sufficient data have been generated to provide a robust analysis.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation.	N/A	N/A

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

Literature search

A systematic review was undertaken to evaluate the efficacy, effectiveness and safety of degarelix for the treatment of advanced hormone-dependent prostate cancer.

Study population

The aim of the literature review was to identify studies conducted in adult men with advanced hormone-dependent prostate cancer (locally advanced or metastatic, including biochemical relapse) in whom orchidectomy was not preferred. Where possible, studies needed to include the following subgroups of patients: those with prostate-specific antigen (PSA) levels >20 ng/ml, spinal metastases with impending or actual spinal cord compression, high tumour volume with impending or actual urinary outflow obstruction and bony metastases associated with intractable pain, patients in whom standard anti-androgen treatment is contraindicated, and those at risk of evolving cardiovascular co-morbidity.

Therapeutic interventions

The search was designed to identify studies investigating the clinical efficacy of degarelix and its comparator agents – comprising luteinising hormone-releasing hormone (LHRH) agonists (leuprorelin, goserelin, triptorelin) in combination with short-term anti-androgen treatment and bicalutamide monotherapy – for the outcomes of overall survival, progression-free survival (PFS), response rate, testosterone response, PSA response (including PSA percentage change from baseline and PSA progression [also known as PSA recurrence or PSA failure]), time to PSA progression, PSA PFS, adverse events (AEs) and health-related quality of life.

Databases searched

The following databases were searched, with no date restrictions, for relevant clinical trials of degarelix:

- Bibliographic databases: MEDLINE®, MEDLINE In-Process, Embase, Web of Science, and the Cochrane Library
- References of retrieved articles and reports
- Ferring Pharmaceuticals Ltd:
  - List of sponsored studies
  - Clinical study reports of completed studies (when available, clinical study reports from Ferring were used as the main data source)
- Clinical trial registries: WHO International Clinical Trials Registry Platform (ICTRP).

The search combined terms to describe the intervention(s) of interest and the population before applying methodological search filters, such as those produced by the Scottish Intercollegiate Guidelines Network (SIGN), to refine the results to the appropriate types of evidence (clinical trials, systematic reviews and economic evidence). The terms within these groups were combined using the Boolean operator OR and then groups were combined using the Boolean operator AND. This approach is the standard 'building block' approach to searching.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Two independent reviewers scanned titles/abstracts of references from the bibliographic databases to identify potentially relevant studies and then assessed the full text of obtained articles or reports to determine whether the studies should be included. All disagreements were resolved by discussion. Table 8 shows the eligibility criteria for study selection.

Table 8. Eligibility criteria used in study selection (clinical effectiveness)

Inclusion criteria	
Population	Relevant population: adult male patients with advanced hormone-dependent prostate cancer*
Interventions	Degarelix
Comparators	Luteinising hormone-releasing hormone agonists • Goserelin • Leuprorelin • Triptorelin Bicalutamide monotherapy
Outcomes	Outcome measures to be considered: • Overall survival • Progression-free survival • Response rate • Testosterone response • PSA response (PSA percentage change from baseline and PSA progression [recurrence or failure]) • PSA PFS • Time to PSA progression • Adverse effects of treatment • Health-related quality of life
Study design	Randomised controlled trials and non-randomised clinical trials
Language restrictions	No language restrictions
Exclusion criteria	
Population	Not further specified
Interventions	Not further specified
Comparators	Not further specified
Outcomes	Not further specified
Study design	Phase I pharmacokinetic studies
Language restrictions	N/A

Key: N/A = not applicable; PSA = prostate-specific antigen; PFS = progression-free survival

* Available clinical trials of degarelix usually included patients with prostate cancer of all stages, so studies of patients with all stages of prostate cancer suitable for treatment with hormonal therapy were included.

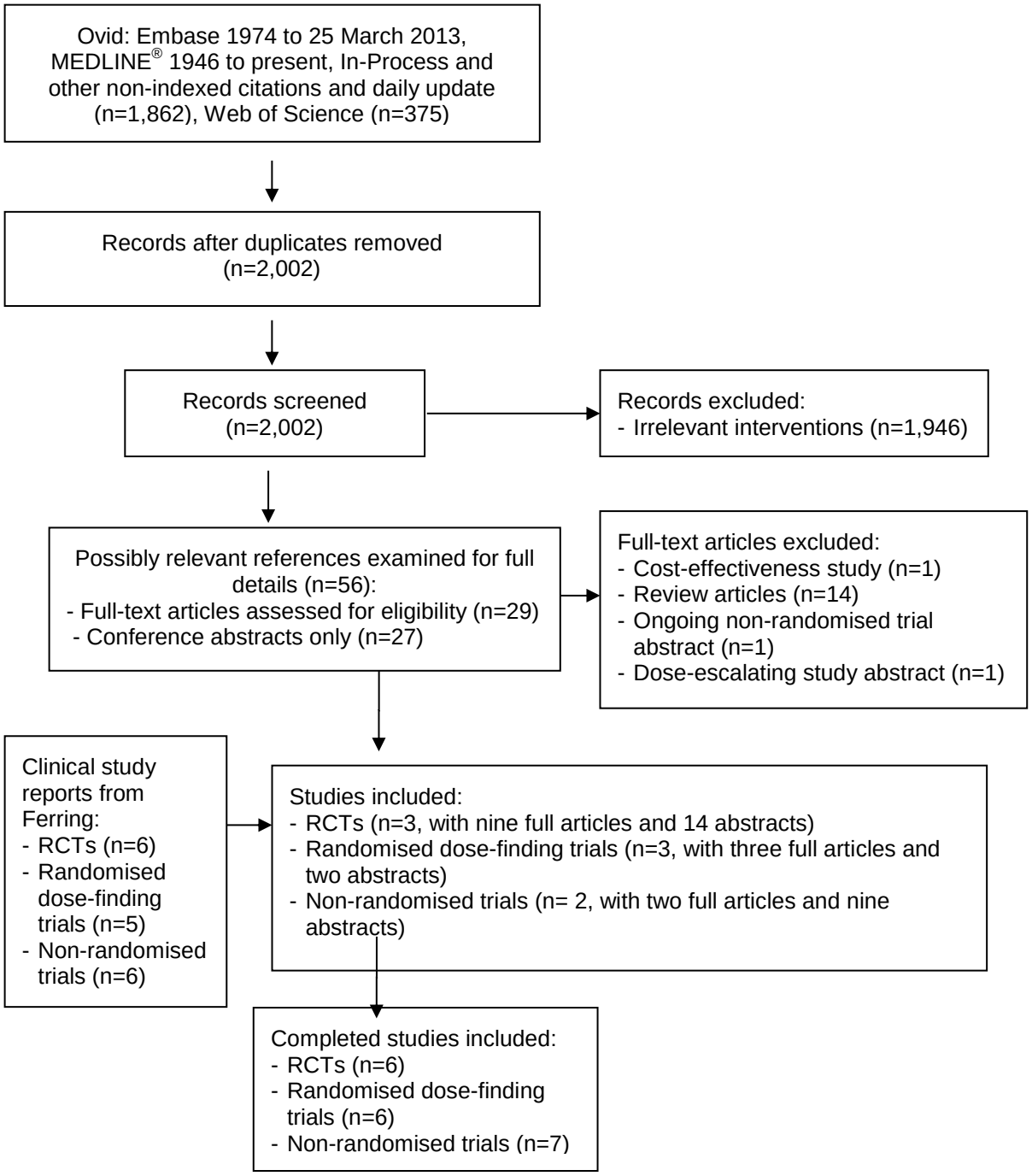
Types of studies

The systematic review included randomised controlled trials (RCTs) that compared degarelix with LHRH agonists alone or in combination with short-term anti-androgen treatment. The review also considered clinical trials of degarelix for the treatment of patients with prostate cancer, in which LHRH agonist or anti-androgen control was not used; these were considered to be non-RCTs and included degarelix dose-finding trials and extensions of completed RCTs. Pharmacokinetic (mostly Phase I) studies were not considered.

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

Once duplicate references were removed, the initial literature search included 2,002 references (see Figure 3). After screening of titles and abstracts, 56 references (29 full papers and 27 conference abstracts) that were possibly relevant to the treatment of prostate cancer with degarelix were identified. After examining further details (that is, the full text if available) and adding the clinical study reports from Ferring Pharmaceuticals, six completed RCTs that compared degarelix and LHRH agonists,[9-38,106] six randomised dose-finding trials of degarelix,[39-53] and seven non-randomised studies[21,54-65,67-71] (mostly extensions of the completed RCTs) remained.

Figure 3. Flow diagram for identification of clinical trials of degarelix for prostate cancer



Key: RCTs = randomised controlled trials

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

For all six identified Phase III/IIIb RCTs, data and information were extracted from the clinical study reports and end-of-trial (EOT) tables. In addition, information was extracted from published RCT reports and conference abstracts, where available, for the CS21, CS28, CS30 and CS31 trials (see Table 9 for trial details).

The main findings from post hoc pooled analyses of the six identified RCTs are also summarised in this submission (see Sections 6.5.3 and 6.9.2). These post hoc analyses of pooled data evaluated both safety and efficacy endpoints, using Kaplan–Meier or Cox-proportional hazards model estimates on individual patient-level data. The endpoints evaluated include the incidence of cardiovascular AEs, musculoskeletal events (including joint-related signs and symptoms, and fractures) and urinary tract events [76] In addition, post hoc exploratory analyses of secondary endpoint efficacy data from CS21 are reported upon.[21,73]

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table 9 lists the six completed RCTs identified by the literature review, which compared degarelix with LHRH agonists.[9-38,106]

Table 9. List of included randomised controlled trials

Trial (acronym)	Intervention (n=randomised/analysed)	Comparator (n=randomised/analysed)	Population	Main references

CS21 (2008)	Degarelix: initial dose 240 mg on Day 0, then 12 monthly (every 28 days) maintenance doses of 160 or 80 mg:
	(A) Degarelix 240/160 mg (n=206/202)
	(B) Degarelix 240/80 mg (n=210/207)
		(C) Leuprorelin 7.5 mg on Day 0, then 12 monthly (every 28 days) doses:
		(n=204/201)
		23/201 (11%) received concomitant bicalutamide for flare protection at the start of treatment
			• Patients aged ≥18 years with histologically confirmed adenocarcinoma of prostate (all stages), for whom endocrine treatment was indicated (except for neoadjuvant hormonal therapy)
			• Included patients with:
			  • Increasing PSA levels after treatment with curative intent, i.e. those with biochemical failure and those with metastatic disease (hormone-sensitive)
			  • Screening serum testosterone levels of >1.5 ng/ml, ECOG score ≤2 and PSA levels ≥2 ng/ml
			• Previous or current hormonal management of prostate cancer was not allowed, except in patients who had undergone localised therapy of curative intent in which case neoadjuvant or adjuvant hormonal therapy for ≤6 months was accepted (discontinued >6 months before inclusion)
			• Patients considered to be candidates for curative therapy were excluded
				Clinical study report (FE200486 CS21)[9]
				Klotz *et al* (2008)[10]
				Damber *et al* (2012)[106]
				Schroder *et al* (2010)[20]
				Tombal *et al* (2010)[21]
				Smith *et al* (2010)[22]
				Iversen *et al* (2011)[23]
				Sommerauer *et al* (2009)[24]
				Conference abstracts[19,25-35]
				Other source:
				Gittleman *et al* (2011)[36]

CS28 (2011)	(A) Degarelix 240 mg on Day 0, then 80 mg on Days 28 and 56 (n=29/27)	(B) Goserelin 3.6 mg on Days 3, 31 and 59 and bicalutamide on Days 0–17 (n=13/13)	• Histologically confirmed prostate cancer • PSA >10 ng/ml at screening • TNM staging at baseline: any T, any N, any M • IPSS ≥12 • Maximum urine flow (Qmax) ≤12 ml/sec (voided volume had to be ≥150 ml unless in acute retention or obstructed with residual urine volume (Vresidual) >100 ml) at screening • ECOG score ≤2 • Estimated life expectancy ≥12 months • Prostate size >30 cm^3, measured by TRUS • Demonstrated response to previous hormonal prostate	Clinical study report (FE200486 CS28)[11] Anderson *et al*. (2012)[12]

Trial (acronym)	Intervention (n=randomised/analysed)	Comparator (n=randomised/analysed)	Population	Main references
			cancer treatment for patients who had received hormonal prostate cancer treatment	
CS30 (2012)	(A) Degarelix 240 mg on Day 0, then 80 mg on Days 28 and 56 (n=181/180)	(B) Goserelin + bicalutamide: goserelin 3.6 mg on Days 3, 31 and 59 and bicalutamide: 50 mg daily on days 0–16 (n=65/64)	• Patients who planned to undergo radical radiotherapy treatment and in whom neoadjuvant endocrine treatment was indicated • TNM stage T2 (b or c)/T3/T4, N0 or M0, Gleason score ≥7 or PSA ≥10 ng/ml • ECOG score ≤2 • Estimated life expectancy ≥30 months • Prostate size >30 cm^3, measured by TRUS	Clinical study report (FE200486 CS30)[13] Mason *et al* (2013)[14] Conference abstract[37]
CS31 (2011)	(A) Degarelix 240 mg on Day 0, then 80 mg on Days 28 and 56 (n=84/82)	(B) Goserelin + bicalutamide: goserelin 3.6 mg on Days 0, 28 and 56 and bicalutamide 50 mg once daily orally on Days 0–28 (n=98/97)	• Histologically confirmed prostate cancer (Gleason-graded, all stages; any T, any N, any M) • Serum PSA at screening >2 ng/ml • Prostate size >30 cm^3, measured by TRUS • Bone scan within 12 weeks before inclusion • Able to undergo transrectal examinations • Estimated life expectancy ≥12 months	Clinical study report (FE200486 CS31)[15] Axcrona *et al* (2012)[16] Conference abstract[38]

Trial (acronym)	Intervention (n=randomised/analysed)	Comparator (n=randomised/analysed)	Population	Main references

CS35 (2012)	(A) Degarelix 240 mg on Day 0, followed by four doses of 480 mg at three-monthly intervals on Days 28, 112, 196 and 280
	(n=572/565)
		(B) Goserelin 3.6 mg on Day 0, followed by three-month regimen of 10.8 mg on Days 112, 196 and 280
		(n=287/282)
		
		Bicalutamide could be given for 28 days; 38/282 (13.5%) patients used this anti-androgen on Days 1–38
			• Histologically confirmed adenocarcinoma of the prostate for which endocrine treatment (except for neoadjuvant hormonal therapy) was indicated
			• PSA level meeting one of these criteria:
			  • Treatment-naive patients: PSA ≥2 ng/ml
			  • Patients with recurrence after radical prostatectomy: serum PSA increase of ≥0.2 ng/ml from the previous test on two consecutive measurements
			  • Patients with recurrence after radiotherapy or cryotherapy: serum PSA (two measurements) >2 ng/ml higher than previously confirmed PSA nadir
			• Aged ≥18 years
			• Screening serum testosterone level above the lower limit of normal range in an elderly male population, globally defined as >1.5 ng/ml
			• ECOG score ≤2
			• Life expectancy ≥1 year
				Clinical study report (FE200486 CS35)[17]

CS37 (2013)	**Phase A** (7 months): (A) Degarelix intermittent: initial dose 240 mg, followed by maintenance regimen of six one-monthly doses (80 mg) (n=177/175) (B) Degarelix continuous: initial dose 240 mg, followed by maintenance regimen of six one-monthly doses (80 mg) (n=50/50)	**Phase A** (7 months): (C) Leuprorelin continuous: initial 7.5 mg, followed by two three-monthly injections (22.5 mg) (n=182/178) **Phase B** (7 months; only included patients with PSA ≤2 ng/ml at end of Phase A): (C) Leuprorelin continuous: maintenance regimen of three three-monthly injections (22.5 mg)	• Rising PSA (≥2.2 ng/ml) after primary therapy for localised prostatic carcinoma for which androgen-deprivation therapy was warranted • Histologically confirmed (Gleason-graded) adenocarcinoma of the prostate (non-metastatic) • Screening testosterone within normal range (≥1.5 ng/ml) • Aged ≥18 years • ECOG score ≤2 • Life expectancy of ≥15 months • Bone scan mandatory to rule out metastatic disease; if bone scan was inconclusive, suspicious or required further testing, a full body CT scan was required	Clinical study report (FE200486 CS37)[18]

Trial (acronym)	Intervention (n=randomised/analysed)	Comparator (n=randomised/analysed)	Population	Main references
	Phase B (7 months; only included patients with PSA ≤2 ng/ml at end of Phase A): (A) Degarelix intermittent: off treatment (n= 177/137) (B) Degarelix continuous: maintenance regimen of seven one-monthly doses (80 mg) (n=50/41)	(n=182/150)		

Key: ECOG = Eastern Cooperative Oncology Group; IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; TNM = tumour, nodule and metastasis; TRUS = transrectal ultrasound

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The study CS21 (by Klotz *et al*) compared degarelix with the main comparator leuprorelin, with or without concomitant bicalutamide therapy, with reference to the decision problem.[9,10]

Studies CS28 (Anderson *et al*), CS30 (Mason *et al*), CS31 (Axcrona *et al*) and CS35 compared degarelix with goserelin, with or without concomitant bicalutamide therapy, with reference to the decision problem.[11-17]

Study CS37 compared intermittent administration of the intervention degarelix with continuous administration of degarelix and continuous administration of the main comparator leuprorelin with reference to the decision problem.[18]

These studies are described in detail in Sections 6.3–6.5.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

All identified RCTs were evaluated, although some trial data were excluded from the meta-analysis described in Section 6.6.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

In addition to the RCTs involving comparators to degarelix, the systematic literature review also identified six randomised degarelix dose-finding trials[39-53] and seven non-randomised studies (mostly extensions of the completed RCTs)[54-71] (see Appendix B, Table B1). One of the six dose-finding trials (CS02) was not considered further in this report, as the initial dose of degarelix used was much lower than the approved regimen (see Section 6.8).[39,40]

6.3 *Summary of methodology of relevant RCTs*

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

The six included RCTs were conducted in America and Europe from 2006 onward. All six RCTs were sponsored by Ferring Pharmaceutical A/S. The methods of these RCTs are summarised in Appendix B, Table B2.[9-18]

RCT design

The included RCTs were primarily designed to demonstrate that degarelix was non-inferior to LHRH agonists in the treatment of patients with prostate cancer.[9-18] Randomisation lists were appropriately prepared centrally, using a validated computer program.[9-11,13,15,17,18] All six RCTs were open label, as blinding of patients and care providers was impossible due to the different routes of administration and formulations of degarelix and the comparators (leuprorelin or goserelin.[9,11,13,15,17,18] In study CS21, the treatment was blinded for the central laboratory personnel.[9]

Intervention and dosing

Degarelix

The initial dose of degarelix in all six of the included RCTs was 240 mg, administered on Day 0.[9,11,13,15,17]

Five RCTs used a monthly maintenance dose of degarelix from Day 28:

- 80 or 160 mg for 12 months in CS21
- 80 mg for three months in CS28, CS30 and CS31
- 80 mg for 7 or 14 months in CS37.[9-16,18]

In CS35, a three-monthly maintenance regimen of degarelix (480 mg) was administered after the initial dose of degarelix.[17]

LHRH agonists

The LHRH agonist comparator used in the control group was:

- Leuprorelin 7.5 mg monthly in CS21
- Goserelin 3.6 mg monthly in CS28, CS30 and CS31
- Goserelin 10.8 mg three-monthly in CS35.[1-17]

The LHRH agonist control in CS37 was leuprorelin, at an initial dose of 7.5 mg followed by a three-monthly maintenance dose of 22.5 mg for 14 months.[18]

Anti-androgen flare (surge) protection

Only 11% of patients in the LHRH agonist group in CS21 received bicalutamide for flare protection at the start of treatment and only 13.5% of patients in the control group in CS35 received bicalutamide from Day 1 to Day 38 for flare protection.[9,10,17] All patients in the LHRH agonist groups received bicalutamide (50 mg once-daily) from Day 0 to Day 28 in CS31 and from Day 0 to Day 16 in CS28 and CS30.[11,13,15]

Study endpoints

The primary endpoint was:

- Suppression of serum testosterone levels to ≤0.5 ng/ml (castrate level) between Day 28 and 364 in CS21 and CS35[9,10]
- Reduction of prostate volume (measured by transrectal ultrasound) at 12 weeks in CS30 and CS31[13-16]
- Change in the International Prostate Symptom Score (IPSS) at 12 weeks in CS28[11,12]
- PSA suppression (≤4 ng/ml) at 14 months in CS37.[18]

The primary objective of CS37 was to establish non-inferiority of intermittent degarelix treatment compared with continuous androgen-deprivation (continuous leuprorelin and continuous degarelix) in maintaining PSA suppression.[18]

In addition, a variety of secondary outcomes, including PSA progression, were measured in the included RCTs (see Appendix B, Table B1).[9-18] The key secondary efficacy outcome included in the cost-effectiveness analysis that forms part of this STA submission is PSA progression.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Inclusion criteria

Table B3 in Appendix B provides a summary of the inclusion criteria for the six RCTs that compared degarelix with an LHRH agonist.[9,11,13,15,17,18]

All trials included adult patients (aged ≥18 years) with histologically confirmed prostate cancer in whom endocrine treatment was indicated.[9-18] CS30 only included patients in whom neoadjuvant hormonal therapy before planned radical radiotherapy was indicated.[13,14] Patients' screening serum testosterone levels were an inclusion criterion in three of the trials: levels had to be >1.5 ng/ml in CS21,[9,10] above the lower limit of the normal range in an elderly male population (globally defined as >1.5 ng/ml) in CS35,[17] and within the normal range (≥1.5 ng/ml) in CS37.[18] Baseline serum testosterone levels were not an inclusion criterion in the remaining three RCTs (CS28, CS30 and CS31).[11-16]

PSA levels were an eligibility criterion in all six RCTs. Baseline PSA levels had to be ≥2 ng/ml in three studies (CS21, CS31 and CS35) and ≥10 ng/ml in two studies (CS28 and CS30).[9,10,15-17] For patients with recurrence after radical prostatectomy in CS35, PSA levels needed to have shown a ≥0.2 ng/ml increase from the previous test on two consecutive measurements.[17] Patients were eligible to enter CS37 only if they had rising PSA levels after having undergone primary therapy for localised prostatic carcinoma – either a rise in PSA levels ≥0.2 ng/ml after radical prostatectomy or three PSA levels higher than the nadir PSA after radiation, cryotherapy or LHRH treatment – and the investigator assessed that androgen deprivation therapy was warranted.[18]

An Eastern Cooperative Oncology Group (ECOG) score ≤2 was an eligibility criterion in five of the six RCTs: CS21, CS28, CS30, CS35 and CS37.[9-13,17,18] Total prostate volume of >30 ml (30 cm^3), measured by transrectal ultrasound scan (TRUS), was required in two RCTs (CS30 and CS31).[13-16] It was added as an eligibility criterion in CS28 following a protocol amendment.[11,12] One of the eligibility criteria in CS28, in which change in IPSS was defined as the primary outcome, was an IPSS ≥12.[11,12]

Exclusion criteria

Table B4 in Appendix B provides a summary of the exclusion criteria for the six RCTs.[9,11,13,15,17,18] CS21 excluded patients in whom neoadjuvant hormonal therapy was indicated.[9,10] Patients with any previous treatments for prostate cancer were excluded from three of the RCTs: CS28, CS30 and CS31.[11-16]

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table 10 shows the main baseline characteristics of participants in the six included RCTs.[9-18] No statistically significant differences were observed between the groups within each RCT. The proportion of patients with either locally advanced or metastatic prostate cancer was 49% in CS21, 48% in CS28, 34% (metastatic prostate cancer 0%) in CS30, 60% in CS31, 56% in CS35 and only 5.5% (metastatic prostate cancer <1%) in CS37.

Table 10. Characteristics of participants across randomised controlled trials[9-18]

Trial no	Characteristics	Treatment groups		
CS21[9,10]		**Group A (degarelix 240/160 mg, n=202[a])**	**Group B (degarelix 240/80 mg, n=207[a])**	**Group C (leuprorelin 7.5 mg, n=201[a])**
	Median (range) age (years)	72 (50–88)	72 (51–89)	74 (52–98)
	Race, white (n, %)	168 (83)	171 (83)	172 (86)
	Mean (SD) weight (kg)	78.7 (13.0)	79.8 (14.9)	79.4 (12.2)
	Median (25–75 percentile)			
	Testosterone (ng/ml)	3.78 (2.86–5.05)	4.11 (3.05–5.32)	3.84 (2.91–5.01)
	PSA (ng/ml)	19.9 (8.2–68)	19.8 (9.4–46)	17.4 (8.4–56)
	Stage of disease (n, %)			
	Localised	59 (29)	69 (33)	63 (31)
	Locally advanced	62 (31)	64 (31)	52 (26)
	Metastatic	41 (20)	37 (18)	47 (23)
	Not classifiable	40 (20)	37 (18)	39 (19)
	Gleason grade (n, %)			
	2–4	21 (11)	20 (10)	24 (12)
	5–6	67 (34)	68 (33)	63 (32)
	7	56 (28)	63 (30)	62 (31)
	8–10	56 (28)	56 (27)	51 (26)

Trial no	Characteristics	Treatment groups	
CS28[11,12]		**Group A (degarelix, n=27)**	**Group B (goserelin, n=13)**
	Median (range) age (years)	68 (53–87)	72 (57–85)
	Median (range) testosterone (ng/ml)	4.2 (1.1–6.7)	3.9 (2.7–7.4)
	Median (range) PSA level (ng/ml)	54.5 (8–1,914)	41.1 (14.6–348)
	Stage of prostate cancer (n, %)		
	Localised	4 (15)	0
	Locally advanced	4 (15)	1 (8)
	Metastatic	10 (37)	4 (31)
	Not classifiable	9 (33)	8 (62)
	T staging (n, %)		
	T1/2	5 (19)	2 (15)
	T3/4	21 (78)	11 (85)
	TXa	1 (4)	0 (0)
	Gleason score (n, %)		
	5–6	2 (7)	0 (0)
	7–10	25 (93)	13 (100)
	ECOG performance status (n, %)		
	Fully active	22 (81)	11 (85)
	Restricted but ambulatory	4 (15)	1 (8)
	Ambulatory but unable to work	1 (4)	1 (8)
	Mean (SE) IPSS total score	20.1 (1.1)	21.1 (1.6)
	Mean (SE) IPSS quality of life score	3.6 (0.3)	3.2 (0.5)
	Mean (SE) Qmax (ml/s)	9.3 (0.8)	8.3 (0.8)
	Mean (SE) prostate volume (ml)	53.5 (5.5)	50.3 (4.5)
CS30[13,14]		**Group A (degarelix, n=180[b])**	**Group B (goserelin, n=64[b])**
	Mean (SD) age (years)	70.6 (6.37)	70.8 (5.96)
	Mean (SD) weight (kg)	83.6 (14.2)	80.9 (12.4)
	Mean (SD) BMI (kg/m^2)	27.8 (3.99)	26.8 (3.69)
	Mean (SD) testosterone (ng/ml)	4.18 (1.72)	4.45 (1.49)
	Median (range) testosterone (ng/ml)	3.92 (0.58–11.2)	4.42 (0.19–8.16)
	Mean (SD) PSA (ng/ml)	17.4 (30.1)	13.4 (12.9)
	Median (range) PSA	10.0 (2.5–339)	9.75 (2.9–80)
	Tumour stage[a] (n, %)		
	Localised	111 (62)	41 (64)
	Locally advanced	63 (35)	20 (31)
	Not classifiable	6 (3)	3 (5)
	Gleason score (n, %)		
	2–6	41 (23)	12 (19)
	7	97 (54)	42 (66)
	8–10	42 (23)	10 (16)
	ECOG score (n, %)		
	Fully active	154 (86)	58 (91)
	Restricted but ambulatory	21 (12)	16 (9)
	Ambulatory but unable to work	5 (3)	0
	Capable of only limited self-care	0	0
	Mean (SD) IPSS	9.5 (6.71)	8.5 (6.30)
	Mean (SD) IPSS quality of life	2.27 (1.63)	1.94 (1.56)
	Mean (SD) total prostate volume (ml)	50.9 (20.3)	52.5 (18.8)
	Median (range) days since prostate cancer diagnosis	75 (14–1,378)	72 (17–1,526)

Trial no	Characteristics	Treatment groups	
CS31[15,16]		**Group A (degarelix, n=82)**	**Group B (goserelin, n=97)**
	Mean (SD) age (years)	71.9 (7.71)	73 (7.1)
	Mean (SD) weight (kg)	79.7 (12.4)	79.7 (12.2)
	Mean (SD) BMI (kg/m)	26.8 (4.07)	26.5 (3.72)
	Testosterone (ng/ml)		
	Mean (SD)	4.25 (1.88)	4.43 (1.64)
	Median (range)	4.08 (0.32–10.8)	4.33 (0.13–9.61)
	PSA level (ng/ml)		
	Mean (SD)	277 (937)	148 (438)
	Median (range)	27.8 (1.9–6,206)	15.6 (3–2,829)
	Tumour stage (n, %)		
	Localised	24 (29)	32 (33)
	Locally advanced	30 (37)	23 (24)
	Metastatic	22 (27)	31 (32)
	Not classifiable	6 (7)	11 (11)
	T stage (n%)		
	T1/2	35 (43)	42 (43)
	T3/4	47 (57)	55 (57)
	Gleason score (n, %)		
	2–6	17 (21)	16 (16)
	7	24 (29)	31 (32)
	8–10	41 (50)	50 (52)
	ECOG score (n, %)		
	Fully active	52 (63)	65 (67)
	Restricted but ambulatory	28 (34)	31 (32)
	Ambulatory but unable to work	2 (2)	0
	Capable of only limited self-care	1 (1)	1 (1)
	Mean (SD) IPSS	14.3 (6.91)	13.4 (7.36)
	Mean (SD) IPSS QoL	2.85 (1.62)	2.73 (1.66)
	Mean (SD) BPH Impact Index	5.06 (3.39)	4.58 (3.58)
	Total prostate volume (ml)	54.8 (26)	49.9 (15.5)
	Mean (SD) days since diagnosis of prostate cancer	89 (217)	102 (270)
CS35[17]		**Group A (degarelix, n=565[b])**	**Group B (goserelin, n=282[b])**
	Mean (SD) age (years)	71.9 (8.32)	71.1 (7.9)
	Race (n, %)		
	White	475 (84)	239 (85)
	Black/African American	41 (7)	16 (6)
	American Indian/Alaskan native	45 (8)	25 (9)
	Mean (SD) weight (kg)	79.6 (15.9)	80.2 (14.4)
	Mean (SD) testosterone (ng/ml)	4.72 (2.01)	4.92 (1.94)
	Baseline PSA (ng/ml) (n, %)		
	0–10	163 (29)	96 (34)
	10–20	125 (22)	48 (17)
	20–50	105 (19)	62 (22)
	≥50	170 (30)	76 (27)

Trial no	Characteristics	Treatment groups		
		Group A (degarelix, n=565[b])		**Group B (goserelin, n=282[b])**
	Stage of prostate cancer (n, %)			
	Localised	165 (29)		90 (32)
	Locally advanced	152 (27)		74 (26)
	Metastatic	172 (30)		71 (25)
	Not classified	76 (13)		47 (17)
	Gleason score (n, %)			
	2–4	49 (9)		16 (6)
	5–6	187 (33)		89 (32)
	7–10	324 (58)		177 (63)
	ECOG performance score (n, %)			
	Fully active	430 (76)		226 (80)
	Restricted but ambulatory	120 (21)		49 (17)
	Ambulatory but unable to work	15 (3)		7 (2)
	Capable of only limited self-care	0		0
	Completely disabled	0		0
	Curative intent (n, %)			
	Yes	70 (12)		39 (14)
	No	495 (88)		243 (86)
CS37[18]		**Group A (degarelix intermittent 240/80 mg, n=175[b])**	**Group B (degarelix continuous 240/80 mg, n=50[b])**	**Group C (leuprorelin 7.5/22.5 mg, n=178[b])**
	Mean (SD) age (years)	71.9 (8.89)	71.7 (8.14)	71 (8.44)
	Race (n, %)			
	American Indian/Alaskan Native	2 (1)	1 (2)	2 (1)
	Asian	0	1 (2)	1 (<1)
	Black/African American	32 (18)	9 (18)	38 (21)
	White	140 (80)	39 (78)	137 (77)
	Mean (SD) weight (kg)	90.3 (19.4)	88.4 (15.8)	91.9 (16.9)
	Mean (SD) BMI (kg/m^2)	28.9 (5.45)	29.2 (4.89)	29.6 (4.94)
	Prostate cancer stage (n, %)			
	Localised	65 (37)	17 (34)	60 (34)
	Locally advanced	7 (4)	1 (2)	13 (7)
	Metastatic	0	0	1 (<1)
	Not classifiable	103 (59)	32 (64)	104 (58)
	Gleason score (n, %)			
	2–4	4 (2)	1 (2)	3 (2)
	5–7	56 (32)	22 (44)	61 (35)
	7–10	115 (66)	27 (54)	112 (64)
	ECOG score (n, %)			
	0: fully active	144 (82)	41 (82)	160 (90)
	1: restricted but ambulatory	26 (15)	8 (16)	16 (9)
	2: ambulatory but unable to work	5 (3)	1 (2)	2 (1)

Key: BMI = body mass index; BPH = benign prostate hyperplasia; ECOG = Eastern Cooperative Oncology Group; IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; Qmax = maximum urine flow; QoL = quality of life; SD = standard deviation; SE = standard error
[a] Intention-to-treat population; [b] Full analysis set

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

The main outcome measures of the six RCTs are summarised in Table 11 below,[9,11,13,15,17,18] while Table B5 in Appendix 5 provides a more detailed overview of the primary and secondary outcomes of these trials.[9-18]

Four outcomes were defined as the primary endpoints in the trials: serum testosterone response (CS21 and CS35), prostate volume (CS30 and CS31), IPSS (CS28) and PSA response (CS37).

Table 11. Main outcome measures in included randomised controlled trials[9,11,13,15,17,18]

Main outcomes	CS21	CS28	CS30	CS31	CS35	CS37
Overall survival	x	x	x	x	x	x
Progression-free survival	x				x	x
Testosterone response [a]	x (primary)	x	x	x	X (primary)	x
PSA response	x	x	x	x	x	X (primary)
Prostate volume (size)		x	X (primary)	X (primary)		
IPSS		X (primary)	x	x	x	
Health-related QoL	x	x	x	x	x	x
Adverse effects	x	x	x	x	x	x

Key: IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; QoL = quality of life

[a] Serum testosterone levels

Serum testosterone level

Serum testosterone level is an objective laboratory parameter that is relevant to clinical practice. Serum testosterone levels were determined using a validated liquid chromatography–mass spectrometry (LC-MS)/MS assay, which is considered to be the most precise method for the detection of low testosterone levels. Samples for each timepoint were analysed in triplicate and the median value was reported. The laboratory personnel were blinded to the treatment.[9]

PSA response

All six of the included RCTs measured PSA response, although this was only defined as the primary endpoint in one trial (CS37).[9,11,13,15,17,18]

PSA measurements can be used to monitor response to treatment for prostate cancer, disease recurrence and progression. Clinical experts consulted during the compilation of this submission confirmed that PSA progression (also known as PSA recurrence or PSA failure) – defined as two increases >50% above baseline – is used routinely in clinical practice as a prognostic indicator to assess disease progression and/or treatment response.[7] The published literature also corroborates the use of PSA progression as a prognostic indicator; for example, Hussain *et al* found that PSA progression – defined as an increase of ≥25% over nadir and an absolute increase of ≥2 or 5 ng/ml – predicts overall survival in patients with hormone-sensitive or hormone-refractory prostate cancer and, so, is a suitable endpoint for Phase II studies in these patients.[107] In addition, Caire *et al* concluded that in patients with prostate cancer, lower pathological Gleason scores and lower PSA levels at diagnosis were associated with a delayed time to PSA progression, and that those patients with delayed PSA progression had a disease-specific survival advantage compared with men with early PSA progression.[108]

Prostate volume

A symptom of prostate cancer is urinary obstruction with lower urinary tract symptoms (LUTS).[109] An effective hormonal treatment can, in most cases, give the patient relief from these symptoms. The mechanism to achieve this relief is a reduction in the size of the prostate gland, which reduces obstruction and, therefore, the LUTS. Prostate volume was measured directly by TRUS, using suitable, well maintained, locally available equipment. All trial sites were provided with a manual for standardised TRUS measurements in a separate document. All evaluations for a single patient were to be performed using the same equipment.

IPSS

The IPSS questionnaire is commonly used to assess the severity of LUTS and to monitor the progress of the disease process once treatment has been initiated.[11,13,15] Version 1 of the IPSS questionnaire has been validated for multinational use and was provided to sites in each country in the local language. The IPSS questionnaire included an additional single question to assess a patient's quality of life in relation to his urinary symptoms: 'If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?' The answers to this question ranged from 'delighted' (a score of 0) to 'terrible' (a score of 6). The

response to this question was analysed separately and was not included in the total IPSS.

Quality of life

In CS21, the effects of degarelix and leuprorelin on patients' quality of life were evaluated using version 2 of the 12-item short form survey (SF-12 v2) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) to measure generic and cancer-specific quality of life, respectively.[9]

As described above, quality of life in relation to the patient's urinary symptoms was assessed in three RCTs (CS28, CS30 and CS31) using a single question related to urological symptoms that was added to the IPSS: 'If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?'[11,13,15] Study CS31 also included the Benign Prostatic Hyperplasia Impact Index (BPHII), a self-administered questionnaire comprising four items, which measures how much urinary problems affect various domains of health.[15]

In CS35, generic health-related quality of life was measured using version 2 of the 36-item short-form survey (SF-36 v2). This study also measured changes in arthralgia on a visual analogue scale (VAS), using the question: 'Please rate how much pain you have felt on average during the last week?' The VAS was 100 mm in length, where 0 mm was 'No pain' and 100 mm was 'worst possible pain'.[17]

In CS37, quality of life was assessed by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) instrument and sexual function by the Sexual Function Inventory (SFI). Both outcomes were compared between the degarelix intermittent treatment group and the continuous androgen-deprivation treatment group.[18]

Adverse events

An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational medicinal product (IMP) that did not necessarily have a causal relationship with the study treatment. An AE was, therefore, any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the product, whether or not related to the IMP. An adverse drug reaction (ADR) was defined as an AE rated by the investigator and/or the sponsor as probably or possibly related to treatment with the IMP.[9,11,13,15,17,18]

AEs were graded according to the common terminology criteria for adverse events (CTCAE) issued by the National Cancer Institute. In accordance with the CTCAE, AEs were rated on a five-point scale corresponding to mild, moderate, severe, life-threatening or disabling, and death. A separate five-point rating scale was used to rate the intensity of AEs not described in the CTCAE.[9,11,13,15,17,18]

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table B6 in Appendix B provides an overview of the methods used for statistical analysis and data management in the included RCTs.[9-18]

Statistical hypotheses tested

The two RCTs that used testosterone levels as the primary outcome (CS21 and CS35) assessed the response to degarelix based on the following non-comparative criterion of the US Food and Drug Administration (FDA) and non-inferiority criterion of the European Medicines Agency (EMA):[9,17]

- **FDA criterion – *degarelix response rate estimation:*** this non-comparative primary objective was met if the lower limit of the obtained 95% two-sided confidence interval (CI) was >90%; that is, if the one-year suppression rate was of statistical significance greater than 90%.
- **EMA criterion – *non-inferiority assessment:*** in CS21, the non-inferiority limit was –10 percentage points for the difference between degarelix and leuprorelin in the cumulative probability of testosterone ≤0.5 ng/ml from Day 28 to Day 364. In CS35, the pooled standard error (SE) was used to construct the 95% two-sided CI of the difference between degarelix and goserelin in cumulative probability of testosterone ≤0.5 ng/ml from Day 3 to Day 364, and non-inferiority was to be claimed if the lower limit of this CI was >–Δ (change), where Δ=5% was the non-inferiority margin.

The two RCTs that used prostate volume as the primary outcome (CS30 and CS31) assumed that degarelix was non-inferior to goserelin plus bicalutamide. Non-inferiority was to be established if the treatment difference in mean percentage reduction in prostate volume (adjusted for baseline volume and baseline total IPSS) was significantly greater (two-sided at α=0.05 level) than Δ=–10 points (non-inferiority margin) in both the full analysis set (FAS) and per-protocol (PP) analysis set.[13,15]

In CS28, non-inferiority was to be established if the difference between degarelix and goserelin plus bicalutamide in mean change from baseline in total IPSS (adjusted for baseline total IPSS, age and country) was statistically significantly smaller (two-sided at α=0.05 level) than Δ=3 points in both the FAS and PP analysis set.[15]

In CS37, the primary efficacy analysis was examination of the non-inferiority of the intermittent treatment compared with the continuous treatment. The primary efficacy analysis was evaluated for the FAS for Phase B. This assessment was made by obtaining the 95% CI for the difference between the intermittent and continuous treatments (intermittent–continuous). If the lower bound of this CI was >–12.5% (the non-inferiority margin) the intermittent treatment was to be considered non-inferior to the continuous treatment with respect to the primary efficacy variable. Each of the CIs was determined using a normal approximation to the binomial distribution.[18]

Sample size calculation

The sample size calculation was generally based on the assumed non-inferiority margin of α=0.05 and statistical power=0.9, except in CS37, in which a conservative approach that assumed 0.8 power was adequate because there was no precedent for intermittent treatment.[9,11,13,15,17,18] CS28 was stopped early due to poor recruitment, and the power of the trial was reduced from 90% to 25%.[11]

Data management and patient withdrawals

For CS21, the intention-to-treat (ITT) and safety analysis sets were identical, comprising all 610 randomly assigned patients who received at least one dose of study medication. The population in all safety summaries was, therefore, labelled as the ITT analysis set. The PP analysis set consisted of all patients in the ITT analysis without any major protocol deviations.[9,10]

For four of the other included RCTs (CS28, CS30, CS31 and CS35), the following data sets were used:[11,13,15,17]

- ITT analysis set: data of all patients who were randomly assigned
- FAS: data of all patients who received at least one dose of IMP and had at least one efficacy assessment after dosing
- PP analysis set: patients in the FAS, except for those who met specified protocol variation criteria
- Safety analysis set: data of all patients who received at least one dose of IMP.

CS37 had two phases: Phase A and Phase B, in which the following datasets were used:[18]

- FAS: all randomly assigned patients who received at least one dose of IMP and had at least one efficacy assessment after dosing.
- FAS for Phase B: a subset of all randomly assigned patients who completed seven months of treatment and had PSA levels ≤2.0 ng/ml at the end of Month 7 and had at least one primary endpoint efficacy assessment (that is, PSA measurement) after Month 7.
- PP analysis set: patients in the FAS were excluded from the PP analysis set if they met any of the criteria for serious protocol violations, with the exception of dosing violations, in which case the subject data were included in the PP analysis set up to the timepoint when the dosing violation occurred.
- PP for Phase B analysis set: patients in the FAS for Phase B were excluded from the PP analysis set for Phase B if they met any of the criteria for protocol violations, with the exception of the dosing violations, which could have occurred in

either the leuprorelin continuous or degarelix continuous treatment arms, in which case the patient data were included in the PP for Phase B analysis set up to the timepoint when the dosing violation occurred.

- Safety analysis set: all patients who received at least one dose of IMP were included.
- Safety analysis set for Phase B: the data of all patients who received at least one dose of trial drug and who had PSA levels <2.0 ng/ml at the end of Month 7 were included.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Post hoc exploratory subgroup analyses of PSA response data from the CS21 trial were performed, analysing PSA PSF, overall survival, PSA progression by baseline disease stage and PSA progression by baseline PSA level.[21] PSA response was explored further, as it has been suggested to play an important role in monitoring the response to treatment for prostate cancer, disease recurrence and progression.[107,108]

An independent academic group completed a pooled analysis of the six RCTs (CS21, CS28, CS30, CS31, CS35 and CS37) to perform a post hoc exploratory analysis of the risk of cardiovascular events and mortality in the entire RCT population and in a subgroup of patients with a history of cardiovascular disease (CVD).[73] The same pooled individual patient level data[110] have been analysed, using the Kaplan–Meier method, for the purpose of inclusion in the cost-effectiveness model described in Section 7 of this submission. CVD AEs were explored further because an association between LHRH agonists, with/without anti-androgen treatment, and an increased risk of cardiovascular events (including myocardial infarction and cardiovascular mortality) in patients with prostate cancer has previously been suggested.[94,111-115] This risk association was corroborated by the request of the US FDA in 2010 for manufacturers of LHRH agonists to add new safety information to the '*Warnings and Precautions*' labelling section regarding an increased risk of diabetes and certain CVDs (myocardial infarction, sudden cardiac death, stroke).[105]

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

CONSORT flow charts for each RCT are shown in Figure 4 to Figure 9 below.

In addition, Table B7 in Appendix B shows the participant flow for each of the included RCTs.[9,11,13,15,17,18]

Figure 4. CONSORT flow chart for CS21[9,10]

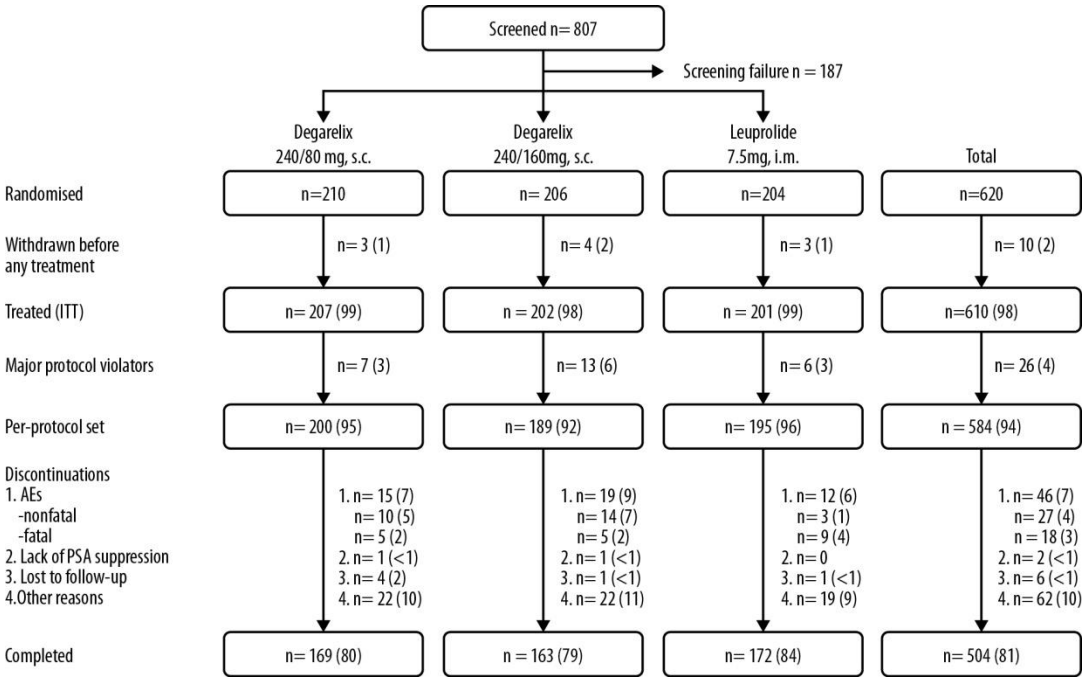


Figure 5. CONSORT flow chart for CS28[11,12]

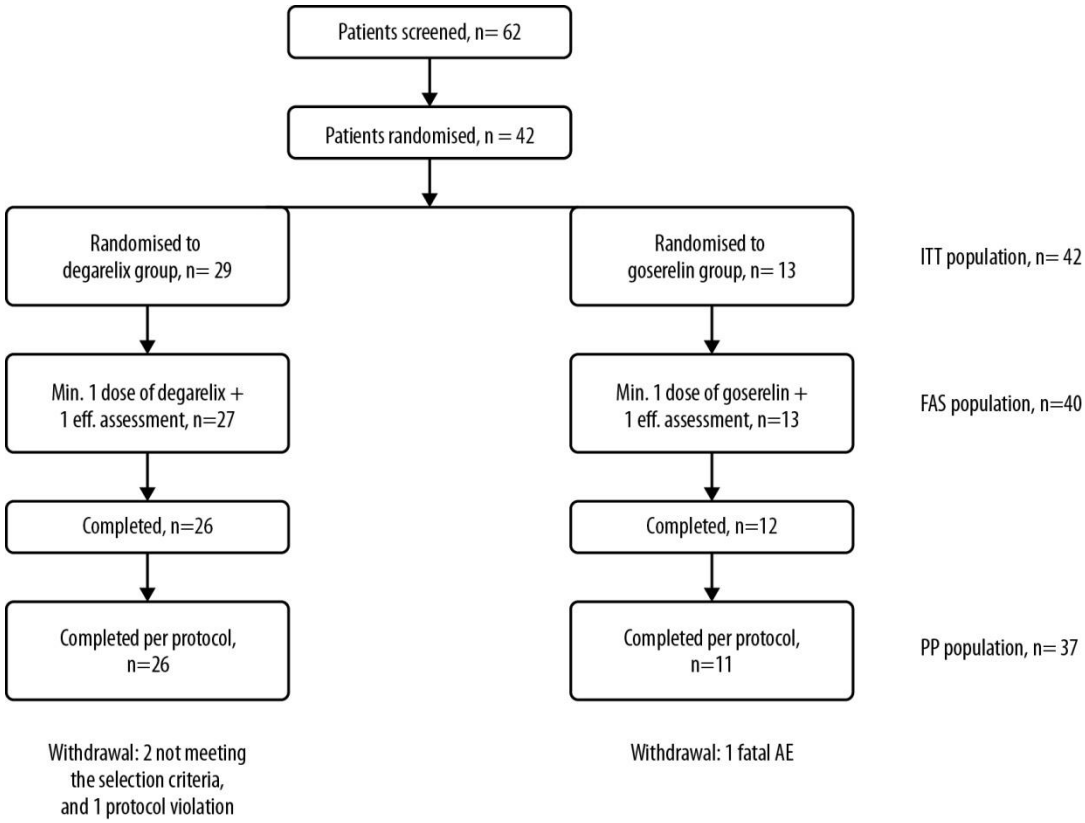


Figure 6. CONSORT flow chart for CS30[13,14]

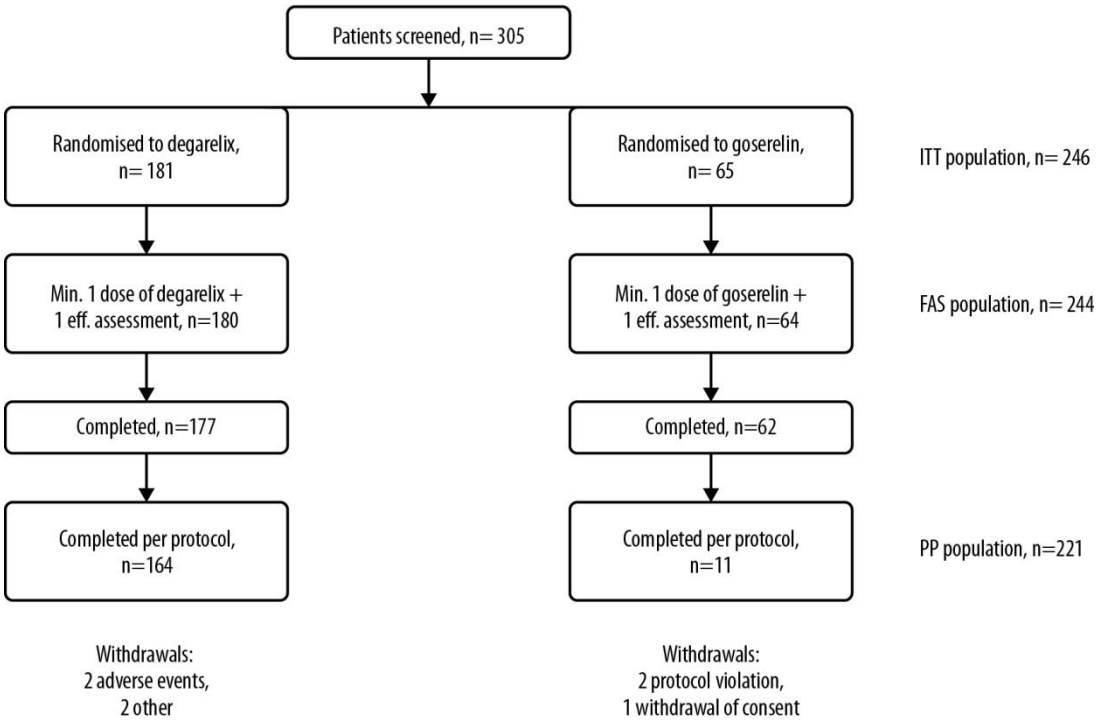


Figure 7. CONSORT flow chart for CS31[15,16]

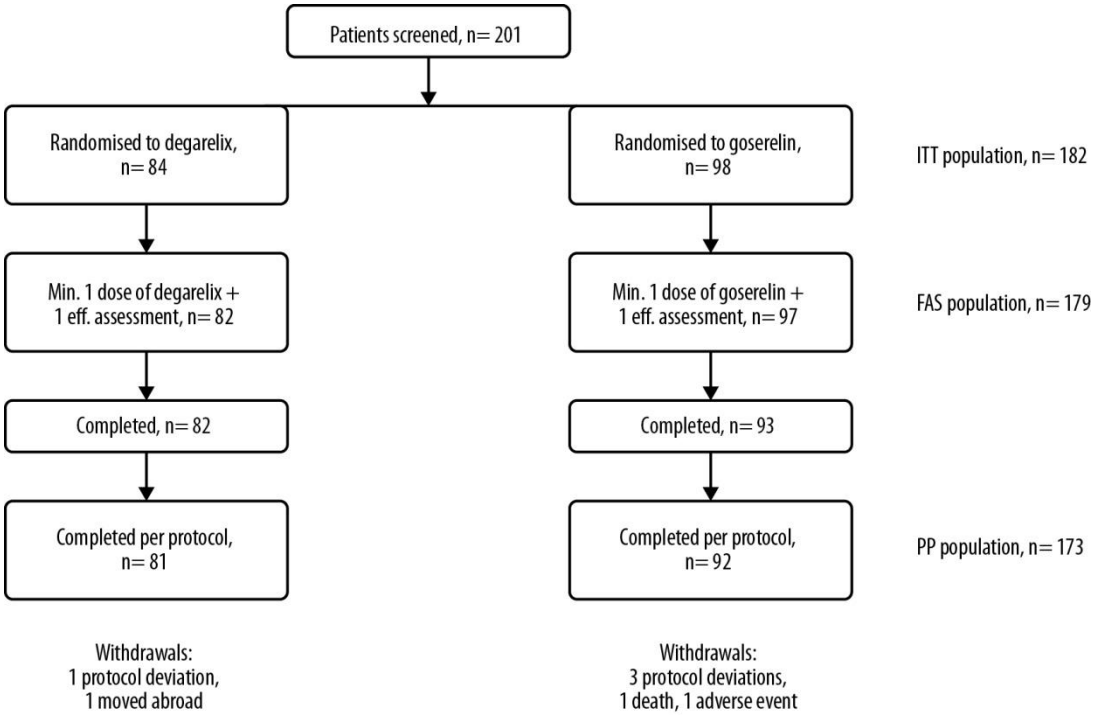


Figure 8. CONSORT flow chart for CS35[17]

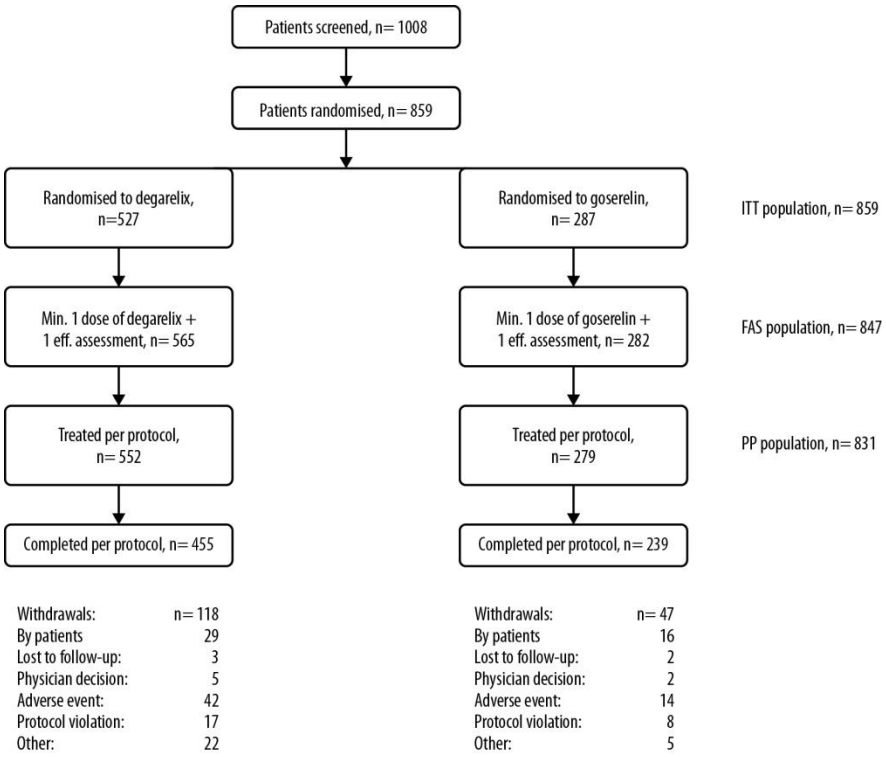
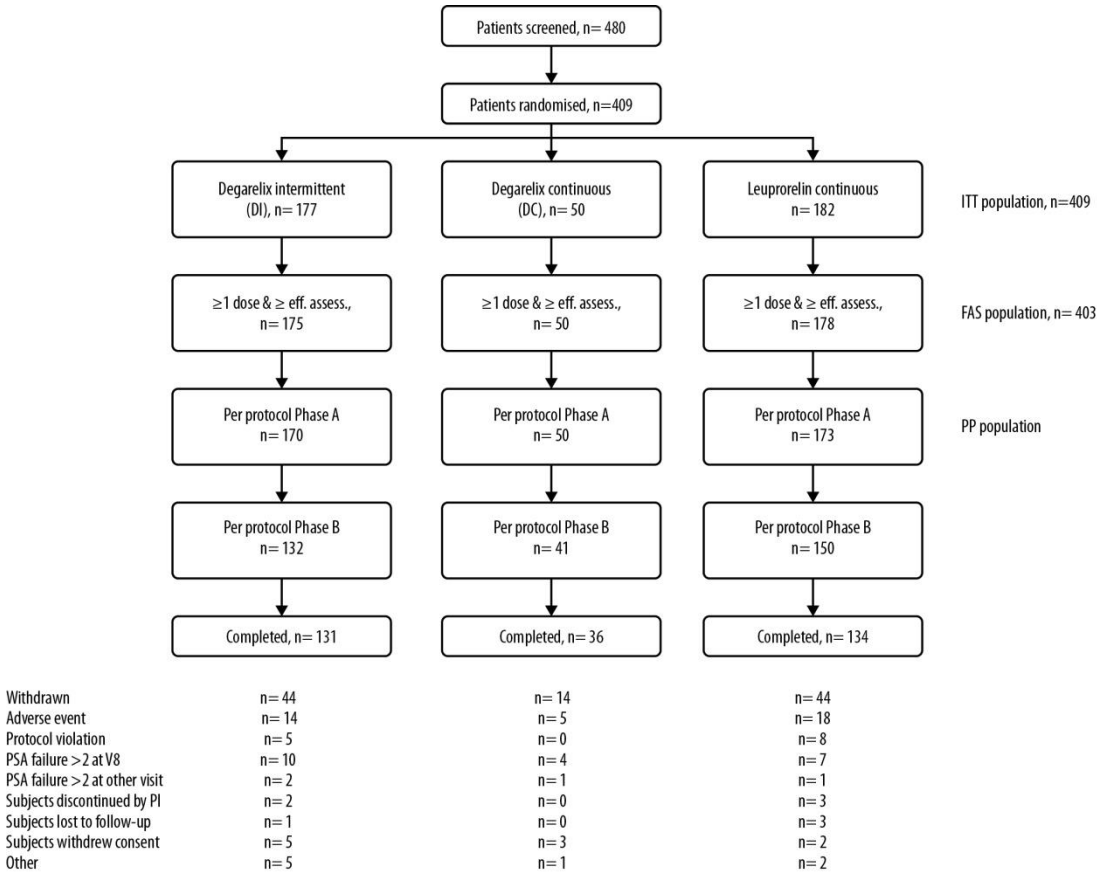


Figure 9. CONSORT flow chart for CS37[18]



6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below

Table B8 in Appendix B shows the results of validity assessment of the included RCTs.[9,11,13,15,17,18]

Randomisation was appropriately conducted (see also Appendix B, Table B2); however, the concealment of treatment allocation was generally unclear. No statistically significant differences between groups were seen in the main baseline characteristics of participants (see also Table 10).[9-18]

Due to the different formulations and methods of administration of degarelix and LHRH agonists, blinding of patients and care providers was impossible.[9,11,13,15,17,18] The protocol for CS21 explicitly stated that the treatment was blinded to the central laboratory personnel.[9] The lack of blinding may not introduce important bias in objectively measured outcomes, such as serum testosterone level and prostate volume; however, assessment of subjectively measured outcomes, such as AEs, IPSS and other items around quality of life, may be subject to bias.

Clinical study reports and published papers provided details on patient withdrawals and exclusions.[9-18] No unexpected imbalance between treatment groups occurred in the dropouts of each RCT (see also Appendix B, Table B7 and Figure 4 to Figure 9).

Clinical study reports were available for all the included RCTs.[9,11,13,15,17,18] Any selective outcome reporting will have limited impact.

The FAS included data of all patients who received at least one dose of IMP and had at least one efficacy assessment after dosing.[9-18] The PP analysis set included patients in the FAS except those who met specified protocol variation criteria. Results from the FAS and PP analysis set were routinely reported in the clinical study reports, and the two results were generally similar.

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.

- Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Testosterone response

Testosterone response during the first two weeks

In CS21, a patient was defined as having a testosterone flare (surge) if testosterone levels exceeded those measured at baseline by ≥15% on any two days during the first two weeks of treatment – that is, two of Days 1, 3, 7 and 14. Only one (0.2%) patient treated with degarelix (from the 240/160 mg group) had a slight testosterone increase during the first two weeks of treatment, compared with 161 (80.1%) patients in the leuprorelin 7.5 mg group ($p<0.0001$, Fisher's exact test).[9]

In the leuprorelin group, 11% of patients received anti-androgen protection against a testosterone flare at the start of the treatment. The proportion of patients who had a testosterone flare during the first two weeks of treatment was lower among the 11% who started anti-androgen therapy before starting leuprorelin or at Day 7 after starting leuprorelin (72.7%) compared with those who did not use anti-androgen therapy (80.9%).[9]

On Day 3 of CS21, 193 (95.5%) patients from the degarelix 240/160 mg group and 199 (96.1%) from the 240/80 mg group had testosterone levels ≤0.5 ng/ml, compared with no patients in the leuprorelin 7.5 mg group ($p<0.0001$). Rapid suppression of testosterone was observed for patients in the two degarelix groups, with median testosterone levels reduced by >90% from baseline by Day 3. In contrast, patients in the leuprorelin group had a 65% increase in testosterone levels by Day 3. The use of anti-androgen therapy did not affect the lack of testosterone suppression observed for patients in the leuprorelin 7.5 mg group.[9]

The rapid suppression of testosterone levels seen with degarelix indicates a rapid onset of action and, as a result, the possibility of rapid disease control. Avoidance of testosterone flare also reduces the risk of exacerbating bone pain, compression of a nerve root, spinal cord compression and obstructive uropathy.

In CS35, in which degarelix was administered as a three-monthly regimen, the cumulative probability (95% CI) of testosterone levels ≤0.5 ng/ml from Day 3 to Day 364 was 85.0% (81.6% to 87.8%) for degarelix compared with 5.3% (3.1% to 8.4%) for goserelin. It should be noted that only 13.5% of patients in the goserelin group received anti-androgen protection against a testosterone flare (surge) at the start of the treatment.[18]

Cumulative probability of testosterone levels ≤0.5 ng/ml from Day 28

Table 12 shows the results from the included RCTs for the cumulative probability of testosterone levels ≤0.5 ng/ml from Day 28.[9-17]

Table 12. Kaplan–Meier estimated cumulative probability of testosterone ≤0.5 ng/ml[9,11,13,15,17]

Study	Intervention	Duration	Estimate (95% CI)
Monthly maintenance dosing regimens			
CS21[9,10]	Degarelix 240/80 mg	Day 28–84	99.5% (96.5% to 99.9%)
	Leuprorelin 7.5 mg	Day 28–84	97.6% (92.7% to 99.2%)
	Degarelix 240/160 mg	Day 28–364	98.3% (94.8% to 99.4%)
	Degarelix 240/80 mg	Day 28–364	97.2% (93.5% to 98.8%)
	Leuprorelin 7.5 mg	Day 28–364	96.4% (92.5% to 98.2%)
CS28[11,12]	Degarelix 240/80 mg	Day 28–84	100%
	Goserelin 3.6 mg + bicalutamide	Day 28–84	92%
CS30[13,14]	Degarelix 240/80 mg	Day 28–84	96.0% (91.8% to 98.1%)
	Goserelin 3.6 mg + bicalutamide	Day 28–84	92.0% (81.9% to 96.6%)
CS31[15,16]	Degarelix 240/80 mg	Day 28–84	97.6% (90.6% to 99.4%)
	Goserelin 3.6 mg + bicalutamide	Day 28–84	95.9% (89.4% to 98.4%)
Three-monthly maintenance dosing regimen			
CS35[17]	Degarelix 240/480 mg	Day 28–364	90.0% (87.0% to 92.3%)
	Goserelin 3.6/10.8 mg	Day 28–364	96.7% (93.7% to 98.2%)

Key: CI = confidence interval

In CS21, the primary endpoint was the probability of testosterone levels ≤0.5 from Day 28 to Day 364. For the ITT dataset, the Kaplan–Meier method estimated a cumulative probability (95% CI) of testosterone ≤0.5 ng/ml from Day 28 to Day 364 of 98.3% (94.8% to 99.4%) in the degarelix 240/160 mg group, 97.2% (93.5% to 98.8%) in the degarelix 240/80 mg group and 96.4% (92.5% to 98.2%) in the leuprorelin 7.5 mg group. For each of the two degarelix groups, the lower boundary of the two-sided 95% CI was above the 90% threshold. The difference in the cumulative probability of testosterone ≤0.5 ng/ml was 1.9% (–1.8% to 5.7%) between degarelix 240/160 mg and leuprorelin 7.5mg and 0.9% (–3.2% to 5.0%) between degarelix 240/80 mg and leuprorelin 7.5 mg. For both degarelix groups, the entire two-sided (multiplicity-adjusted) 97.5% CI was greater than the non-inferiority limit of –10 percentage points, demonstrating the non-inferiority of degarelix to leuprorelin 7.5 mg.[9]

As a secondary outcome, testosterone response (cumulative probability of testosterone levels ≤0.5 ng/ml from Day 28 to 84) was also measured in three other RCTs that compared a monthly maintenance regimen of degarelix 240/80 mg with LHRH agonist treatment (CS28, CS30 and CS31).[11,13,15] Results from these RCTs were consistent with the findings from CS21, indicating that a monthly maintenance regimen of degarelix is at least as effective as LHRH agonist therapy in reducing serum testosterone to the castrate level.

In Study CS35, which compared a three-monthly regimen of degarelix (240/480 mg) with a three-monthly regimen of goserelin (3.6/10.8 mg), the cumulative probability of testosterone levels ≤0.5 ng/ml from Day 28 to Day 364 was 90.0% for degarelix compared with 96.7% for goserelin. For this endpoint, goserelin was statistically superior to degarelix, with a difference of –6.7% (95% CI –10.1 to –3.3%). The pattern of testosterone escapes (testosterone >0.5 ng/ml) for the first 168 days was similar for degarelix and goserelin. Thereafter, additional testosterone escapes occurred, particularly at trough levels of degarelix (that is, at Days 196, 280 and 364) during degarelix treatment, whereas testosterone suppression ≤0.5 ng/ml was maintained in all patients who received goserelin treatment. It is important to note that this study was part of the development programme for degarelix and used a three-monthly regimen of 240/480 mg, which involves a maintenance dose that is not licensed in the UK, so the results are not fully applicable to the decision problem.[17]

Time to return to testosterone >0.5 ng/ml (above castration level) during Phase B of CS37

The number of patients in the FAS who had testosterone levels >0.5 ng/ml during Phase B of CS37 was 116 in the degarelix intermittent group, three in the degarelix continuous group and one in the leuprorelin group. Log-rank tests confirmed that the differences between the groups in time to testosterone >0.5 ng/ml and in the number of patients who achieved this were statistically significant (p<0.0001). The median time to testosterone levels >0.5 ng/ml in the degarelix intermittent group was 112 days (95% CI 112 to 140 days), counted from the start of Phase B at Day 196 (that is, 28 days after the last injection of trial drug). The majority of patients in the degarelix intermittent group (74.4%) who had a testosterone level >0.5 ng/ml experienced this event between four and five months after the last degarelix treatment. The pattern observed in the degarelix intermittent group and the continuous treatment group (degarelix and leuprorelin combined) was similar for both the Phase B FAS and the Phase B PP analysis set.[18]

Prostate size reduction

The change in prostate volume from baseline to Week 12 was the primary outcome in two RCTs (CS30 and CS31) and a secondary outcome in one RCT (CS28).[11-16]

In CS30, the mean change in prostate volume at 12 weeks from baseline was –36% in the degarelix group and –35.3% in the goserelin plus bicalutamide group. After adjusting for baseline prostate volume and baseline total IPSS, the difference between treatment groups was –0.30% (95% CI –4.74% to 4.14%; p=0.894) for the FAS and –0.27% (95% CI –5.05% to 4.52%; p=0.912) for the PP analysis set. The

upper limit of the two-sided 95% CI for the adjusted mean difference between the degarelix and goserelin plus bicalutamide groups was thus below the non-inferiority margin of 10 and, therefore, non-inferiority of degarelix was established.[13]

In CS31, the mean change from baseline in prostate volume at Week 12 was –37.2% in the degarelix group, compared with –39% in the goserelin plus bicalutamide group. The difference between groups (adjusted for baseline prostate volume and total IPSS) was 2.37% (95% CI –2.78% to 7.52%) for the FAS and 2.24% (95% CI –3.1 to 7.58%) for the PP analysis set. The upper limit of the two-sided 95% CI for the adjusted mean difference was below the non-inferiority margin of 10.[15]

In CS28, the mean decrease at Week 12 from baseline in prostate size was 22.4 ml in the degarelix group and 13.4 ml in the goserelin plus bicalutamide group. The difference between the two groups was –7.83% (95% CI –17.3% to 1.64%; p=0.10).[11]

IPSS

Change in IPSS was the primary outcome in the early-terminated CS28 trial and a secondary outcome in CS30, CS31 and CS35.[11,13,15,17]

In CS28, a mean change in total IPSS at Week 12 of –11.2 in the degarelix group and –7.69 in the goserelin plus bicalutamide group was recorded for the FAS. The adjusted mean difference between the groups was –2.95 (95% CI –7.51 to 1.61; p=0.197). The upper limit of the two-sided 95% CI for the adjusted mean difference for total IPSS (1.61) was below the non-inferiority margin of Δ=3, so non-inferiority could be established. For the PP analysis set, the difference was –5.88 (95% CI –11.5 to –0.29; p=0.0398), which was statistically significant, and the upper limit of the two-sided 95% CI for total IPSS at Week 12 (–0.29) was below zero; therefore, not only could non-inferiority be concluded, but also a statistical superiority of degarelix over goserelin plus bicalutamide).[11]

In CS30, the mean change in IPSS recorded at Week 12 for the FAS was –1.71 with degarelix and 0.11 with goserelin plus bicalutamide. The difference at Week 12 (adjusted for baseline IPSS) was statistically significant at –1.42 (95% CI –2.81 to –0.035; p=0.044). In addition, 37% of patients in the degarelix group and 27% in the goserelin group experienced a clinically meaningful IPSS decrease of ≥3 points at Week 12. When the clinically meaningful response was set at a ≥30% decrease in IPSS, the corresponding numbers were 40% and 30%, respectively. For the PP analysis set, the adjusted difference at Week 12 was –1.23 (95% CI –2.62 to 0.149; p=0.08).[13]

In CS31, the mean change from baseline in total IPSS at Week 12 was –4.39 in the degarelix group and –2.74 in the goserelin plus bicalutamide group. The difference adjusted for baseline IPSS was –1.24 (95% CI –2.92 to 0.43; p=0.15).[15]

In CS35, in which three-monthly regimens were administered, the mean change in total IPSS at Week 4 was –1.06 (SE 6.27) in the degarelix group and –0.211 (SE 6.22) in the goserelin group; the difference was –0.80 (95% CI –1.62 to 0.02; p=0.056). The corresponding changes at Day 364 were –2.04 (SE 7.28) and –1.52

(SE 6.25), respectively, which represented a statistically non-significant difference of –0.39 (95% –1.28 to 0.49; p=0.382).[17]

PSA response

The PSA response was measured in all relevant RCTs.[9,11,13,15,17,18]

PSA results from trial CS21

In CS21, PSA progression (recurrence/failure) was defined as two consecutive increases in PSA levels of ≥50% and of ≥5 ng/ml compared with nadir. The Kaplan–Meier-estimated probabilities of completing the study without PSA progression on Day 364 were 85.8% (95% CI 79.8% to 90.1%) for degarelix 240/160 mg, 91.1% (95% CI 85.9% to 94.5%) for degarelix 240/80 mg and 85.9% (95% CI 79.9% to 90.2%) for leuprorelin 7.5 mg (see Table 13).[3]

Table 13. Kaplan–Meier analysis for the cumulative probability of completing the study without PSA failure from Day 0 to Day 364: ITT analysis set[9]

	Degarelix 240/160 mg				Degarelix 240/80 mg				Leuprorelin 7.5 mg			
	No. at risk	**PSA failure[a]**	**No of censured observations**	**%**	**No. at risk**	**PSA failure[a]**	**No of censured observations**	**%**	**No. at risk**	**PSA failure[a]**	**No of censured observations**	**%**
ITT analysis set	202				207				201			
Day 0 to 28	193	1	8	99.5	201	0	6	100	194	1	5	99.5
To Day 56	192	1	1	99.5	197	0	4	100	192	1	2	99.5
To Day 84	190	1	2	99.5	193	0	4	100	190	1	2	99.5
To Day 112	190	1	0	99.5	189	1	3	99.5	188	3	0	98.4
To Day 140	187	2	2	99.0	187	2	1	99.0	182	7	2	96.4
To Day 168	179	7	3	96.3	185	4	0	97.9	180	9	0	95.3
To Day 196	173	11	2	94.2	181	4	4	97.9	175	11	3	94.2
To Day 224	168	14	2	92.5	175	7	3	96.3	173	12	1	93.7
To Day 252	165	16	1	91.4	169	9	4	95.2	168	14	3	92.6
To Day 280	157	20	4	89.2	165	11	2	94.0	163	18	1	90.4
To Day 308	153	23	1	87.5	161	12	3	93.5	156	21	4	88.7
To Day 336	149	26	1	85.8	156	15	2	91.7	150	24	3	87.0
To Day 364	0	26	149	85.8	0	16	155	91.1	0	26	148	85.9
95% CI	(79.8 to 90.1%)				(85.9 to 94.5)				(79.9 to 90.2)			

Key: CI: confidence interval; ITT = intention-to-treat; PSA = prostate-specific antigen

NB Within-treatment group 95% CI calculated by log-log transformation of survivor function

[a] PSA failure = two consecutive increases in PSA from nadir ≥50% and >5 ng/ml at least two weeks apart

Data from post hoc exploratory subgroup analyses of PSA from trial CS21

Post hoc exploratory subgroup analyses of PSA response data from the CS21 trial were performed. These included an analysis of PSA progression (recurrence/failure) in CS21 by baseline disease stage and baseline PSA level (Figure B1 in Appendix B).[21]

In both treatment groups, PSA progression occurred more frequently in patients with advanced disease. Among patients with metastatic disease, 21.6% of those in the degarelix 240/80mg group and 36.2% of those in the leuprorelin group experienced PSA progression (p=0.156). The proportion of patients with locally advanced disease who experienced PSA progression was also similar in the 240/80 mg degarelix group (10.9%) and the leuprorelin group (11.5%).[21]

PSA progression was positively associated with higher baseline PSA levels, and all cases of PSA progression in CS21 occurred in patients with baseline PSA levels >20 ng/ml. The proportion of patients with baseline PSA >20 ng/ml who experienced PSA progression was 16.0% (16/100) in the degarelix 240/80 mg group and 28.0% (26/93) in the leuprorelin group; the between-group difference was statistically significant (p=0.04).[21]

In trial CS21, the median percentage change in PSA levels from baseline to Day 14 was –64.6% (interquartile range –77.8% to –40.8%) in the degarelix 240/160 mg group, –63.4% (interquartile range –77.1% to –48.4%) in the degarelix 240/80 mg group and –17.9% (interquartile range –35.5% to –5.2%) in the leuprorelin group. The median percentage change in PSA levels at Day 28 was –82.3% (interquartile range –91.4% to –68.3%) in the degarelix 240/160 mg group, –84.9% (interquartile range –91.6% to –73.2%) in the degarelix 240/80 mg group and –66.7% (interquartile range –81.3% to –47.7%) in the leuprorelin group. The difference in the median change between degarelix and leuprorelin was statistically significant on Days 14 and 28 (p<0.0001, Wilcoxon test), indicating that treatment with degarelix achieved more rapid PSA control than treatment with leuprorelin.[9]

PSA results from other included RCTs

In CS28, the median percentage changes in PSA levels from baseline to Week 8 were –89.2% (min–max range –99.5% to –31.6%) for degarelix and –97.3% (–99.7% to –87.6%) for goserelin plus bicalutamide. At Week 12, median percentage changes in PAS levels from baseline were –93.9% (–99.8% to –64.7%) for degarelix and –97.8% (–99.7% to –94.5%) for goserelin plus bicalutamide.[11]

In CS30, the median percentage changes in PSA levels at Week 4 were –71.6% (min–max range –98.3% to 64.3%) for degarelix and –72.2% (–97.0% to 65.5%) for goserelin plus bicalutamide.[14] Median percentage changes in PSA levels at Week 12 were 89.2% (–99.8% to –37.2%) for degarelix and 93.0% (–98.9% to –54.6%) for goserelin plus bicalutamide.[13]

In CS31, the median percentage changes in PSA levels from baseline to Week 4 were –80.6% (min–max range –99.1% to 45.5%) for degarelix and –85.2% (–99.8% to 47.8%) for goserelin plus bicalutamide. Median percentage changes at Week 12 were –92% (–99.9% to 27.7%) for degarelix and 97.3% (–99.9 to –18.2%) for goserelin plus bicalutamide.[15]

In CS35, in which degarelix was administered as a three-monthly regimen, median changes from baseline in PSA levels at Day 28 were –84% (interquartile range –92% to –71%) for degarelix and only –66% (–83 to –49%) for goserelin (p<0.0001). Thereafter, median reductions in PSA levels in both treatment groups were similar (94% versus 94% at Day 84, and 96% versus 98% at Day 364). The cumulative probabilities of no PSA progression (recurrence/failure) from Day 0 to Day 364 were 86.5% (95% CI 83.2% to 89.2%) and 86.5% (81.7% to 90.1%), respectively.[17]

In CS37, the primary objective was to establish non-inferiority of intermittent degarelix treatment (seven months of treatment followed by seven months of non-treatment) compared with continuous androgen-deprivation treatment, as determined by the primary endpoint of the proportion of patients with serum PSA levels ≤4.0 ng/ml at Month 14 (or the last post-Month 7 value prior to Month 14 if the value for the Month 14 visit was not available). All patients in the degarelix intermittent treatment group had PSA values <4.0 ng/ml at Month 14 (100% responder rate) and three patients in the continuous androgen-deprivation treatment group (one in the degarelix continuous group and two in the leuprorelin continuous group) had PSA values of >4.0 ng/ml at Month 14 (98.4% responder rate). The lower limit of the CI for the comparison of intermittent degarelix versus continuous androgen-deprivation treatment was –0.19 percentage points, which, under the conditions of this study, established non-inferiority of the intermittent regimen degarelix compared with the continuous androgen-deprivation treatment regimen.[18]

PSA results taking into account anti-androgen flare protection

Data were pooled from the randomised one-year studies CS21 (monthly degarelix versus monthly leuprorelin) and CS35 (three-monthly degarelix versus three-monthly goserelin). In both trials, anti-androgen therapy was administered in the LHRH agonist group at the investigator's discretion. Estimates of the probability of PSA PFS were made by the Kaplan–Meier method and log-rank test, and adjusted HRs for PSA PFS failure were calculated using Cox regression.[116]

In the pooled population (n=1,457), 974 patients received degarelix, 414 received an LHRH agonist and 69 received an LHRH agonist plus anti-androgen. Pooled data showed slower PSA suppression with LHRH agonist plus anti-androgen treatment compared with degarelix. In patients with metastatic disease, mean percentage PSA reduction was greater in those receiving degarelix than those receiving an LHRH agonist plus anti-androgen during the first seven months. In addition, the PSA PFS failure rate (adjusted for baseline PSA levels, stage of prostate cancer and Gleason score) was significantly lower with degarelix than with LHRH agonist plus anti-androgen treatment for all patients (HR 0.490; p=0.0028) and for those with baseline PSA levels >20 ng/ml (HR 0.500; p=0.0073). It should be noted that the number of

patients who received anti-androgen flare protection with LHRH agonist treatment was small.[116]

Overall and progression-free survival

Table 14 summarises the death outcome results from the included RCTs.[9,11,13,15,17,18]

Table 14. Death outcome results from included RCTs[9-18]

Trial	Intervention	Deaths/N (%)
CS21[9,10]	Degarelix 240/160 mg Degarelix 240/80 mg Leuprorelin 7.5 mg	5/202 (2) 5/207 (2) 9/201 (4)
CS28[11,12]	Degarelix 240/80 mg Goserelin 3.6 mg + bicalutamide	0/27 (0) 1/13 (7.7)
CS30[13]	Degarelix 240/80 mg Goserelin 3.6 mg + bicalutamide	0/181 (0) 0/64 (0)
CS31[15,16]	Degarelix 240/80 mg Goserelin 3.6 mg + bicalutamide	0/84 (0) 1/98 (1.0)
CS35[17]	Degarelix 240/480 mg Goserelin 3.6/10.8 mg	8/565 (1) 8/283 (3)
CS37[18]	Degarelix intermittent 240/80mg Degarelix continuous 240/80mg Leuprorelin continuous 7.5/22.5 mg	2/175 (1) 0/50 (0) 2/178 (1)

Post hoc subgroup analyses of survival data in trial CS21

Tombal *et al* (2010) provided additional results on overall survival and the risk of PSA progression (recurrence/failure) or death from the CS21 trial (see Figures B2 and B3 in Appendix B).[21] The risk of death was 2.6% (95% CI 1.1% to 6.2%) in the degarelix 240/80 mg group and 4.9% (2.6% to 9.3%) in the leuprorelin group. Patients receiving degarelix had a lower risk of PSA progression (recurrence/failure) or death compared with patients in the leuprorelin group; this difference was statistically significant (log-rank test, p=0.05).[21]

In CS35, which used three-monthly regimens, disease progression was defined as PSA progression (recurrence/failure), death from any cause or the introduction of additional therapy related to prostate cancer, whichever occurred first. Additional therapy related to prostate cancer included radiation, anti-androgens, second-line treatment and concomitant therapy used for the treatment of prostate cancer, as recorded by the investigators. The Kaplan–Meier estimate of the cumulative probabilities of no disease progression were similar for degarelix (79.0% [95% CI 73.4% to 83.6%]) and goserelin (77.3% [95% CI 70.9% to 82.6%]); p=0.328.[17]

In CS37, three patients receiving the intermittent degarelix regimen experienced disease progression prior to Phase B and one patient in the continuous degarelix group experienced disease progression during Phase B (Visit 12). The differences in the analyses across all three groups for the FAS for Phase B and the PP set for Phase B were statistically significant (p=0.0298) but were not considered medically significant. None of the differences between groups for any analysis comparing intermittent degarelix versus continuous androgen deprivation therapy were statistically significant (p≥0.3842).[18]

Clinically significant changes in laboratory values

Serum alkaline phosphatase levels

Levels of alkaline phosphatase in serum (s-ALP) are a marker of progression of metastatic disease,[117-119] and suppression of serum ALP is, therefore, an indicator of effective control of metastatic disease.

In CS21, s-ALP levels were prospectively measured in all patients as part of the laboratory tests included in the overall safety analysis.[9,20] The effect on s-ALP levels in patients in CS21 was assessed through a post hoc analysis, focusing on the licensed 240/80 mg dose of degarelix compared with leuprorelin 7.5 mg. Levels of s-ALP were assessed for three subgroups: patients with metastases, patients with baseline PSA levels >50 ng/ml and patients with metastases and baseline haemoglobin levels <13 g/dl. Baseline s-ALP levels were high in patients with metastatic disease, due to the presence of skeletal metastases, and highest in patients with metastatic disease and haemoglobin levels <13 g/dl at baseline.[20]

After initial peaks in both treatment groups, s-ALP levels were suppressed below baseline levels with degarelix 240/80 mg in 37 patients with metastatic disease, including 16 with metastatic disease and Hb levels <13 g/dl. Levels of s-ALP were also suppressed with leuprorelin acetate, dropping below baseline levels by Day 84, although the trough levels achieved in the 26 patients with metastases and haemoglobin levels <13 g/dl did not match the levels in the 47 metastatic patients overall receiving leuprorelin. The increase in s-ALP levels observed in patients treated with leuprorelin was not observed in those treated with degarelix 240/80 mg. Overall, the difference in s-ALP suppression in patients with metastatic prostate cancer was statistically significant between degarelix 240/80 mg and leuprorelin at Day 364 (96 versus 179 IU/l; p=0.014). In general, s-ALP levels were maintained around baseline in patients with localised or locally advanced disease, irrespective of treatment received.[20]

The same significant difference in improvement in s-ALP response between degarelix 240/80 mg and leuprorelin was also observed in the subgroup of patients with metastases as a whole (without grouping by Hb level) and patients with baseline PSA levels ≥50 ng/ml. This post hoc analysis thus suggests more effective control of metastatic disease with degarelix than with leuprorelin.[20]

Pooled data for 2,328 patients from six RCTs (CS21, CS28, CS30, CS31, CS35 and CS37) found that s-ALP levels in patients with metastatic disease were suppressed to a greater extent throughout one-year treatment by degarelix (p=0.0383). The mean adjusted change from baseline was significantly lower throughout 12 months.[74,75]

Quality of life

In CS21, the effects of degarelix and leuprorelin on patients' quality of life were evaluated using the SF-12 v2, which measures generic quality of life, and the EORTC QLQC30 to measure cancer-specific quality of life. All SF-12 v2 scores were comparable across treatment groups and study days. Throughout, no changes from baseline scores in any of the eight SF-12 domains assessed were observed. The

EORTC QLQ-C30 scores for all three groups were stable, with no changes from baseline in median scores for all subscales of the questionnaire at any time point in the study (please note: technical problems and problems with patient compliance occurred with respect to data transfer and collection for assessment of quality of life. The removal of irregular data from the EORTC QLQ-C30 scores had no effect, and all of the values for median changes from baseline remained the same).[9]

In CS28, quality of life was measured using a supplementary question about urinary symptoms in the IPSS. The mean QoL scores showed a decrease (that is, quality of life improved) from baseline at each visit in both treatment groups. The mean decreases from baseline in quality of life scores at Weeks 4, 8 and 12 were greater with degarelix (0.96, 1.54 and 1.77, respectively) than with goserelin plus bicalutamide (0.54, 0.73 and 0.55, respectively).[11]

In CS30, no overall significant differences in the change in quality of life scores from baseline to Week 4, 8 or 12 were seen between treatment groups. This was also the case when the observed case (OC) method was used. Findings were similar when a logistic regression model categorised the response as 0–3 (delighted to mixed) and 4–6 (dissatisfied to terrible) for the FAS, using both the last observation carried forward (LOCF) and OC methods. Results were also similar for the PP analysis set.[13]

In CS31, the proportion of patients who felt delighted, pleased or mostly satisfied with their urinary condition increased from baseline to Week 12 from 38% to 72% in the degarelix group and from 48% to 76% in the goserelin plus bicalutamide group. The burden of urinary symptoms was decreased, and the mean reduction in the BPHII score at Week 12 was similar for degarelix (–1.28) and goserelin plus bicalutamide (–1.16).[15]

In CS35, all SF-36 scores were comparable across treatment groups and trial days, and no changes from baseline scores occurred during the trial in any of the eight domains. For improvement of arthralgia, the onset of action seemed to be faster in patients receiving degarelix; however, the VAS score decreased to a similar extent in the two treatment groups by Day 196. The change in VAS from baseline was generally similar for degarelix and goserelin when analysed according to the stage of prostate cancer, with the exception of metastatic prostate cancer, when a greater decrease with degarelix than with goserelin was observed at Day 28, and this was statistically significant (p=0.0438).[17]

In CS37, a cross-sectional analysis of covariance (ANCOVA) was performed on the results of the FACT-P survey for the intermittent degarelix and continuous androgen-deprivation treatment groups for four analysis sets. With the exception of a few random FACT-P domains at specific visits, no statistically significant difference was observed over a range of visits or through to the end of the study for any domains. Patients in the intermittent degarelix treatment group reported a higher SFI mean score on the sexual drive domain at month 14 compared with those in the continuous androgen-deprivation treatment group; this difference was statistically significant. There appeared to be a relationship between return to testosterone levels >0.5 ng/ml and improved SFI scores in those receiving intermittent degarelix.[18]

6.6 *Meta-analysis*

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

The cumulative probability of testosterone levels ≤0.5 ng/ml

To improve the homogeneity and comparability of RCTs, only those that compared degarelix 240/80 mg (the dose licensed in the UK) with leuprorelin or goserelin were included in the meta-analysis (see Table 15).[9-11,13-16] Raw data from four RCTs (CS21, CS28, CS30 and CS31) were combined into a pooled dataset, and the Kaplan–Meier method was used to estimate the pooled cumulative probability of testosterone levels ≤0.5 ng/ml from Day 28 to Day 84 or Day 364. The pooled cumulative probability of testosterone levels ≤0.5 ng/ml from Day 28 to Day 84 was 98.0% (95% CI 96.2% to 98.9%) for degarelix 240/80 mg and 96.2% (95% CI 93.7% to 97.7%) for LHRH agonist treatments. The cumulative probability from Day 28 to Day 364 was 95.7% (95% CI 92.4% to 97.6%) for degarelix 240/80 mg and 94.7% (95% CI 91.4% to 96.7%) for LHRH agonist treatments.

Table 15. Kaplan–Meier estimated cumulative probability of testosterone ≤0.5 ng/ml, combining data from CS21, CS28, CS30 and CS31

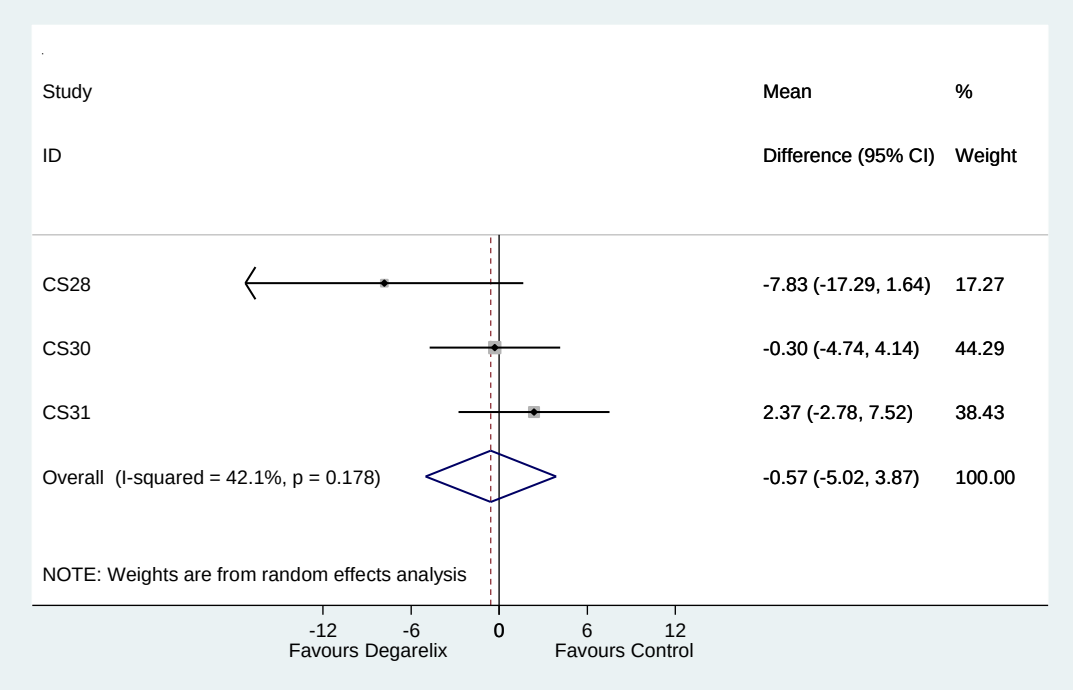
Intervention	Estimate (95% CI)
Day 28–84	
Degarelix	98.0% (96.2% to 98.9%)
LHRH agonists	96.2% (93.7% to 97. 7%)
Day 28–364	
Degarelix	95.7% (92.4% to 97.6%)
LHRH agonists	94.7% (91.4% to 96.7%)

Key: CI = confidence interval; LHRH = luteinising hormone-releasing hormone

Reduction in prostate size

The percentage change in prostate volume from baseline to Day 84 (Week 12) was evaluated in three RCTs (CS28, CS30 and CS31).[11-16] The differences between degarelix and control treatment in percentage change in prostate volume recorded in the three RCTs were combined in a meta-analysis (see Figure 10), using the reported adjusted differences and 95% CIs from the clinical study reports. No statistically significant heterogeneity was seen across the three studies (I^2=42%; p=0.178). The pooled mean difference between degarelix and LHRH agonists was –0.57 (95% CI –5.02 to 3.87), indicating that degarelix is non-inferior to leuprorelin or goserelin plus bicalutamide.

Figure 10. Difference between degarelix and control treatment in percentage change of prostate volume from baseline to Day 84 (Week 12)

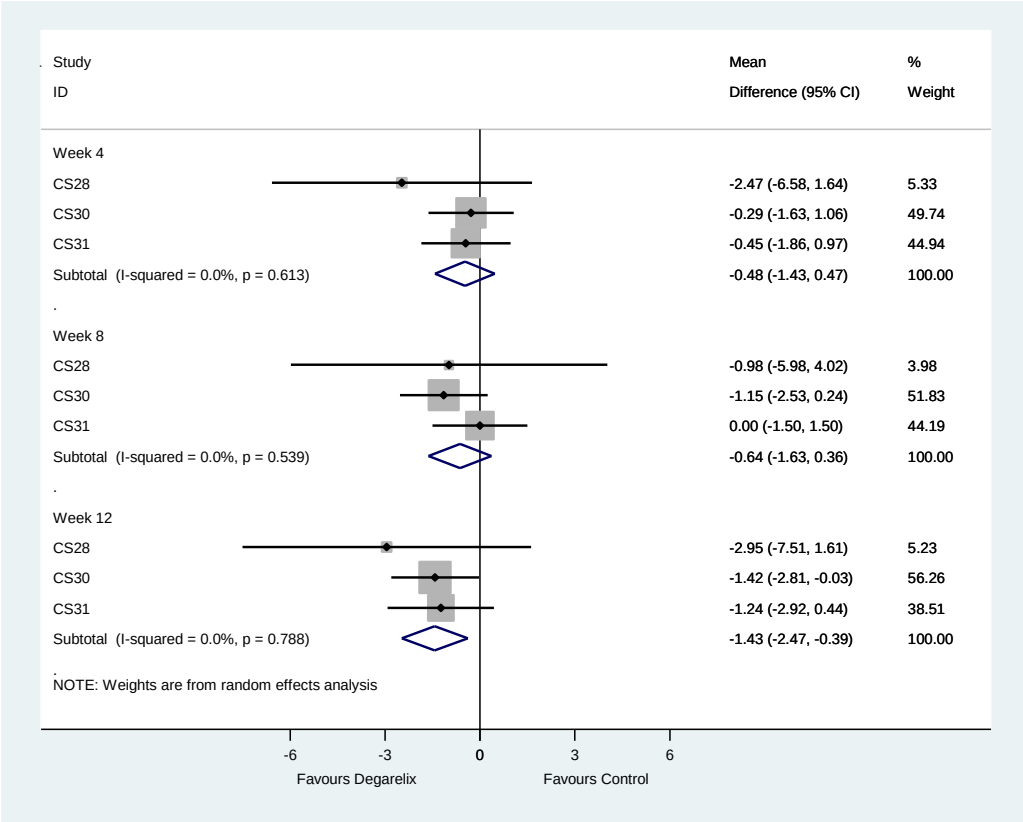


IPSS

The IPSS is used to assess the severity of LUTS and to monitor the progress of the disease process once treatment has been initiated.[11,13,15] A higher overall score indicates increased severity of LUTS, so a reduction in IPSS indicates improvement in LUTS.

Three RCTs (CS28, CS30 and CS31) measured change in IPSS from baseline.[11-16] A meta-analysis was conducted, using the reported mean estimates of change and 95% CIs at Weeks 4, 8 and 12 (see Figure 11). No significant heterogeneity was observed across studies (I^2=0.0%; p=0.613, p=0.539 and p=0.788 at Weeks 4, 8 and 12, respectively). The pooled difference in change from baseline in IPSS was –0.48 (95% CI –1.43 to 0.47; p=0.323) at Week 4, –0.64 (–1.63 to 0.36, p=0.212) at Week 8 and –1.43 (–2.47 to –0.39, p=0.007) at Week 12. The difference between degarelix and LHRH agonist control, thus, tended to increase over time and was statistically significant at Week 12.

Figure 11. Difference between degarelix and control treatment in change from baseline in international prostate symptom score (IPSS)



PSA response

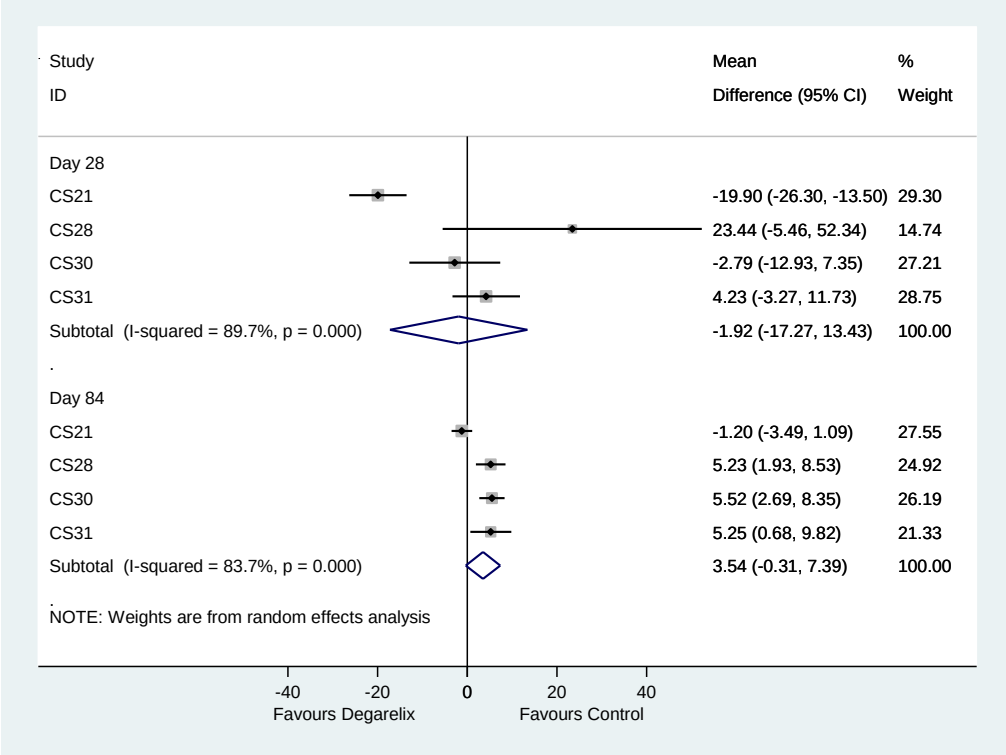
This meta-analysis used data from the RCTs that compared a monthly maintenance regimen (240/80 mg) of degarelix with monthly maintenance LHRH agonist therapy (CS21, CS28, CS30 and CS31).[9-16] As the differences between degarelix and the LHRH agonists were symmetrically distributed, the mean differences between the treatment groups have been used for this meta-analysis rather than the median values reported in Section 6.5.3.

For percentage change in PSA levels, the pooled mean difference between degarelix and LHRH agonists was –1.92 (95% CI –17.27 to 13.43; p=0.806) at Day 28 and 3.54 (–0.31 to 7.39; p=0.072) at Day 84. However, statistically significant heterogeneity between the individual RCTs was detected (I^2=89.7% at Day 28 and I^2=83.7% at Day 84; p<0.001) (see Figure 12).

Results of this meta-analysis for the percentage change in PSA levels should be interpreted with caution for a number of reasons. First, the baseline PSA level may be a cause of significant heterogeneity across RCTs at Week 4 as a consequence of different eligibility criteria in the four studies: CS28 included patients with much higher baseline PSA levels (median PSA levels: 41–55 ng/ml) than the other RCTs (median PSA levels: 17–20 ng/ml in CS21, 10 ng/ml in CS30 and 16–28 ng/ml in CS31) (see Appendix B, Table B4).[9,11,12,15] In addition, clinical expert opinion indicates that PSA progression, rather than absolute PSA percentage change from baseline, is routinely used in clinical practice as a prognostic indicator for treatment response[7] because it is a more appropriate outcome to measure disease progression

when using PSA as a surrogate clinical marker. However, no meta-analyses could be completed for PSA progression, as only one trial that evaluated monthly dosing regimens (CS21) assessed PSA progression (see Section 6.5.3).

Figure 12. **Meta-analysis of percentage change in PSA from baseline**

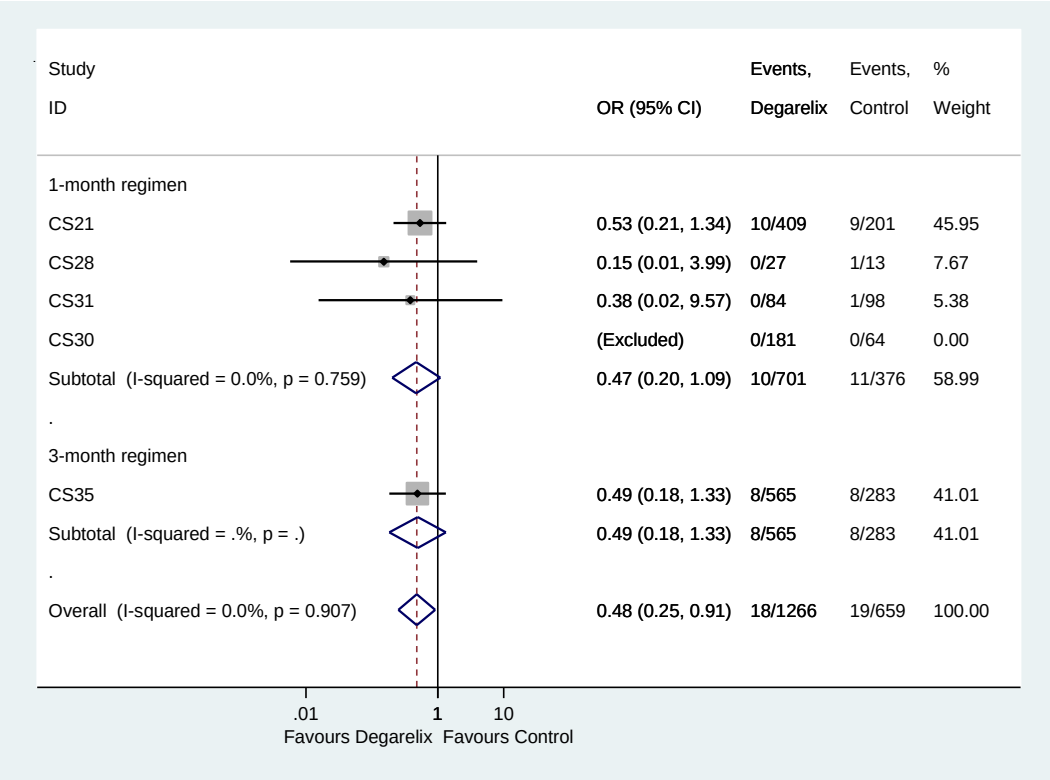


Overall survival

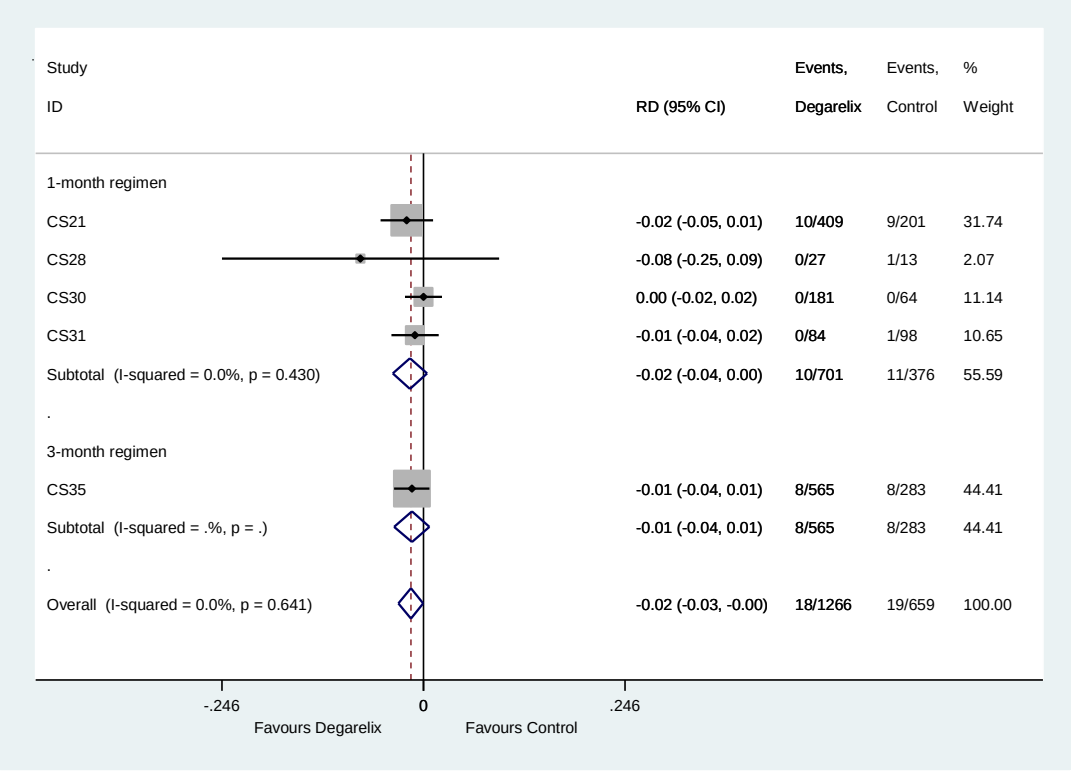
Data from CS37 were not used in this meta-analysis, because the degarelix monthly maintenance dose may not be comparable with the leuprorelin three-month regimen. Using the odds ratio (OR) as the outcome statistic, no significant heterogeneity was present across the other five RCTs for the outcome of death. [9,11,13,15] Pooled data from the included RCTs indicate that mortality tended to be lower in the degarelix group than in the LHRH agonist control group (pooled OR 0.48; 95% CI 0.25 to 0.91; p=0.025) (see Figure 13a). Similar results were obtained when the difference in rate was used (see Figure 13b). The pooled difference in death rate between degarelix and the control treatments was –1.5% (95% CI –3.0% to 0.0%; p=0.045). The overall rate of death was 1.4% (18/1,266 patients) in the degarelix group and 2.8% (19/659 patients) in the control group.

Figure 13. Deaths in the included RCTs: (a) odds ratio (OR) and (b) rate difference (RD)

(a)



(b)



6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Meta-analyses were completed for the following outcomes: testosterone response, prostate size reduction, IPSS, PSA response and overall survival.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Reasons for inclusion/exclusion for each outcome assessed in meta-analyses has been provided in the appropriate sections.

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

The comparators for degarelix specified in the NICE STA scope are leuprorelin, goserelin, triptorelin and bicalutamide monotherapy.[83] Degarelix was not directly compared with triptorelin or bicalutamide monotherapy in the identified RCTs. According to findings from previous meta-analyses by Seidenfeld *et al*[120] and Hemels *et al*,[121] different single-therapy LHRH agonists had similar effectiveness in patients with prostate cancer. A mixed-treatment comparison (MTC) was, therefore, conducted to explore whether or not the previous meta-analyses' findings that none of the LHRH agonists has superior clinical efficacy or effectiveness over another could be supported. The MTC also evaluated the evidence available to compare bicalutamide monotherapy with degarelix. The relevant outcomes for the MTC were overall survival and PSA progression.

The literature search strategy used to identify RCTs involving degarelix (described in Sections 6.1 and 6.2) was also used to identify clinical trials that directly compared different LHRH agonists in the treatment of patients with prostate cancer. Study inclusion and data extraction for the MTC were conducted by a senior systematic reviewer (University of East Anglia). From the 2,002 records identified by the initial search (see Figure 3), ten trials directly compared the relevant comparators specified in the NICE STA scope.[83]

Details of these ten trials and the reasons for their inclusion in, or exclusion from, the MTC analysis are shown in Table 16.

Table 16. Identified RCTs that directly compared triptorelin or bicalutamide with leuprorelin or goserelin, with reasons for inclusion in, or exclusion from, the mixed treatment comparison

Study (n)	Interventions compared	Study participants	Outcome measures reported	Main conclusions	Inclusion/exclusion (reasons) in MTC
Chodak *et al* (1995) (n=486)[122]	• Bicalutamide 50 mg • Castration (surgical or goserelin)	Patients with untreated stage D2 prostate cancer	• Time to treatment failure • Objective disease progression • Survival • QoL	Bicalutamide 50 mg was not as effective as castration, but with favourable QoL outcomes and low incidence of non-hormonal AEs	Exclude (percentage of patients that received goserelin in castration group is unknown)
Dias Silva *et al* (2012) (n=60)[123]	• Leuprorelin 3.75 mg • Leuprorelin 7.5 mg • Goserelin 3.6 mg	Patients with advanced prostate cancer, with indication for hormonal therapy	• Serum testosterone	• Leuprorelin 7.5 mg showed better results in reaching castration levels than leuprorelin 3.75 mg • The difference between leuprorelin and goserelin was non-significant	Exclude (no overall survival or PSA progression [recurrence/failure] outcomes)
Heyns *et al* (2003) (n=284)[124]	• Triptorelin 3.75 mg • Leuprorelin 7.5 mg	Men with advanced prostate cancer	• Testosterone suppression • Serum LH • Bone pain • Median PSA • Survival • Safety	Triptorelin reduced testosterone levels less rapidly but maintained castration as effectively as leuprorelin	**Include** (overall survival reported)
Iversen *et al* (1998) (n=480)[125]	• Bicalutamide 100 mg • Bicalutamide 150 mg • Castration (surgical or goserelin 3.6 mg)	Patients with previously untreated non-metastatic (M0) advanced prostate cancer	• Time to death • Objective progression • Treatment failure • QoL • Safety	Bicalutamide 150 mg provided similar survival outcome to castration, and improved sexual interest and physical capacity	**Include** (most patients [86%] in the castration group received goserelin; overall survival reported)

Study (n)	Interventions compared	Study participants	Outcome measures reported	Main conclusions	Inclusion/exclusion (reasons) in MTC
Kaisary *et al* (1995) (n=245)[126]	• Bicalutamide 50 mg • Castration (surgical or goserelin)	Patients with advanced prostate cancer	• Time to treatment failure • Time to objective progression • Survival • QoL • Tolerability	• Survival was similar in the two groups • Bicalutamide 50 mg was associated with a low incidence of diarrhoea and sexual dysfunction	Exclude (<50% in castration group received goserelin)
Kuhn *et al* (1997) (n=67)[127]	• Triptorelin 3.75 mg • Leuprorelin 3.75 mg	Patients with prostate cancer not suitable for surgery	• Pain • UTI symptoms • Prostate volume • Mean serum PSA • Testosterone level	Triptorelin induced a greater decrease in testosterone levels than leuprorelin	Exclude (leuprorelin 3.75 mg; no survival or PSA recurrence outcomes)
Sieber *et al* (2004) (n=103)[128]	• Bicalutamide 150 mg • Medical castration	Patients with localised or locally advanced prostate cancer	• Bone mineral density • Fat-free mass • Serum lipids	Bicalutamide 150 mg may offer an important advantage compared with castration in bone loss and body composition	Exclude (LHRH agonists not specified; no survival or PSA progression [recurrence/failure] outcomes)
Smith *et al* (2004) (n=52)[129]	• Bicalutamide 150 mg • Leuprorelin (three-month regimen 22.5mg)	Patients with prostate cancer and no bone metastases	• Bone mineral density • Body composition	Bicalutamide increased bone mineral density, lessened fat accumulation and had fewer bothersome side-effects than Leuprorelin	Exclude (leuprorelin three-month regimen; no overall survival or PSA progression [recurrence/failure] outcomes)
Williams *et al* (2003) (crossover, n=50)[130]	• Leuprorelin • Goserelin	Patients with advanced prostate cancer	• Discomfort score	Patients tolerated leuprorelin better than goserelin ($p<0.01$)	Exclude (no overall survival or PSA progression [recurrence/failure] outcomes)

Study (n)	Interventions compared	Study participants	Outcome measures reported	Main conclusions	Inclusion/exclusion (reasons) in MTC
Tyrrell et al 1998 (n=1,453)[131]	• Bicalutamide 100 • Bicalutamide 150 mg • Castration (surgical or goserelin 3.6 mg)	Patients with metastatic (M1) prostate cancer	• Time to death • Objective progression • Treatment failure • QoL • Safety	Bicalutamide 150 mg was less effective than castration in terms of survival outcome, but showed a benefit in terms of QoL and subjective response compared with castration.	Exclude (proportion of patients who received goserelin in the castration group is unknown)

Key: AE = adverse event; LH = luteinising hormone; LHRH = luteinising hormone-releasing hormone; MTC = mixed-treatment comparison; PSA = prostate-specific antigen; QoL = quality of life; UTI = urinary tract infection

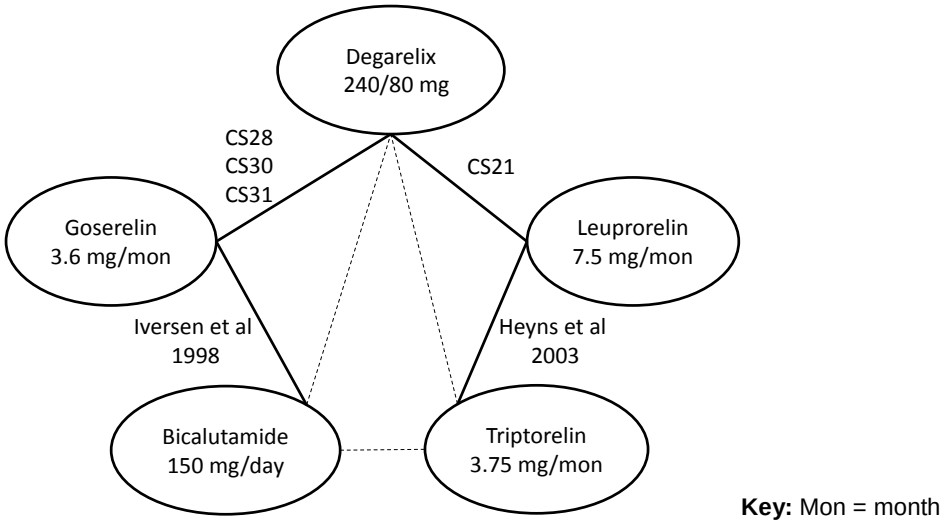
6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

A quality assessment for each comparator trial identified has been included in appendix 5.

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Figure 14 shows the network of trials involved in the MTC of degarelix and the relevant comparators. To reduce heterogeneity across studies and ensure relevance to the decision problem,[132,133] only degarelix data from the 240/80 mg group and only data from those RCTs that compared one-monthly dosing regimens were used. The trials CS35, in which a three-monthly degarelix dosing regimen was compared with a three-monthly goserelin regimen,[17] and CS37, in which degarelix 240/80 mg (monthly maintenance regimen) was compared with leuprorelin 7.5/22.5 mg (three-monthly maintenance regimen), were excluded.[18] Although a HR of the overall survival is the most desirable outcome statistic, available data from the included RCTs were not sufficient and an OR was, therefore, used.

Figure 14. Network of trials used in mixed-treatment comparison – overall survival outcome



6.7.4 For the selected trials, provide a summary of the data used in the analysis.

Of the direct comparison trials, one RCT that compared triptorelin and leuprorelin (Heyns *et al*, 2003[124]) and one that compared bicalutamide monotherapy and goserelin (Iversen *et al,* 1998[125]) were suitable for inclusion in the MTC analysis. The

overall survival outcome was reported in the two included RCTs, although PSA progression (recurrence/failure) data were not available.

Heyns *et al* compared monthly treatment regimens of triptorelin 3.75 mg and leuprorelin 7.5 mg in 284 patients with advanced prostate cancer. Median PSA level was a reported outcome in this trial, but PSA progression was not. The probability of survival at nine months was 97.0% in the triptorelin group and 90.5% in the leuprorelin group (p=0.033). The authors concluded that 'long-term data are required to determine the clinical significance of this observation' (that is, the higher nine-month survival rate in the triptorelin group).[124]

The study by Iversen *et al* combined data from two similar RCTs, in which daily bicalutamide 150 mg was compared with surgical castration or monthly goserelin 3.6 mg in a total of 480 patients with advanced prostate cancer. As the proportion of patients receiving goserelin in the castration group was known (86%), this trial was included in the MTC. The median follow-up for the survival outcome was four years. The reported HR was 0.93 (95% CI 0.66 to 1.31),[125] indicating equivalence between bicalutamide and goserelin in the survival outcome.

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Markov chain Monte Carlo methods in WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) were used to conduct the random-effects MTCs. The WinBUGS code for Bayesian analysis is available from a report by Dias *et al*[134] (see Appendix C for the WinBUGS code used). A non-informative or vague prior was used, and results were obtained by 200,000 iterations after a burn-in of 100,000.

6.7.6 Please present the results of the analysis.

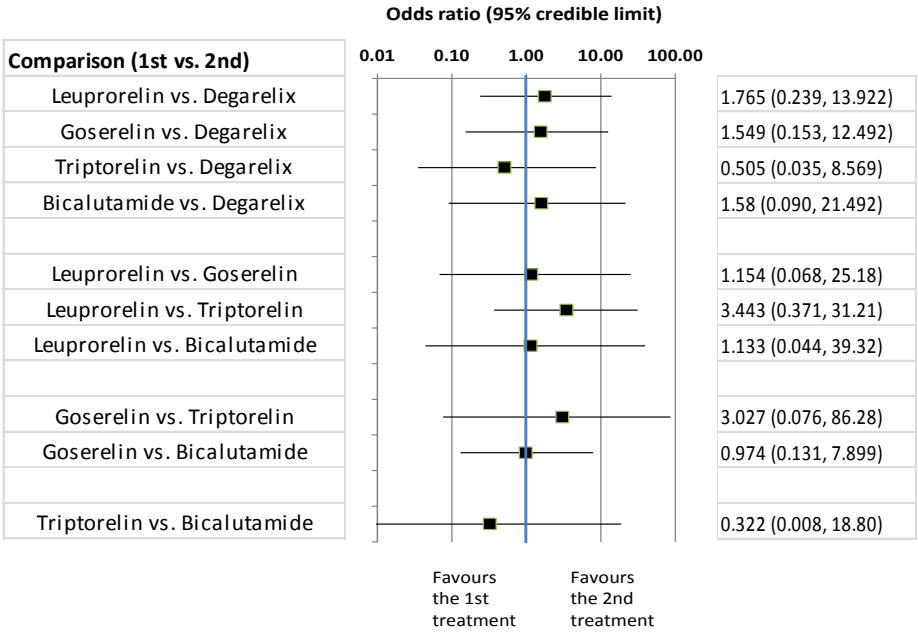
The results of the MTC analysis are shown in Figure 15. These show no statistically significant differences in the overall survival outcome between the different LHRH agonists (leuprorelin, goserelin and triptorelin), thus supporting previous reports by Seidenfeld *et al*[120] and Hemels *et al*[121] that none of the LHRH agonists exhibit superior clinical efficacy or effectiveness over another.

As bicalutamide monotherapy is one of the comparators listed within the final NICE scope, the MTC also evaluated the evidence available to allow a comparison between degarelix and bicalutamide monotherapy. As detailed in Table 16 only two suitable RCTs that compared bicalutamide at its monotherapy dose (150 mg) versus castration (medical or surgical) were identified.

The first of these trials, reported by Tyrell *et al,* showed that bicalutamide monotherapy was less effective than castration (medical or surgical) in patients with metastatic prostate cancer, in terms of the survival outcome. In addition, neither the percentage breakdown of patients who received surgical versus medical castration nor the absolute numbers of deaths in each treatment arm were explicitly described

in this study.[131] These factors, therefore, circumvent the inclusion of this study in the MTC network required to compare the clinical efficacy of bicalutamide monotherapy versus degarelix.

Figure 15. Results of mixed treatment comparison between degarelix and relevant comparators – death outcome (odds ratio [95% credible limit])



The second RCT identified, reported by Iversen *et al,* compared bicalutamide monotherapy (150 mg) with either surgical (14% of patients) or medical (86% of patients) castration in men with non-metastatic advanced prostate cancer. The authors concluded that bicalutamide monotherapy provides a similar survival outcome to castration in previously untreated patients with non-metastatic advanced prostate cancer.[125] Although this trial could be included in a subsequent MTC, the resulting non-closed MTC network would rely on only one clinical outcome (overall survival), because no other suitable outcomes required for an adequate comparison of bicalutamide monotherapy were reported on. The resulting MTC network would also lack any head-to-head RCTs that directly compare degarelix with bicalutamide monotherapy. This paucity of evidence to compare bicalutamide monotherapy with degarelix, therefore, prevents a robust comparison from both a clinical and a health economic perspective.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Heterogeneity across the trials used in the MTC analysis could not be evaluated, as only a single trial was available for goserelin versus bicalutamide, as well as one for leuprorelin versus triptorelin (see Figure 14). In addition, inconsistency between the direct and indirect estimates could not be assessed because the available evidence

was insufficient (that is, there were no closed loops in the MTC network presented in Figure 14).

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Reasons for inclusions and exclusions from the ten studies identified are detailed in Table 16.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

As detailed in Section 6.7.7, heterogeneity across the comparator trials used in the MTC analysis could not be evaluated.

6.8 *Non-RCT evidence*

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

Efficacy results from the included non-RCTs are described in this section. Safety and tolerability results from these trials will be discussed in Section 6.9.

Findings from the included dose-finding trials

The systematic review identified six dose-finding trials (see Appendix B, Table B1).[41,45,48,49,52] Because of a lack of LHRH agonist controls in these trials, their results are reported as findings from non-controlled, observational studies only to provide supplementary evidence on the clinical efficacy and safety of degarelix. One of the six dose-finding studies (CS02[40]) was not further considered, because the initial dose of degarelix used was much lower than that of the approved regimen. A summary of the methodological characteristics of the remaining five relevant dose-finding trials is provided in Table B9 in Appendix B.

The initial dose of degarelix used in three of these trials was 200 mg (CS12[41] and CS14[45]) and 240 mg (CS12[41] and Ozono *et al*, 2012[52]) Three trials evaluated monthly degarelix maintenance doses of 80, 120 or 160 mg (CS12:[41] 80, 120 and 160 mg, CS14:[45] 60 and 80 mg and Ozono *et al*, 2012:[52] 80 or 160 mg). Two trials investigated degarelix three-month maintenance regimens: 240 mg in CS15[48] and 360 or 480 mg in CS18.[49]

The length of follow-up was 12 months for all five of the dose-finding trials.[41,45,48,49,52] The primary outcome was the proportion of patients with (CS12, CS14, CS15, Ozono et al) or cumulative probability of (CS18) testosterone levels ≤0.5 ng/ml from Day 28 to Day 364.[41,45,48,49,52] Characteristics of patients included in these dose-finding trials were similar to those of patients in the included RCTs.[9-18,41,45,48,49,52]

Table B10 in Appendix B provides a summary of the main baseline characteristics of participants in the five dose-finding trials, while Table B11 provides an overview of the main results of these trials.[41,45,48,49,52]

The most relevant regimen for degarelix is the licensed regimen with an initial dose of 240 mg followed by a maintenance dose of 80 mg. This was used in two dose-finding trials (CS12 and Ozono *et al*, 2012).[41,52] The proportion of patients with serum testosterone levels ≤0.5 ng/ml from Day 28 to Day 364 in the 240/80 mg group was 90% (95% CI 73% to 98%) in CS12[41] and 94.5% (95% CI 88.5% to 98.0%) in Ozono *et al* 2012.[41,52]

The three-month maintenance regimens evaluated in two of the dose-finding trials were 240 mg in CS15 and 360 or 480 mg in CS18.[48,49] The proportion of patients with testosterone levels ≤0.5 ng/ml from Day 28 to the end of the study was low in CS15 due to inadequate testosterone suppression.[48] When the maintenance dose of the three-month regimen was increased from 240 mg in CS15 to 360 mg or 480 mg in CS18, the proportion of patients with testosterone levels ≤0.5 ng/ml from Day 28 to 364 was higher.[49]

Findings from the included extension trials

Six extension trials were included. Three of these (CS21A, CS34 and CS35A[57,68,69]) were extensions of included RCTs.

The main methodological characteristics, patient characteristics and main findings of the six extension trials are shown in Tables B12–B14 in Appendix B.

The primary objective of these extension trials was to evaluate the long-term safety and tolerability during long-term treatment with degarelix in patients with prostate cancer, so that the primary outcomes were usually clinical safety and laboratory parameters (see Appendix B, Table B12).[54,56,57,68-70] Patients were included in these extension trials after they had completed the main trials.

In CS21A, patients who received degarelix in CS21 continued to do so.[57] Patients switched from leuprorelin to degarelix at a starting dose of 240 mg followed by a monthly maintenance dose of 80 mg or 160 mg (randomly allocated). After Protocol Amendment 2, all patients received a monthly degarelix maintenance dose of 80 mg. Degarelix 240/160 mg and 240/80 mg regimens demonstrated similar efficacy in maintaining suppression of both testosterone to castrate levels (≤0.5 ng/ml) and PSA to levels <2 ng/ml for five years. Sustained suppression of both testosterone and PSA levels was observed with degarelix treatment during CS21A, irrespective of whether patients received degarelix or leuprorelin during the main CS21 trial. No statistically significant differences in the number of patients with PSA progression or who escaped testosterone suppression were observed between the treatment groups after switching from leuprorelin to degarelix in CS21A. For patients switched from leuprorelin, degarelix provided more effective suppression of FSH. The PSA PFS hazard rate decreased significantly after the switch in the leuprorelin/degarelix group, while the rate in those who continued on degarelix was consistent with the rate in Year 1[58] (see Appendix B, Table B14).

CS34 was an extension of three RCTs (CS28, CS30, and CS31[11,13,15]), but only 77 of the patients who completed the three main trials were recruited to CS34.[68] Patients treated with degarelix during the main trials continued to do so. Patients who received goserelin in the main trials were switched to degarelix at a starting dose of degarelix 240 mg on Day 0, followed by a maintenance dose degarelix 80 mg at monthly intervals thereafter. Suppression of PSA and testosterone levels attained during the main trials was maintained long-term in patients receiving degarelix.

Trial CS42A was the extension of a trial (CS42) of degarelix (240/80 mg) in Korean patients with prostate cancer. It reported that the cumulative probability of no PSA progression [recurrence/failure] from Day 28 to 364 was 94.7% (95% CI 89.0% to 97.4%).[25]

CS35A was different from other extension trials of RCTs in two respects: (1) no change was made to the treatment received in the control group when patients entered the extension trial, and (2) PSA PFS failure was the primary outcome.[69] Patients who entered CS35A continued with the same three-monthly treatment they had received in CS35 (that is, degarelix 480 mg or goserelin 10.8 mg every three months). The primary outcome, PSA PFS failure, was defined as either PSA progression or death, whichever occurred first. The planned length of follow-up in CS35A was 24 months, but the study was terminated early after six months. The adjusted HR of PSA PFS failure rates was 0.74 (95% CI 0.54 to 1.11), which showed that the risk of PSA PFS failure was lower with degarelix compared with goserelin, although this difference was not statistically significant (p=0.159). However, the adjusted HR of testosterone escape rates (a secondary outcome) was 3.51 (95% CI 1.74 to 7.09), indicating that patients in the degarelix group were 3.5 times more likely to escape testosterone suppression compared with patients in the goserelin group (p=0.0005). The adjusted HR of mortality was 0.60 (95% CI 0.26 to 1.37), indicating that degarelix treatment was associated with lower mortality compared with goserelin therapy, although this difference was not statistically significant (p=0.221).[17,69]

In CS12A, patients initially received the same maintenance doses as they received in CS12 (that is, 80, 120 or 160 mg degarelix at 28-day intervals). Subsequent to a protocol amendment, all continuing patients received degarelix 160 mg at 28-day intervals. In both the 80–160 mg and 120–160 mg groups, the hazard rate of testosterone escape (testosterone levels >0.5 ng/ml) was significantly higher before than after the dose shift (p=0.004 and p=0.009, respectively). Neither the 80–160 mg nor the 120–160 mg group showed a significant difference in hazard rates for PSA progression before and after dose shift. A tendency for the hazard rate of PSA progression to increase was observed after the dose shift in the 80–160 mg dose group (hazard rate increased from 0.12 to 0.21, p=0.22).[41,54]

In CS15A, patients initially continued with the same three-monthly degarelix maintenance regimen (240 mg every three months) they had received in CS15. The protocol for CS15A was then amended so that the patients shifted to a three-monthly maintenance dose of 360 mg or 480 mg. This maintenance dose shift to 360 mg and

480 mg was found to result in stabilisation of the testosterone escape rates (that is, the probabilities of testosterone suppression remained more or less constant following the dose shift), and the hazard rates for testosterone escape were significantly larger before than after the dose shift in all groups. The PSA progression rate was relatively constant during the trial, with no clear differences between the PSA progression rate before and after the dose shift.[48,56]

Findings from observational studies

Geiges *et al* recorded the safety and efficacy of degarelix in an observational study of 421 patients with prostate cancer who were treated with degarelix and followed up in daily practice for up to 24 months. PSA reduction to levels <4 ng/ml after 12 months was achieved in 83.3% of patients with baseline PSA levels <10 ng/ml (also including patients who previously received hormonal therapy). Prostate volume, measured by TRUS, was reduced by 40.8% within three months compared with baseline. ALP levels were measured in 61 patients; among these patients, ALP was suppressed from a median level of 639.9 IU/l to 108.7 IU/l after two months, and remained suppressed at a level of 78.6 IU/l at Month 12. The authors concluded that 'Efficacy and safety of treatment with degarelix was confirmed in routine daily practise. The efficacy of degarelix is comparable with other androgen-deprivation-therapies. The control of ALP by degarelix in daily clinical practice is in line with previously reported results from the pivotal trial. Also the prostate volume reduction of 40.8% was comparable with that found in a recent randomized clinical trial. Especially patients with high tumour burden or those scheduled for neoadjuvant hormone therapy prior to radiotherapy could benefit from the fast volume reduction offered by degarelix'.[71]

6.9 *Adverse events*

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

None of the RCTs was designed to assess safety as a primary outcome.

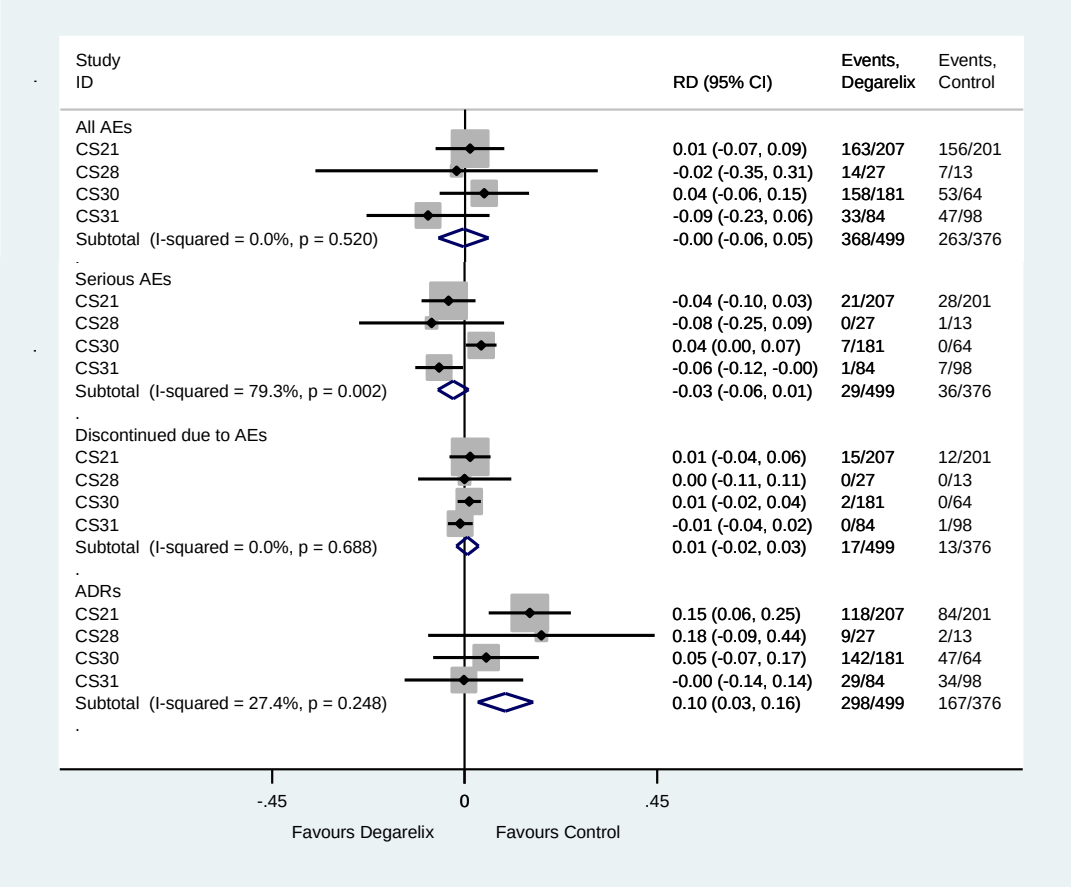
6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Figure 16 shows comparative results of a meta-analysis of AEs, using data from the RCTs in which degarelix 240/80 mg was compared with leuprorelin or goserelin plus bicalutamide.[9,11,13,15] To improve the comparability of the trials, this meta-analysis used data from those RCTs in which the monthly regimen of degarelix 240/80 mg was compared with monthly regimens of leuprorelin or goserelin plus bicalutamide (CS21, CS28, CS30 and CS31). Data from CS35, in which a three-monthly dosing regimen of degarelix was evaluated, were, therefore, not included. Data from CS37 were also not included, because this trial compared the monthly regimen of degarelix 240/80 mg with a three-monthly maintenance regimen of leuprorelin 22.5 mg.

No statistically significant heterogeneity was present across the studies. Overall, no statistically significant difference in the proportion of patients experiencing any AEs,

death or serious AEs (SAEs) was observed between the degarelix 240/80 mg group and the LHRH agonist group. However, the proportion of patients with ADRs (AEs evaluated by the investigator as possibly or probably related to the IMP) was higher in the degarelix group (rate difference 9.5% [95% CI 3.0% to 16.0%]; p=0.004). The higher rate of ADRs in the degarelix group was caused by injection site-related AEs (such as injection site pain, erythema and swelling). Notably, most of the injection-site reactions with degarelix (240/80mg) in CS21 occurred with the initiation dose and decreased over time (32% of injections were associated with an injection site reaction with the initiation dose, compared with only 3% of injections with the first maintenance dose and 2–5% with subsequent maintenance doses).[9] This is likely to be related to the subcutaneous route of administration and the larger volume administered as the initiation dose versus the maintenance dose. In CS21, the percentage of ADRs remaining after exclusion of injection site-related AEs was evaluated and was found to be similar in the three treatment groups: 44% (88/202) for degarelix 240/160, 43% (90/207) for degarelix 240/80 mg and 42% (84/201) for leuprorelin.[9]

Figure 16. Summary adverse events from relevant randomised controlled trials (difference in risk [RD] between degarelix and control treatment)[9,11,13,15]

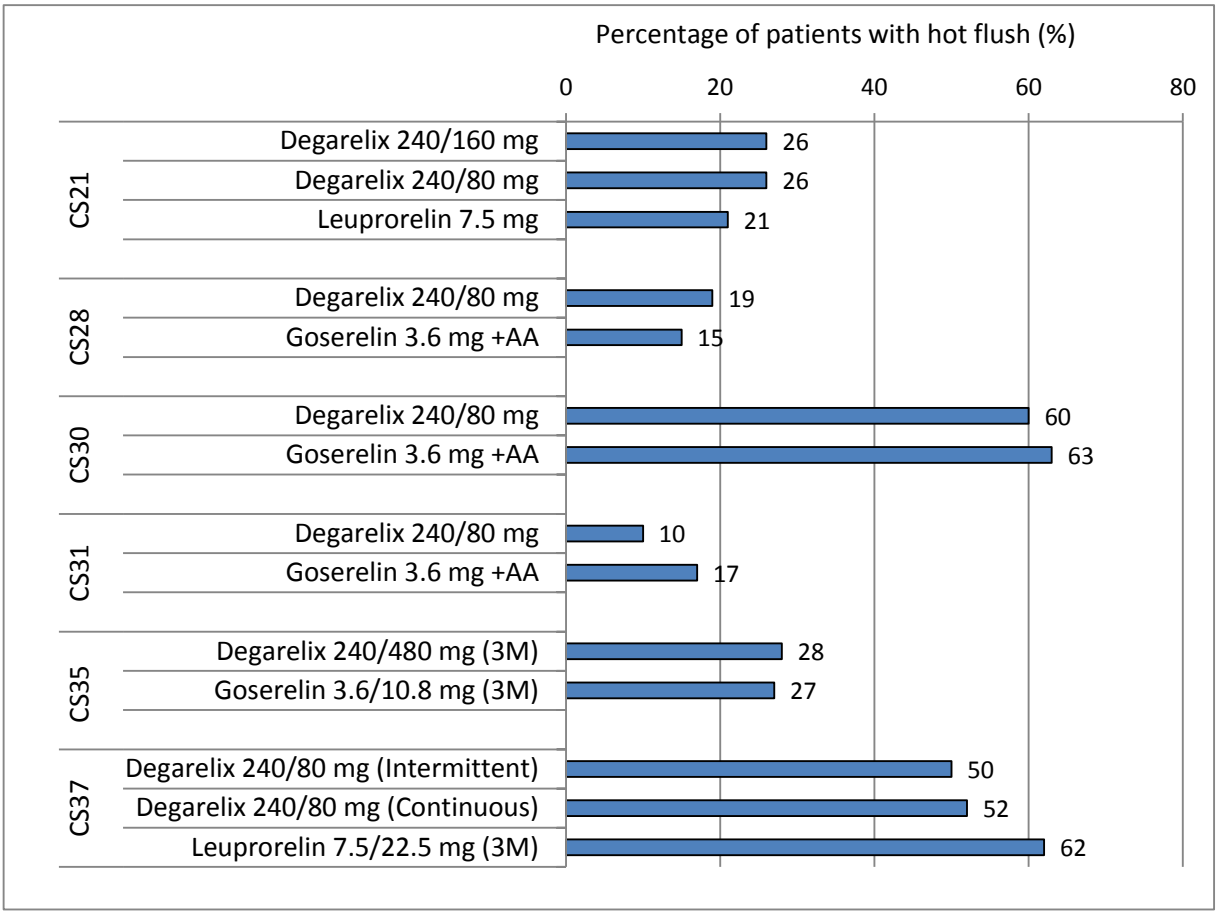


AEs by System Organ Class

In the included RCTs, AEs were separated into groups by 'System Organ Class'.[9,11,13,15,17,18] As a consequence of testosterone suppression, hot flushes were

the most commonly reported AE in both the degarelix and the LHRH control group.[9,11,13,15,17,18] Although the rate of patients with hot flushes varied considerably across trials, the difference in the percentage of patients with hot flushes between groups within each trial was similar (see Figure 17).

Figure 17. Hot flush adverse events reported in the included randomised controlled trials[9,11,13,15,17,18]



AE analysis from individual patient data

As all six RCTs (CS21, CS28, CS30, CS31, CS35 and CS37) identified by the systematic review were conducted by Ferring Pharmaceuticals, patient-level data are available for post hoc exploratory analyses. Conducting Kaplan–Meier analyses of individual patient-level data, rather than using incidence figures alone, allows the timing of events and censoring to be accurately accounted for.[135]

CVD AE analysis of individual patient data

As previously described, LHRH agonists have been associated with an increased risk of CVD AEs.[105] The pooled individual patient data from the six RCTs identified in the systematic review (CS21, CS28, CS30, CS31, CS35 and CS37) were evaluated by post hoc exploratory analysis to compare the risk of cardiovascular events (including and excluding death) in patients treated with degarelix with that of those receiving LHRH agonists. Cardiovascular events included were arterial embolic and thrombotic

events, haemorrhagic and ischaemic cerebrovascular conditions, myocardial infarction and ischaemic heart disease. An independent academic group, external to Ferring Pharmaceuticals A/S, used Kaplan–Meier curves and performed Cox regression model analysis of the pooled data to establish the risk of CVD AEs in the total RCT patient population and in those with a pre-existing CVD at baseline.[73] The following are the main findings of these analyses.

- In total, data from 2,328 patients were analysed; 1,491 received degarelix and 837 received an LHRH agonist (goserelin: n=458; leuprorelin: n=379). The treatment groups were balanced for common baseline characteristics and CVD-related characteristics.
- Among men with pre-existing CVD, the risk of cardiac events within one year of initiating therapy was significantly lower for those treated with degarelix than for those treated with LHRH agonists (HR 0.44; 95% CI 0.26 to 0.75; p=0.0023).
- Among men with no history of CVD, the incidence of cardiac events within one year was comparable between the two treatment groups.

This pooled analysis of data from 2,328 patients indicates that men with a history of CVD, who are in need of androgen deprivation therapy, experience a significantly lower risk of CVD AEs if treated with degarelix compared with an LHRH agonist.[110] The same pooled individual patient-level data have been analysed using the Kaplan–Meier method for the purpose of inclusion in the cost-effectiveness model described in Section 7 of this submission.

Disease-related AE analysis of individual patient data

Several disease-related AEs, including the risk of fractures, joint-related signs and symptoms and urinary tract events were explored, using the pooled analysis of individual patient-level data from six RCTs; the main findings are as follows:[74,75]

- Data from 2,328 patients were analysed; 1,491 received degarelix and 837 an LHRH agonist (goserelin n=458; leuprorelin n=379).
- The overall probability of joint-related signs and symptoms was significantly reduced in the degarelix group compared with the LHRH group (5.3% versus 8.1%, respectively; p=0.0116, log-rank).
- The overall probability of fracture was also significantly reduced in the degarelix group compared with the LHRH group (0.9% versus 2.3%, respectively; p=0.0234, log-rank).
- The overall probability of a urinary tract AE was significantly lower in degarelix- versus LHRH agonist-treated patients (15.0% versus 22.3%; p<0.0001, log-rank).[110]

The same pooled individual patient data have been analysed using the Kaplan–Meier method for the purpose of inclusion in the cost-effectiveness model described in Section 7 of this submission. Similar pooled analyses on these disease-related AEs have been submitted to the peer-reviewed journal *European Urology* and are due to be published within the next six months.[76]

AE findings from the dose-finding and extension trials

AEs reported in the dose-finding trials were similar to those reported in the included RCTs (see Table 6.23). The general conclusion was that degarelix was well tolerated.

In five of the six extension trials, the primary objective was to evaluate the long-term safety and tolerability of degarelix in patients with prostate cancer (see Appendix B, Table B12) According to the results of these extension trials, the long-term use of degarelix was generally safe and well tolerated (see Appendix B, Table B14). The AE results were consistent with those expected in an elderly population with prostate cancer in receipt of long-term androgen-deprivation therapy. The AEs reported were also generally consistent across these extension trials, and similar to those reported in the RCTs. The most commonly reported ADRs in the degarelix treatment groups were injection site reactions. Other ADRs were mostly associated with the pharmacological consequences of testosterone suppression (primarily, hot flushes).

AE findings from observational studies

In an observational study reported by Geiges *et al*, 421 patients with prostate cancer who were treated with degarelix were followed up in daily practice for up to 24 months. The major side-effects observed during this study were hot flushes (8.8 %) and erythema at the injection site (7.9 %). The frequency of pain and back pain was recorded and, at the last documentation, this was reduced by 20.9% and 58.8%, respectively. The authors concluded that their observations confirmed the safety of treatment with degarelix in routine daily practice.[71]

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

- Degarelix provides a well tolerated treatment option for advanced hormone-dependent prostate cancer, and meta-analyses of RCTs indicate that degarelix has a similar overall AE profile to LHRH agonists (see Section 6.9.2).
- In men with pre-existing CVD, the risk of cardiac events within one year of initiating therapy is significantly lower for those treated with degarelix than for those treated with LHRH agonists (see Section 6.9.2). The cardiovascular risk benefit that degarelix offers, compared with LHRH agonists, is of particular relevance to the decision problem, as the population covered by the licensed indication of degarelix has a high prevalence of cardiovascular co-morbidity; indeed, in England the prevalence of CVD for those aged 65–74 and ≥75 years, the age groups with the highest incidence of prostate cancer,[84] is 34.1% and 44.4%,[88] respectively. Degarelix offers an alternative treatment option with significant cardiovascular AE safety benefits for the prostate cancer population.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Testosterone response

Degarelix (240/80 mg) is effective in achieving and maintaining serum testosterone at castrate levels (≤0.5 ng/ml) and, administered as a monthly maintenance regimen, is non-inferior to conventional LHRH agonists. LHRH agonist administration can result in a transient increase in testosterone levels – a testosterone flare (surge) – leading to an increased risk of exacerbating bone pain, compression of a nerve root, spinal cord compression and obstructive uropathy.[78] As treatment with degarelix does not cause the initial rise in serum testosterone levels seen with LHRH agonists, these risks are avoided and anti-androgen treatment to reduce the incidence of testosterone flare (surge) is not required at the start of treatment.

Reduction in prostate size

A common symptom of prostate cancer is urinary obstruction with LUTS.[109] Hormonal treatment may improve LUTS by reducing the size of the prostate gland. Evidence from three RCTs (CS28, CS30 and CS31) indicated that degarelix was non-inferior to the LHRH agonist controls in reducing prostate volume. The estimated overall difference in percentage change in prostate volume was –0.57 ml (95% CI –5.02 ml to 3.87 ml). Importantly, improvement in urinary symptoms has been shown to be associated with increased quality of life for patients with prostate cancer receiving androgen deprivation therapy.[14,16]

IPSS

Combined evidence from three RCTs (CS28, CS30 and CS31) indicated that degarelix was more effective than goserelin plus bicalutamide in reducing the total IPSS at Week 12 (pooled mean difference –1.43; 95% CI –2.47 to –0.39; p=0.007). It should be noted that the IPSS questionnaire was completed by the patients, and the lack of blinding of patients and care providers may cause some bias in the IPSS assessment.

PSA response

As described earlier, PSA progression is used to monitor the response to treatment for prostate cancer, disease recurrence and progression (see ‘PSA response’ in Section 6.5).[7,107,108]

According to data from the pivotal CS21 trial, degarelix achieves more rapid suppression of PSA levels compared with leuprorelin, with a median reduction at Day 28 of 82.3% versus 66.7% (p<0.0001).[9,10] In addition, data from CS21 showed that the risk of PSA progression was lower with degarelix 240/80 mg than leuprorelin for patients with baseline PSA levels >20 ng/ml (16% versus 28%; p=0.04),[21] indicating degarelix offers a lower risk of disease progression compared with LHRH agonists. Thus, degarelix will keep patients on first-line hormonal therapy for longer, which is more cost-effective and associated with better health-related quality of life than subsequent treatment stages (see Section 7.4).

Progression-free and overall survival

Pooled data from the included RCTs indicate that mortality tended to be lower in the degarelix group than in the LHRH agonist control group (pooled OR 0.48; 95% CI 0.25 to 0.91; p=0.025). The overall rate of death was 1.4% (18/1,266) in the degarelix group and 2.8% (19/659) in the control groups. An additional analysis of data from CS21 found that the risk of PSA progression (recurrence/failure) or death was lower in the degarelix 240/80 mg group compared with the leuprorelin group (p=0.05).[21]

AEs

As a consequence of testosterone suppression, flushing was the most commonly reported AE in both the degarelix and LHRH agonist control groups. Overall, no statistically significant difference was seen in the proportion of patients experiencing any AEs, SAEs and discontinuation due to AEs between the degarelix 240/80 mg group and the LHRH agonist group, indicating that degarelix offers a well-tolerated treatment option. However, the proportion of patients with ADRs was higher in the degarelix group, with a rate difference of 9.5% (95% CI 3.0% to 16.0%; p=0.004). The higher rate of ADRs in the degarelix group was caused by injection site-related AEs. Most injection-site reactions occur with the initiation dose (32%), with much lower incidences after the first maintenance dose (3%) and the maintenance doses thereafter (2–5%).

Analyses of pooled individual patient-level data have provided evidence that degarelix offers benefit over LHRH agonists in terms of a reduced risk of several disease-related and disease non-related AEs. Among men with pre-existing CVD, the risk of cardiac events within one year of initiating therapy was significantly lower for those treated with degarelix than for those treated with LHRH agonists (HR 0.44; 95% CI 0.26 to 0.75; p=0.0023).[73] Among men with no history of CVD, the incidence of cardiac events within one year were comparable between the two groups.[73] In terms of disease-related AEs, degarelix was associated with significantly fewer joint-related signs and symptoms (p=0.0116) and fractures (p=0.0234), and urinary tract events (p<0.0001) than LHRH agonists.[74,75]

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Main strengths

- The studies were well designed and conducted RCTs.
- Outcome reporting bias may be minimised by using data from the clinical study reports.

Main limitations

- The studies had an open label design, as it was impossible to blind patients and care providers. Lack of blinding may introduce bias in subjectively measured outcomes such as AEs, IPSS and other quality of life scores.
- The available RCTs included patients with different stages of prostate cancer – localised, locally advanced and metastatic;[9,11,13,15,17,18] however, tests for an

interaction between the disease state and treatment effect showed that treatment effect is not dependent on the stage of disease.[76]

- Degarelix has not been directly compared with triptorelin and bicalutamide in RCTs, and very limited evidence is available for an indirect comparison of degarelix and triptorelin or bicalutamide in patients with prostate cancer.
- Short-term anti-androgen treatment was not consistently used in the LHRH agonist control groups in CS21, CS35 and CS37.[9,17,18] Inadequate flare protection for patients in the LHRH agonist groups should be taken into consideration when interpreting results from these trials.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Table 17 summarises the relevance of the evidence base to the decision problem.

Table 17. The relevance of the evidence base to the decision problem[9-18,83]

	Decision problems	Relevance to problems
Population	The relevant population: adult male patients with advanced hormone-dependent prostate cancer	• RCTs included patients with all stage prostate cancer in trials CS21, CS28, CS31 and CS35, although patients with neoadjuvant hormonal therapy have been excluded from these trials • Trial CS30 only included patients in whom neoadjuvant endocrine treatment was indicated • Trial CS37 included patients with a rising PSA level (≥2.2 ng/ml) after primary therapy for localised prostate cancer • The proportion of patients with locally advanced or metastatic prostate cancer was 49% in CS21, 48% in CS28, 34% (0% metastatic) in CS30, 60% in CS31, 56% in CS35 and only 5.5% in CS37 • Results for patients with advanced or metastatic prostate cancer were not systematically reported • Only limited data were available for relevant subgroup analyses; additional analyses by baseline disease stage (localised, locally advanced and metastatic) and PSA level (>20 ng/ml) were conducted using data from CS21
Interventions	Degarelix	• The licensed starting dose of degarelix is 240 mg and the maintenance dose is monthly 80 mg • Monthly degarelix 160 mg was used in one of the three arms in CS21 • A three-month maintenance regimen of degarelix was evaluated in CS35
Comparators	• LHRH agonists: goserelin, leuprorelin and triptorelin • Bicalutamide monotherapy	• No RCTs directly compared degarelix with triptorelin or bicalutamide • The short-term anti-androgen treatment for flare protection was not consistently used in the LHRH agonist control groups in CS21, CS35 or CS37
Outcomes	• Overall survival • Progression-free survival • Response rate • Testosterone response • Prostate-specific antigen (PSA) response • Adverse effects of treatment • Health-related quality of life	• These outcomes have been assessed in the included RCTs • Overall survival has not been used as the primary outcome measure in the included RCTs • Although not specified in the draft NICE scope, the change in prostate volume was measured in trials CS28, CS30 and CS31 • International Prostate Symptom Score (IPSS) was used in CS28, CS30, CS31 and CS35 to assess changes in patients' quality of life

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in

clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The dose of degarelix licensed in the UK is a combination of a 240 mg initiation dose and 80 mg monthly maintenance doses [240/80 mg].[2,3] As this dose was evaluated in five of the six RCTs identified,[9-16,18] most of the evidence provided in this submission is based on the dose licensed in the UK.

As previously noted, the available RCTs included patients with all stages of prostate cancer (localised, locally advanced and metastatic) although degarelix is indicated for the treatment of locally advanced and metastatic disease.[2,3] However, a pooled analysis concluded that the treatment effect of degarelix is not dependent on disease stage.[76]

Initial concomitant anti-androgen therapy with LHRH agonists is routinely used in the UK to reduce the incidence of testosterone flare. In two (CS21 and CS35) of the six RCTs that form part of the evidence base presented here, only 11% and 13.5% of patients received concomitant anti-androgen therapy. However, pooled data from CS21 and CS35 indicate that LHRH agonist treatment combined with anti-androgen protection against testosterone flare did not achieve the same level of disease control as degarelix during the first year of therapy, even when the 7.5 mg monthly regimen of leuprorelin (which is higher than the 3.75 mg dose indicated for use in the UK) was evaluated (CS21).

The dose of leuprorelin used in CS21 was 7.5 mg, as opposed to the 3.75 mg licensed monthly dose in the UK. Therefore, when interpreting the results, an assumption is made that different dosing regimens of leuprorelin have no effect on the efficacy and safety profile. This assumption is supported by a literature search, which identified seven studies comparing the two doses of leuprorelin (3.75 mg and 7.5 mg).[136-142] These found no statistically significant differences in clinical outcomes between the two doses; thus, it can be assumed that leuprorelin 3.75 mg and 7.5 mg monthly are clinically equivalent.

7 Cost effectiveness

Summary of degarelix cost-effectiveness

- A Markov treatment sequence model has been used to assess the cost-effectiveness of degarelix compared with three-monthly goserelin (the most frequently used luteinising hormone-releasing hormone [LHRH] agonist in England and Wales).
- The model is based on the differences in efficacy between degarelix and LHRH agonists in relation to delaying disease progression and reducing the adverse events associated with disease progression and current treatment (musculoskeletal events and cardiovascular events).
- In the model base case, degarelix is cost saving, saving £1,541 compared with goserelin and improving outcomes by 0.58 quality-adjusted life-years (QALYs).
- A wide range of scenario and sensitivity analyses have been undertaken around model inputs and degarelix remained cost-effective in all scenarios tested.
- Using probabilistic sensitivity analysis, there was a 99.5% chance that degarelix will be cost-effective at a threshold of £20,000 per QALY, and 100% chance at £30,000 per QALY.
- Degarelix is also cost saving in the prostate-specific antigen (PSA) >20 ng/ml high-risk subgroup, saving £1,489 compared with goserelin and improving outcomes by 0.58 QALYs.

A Markov treatment-sequence model was developed in Microsoft® Excel (see Section 7.2.2). This approach was used to estimate outcomes and costs for patients with advanced hormone-dependent prostate cancer over a lifetime horizon (30 years). The model was designed to replicate disease progression over time by estimating outcomes over the treatment sequence typically followed by a patient with the condition (see Section 7.2.4).

Two patient groups are included in the economic evaluation. The first treatment group is the intention-to-treat (ITT) population from the CS21 and CS21A trials. This population reflects the licensed indication for the treatment of advanced hormone-dependent prostate cancer; however, the ITT population also includes some patients with localised prostate cancer, and in UK clinical practice, some of these patients would not be treated with hormonal therapy. A secondary group from the CS21 population is, therefore, also considered: patients with PSA levels >20 ng/ml. These patients are a higher-risk subgroup of the ITT population and are more reflective of the population treated with hormonal therapy in the UK (see Sections 7.2.1 and 7.9).

The model successfully replicates the trial data, and its longer-term predicted outcomes are consistent with the wider clinical literature (see Sections 7.7.1 and 7.8). The model estimates that for the ITT population, patients treated with degarelix will remain on first-line therapy for an additional 0.37 years (9.58 versus 9.21) compared with patients treated with goserelin 10.8 mg, the most commonly-prescribed LHRH agonist in the UK. Over the patient's lifetime, treatment with degarelix results in an incremental QALY gain of 0.58 (5.85 versus 5.28) and a cost saving of £1,541 (£26,095 versus £27,636) (see Section 7.7.6), due to reduced costs of later-line

therapies and reduced numbers of cardiovascular events and musculoskeletal events (MSEs) associated with LHRH agonist treatment. Table 18 shows the base case results.

A range of scenario analyses were undertaken, in addition to deterministic and probabilistic sensitivity analysis. The results of the model were relatively insensitive to variations in the underlying assumptions, with degarelix being the cost-effective treatment option in 100% of the simulations at a willingness-to-pay threshold of £30,000 per QALY (see Section 7.7.8).

Table 18. Base case cost-effectiveness results

	Degarelix	**Goserelin (10.8 mg)**
Technology acquisition cost	£8,524	£3,978
Other costs	£17,571	£23,657
Total costs	£26,095	£27,636
Difference in total costs	N/A	–£1,541
LYG	9.58	9.21
LYG difference	N/A	0.37
QALYs	5.85	5.27
QALY difference	N/A	0.58
ICER	N/A	Dominating

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY(s) = quality-adjusted life year(s)

Subgroup analyses c*onsidered a*nd clinical *a*nd cost-effectiveness r*esults*

Subgroup analysis was undertaken for those patients who had PSA levels >20 ng/ml as this represents a higher-risk population than the ITT population in trials CS21 and CS21A (see section 7.2.1 and 7.9). Table 19 below provides the results for this subgroup and indicates that treatment with degarelix is likely to be cost saving for this subgroup as well as for the base-case population.

Table 19. PSA >20 ng/ml subgroup results

	Degarelix	Goserelin (10.8 mg)
Technology acquisition cost	£6,683	£2,927
Other costs	£21,623	£26,867
Total costs	£28,306	£29,794
Difference in total costs	N/A	–£1,489
LYG	9.22	8.78
LYG difference	N/A	0.44
QALYs	5.36	4.77
QALY difference	N/A	0.58
ICER	N/A	Dominating

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; PSA = prostate-specific antigen; QALY(s) = quality-adjusted life year(s)

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A broad systematic review was conducted in March 2013 to identify cost-effectiveness studies for advanced prostate cancer patients treated with LHRH agonists. A precise search strategy was utilised, incorporating terms for degarelix and its comparators, together with terms for prostate cancer and an economics filter, as reported on the Centre for Reviews and Dissemination (CRD) website.[143] To ensure the published literature was comprehensively reviewed, a wide range of databases were searched, these included:

- Medline and Medline in Process & Other Non-Indexed citations
- EMBASE
- Cochrane CDSR
- Cochrane CCRT
- Cochrane DARE
- Cochrane NHS EED
- Cochrane HTA
- CINAHL
- EconLit
- Science Citation Index
- Conference Proceedings index (Science)

Appendix 10 describes the search strategy used to search the databases. The structure of the search is described by providing the structure and the terms used to search the Medline database. Having identified studies from a wide range of databases the titles and abstracts were reviewed in greater detail to assess their relevance for informing the overall decision problem. Table 20 shows the eligibility criteria employed to assess the relevance of the different studies are outlined below.

Table 20. Eligibility criteria and rationale for each criterion

Inclusion Criteria		
Category	**Inclusion Criteria**	**Rationale**
Population	Adults with advanced hormone-dependent prostate cancer (locally advanced or metastatic, including biochemical relapse) in whom orchidectomy is not preferred	This was the population identified by the NICE final scope and is in accordance with the licensed indication for degarelix.
Study type	Full economic evaluation (including cost-consequence, cost-minimisations, cost-effectiveness, cost-utility and cost-benefit evaluations) that compares two or more interventions	The aim of the review was to identify relevant economic evaluations
Outcomes	Incremental costs and QALYs; any other measure of effectiveness reported together with costs	The aim of the review was to identify relevant economic evaluations, which must report costs
Interventions	The intervention of interest was degarelix (see Appendix 10 for the terms used to filter by this agent)	
Comparators	The comparators included in the search included gonadotrophin hormone agonists and androgen antagonists (see Appendix 10 for a full list of terms)	The comparators for the literature were selected in accordance with the final NICE scope
Other	Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed, and the study's data and results must be extractable	Only studies which provided extractable data and results were usable
Exclusion criteria		
Category	**Exclusion Criteria**	**Rationale**
Publication Type	Letters; editorials; reviews of economic evaluations (although reference lists of these were hand-searched)	Primary study articles were required.

The papers which, from a detailed review of the title and abstract, appeared to meet the inclusion criteria were obtained for a secondary review. This secondary review involved the entire article being assessed according to the criteria outlined in Table 20 above. The studies which, following a secondary review, were still assessed to have met the inclusion criteria are reviewed below.

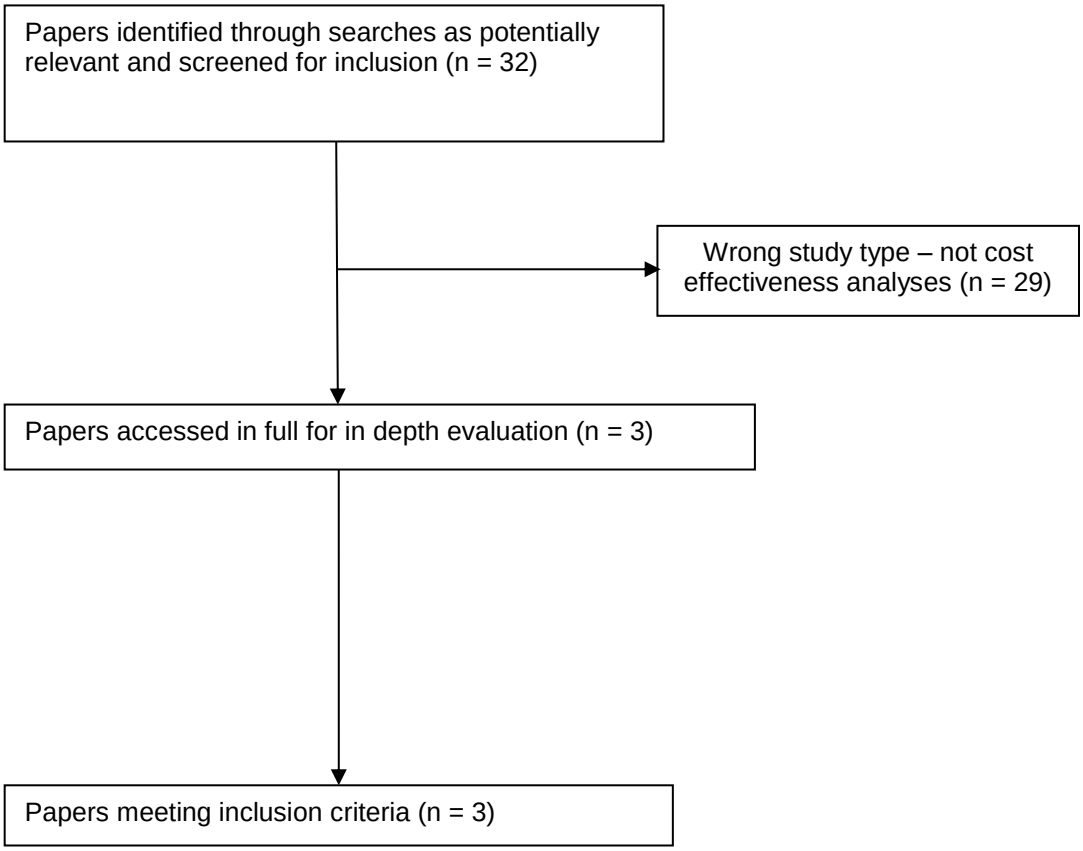
Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Identification of relevant studies

As discussed in 7.1.1 above, a range of studies were identified and their relevance assessed according to the inclusion/exclusion criteria described in Table 20. As illustrated by Figure 18 below, the majority of the studies initially identified failed to meet the inclusion criteria. Three of the studies met the criteria for inclusion both after the primary and the secondary review. These relevant studies are reviewed and critically appraised below.

Figure 18. Identification of cost-effectiveness studies relevant to the decision problem



Overview of the relevant studies

Three studies of relevance were identified. Two studies (Lu *et al* and by Lee *et al*) undertook the cost-effectiveness analysis from the perspective of the UK NHS.[144,145] A further study, undertaken by Hatoum *et al,* undertook the analysis from a US payer's perspective.[146] All three studies compared degarelix with an LHRH agonist. The aim of each of the studies appears to have been to inform clinical decision-making in their respective national contexts.

Lu *et al* used a hybrid model to compare the cost-effectiveness of degarelix (administered monthly) to triptorelin (administered every three months) in combination with short-term anti-androgen treatment. A decision tree was used to estimate the proportion of patients experiencing spinal cord compression (SCC) and bladder outlet obstruction (BOO) as a result of the testosterone flare that is associated with LHRH agonist treatment. From the end of the first month until the ten-year time horizon, a Markov model was used to estimate the costs and QALYs accumulated by patients on both of the treatment options. The model assumed no difference in efficacy between the two treatment options, only a differential safety profile during the first month of treatment.[144,145]

In contrast to the study by Lu *et al,* the study by Lee *et al*[145] used data from the CS21 study to estimate the time to PSA progression. The comparator to degarelix in this cost-effectiveness study was leuprorelin, in combination with short-term anti-androgen treatment, as leuprorelin was the comparator used in the CS21 study. The paper argued that the differential efficacy between the treatments should be reflected in the model structure, as UK clinicians had stated that PSA progression was a good indicator of biochemical disease progression and was used to determine when patients are switched from first-line treatment.[7] Following failure on first-line treatment, patients progressed through a number of treatment sequences, many of which were associated with a lower health-related quality of life (HRQL). In line with the analysis by Lu *et al*, the differential adverse event (AE) profile was incorporated into the modelling approach. The risk of experiencing SCC or an MSE was modelled, which had implications for the costs accumulated by patients and their HRQL.

The study by Hatoum *et al* aimed to inform clinical decision-making in the USA. The model used a similar approach to Lee *et al;* the comparator to degarelix was leuprorelin and data from trial CS21 were used to inform the time patients stayed on first-line treatment. Following PSA progression, patients moved to later lines of treatment. A Markov modeling approach was used to model progression through the different lines of therapy – each line of therapy was associated with different costs, and patient HRQL decreased as they moved through the treatment lines.[146]

Results

Table 21 reports the results for each of the three studies as well as a summary of the method used.

Table 21. Summary list of other cost-effectiveness evaluations

Study	Year	Country where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Lu *et al*[144]	2011	UK	Decision tree and Markov model to evaluate cost-effectiveness of monthly degarelix vs 3-monthly triptorelin plus short-term anti-androgen treatment within a metastatic population (the title states advanced, however, the paper only covers metastatic patients). Time-horizon of 10 years. The decision tree monitored patients from the start of hormonal treatment to the end of Month 1. During this time, patients either: developed severe SCC, developed mild symptomatic SCC, experience BOO or had no complications. After treatment, they entered the Markov model, which consisted of 3 stages: in response, progressive disease and death. A monthly cycle was assumed.	70 years old	Degarelix: 2.45 Triptorelin + AA: 2.44	Degarelix: £3,883 Triptorelin + AA: £3,125	£59,012
Lee *et al*[145]	2012	UK	Markov model including treatment sequencing comparing the cost effectiveness of first line treatment with degarelix compared to leuprorelin. The primary efficacy variable was time to PSA progression (recurrence/failue). The adverse events of SCC and MSE were also included.	Not stated	ITT population Degarelix: 3.77 Leuprorelin + AA: 3.53 PSA >20 ng/ml population Degarelix: 3.55 Leuprorelin + AA: 3.28	ITT population Degarelix: £19,440 Leuprorelin + AA: £24,592 PSA >20 ng/ml population Degarelix: £24,621 Leuprorelin + AA: £30,439	ITT population Degarelix is dominant PSA >20 ng/ml population Degarelix is dominant

Study	Year	Country where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Hatoum *et al*[146]	2013	USA	20-year time horizon semi-Markov model. Costs and QALYs discounted at 3%. Compared monthly degarelix 240/80 with monthly leuprolide 7.5 mg. as first-line treatment of locally-advanced prostate cancer. Patients entered the model when receiving either degarelix or leuprorelin and were then subjected to monthly probabilities of PSA progression or death. A patient transitioned to second-line or a subsequent line of ADT treatments when PSA recurred. Once a patient reached the stages of either 'passive monitoring', 'chemotherapy' or 'palliative care', the patient's utility was then considered to be further reduced since prostate cancer had reached the hormone-resistant stage.	72 years old	Degarelix: 4.20 Leuprorelin +AA: 3.46	Degarelix: $37,174 Leuprorelin +AA: $36,991	$245

Key: AA = anti-androgen; ADT = androgen deprivation therapy; BOO = bladder outlet obstruction; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; MSE = musculoskeletal event; PSA = prostate specific antigen; QALY(s) = quality-adjusted life year(s); SCC = spinal cord compression

Critical appraisal

The models by Lee *et al* and Hatoum *et al* estimate that treatment with degarelix is either dominant or highly cost-effective when compared with leuprorelin.[145,146] In contrast the model by Lu *et al*, estimates that the incremental cost-effectiveness ratio (ICER) resulting from treatment with degarelix is above conventional cost-effectiveness thresholds.[144] The central cause of this difference in results is the approach taken to modelling treatment progression. Lu *et al* assumed no differential efficacy between degarelix and triptorelin with respect to progression-free survival (PFS).[144] The studies by Lee *et al* and Hatoum *et al* model differential PFS for patients treated with degarelix and leuprorelin,[145,146] due to clinician feedback regarding the use of PSA progression in clinical decision-making and the differential time to PSA progression in the CS21 trial. This resulted in improved quality of life for patients treated with degarelix and substantial cost-offsets due to less time being spent in later lines of treatment.

However, the studies as a whole are inadequate to fully inform decision-making in the UK context. The primary limitation of the study by Hatoum *et al*[146] is that it takes a US payer's perspective; as such, the costs incorporated may not be appropriate for the UK. The study by Lu *et al*[144] is limited in that its model structure does not account for all of the additional benefits of treatment with degarelix; the result is that the cost-effectiveness of degarelix is likely to be underestimated. The model reported by Lee *et al*[145] appears to be promising, but as it was only available as a poster, there is a lack of detail on the reported method (as shown by the checklist in Appendix 11 in Section 10.11). Additionally, while a couple of scenario analyses are reported, the analysis of uncertainty is insufficient to fully inform the decision-making problem.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips *et al*. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Please see Appendix 11 in Section 10.11 for full critical appraisal of the studies by Lu *et al,* Lee *et al* and Hatoum *et al.*[144-146]

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[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, *et al*. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

7.2 *De novo analysis*

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The licensed indication for degarelix is the treatment of adult male patients with advanced hormone-dependent prostate cancer.[2,3] Data from the Phase III study CS21 and the extension study CS21A as well as data from five Phase III/IIIb studies were used to support the application for this indication.

Two patient groups are included in the economic evaluation. The first treatment group is the ITT population from the CS21 and CS21A trials. This population reflects the licensed indication for the treatment of advanced hormone-dependent prostate cancer. However, the ITT population includes some patients with localised prostate cancer, and in UK clinical practice, some of these patients would not be treated with hormonal therapy.

A secondary group from the CS21 population is, therefore, also considered. Patients with PSA levels >20 ng/ml are a higher-risk subgroup of the ITT population who are more reflective of the population treated with hormonal therapy in the UK. Results of the subgroup analysis are reported in Section 7.9.

As discussed in Section 6.3.1, the comparator in trial CS21 and CS21A is leuprorelin 7.5 mg. The model assumes the safety and efficacy profile of leuprorelin 7.5 mg is equal to the safety and efficacy profile of leuprorelin 3.75 mg. Additionally, it assumes the efficacy and safety profiles of the alternative LHRH agonists are equal to leuprorelin 7.5 mg. The first assumption, that different dosing regimens have no effect on the efficacy and safety profile, is informed by the available clinical literature. A search was undertaken which identified seven studies comparing the two doses of leuprorelin acetate (3.75 mg and 7.5 mg).[136-141] These found no statistically significant differences in clinical outcomes between the two doses; thus, it can be assumed that leuprorelin acetate 3.75 mg and 7.5 mg monthly are clinically equivalent.

The second assumption, that the LHRH agonists are equally efficacious and safe, is informed by two sources. First, the results from the mixed treatment comparison outlined in Section 6.7 indicate that none of the LHRH agonists offer superior clinical efficacy or effectiveness over another. Second, a previous review conducted by Seidenfeld *et al* (2000) reached the same conclusions.[120]

Goserelin is chosen as the comparator for the base case. In the scenario analyses results are reported for degarelix versus each of the commonly used LHRH agonists.

Goserelin 10.8 mg (three-monthly) is the most commonly prescribed LHRH agonist (39.7% of the market share) in England and Wales, as shown in Table 6 in Section 2.7.

Sensitivity analyses comparing degarelix with the cheapest and most expensive LHRH agonists are presented to indicate the range of cost variability in this class of drug and the impact of this on the cost-effectiveness of degarelix.

Comparison with bicalutamide monotherapy is not provided, as insufficient clinical evidence was found during the systematic review of randomised controlled trial (RCT) data (Section 6.7.6) for the key effectiveness measure of PSA progression. In addition, the evidence available from the two identifed RCTs that included bicalutmide at its monotherapy dose was of poor quality and included low patient numbers. Furthermore, no RCT evidence that directly compared degarelix with bicalutamide monotherapy was identified.

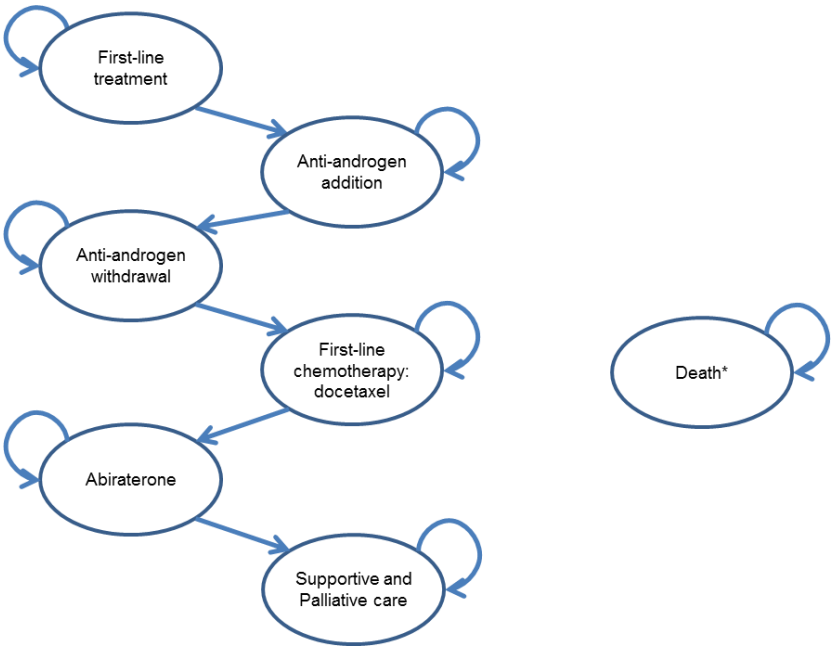
As is the case with the requests and recommendations of other UK HTA bodies, LHRH agonists have routinely been accepted to be the most appropriate comparators to degarelix, as their licensed indication covers the same patient population as that for degarelix. This is not the case when comparing degarelix with bicalutamide monotherapy; while degarelix is indicated in adult male patients with advanced hormone-dependent prostate cancer,[2,3] which includes a spectrum of disease states (locally advanced and metastatic disease), bicalutamide monotherapy is indicated in a smaller patient population that includes only those with locally advanced, non-metastatic prostate cancer.[101] Although an overlap in indications is noted, the non-equivalence in the patient populations represents a further barrier to including bicalutamide monotherapy within cost-effectiveness analysis as the degarelix trials were not sufficiently powered to analyse this subpopulation.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

The base case model structure is illustrated in Figure 19 below. A Markov method is used to model treatment progression over time. The model structure shown below was selected to represent, in as simple a manner as possible, the main aspects of the condition with respect to both its effect on patients HRQL and the current clinical pathway.

Figure 19. Model structure

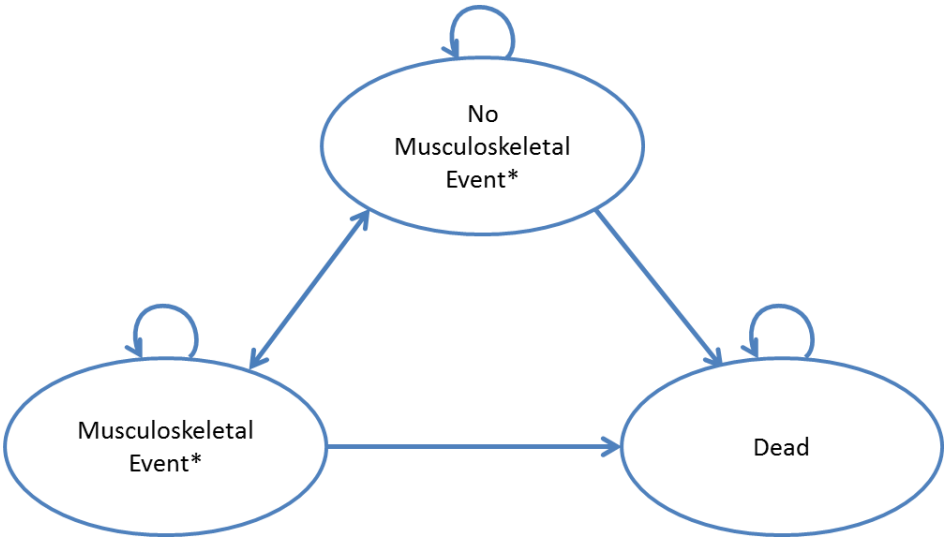


* Individuals can move to 'Death' from all of the states

The structure of the economic model was informed by UK clinicians, who commented that PSA progression (recurrence/failure) is a good indicator of biochemical disease progression. This marker is, therefore, used to determine when patients are taken off first-line treatment and moved onto second-line treatment.[7,145] Disease progression is associated not only with a variation in the treatments administered – it is also linked to a variation in the patient's HRQL (see Section 7.4.4).

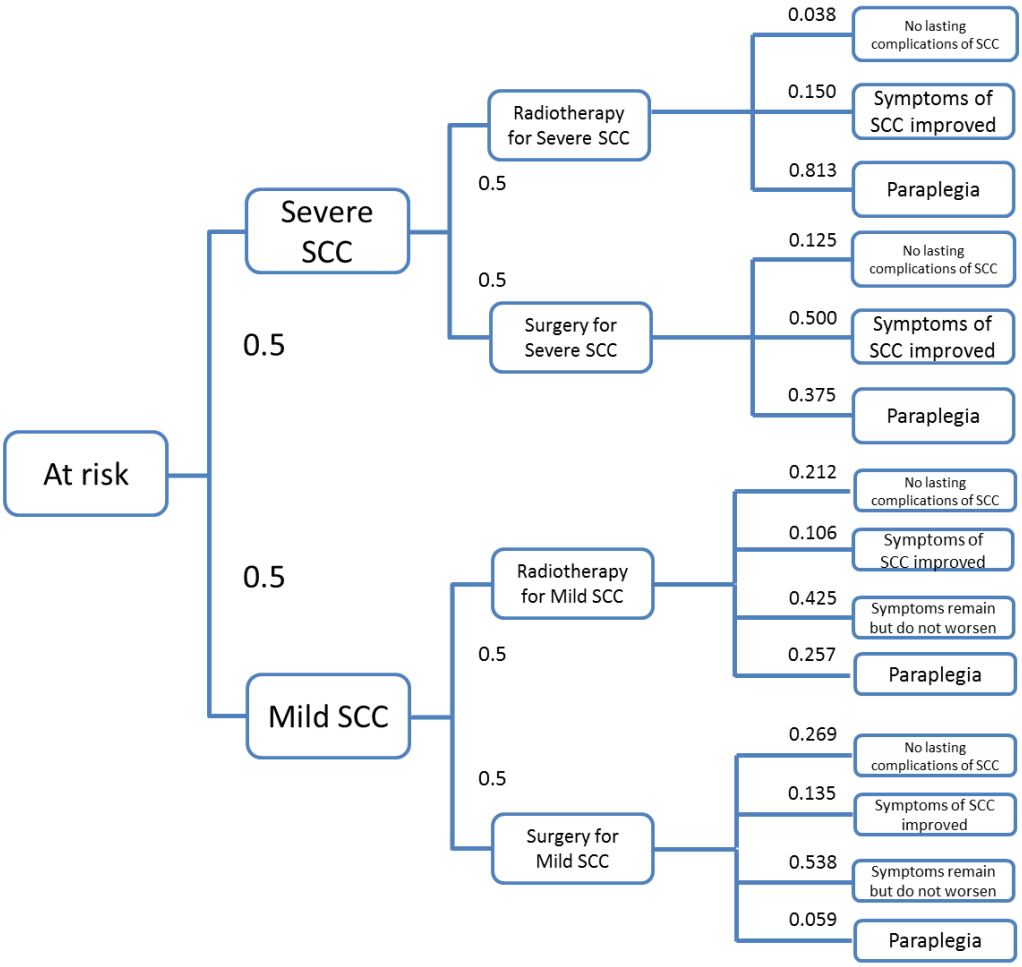
Figure 20 to Figure 22 show the submodels used to incorporate the key AEs associated with disease progression and the treatment of prostate cancer. Two types of AEs are included in the model: MSEs and cardiovascular events. Patients are at risk of both types of events in all lines of treatment.

Figure 20. Structure of the fractures and joint-related signs and symptoms sub-model



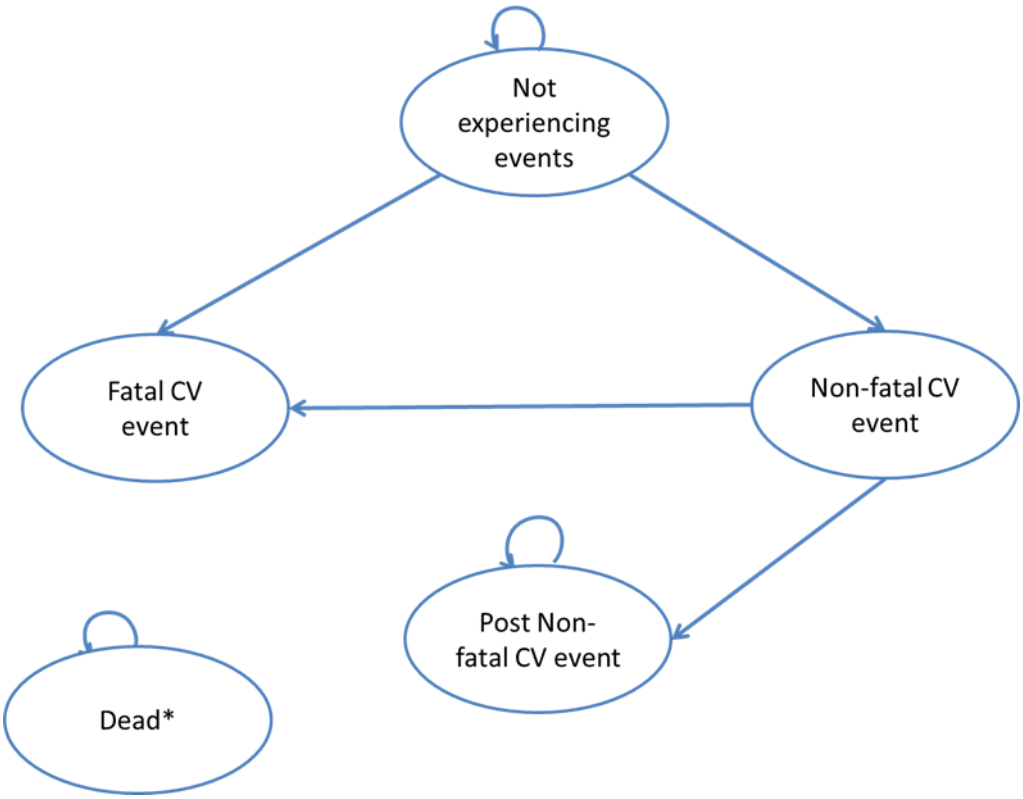
* Fracture or joint-related sign and symptom

Figure 21. Structure of the spinal cord compression sub-model



SCC = spinal cord compression. The numbers shown are probabilities.

Figure 22. Structure of the cardiovascular event sub-model



* Individuals can move to dead from all of the states
CV = cardiovascular.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

Figure 2 in Section 2.5 shows the current clinical pathway of care. The sources consulted for constructing this pathway were: NICE clinical guideline on prostate cancer (CG58), the European Association of Urology (EAU) guidelines on prostate cancer, NICE Technology Appraisal for abiraterone (TA259) and expert opinion from UK clinicians.[7,8,79,99]

As can be seen by comparing Figure 19 in Section 7.2.2 with Figure 2 in Section 2.5 the model structure is both reflective of current first-line treatment and the treatments routinely used post-progression in the UK clinical context.

Taking the approach outlined in Section 7.2.2 enables the model to actively reflect the current standard of care for patients in the UK with advanced hormone-dependent prostate cancer. Given the availability of the appropriate data, the model structure should, therefore, allow the costs and benefits associated with the different treatments throughout the pathway to be accurately incorporated into the decision problem.

The data necessary to model patient progression through the treatment pathway are derived from the CS21 and CS21A trials for first-line treatment and for other lines of therapy from the literature reviewed and critiqued in the EAU guidelines on prostate

cancer and a NICE STA.[10,21,79,99,147] As mentioned previously, PSA progression is used clinically as an indicator of disease progression;[7,107,108] trial data from CS21 were used to compare the time patients would be expected to remain on first-line treatment. Patient progression through subsequent lines of treatment was modelled on the basis of mean duration of response. Response rates to anti-androgen addition, anti-androgen withdrawal and docetaxel treatment were based on estimated response durations reported in the EAU guidelines. Average duration of response to treatment with abiraterone was estimated at 6.45 months, based on mean times reported in an appraisal of abiraterone undertaken by NICE. The method used to calculate the cyclical probability of progression from these sources is outlined in detail in Section 7.3.

The risk of cardiovascular events has been included within the model because these complications are reported to be associated with LHRH agonist treatment, as is reflected by the warning notification published by the US Food and Drug Administration (FDA).

The risk of MSEs is included as such events can be both a side-effect of testosterone flare, associated with LHRH agonists, and associated with disease progression. The following MSEs are included in the model:

- SCC
- Fracture
- Joint-related signs and symptoms (JSS).

These MSEs were included within the model, as reduction in SCCs formed the primary basis of previous modelling of the benefits of degarelix,[144] and new clinical trial data for degarelix have shown a significant benefit in reducing the occurrence of both fractures and JSS.

The rates of SCC were taken from the model published by Lu *et al,* which were taken from a large observational study conducted by Oh *et al*.[78,144] The probabilities of cardiovascular events, fracture and JSS were taken from analysis of pooled degarelix clinical trial data. The clinical trial data indicated that the fractures were not pathological and were, therefore, related to the treatments administered rather than related to disease progression.[10]

The method used to calculate the cyclical probability of AEs from these sources is outlined in detail in Section 7.3.

7.2.4 Please define what the health states in the model are meant to capture.

Each of the health states in the primary model is based on a line of treatment in the standard treatment pathway for patients in the UK with advanced hormone-dependent prostate cancer (illustrated in Figure 19). As the disease progresses, patients move through the pathway. The HRQL associated with each disease state either falls or remains constant as patients progress. This downward trend in HRQL, taken from the results of the systematic literature review reported in Section 7.4.5 is

consistent with the notion that as patients move to later lines of therapy, their condition has progressed (that is, it is becoming more severe).

In addition to capturing the worsening HRQL associated with disease progression, the model states capture the treatment costs, administration costs and monitoring costs associated with each of the treatments in the pathway.

The adverse events experienced while on the different treatments are a further influence on cost, patient HRQL and, in the case of cardiovascular events, mortality.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model structure captures the main aspects of the condition for patients; it is based on the current clinical pathway of treatments used to assist those with advanced hormone-dependent prostate cancer. The differentiating efficacy parameter, PSA progression, used in the model is meaningful for clinicians, who report using PSA progression to determine when patients move to subsequent treatment options.[7,145]

As discussed previously in Sections 7.2.2 and 7.2.3, underlying disease progression is assumed to be reflected by the progression through the treatment pathway. The assumption is that patients are moved through the pathway as each treatment fails and that this failure on treatment is related to the disease progressing.

The impacts of the key AEs associated with prostate cancer and the treatment of prostate cancer are captured in the three sub-models presented in Figure 20 to Figure 22.

The model structure should, therefore, capture the main aspects of the condition for patients, as it reflects:

- Their HRQL while on first-line treatment
- The relative time an individual would be expected to remain on first-line treatment
- Their HRQL on later lines of treatment
- The reductions in HRQL associated with key AEs.

As mentioned in Section 7.2.2 and discussed in greater detail in Section 7.4.5, patient HRQL decreases as their disease progresses and they move into later lines of the treatment pathway.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 22. Key features of analysis

Factor	Chosen values	Justification	Reference
Patient population (age in years)	72	This is the average age of patients in CS21	Klotz *et al*, 2008[10]
Time horizon	30 years	By this time over 99% of patients are dead	
Cycle length	28 days	A 4-week cycle is sufficient to allow for the fitting of survival data (typically given in years) and the incorporation of published cost data. Both degarelix and the LHRH agonists are actually given every 28 days (when administered monthly)	
Half-cycle correction	No	Patients incur the cost of degarelix and the LHRH agonists at the beginning of a cycle – these are the largest costs. In addition, the inclusion of a half cycle correction would make no substantial difference to the ICER given that cycle length is short compared to average survival, and instead would add spurious precision.	
Were health effects measured in QALYs; if not, what was used?	Yes	QALYs are used as per the NICE reference case.	
Discount of 3.5% for utilities and costs	Yes		NICE (2013)[148]
Perspective (NHS/PSS)	NHS		

Key: ICER = incremental cost-effectiveness ratio; LHRH = luteinising-hormone releasing hormone; PSS = personal social services; QALYs = quality-adjusted life years

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Yes, the intervention is implemented in the model as per the marketing authorisation.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

In line with the SPC, in the base case model, patients are treated with degarelix or one of the comparator treatments until their condition is no longer defined as being hormone-dependent.[2,3] At this stage, their condition has progressed beyond the licensed indication of degarelix and the other comparator treatments. In the model, patients are considered as no longer having hormone-dependent prostate cancer once they receive chemotherapy. Once patients enter the model state labelled 'First-line chemotherapy: docetaxel' (see Figure 19) they no longer receive degarelix or the comparator treatments.

Patients can receive LHRH agonists or degarelix, even if the disease becomes hormone refractory. The impact of this treatment practice is tested within scenario analyses.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Progression-free survival on first-line treatment

Variations in PSA progression between degarelix and the comparators form the primary efficacy variable for the cost-effectiveness model.

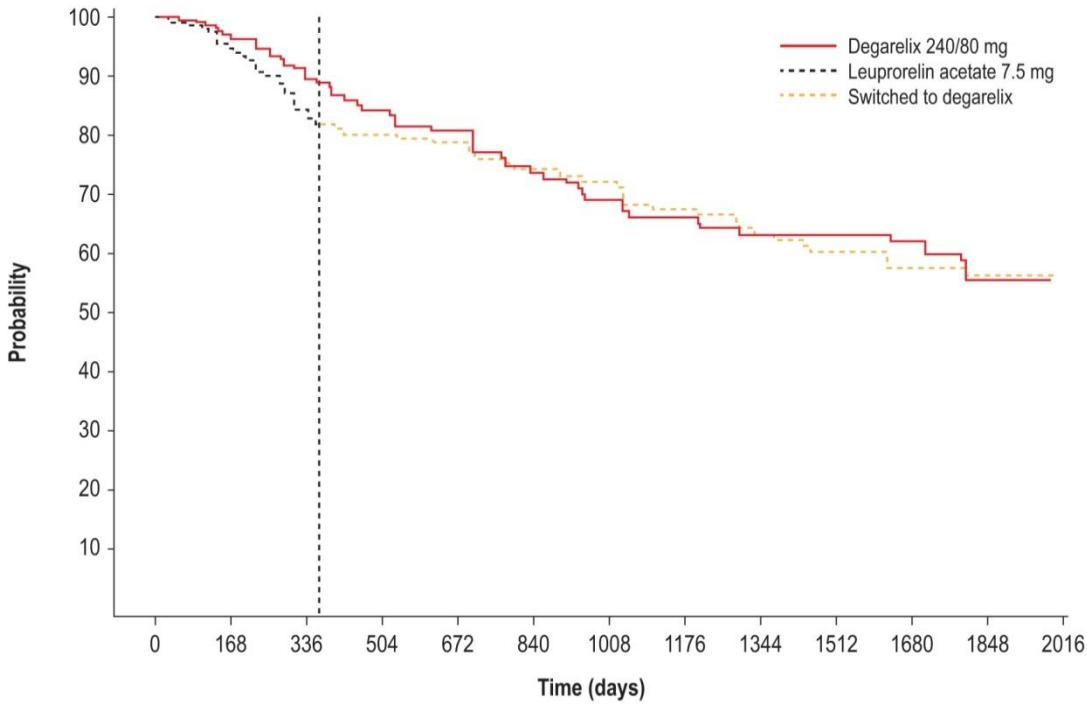
PSA progression is an important prognostic indicator for patients with prostate cancer, and is frequently used to assess disease progression.[7,107,108] PSA progression has, therefore, been used as an efficacy outcome in clinical trials, and it is used as an indication of disease progression in this evaluation. In CS21, PSA progression was defined as two consecutive increases of 50% or more above the PSA nadir (the lowest level observed), accompanied by an absolute increase of 5 ng/ml or more on two consecutive occasions at least two weeks apart. Using this definition, PSA progression is said to have occurred at the time of the second observation.

Degarelix reduces the rate of PSA progression. The treatment effect is modelled using the hazard ratio (HR) reported by the CS21 and CS21A clinical trials.[10,21,57] Model outputs show that patients are expected to remain on first-line treatment for a greater period of time, avoiding the high costs and lower quality of life associated with subsequent lines of treatment.

Based on the ITT population from the trial, the chance (Kaplan–Meier-estimated probabilities) of a patient reaching the end of the trial (Day 364) without suffering PSA progression was 91.1% for patients treated with degarelix (240/80 mg treatment arm) and 85.9% for those receiving leuprorelin 7.5 mg.[10] After the 1-year comparative

period, patients still on treatment were enrolled in the CS21A extension trial. Patients who received degarelix during CS21 continued on the same maintenance dosing regimen and those who received leuprorelin were randomly assigned in a 1:1 ratio to receive either degarelix 240/160 mg or 240/80 mg. The five-year PSA PFS data for the licensed dose of degarelix is shown below in Figure 23.

Figure 23. Five-year PFS data (taken from clinical trial report)[57]



PFS = progression-free survival.

A survival regression was used to fit five parametric curves to the Kaplan–Meier data for the degarelix-treated cohort (Weibull, log-logistic, log-normal, Gompertz and exponential). From these, the curve with the lowest Akaike Information Criterion (AIC) score was chosen as the best fit. Figure 24 to Figure 26 show the parametric curves and trial data, and Table 23 show the goodness of fit for each curve. The log-normal distribution proved the best curve fit to the trial data for both the ITT and PSA >20 ng/ml populations. Sensitivity of the model to choice of curve was tested in the additional analyses (see Section 7.7.9).

Figure 24. Curve fits to trial Kaplan–Meier data – ITT population

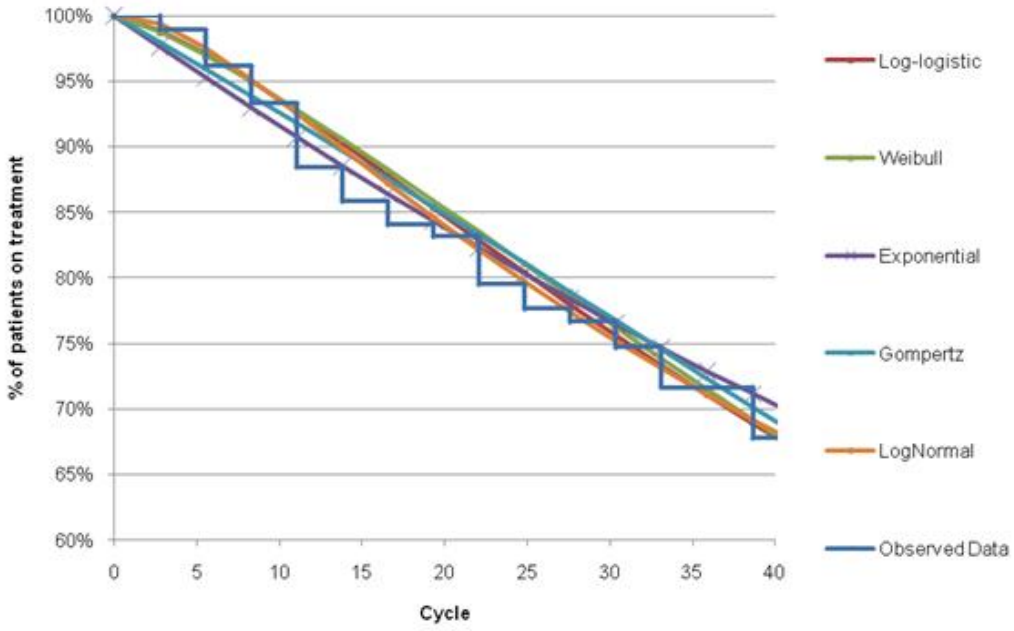


Figure 25. Long-term curve fit – ITT population

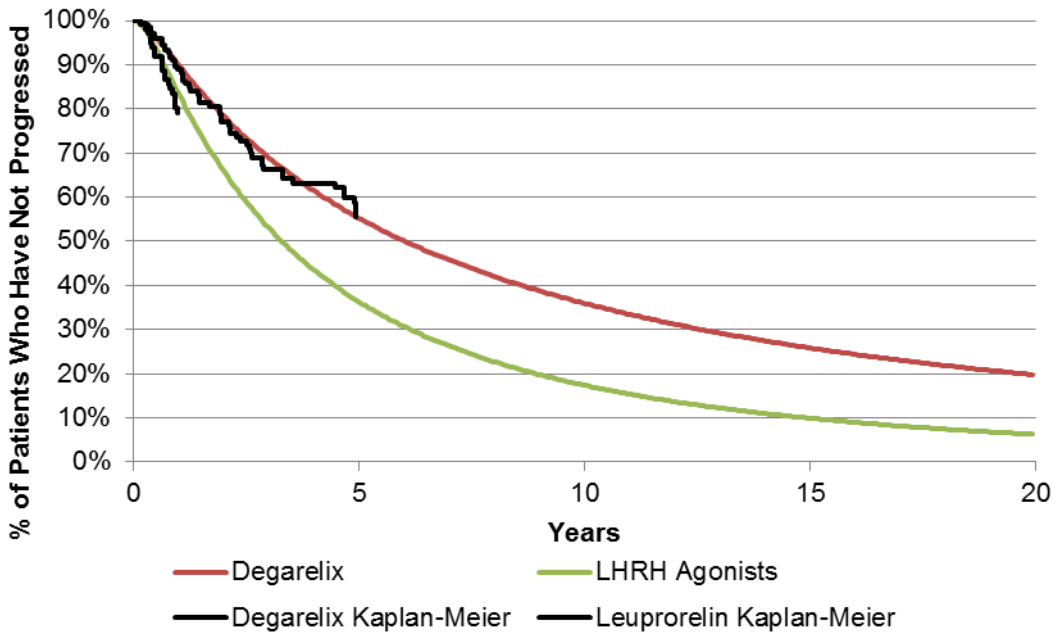


Figure 26. Long-term curve fit – PSA >20 ng/ml population

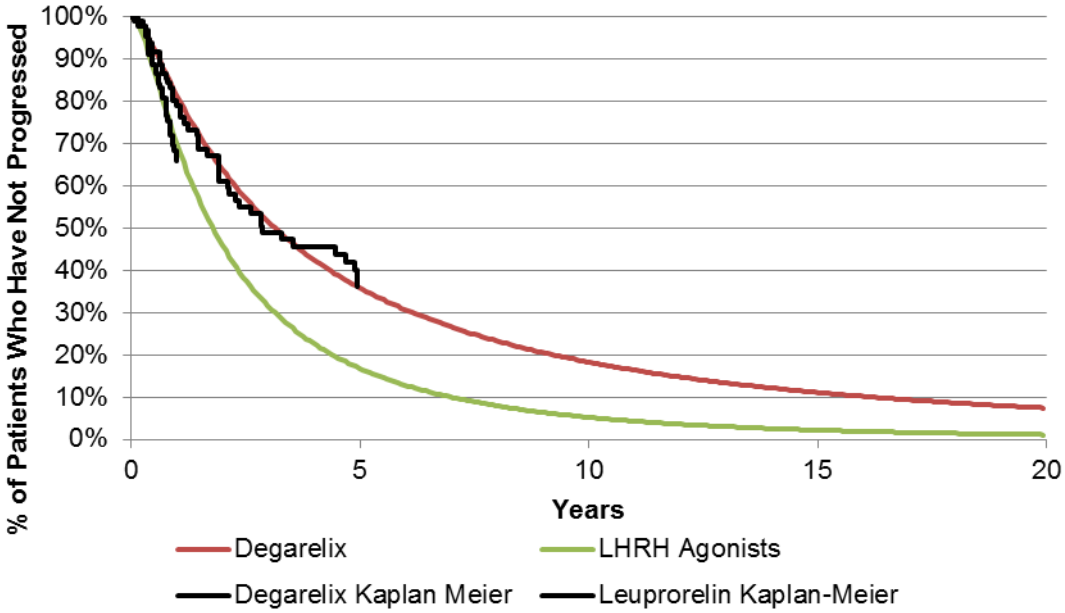


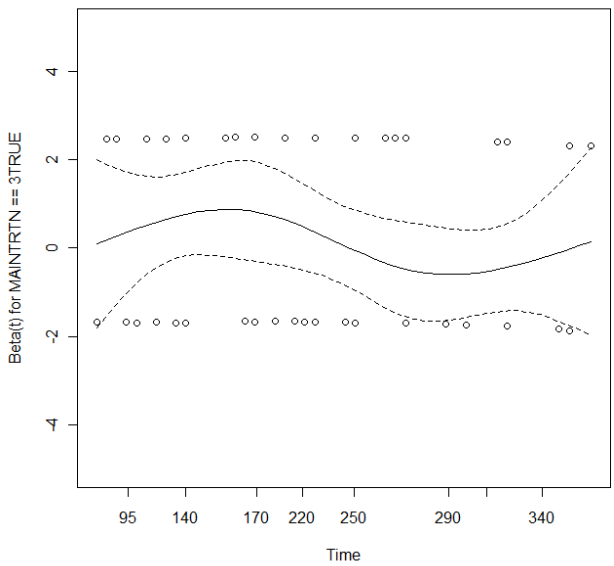
Table 23. Goodness of fit of parametric curves

Curve	AIC score	
	ITT	**PSA >20 ng/ml**
Log-normal	1,029.58	795.22
Log-logistic	1,033.42	797.87
Exponential	1,034.92	799.84
Weibull	1,036.24	801.68
Gompertz	1,099.46	857.57

Key: AIC = Akaike's Information Criterion; ITT = intention to treat; PSA = prostate-specific antigen

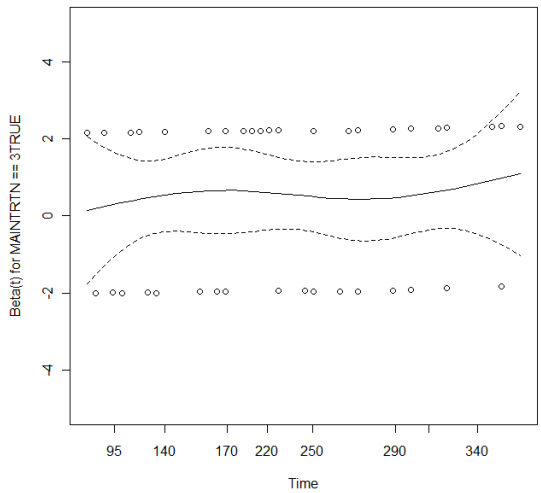
Log-rank tests were performed on the comparative one-year trial data to test for statistical difference in the rates of PSA progression between the treatment groups. The HR estimates produced are shown in Table 24. In the absence of long-term comparative data, these HRs were applied to the parametric curve fits, assuming proportional hazards.[10] The validity of the proportional hazards assumption was tested with the scaled Schoenfeld residuals (see Figure 27 and Figure 28). No violations of proportional hazards were found for the ITT population (p=0.91) or the PSA >20 ng/ml population (p=0.69).

Figure 27. Plots of scaled Schoenfeld residuals against transformed time for the ITT population



ITT = intention to treat. The solid line is a smoothing-spline fit to the plot, with the broken lines representing a ± 2-standard-error band around the fit

Figure 28. Plots of scaled Schoenfeld residuals against transformed time for the PSA >20 ng/ml population



PSA = prostate-specific antigen. The solid line is a smoothing-spline fit to the plot, with the broken lines representing a ± 2-standard-error band around the fit.

The sensitivity of the model results to the assumption of proportional hazards is explored in Section 7.7.9. One of the scenarios in this section investigates the sensitivity of the model to a change in the assumption around a continuing differential treatment effect. In the scenario after one year, the same cyclical risk of progression is applied to those on degarelix and on the comparator treatments assuming that all benefits from degarelix are obtained within the first year of treatment (that is, the

observed duration of benefits from CS21) and benefits do not continue to accrue after this time.

Table 24. Hazard ratio for degarelix versus leuprorelin

Population	Hazard ratio (95% CI)	p-value
ITT	1.71 (1.00-2.93)	0.05
PSA>20 ng/ml	1.74 (0.99-3.07)	0.05
CI = confidence interval; ITT = intention-to-treat; PSA = prostate-specific antigen.		

Although leuprorelin was the control therapy in the clinical trial, the alternative LHRH agonists included in the model are assumed to be equally efficacious as detailed previously in Section 7.2.1.

The parametric curves for the comparator were estimated using the formula:

$$pr_{C,t} = pr_{I,t}^{HR}$$

$pr_{C,t}$ is the proportion of patients on the comparator therapy remaining on first-line treatment.

$pr_{I,t}$ is the proportion of patients treated with degarelix remaining on first-line treatment – estimated using the parametric curve for degarelix.

HR is the hazard ratio reported in Table 24.

From the fitted curves, per-cycle risks of PSA progression were derived for both degarelix and the comparators. These per cycle risks of progression function as time-dependent transition probabilities between the Markov model health states. The method used to calculate these time-dependent transition probabilities is outlined in Section 7.3.2 below.

Duration of response to subsequent lines of therapy

Patient progression through subsequent lines of treatment was modelled based on mean duration of response (see Table 25). Response rates to anti-androgen addition, anti-androgen withdrawal and docetaxel were based on estimated response durations reported in the EAU guidelines.[79] Mean duration of response to treatment with abiraterone was based on curves reported in an appraisal of abiraterone by NICE.[99] No differential response rate was assumed for patients on degarelix compared with patients on LHRH agonists (see Table 25).

Table 25. Duration of response to subsequent lines of therapy

Treatment line	Mean duration of response (months)	Source
Anti-androgen addition	6.0	EAU guidelines[79]
Anti-androgen withdrawal	6.0	EAU guidelines[79]
Docetaxel	12.0	EAU guidelines[79]
Abiraterone	6.45	NICE[99]

The calculation for the cycle risk of non-response for each of the subsequent lines of therapy is outlined in Section 7.3.2 below.

Adverse events

As detailed previously patients treated with androgen-deprivation therapy can suffer a number of AEs associated with treatment, including disorders of the musculoskeletal and cardiovascular system. Patients treated with LHRH agonists are at a greater risk of AEs compared with degarelix-treated patients, due to both the initial increase in testosterone levels that results from LHRH stimulation and metabolic changes associated with LHRH agonist therapy.[73,105,114,144,149,150]

As part of the model, fractures, JSS and cardiovascular events are assumed to be suffered by patients treated with degarelix and LHRH agonists, whereas SCC is assumed to be unique to LHRH agonist-treated patients, in line with assumptions made by Lu *et al*.[144]

MSEs and cardiovascular events are modelled using parametric curves fitted to the pooled observations of six clinical trials (n=2,328 patients) comparing treatment with degarelix to treatment with LHRH agonists.[110] Pooled data have been used to provide a more confident estimate of the incidence of these events, given the relative rarity of these events within the population. As the different trials included in the pooled dataset used different doses of degarelix, analyses were performed to determine whether the incidence of events was significantly different for different degarelix dosing regimens. The results of these significance tests are shown in Appendix E. None of the AEs included in the base case model were significantly different for the doses included in the pooled analyses.

In the base case analysis, the impacts of fractures, JSS, SCC and cardiovascular events are included. Scenario analyses examined alternative assumptions, by adding and removing the impacts of events or changing their application. The scenarios modelled are outlined in Section 7.6.1.

Musculoskeletal events

Exponential and Weibull parametric curves were fitted to the events suffered by patients over the treatment period of the clinical trials. Figure 29 and Figure 30 below show the Kaplan–Meier plots and parametric curve fits for the MSEs incorporated in the model, which rely on data from the pooled observations of the six clinical trials.[110] Table 26 and Table 27 report the statistics of the parametric curves illustrated in Figure 29 and Figure 30, respectively. The data contradicted the assumption that, over time, the hazard of experiencing an MSE was constant and, therefore, the Weibull curves shown in Figure 29 and Figure 30 were incorporated into the model.

Figure 29. Kaplan–Meier plots and parametric curve fits, fractures

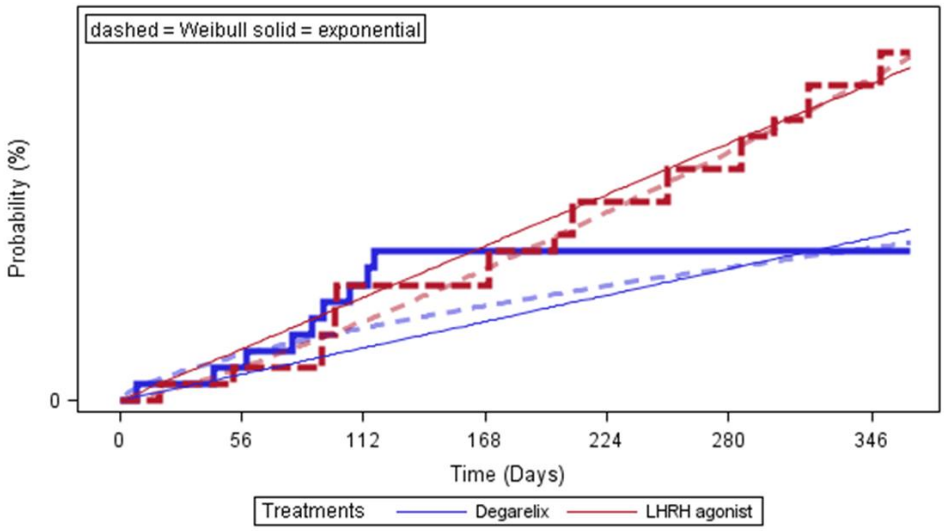


Figure 30. Kaplan–Meier plots and parametric curve fits, joint-related signs and symptoms

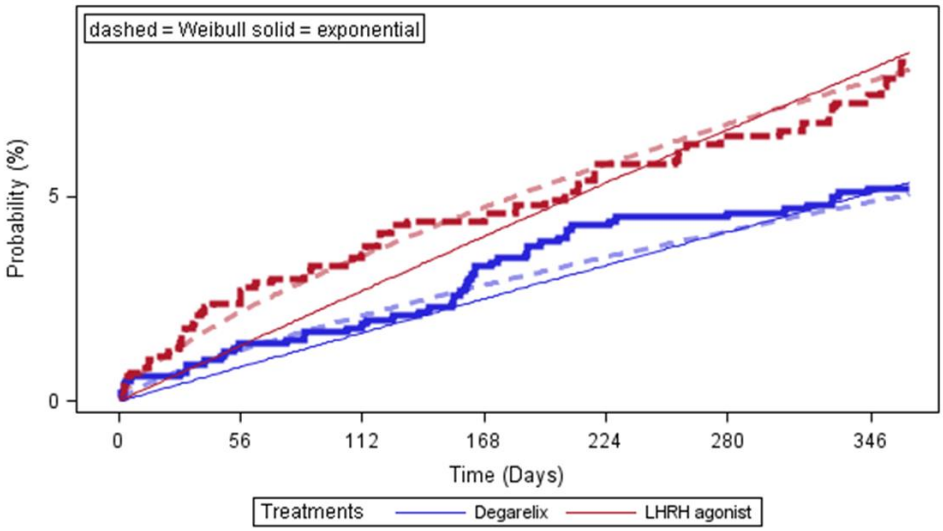


Table 26. Fracture fitted curve statistics

Treatment	Parameter	Weibull Model			Exponential model	
		Estimate	Covariance (I)	Covariance (S)	Estimate	Variance (I)
Degarelix	Intercept	7.046	4.581	0.905	4.565	0.091
	Scale	1.517	0.905	0.187		
Leuprorelin	Intercept	3.091	0.715	0.167	3.893	0.077
	Scale	0.800	0.167	0.042		

Table 27. Joint-related signs and symptoms fitted curve statistics

Treatment	Parameter	Weibull Model			Exponential model	
		Estimate	Covariance (I)	Covariance (S)	Estimate	Variance (I)
Degarelix	Intercept	3.887	0.295	0.084	2.898	0.018
	Scale	1.315	0.084	0.026		
Leuprorelin	Intercept	3.431	0.249	0.082	2.414	0.018
	Scale	1.391	0.082	0.031		

Long-term quality of life and cost decrements are applied for patients who remain in pain for severe JSS and severe fractures. The proportion of patients remaining in pain each cycle is taken from Hollingworth *et al* (2% per 28 days, based upon the original proportions of 4.6% per month for mild SCC).[151] Patients who do not remain in pain transfer back to being in the 'No musculoskeletal event state' after one cycle and, therefore, have no continuous cost or utility decrement.

The impact of SCC is modelled, using risks reported by Lu *et al*.[144] In the first cycle of the model, a proportion of patients treated with LHRH agonists (0.96%) is expected to suffer SCC with lasting complications and will suffer long-term reduced quality of life and incur additional costs. Lu *et al* used data from a study exploring the use of oral anti-androgen use before LHRH therapy to prevent consequences of a testosterone flare to estimate the probability that patients experience severe or mild SCC.[78] A UK clinician's opinion was used, in line with Lu *et al,* to estimate rescue treatments allocated to patients suffering from SCC.[144] The probability of the different outcomes associated with these therapies is estimated from two clinical studies that investigate the outcomes associated with different treatments for SCC.[152,153]

The probability of experiencing a repeat SCC within a year is estimated to be 6.2%.[154] This is applied as an addition to the first-year cost within the model as a simplifying assumption.

The mortality of patients experiencing SCC is assumed to be equal to the patient cohort as a whole. Patients who experience an SCC and whose symptoms are not resolved are tracked through the model in line with the approach taken by Lu *et al*.[144]

Differential costs and HRQL are associated with these patients due to the management of their condition. The estimated HRQL and cost impact associated with the condition are outlined in Sections 7.4.8 and 7.5.7, respectively.

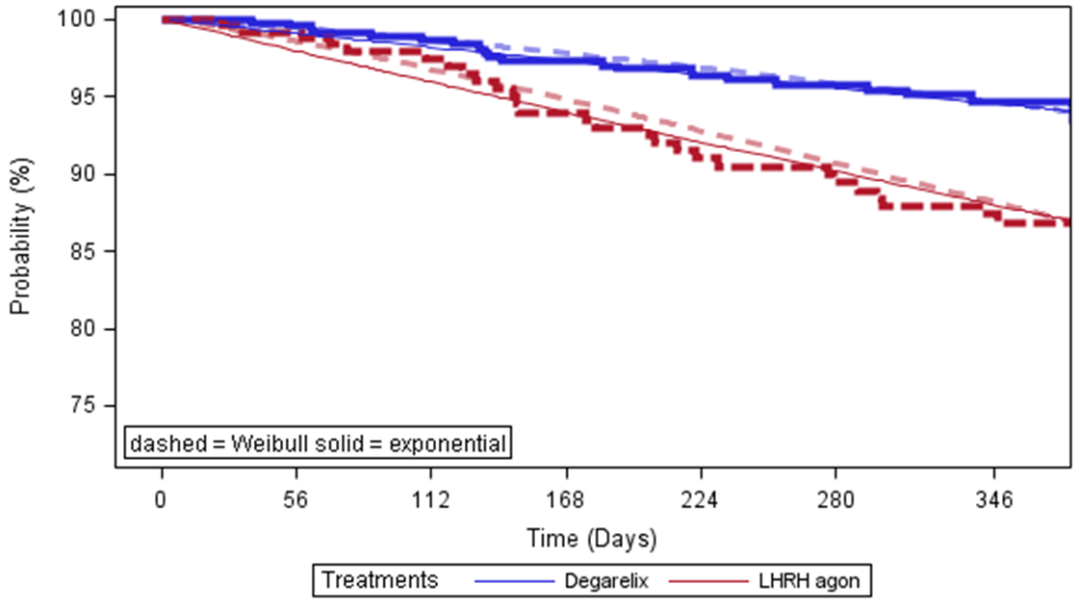
Cardiovascular events

In the base case, cycle-based risks of patients suffering cardiovascular events are generated from exponential parametric curves fit to trial data (as the data did not contradict the assumption of constant hazards). Separate curves are applied to account for fatal and non-fatal events. The cost-effectiveness model only applies the risk of experiencing a cardiovascular event to those patients who had cardiovascular disease (CVD) at baseline (30.67% of patients had prior CVD at baseline across the six pooled trials).[110] This is because the pooled trial data only indicated a significant difference between degarelix and leuprorelin for this subpopulation.[73] The parametric

curves incorporated into the model were, therefore, fitted to the time-to-event data from this subpopulation.

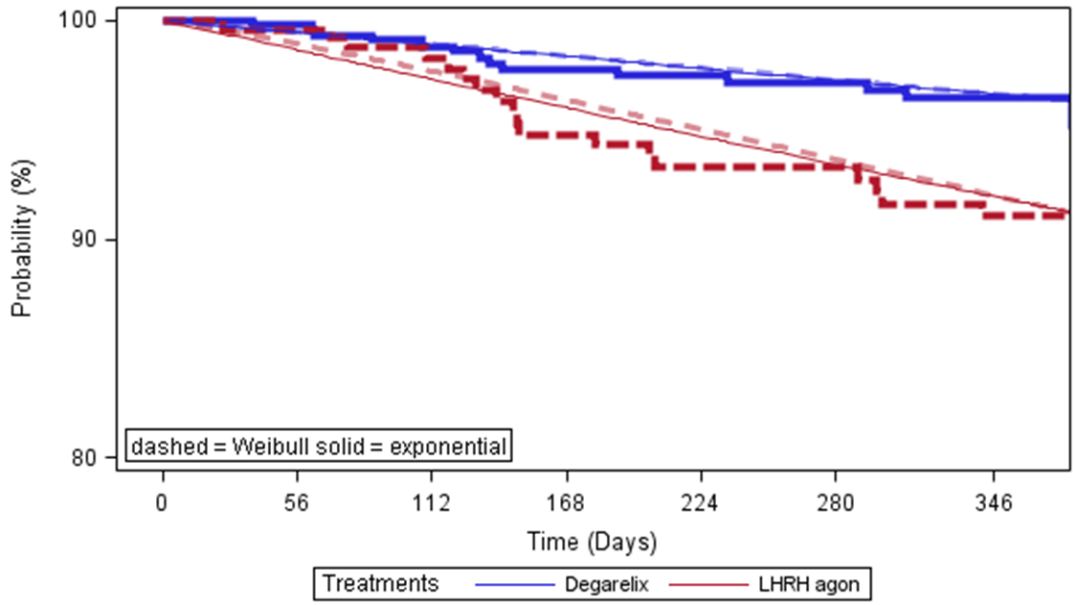
Figure 31 and Figure 32 below show the Kaplan–Meier plots and parametric curve fits for the cardiovascular events incorporated in the model.

Figure 31. Kaplan–Meier plots and parametric curve fits, CV events with death



CV = cardiovascular; LHRH = luteinising hormone-releasing hormone.

Figure 32. Kaplan–Meier plots and parametric curve fits, CV events without death



CV = cardiovascular; LHRH = luteinising hormone-releasing hormone.

Fatal events incur a one-off cost and the patient moves to the 'Death' health state. Non-fatal events incur a one-off multiplicative utility decrement for the duration of the cycle in which the event is suffered (outlined in Section 7.4.8). Patients experiencing

a non-fatal cardiovascular event experience ongoing costs for the management of the condition. The management costs for the non-fatal cardiovascular event state, shown in Figure 22, are weighted according to the proportion of each cardiovascular event reported in the pooled clinical trials. The breakdown of cardiovascular events from the trial is shown in Table 28. The approach to calculating the ongoing costs of managing patients who have had a non-fatal cardiovascular event is outlined in Section 7.5.7.

Table 28. Cardiovascular events recorded in pooled clinical trials

Cardiovascular event subcategory	Fatal events		Non-fatal events	
Ischaemic cerebrovascular conditions	24	23.08%	7	14.29%
Myocardial infarction	27	25.96%	10	20.41%
Other ischaemic heart disease	31	29.81%	13	26.53%
Haemorrhagic cerebrovascular conditions	22	21.15%	4	8.16%
Embolic and thrombotic events, arterial	0	0.00%	15	30.61%
Total events	104		49	

No additional treatment-specific AEs are incorporated into the cost-effectiveness model. One AE that was more commonly experienced by patients treated with degarelix was injection site reactions; however, as discussed in Section 6.9.2, most of the injection site reactions with degarelix (240/80mg) in CS21 occurred with the initiation dose and decreased over time. Additionally, they were also mainly mild or moderate in intensity.[10] As such, they would have neither a substantial cost nor a substantial HRQL impact and would, therefore, only have had a negligible effect on the overall cost-effectiveness estimate.

Mortality

Age-specific mortality rates from the Office of National Statistics (ONS) form the basis of patient survival in the model.[155] To this, the relative survival of prostate cancer patients is applied, using age-specific survival data from the Scottish Cancer Registry.[156] These data have been chosen, as neither data for the UK as a whole nor for England separately are available in the format of individual survival probabilities over time for given age bands at diagnosis. A log-logistic curve was fit to one-, three- and five-year survival data, as this fit produced the lowest mean absolute error compared with the observed data. The other curve fits that were examined were Weibull, log-normal, exponential and Gompertz curves. The fitted curve was used to estimate the additional mortality at extrapolated time points, above the rate that would be expected on the basis of general population mortality rates.

The relative survival curve was split to generate separate curves for patients with metastatic and non-metastatic disease. It was assumed that 9.4% of the prevalent prostate cancer population within the Scottish Cancer Registry has metastatic disease, based on estimates from the NICE STA of abiraterone and prostate cancer prevalence figures published by the National Cancer Intelligence Network.[147,157] The Solver add-in for Microsoft® Excel was used to estimate survival in each model cycle, based on the following equation:

Equation 1: Solver function used to estimate prostate cancer mortality

$$s = (1 - p)(n) + p(m)$$

Where:

s is the combined survival from the ONS life tables and Scottish relative prostate cancer survival

m is the relative survival for metastatic patients, *n* is the relative survival for non-metastatic patients

p is the proportion of prevalent patients that are metastatic (0.094).

To solve the equation, the relationship between *n* and *m* is given as:

Equation 2: Application of metastatic prostate cancer mortality hazard ratio

$$m = 1 - (1 - n)^{\frac{1}{h}}$$

Where *h* is the hazard ratio of mortality for patients with metastatic cancer who progress whilst receiving treatment, reported by Hussain *et al* as 2.39.[107]

Using these two curves, differing levels of relative prostate cancer mortality are applied to the background survival for the patient cohort as they progress through each line of treatment. Patients on first-line treatment with degarelix or an LHRH agonist are assigned a weighted survival, based on the proportions of patients that are expected to have localised, locally-advanced and metastatic disease. These proportions are based on the characteristics of the participants of the CS21 clinical trial. Although using the trial breakdown is likely to overestimate the number of patients with localised disease being treated with LHRH agonists and degarelix, the results of the trial suggest that the efficacy of degarelix is greatest in patients with metastatic disease, and that the ITT analysis of the mixed cohort is, therefore, likely to underestimate the benefit of degarelix.[21] Table 29 shows the distribution of patients by prostate cancer stage at enrolment in both the ITT and the PSA >20 ng/ml populations.

Table 29. Distribution of patients by prostate cancer stage at enrolment

Enrolment cancer stage	Degarelix 240/80 mg, n (%)	Degarelix 240/160 mg, n (%)	Leuprorelin 7.5 mg, n (%)	Total N (%)
ITT population				
Localised	69 (33)	59 (29)	63 (31)	191 (31)
Locally advanced	64 (31)	62 (31)	52 (26)	178 (29)
Metastatic	37 (18)	41 (20)	47 (23)	125 (20)
Non Classifiable	37 (18	40 (20)	39 (19)	116 (19)
PSA >20 ng/ml population				
Localised	18 (18)	19 (19)	16 (17)	53 (18)
Locally advanced	35 (35)	36 (36)	29 (31)	100 (34)
Metastatic	33 (33)	31 (31)	38 (41)	102 (35)
Non classifiable	14 (14)	14 (14)	10 (11)	38 (13)

Key: ITT = intention-to-treat; PSA = prostate-specific antigen

Once patients have progressed onto chemotherapy, 100% are assumed to have metastatic disease that has progressed, in line with the indications for treatment with docetaxel and abiraterone.[97,99]

A scenario analysis, outlined in greater detail in Section 7.6.1, explores the effect on the ICER of not applying an increased hazard of mortality once patients with metastatic disease have progressed onto second and subsequent lines of treatment.

A relative risk was applied to account for lower mortality in patients with metastatic disease treated with abiraterone, in line with a report published by NICE.[99] The report indicates a mean survival of 825 days for patients treated with abiraterone, compared with 550 days for those receiving standard care. A relative risk of mortality of 0.67 (550/825) is, therefore, applied to the mortality risk of patients receiving abiraterone in the model.

As mentioned previously, patients can suffer death due to cardiovascular events associated with their disease and treatment. As this is assumed to be captured in the current relative prostate cancer mortality rates, the differential risk of experiencing a fatal cardiovascular event is applied as a reduced risk of death for degarelix-treated patients.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Probability of remaining on first-line treatment

As discussed in Section 7.3.1, PFS data from CS21 and CS21A are used to estimate the time individuals remain on first-line treatment. Parametric curves were fitted to the trial data and time-dependent transition probabilities are calculated from these curves. The calculation used is shown below.

$$p_{t+1} = \frac{pr_{t+1}}{pr_t} * (1 - p_{d,t+1})$$

Where:

p_{t+1} is the probability of remaining on first-line treatment in the next cycle

pr_{t+1} is the proportion of patients remaining on first-line treatment in the next model cycle according to the parametric curves estimated

pr_t is the proportion of patients remaining on first-line treatment in the current cycle according to the parametric curves estimated

$p_{d,t+1}$ is the probability of transitioning to death in the next model cycle.

The probability of transition onto the second-line treatment is, therefore, 1- p_{t+1} - $p_{d,t+1}$

Probability of remaining on subsequent lines of treatment

As outlined in Section 7.3.1, after the first-line treatments, the probability of transitioning from one line of therapy to another was calculated using clinical data on the mean duration of response for the subsequent lines of therapy.[79,147]

The probability of non-response was estimated using the following formulae:

$$\lambda = \frac{1}{T}$$

$$p_{NR} = e^{-\lambda}$$

Where:

T is the mean duration of response in months

λ is the rate parameter and p_{NR} is the monthly probability of non-response. The probability of non-response stays constant over time.

The probability of remaining in response and therefore on the same line of treatment in the subsequent cycle ($p_{R,t}$) can be expressed as follows:

$$p_{R,t} = 1 - p_{NR} - p_{D,t}$$

Where $p_{D,t}$ is the probability of dying in the current cycle

Table 30 shows the estimated cycle risks of non-response for each of the subsequent lines of therapy.

Table 30. Cycle risk of non-response to subsequent lines of therapy

Treatment line	Mean duration of response (months)	Cycle risk of non-response	Source
Anti-androgen addition	6.00	0.17	EAU guidelines[79]
Anti-androgen withdrawal	6.00	0.17	EAU guidelines[79]
Docetaxel	12.00	0.09	EAU guidelines[79]
Abiraterone	6.45	0.16	Abiraterone submission[99]

Cyclical risk of fractures and joint-related signs and symptoms

As illustrated by the fractures and JSS sub-model diagram (see Figure 20, Section 7.2.2), patients in the model experience a cyclical risk of experiencing a fracture or a JSS The sub-model replicates approach to modelling MSEs by Lu *et al* (2011) – individuals who experience an MSE are assumed to need this complication managed for the duration of the model. As discussed in Section 7.3.1, the risk of experiencing a fracture or JSS was estimated from the pooled data of the six clinical trials.[110] Weibull curves were fitted to the time to JSS data (as discussed in Section 7.3.1, Weibull curves were used as the data contradicted the assumption of constant hazards). The cyclical risk of experiencing a a fracture or a joint-related sign or symptom in the current cycle ($r_{MSE,t}$) is then calculated as follows:

$$r_{MSE,t} = \frac{pr_{NMSE,t}}{pr_{NMSE,t-1}} \quad r_{MSE,t+1} = \frac{pr_{NMSE,t+1}}{pr_{NMSE,t}}$$

Where:

$pr_{NMSE,t}$ is the proportion of individuals with neither of the MSEs in the current time period as estimated by the fitted weibull curves

$pr_{NMSE,t-1}$ is the proportion of individuals with neither of the MSEs in the previous time period as estimated by the fitted weibull curves.

Calculation of risk of spinal cord compression in the initial testosterone flare associated with treatment with LHRH therapy

The model replicates the approach taken by Lu *et al* (2011) to estimate the risk that patients treated with LHRH agonists experience SCC as a result of the testosterone flare associated with these treatments. As shown in Figure 21 (see Section 7.3.1), a decision tree is used to estimate the likelihood of all of the outcomes. The probabilities at each branch of the decision tree are reported in Table D1 in Appendix D. The branches are then multiplied together to estimate the final outcomes.

Cyclical risk of fatal and non-fatal cardiovascular events

As illustrated by the cardiovascular event sub-model diagram (Figure 22, Section 7.3.1), patients in the model experience a cyclical risk of experiencing either a fatal or a non-fatal cardiovascular event. While these events are estimated using different

parametric exponential curves, the approach is similar where the risk of experiencing a cardiovascular event, either fatal or non-fatal, can be summarised as:

$$r_{CV,t} = \left(1 - \frac{pr_{CV,t}}{pr_{CV,t-1}}\right) * x_{CVD}$$

Where:
$r_{CV,t}$ is the risk of the cardiovascular event of interest (either fatal or non fatal)
$pr_{CV,t}$ is the proportion of individuals who have not experienced the cardiovascular event of interest in the current time period as estimated by the fitted exponential curve
$pr_{CV,t-1}$ is the proportion of individuals who have not experienced the cardiovascular event of interest in the previous time period as estimated by the fitted exponential curve
x_{CVD} is the prevalence of CVD at baseline.

Mortality

As discussed above in Section 7.3.1, two curves were constructed to estimate the mortality risk experienced by patients as a result of prostate cancer. First, a parametric curve was used to estimate the general prostate cancer mortality risk; this was applied to all patients in the first line of treatment. Second, a curve was constructed that incorporated the increased hazard of mortality for patients with metastatic disease once they had progressed from first-line treatment; this was weighted to account for the proportion of patients who had metastatic disease at baseline in CS21. This weighted mortality curve was used to estimate the mortality risk for all patients who had progressed from baseline, apart from when being treated with abiraterone.

Each curve was incorporated into the model through the calculation of a cyclical mortality risk. The calculated risks were then applied to the relevant disease states. Section 7.3.1 outlined the formulae used to estimate each curve. The cyclical risk of death can be estimated from each curve using the following approach:

$$r_{D,t} = \left(1 - \frac{pr_{D,t}}{pr_{D,t-1}}\right)$$

Where:
$r_{D,t}$ is the risk of death in the current cycle
$pr_{D,t}$ is the proportion dead on the current cycle according to the relevant mortality curve
$pr_{D,t-1}$ is the proportion dead on the previous cycle according to the relevant mortality curve.

A different mortality risk was estimated for patients on abiraterone. This was based on the mortality risk for patients on second and subsequent lines of treatment, but was adjusted to reflect the lower risk of mortality when on treatment with abiraterone.[147] The calculation was undertaken using the following approach:

$$r_{DAb,t} = r_{D2,t} * RR_{DAb}$$

Where:

$r_{Dab,t}$ is the risk of death on abiraterone in the current model cycle
$r_{D2,t}$ is the risk of death second and subsequent lines of treatment (excluding Abraxane) in the current model cycle
RR_{Dab} is the relative risk of death when treated with abiraterone.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The transition probabilities for the clinical parameters have been estimated in a manner that allows them to vary over time, when the data available suggest that the hazard of an event occurring is not constant. The methods used to estimate the time-dependent risks of an event occurring are outlined in Sections 7.3.1 and 7.3.2.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Two intermediate outcomes were linked to final outcomes. First, as discussed in Sections 7.2.2, 7.2.3 and 7.3.1, time to PSA progression was linked to time on first-line treatment – this determined the speed at which patients transitioned from first-line treatment to subsequent lines of treatment. The evidence supporting this relationship comes from the published literature[107,108] and feedback from clinicians, who indicated that PSA is a good indicator of biochemical disease progression and that PSA progression is used to determine when patients are switched to subsequent lines of treatment.[7]

The second intermediate outcome linked to a final outcome is the association between progression from first-line treatment and an increased risk of death for patients with metastatic disease. As discussed in greater detail in Section 7.3.1, this relationship is estimated using the HR from Hussain *et al* (2009).[107] The effect of incorporating this link is that delayed progression from the first-line treatment model states results in a lower mortality risk. The HR of 2.39 applied in the model is derived from the same definition of PSA progression as used in trial CS21 (PSA increase of 50% from nadir and ≥5 ng/ml on two consecutive occasions ≥2 weeks apart) and is estimated using a similar population to the CS21 trial (hormone-sensitive prostate cancer). No other studies investigated the link between mortality and disease

progression for this patient population. To test the sensitivity of the ICER to this link, a scenario is outlined in Section 7.6.1 for which no link is assumed between treatment progression and increased mortality risk.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Table 31. Advisory board details

Criteria for selecting the experts	Experience in the urology and oncology therapy areas. Experience in procuring and/or prescribing degarelix and comparator therapies. Availability during the STA submission time-line.
Number of experts approached	Six
Number of experts who participated	Four
Declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought	Yes – declarations of potential conflicts of interest were sought prior to the meeting. No experts declared a conflict of interest.
Background information provided and its consistency with the totality of the evidence provided in the submission	All four advisors were presented with draft versions of section A and clinical sections of Section B prior to the advisory board. Therefore, a summary of all the RCT evidence presented in this submission was made to clinical advisors prior to the advisory board. A draft version of the cost–utility model was presented to the advisors at the advisory board.
Method used to collect the opinions	A face-to face advisory board meeting was held, during which questions and answers were recorded. After the advisory board, the answers collated were confirmed by the clinical advisors via distribution of a follow-up questionnaire. Three of the four experts responded to the follow-up questionnaire.

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Medium used to collect opinions	Initial opinion collation: Face-to-face meeting Corroboration of answers: Response to questionnaire
Questions asked	Please comment of the prostate cancer clinical pathway presented and the positioning of degarelix within this pathway. Is PSA progression routinely used to as a prognostic indicator to assess disease progression and/or treatment response? Is PSA progression widely used to inform treatment decisions? Do the model HRQL estimates with the cost-utility model look reasonable? What aspects of the condition most affect patient's quality of life? Is the resource use applied within the cost-utility model in line with routine clinical practice?
Whether iteration was used in the collation of opinions	Initial opinions were collated at the advisory board. Corroboration of the clinical opinion given was gained via a follow-up questionnaire.[7]

Key: HRQL = health-related quality of life; PSA = prostate-specific antigen; RCT = randomised controlled trial

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 32. Summary of variables applied in the economic model

Variable	Value	CI (distribution)	References ections
Clinical Parameters			
Age	72 years		6.3.4
Overall survival parameters			
Mortality hazard ratio metastatic progressed vs. Prostate Cancer Specific	2.39	1.67 – 3.11 (+/- 30%)	7.3.1 & 7.3.2
Progression-free survival parameters – progression from first-line			
LHRH PSA progression Hazard Ratio: ITT Population	1.71	1.01 – 2.93 (Uniform distribution)	7.3.1 & 7.3.2
LHRH PSA progression Hazard Ratio: PSA>20 ng/ml Population	1.74	0.99 – 3.07 (Uniform distribution)	7.3.1 & 7.3.2
Treatment response – proportion responding each cycle			
Anti-androgen addition % responding each cycle	0.834	0.751 -0.918 (Uniform distribution)	7.3.1 & 7.3.2
Anti-androgen withdrawal % responding each cycle	0.834	0.751 -0.918 (Uniform distribution)	7.3.1 & 7.3.2
Docetaxel % responding each cycle	0.913	0.822-0.980 (Uniform distribution)	7.3.1 & 7.3.2
Abiraterone % responding each cycle	0.845	0.760-0.929 (Uniform distribution)	7.3.1 & 7.3.2
Mortality			
Mortality hazard ratio metastatic progressed vs. PC specific	2.39	2.05 - 2.80 (Uniform distribution)	7.3.1 & 7.3.2
Relative risk of mortality on abiraterone	0.67	0.60 - 0.73 (Uniform distribution)	7.3.1 & 7.3.2
CV history			
Proportion of patient with previous CVD	30.67%	0.28 – 0.34 (Uniform distribution)	6.9.2
Probabilities for SCC decision tree (LHRH agonists only)			
Proportion experiencing SCC	0.010	0.006 – 0.013 (Uniform distribution)	7.3.1 & 7.3.2
Proportion with severe SCC	0.500	0.45 – 0.55 (Uniform distribution)	
Proportion of those experiencing SCC who have mild SCC	0.500	0.55 – 0.45 (Uniform distribution)	7.3.1 & 7.3.2
Severe SCC: proportion receiving RT	0.950	0.855 – 1 (Uniform distribution)	7.3.1 & 7.3.2
Patients with severe SCC, proportion receiving Surgery	0.050	0 - 0.145 (Uniform distribution)	7.3.1 & 7.3.2
Mild SCC: proportion receiving RT	0.950	0.855 - 1 (Uniform distribution)	7.3.1 & 7.3.2
Patients with mild SCC, proportion receiving Surgery	0.050	0 - 0.145 (Uniform distribution)	7.3.1 & 7.3.2
Severe SCC treated with RT: proportion cured	0.038	0 – 1.88 (Uniform distribution)	7.3.1 & 7.3.2
Severe SCC treated with RT: proportion improved (to mild SCC)	0.150	0.188 – 0 (Uniform distribution)	7.3.1 & 7.3.2
Severe SCC treated with RT: proportion paraplegic	0.813	0.813 – 0.813 (Uniform distribution)	7.3.1 & 7.3.2
Severe SCC treated with surgery: proportion cured	0.125	0 – 0.625 (Uniform distribution)	7.3.1 & 7.3.2
Severe SCC treated with surgery: proportion improved (to mild SCC)	0.500	0.625 – 0 (Uniform distribution)	7.3.1 & 7.3.2
Severe SCC treated with surgery: proportion paraplegic	0.375	0.375 – 0.375 (Uniform distribution)	7.3.1 & 7.3.2

Mild SCC treated with RT: proportion cured	0.212	0 – 0.743 (Uniform distribution)	7.3.1 & 7.3.2
Mild SCC treated with RT: proportion improved	0.106	0.371 – 0 (Uniform distribution)	7.3.1 & 7.3.2
Mild SCC treated with RT: proportion no response	0.425	0.371 – 0 (Uniform distribution)	7.3.1 & 7.3.2
Mild SCC treated with RT: proportion paraplegic	0.257	0.257 – 0.257 (Uniform distribution)	7.3.1 & 7.3.2
Mild SCC treated with surgery: proportion cured	0.269	0 – 0.941 (Uniform distribution)	7.3.1 & 7.3.2
Mild SCC treated with surgery: proportion improved	0.135	0.471 – 0 (Uniform distribution)	7.3.1 & 7.3.2
Mild SCC treated with surgery: proportion no response	0.538	0.471 – 0 (Uniform distribution)	7.3.1 & 7.3.2
Mild SCC treated with surgery: proportion paraplegic	0.059	0.059 – 0.059 (Uniform distribution)	7.3.1 & 7.3.2
Probabilities for Markov model for adverse events			
Proportion severe fracture degarelix	0.31	0.235 - 0.390 (Beta distribution)	7.3.1 & 7.3.2
Proportion moderate fracture degarelix	0.55	0.461 - 0.640 (Beta distribution)	7.3.1 & 7.3.2
Proportion mild fracture degarelix	0.14	0.097 - 0.183 (Beta distribution)	7.3.1 & 7.3.2
Proportion severe fracture comparator	0.31	0.235 - 0.390 (Beta distribution)	7.3.1 & 7.3.2
Proportion moderate fracture comparator	0.55	0.461 - 0.640 (Beta distribution)	7.3.1 & 7.3.2
Proportion mild fracture comparator	0.14	0.097 - 0.183 (Beta distribution)	7.3.1 & 7.3.2
Proportion Severe JSS Degarelix	0.05	0.045 - 0.056 (Beta distribution)	7.3.1 & 7.3.2
Proportion Moderate JSS Degarelix	0.41	0.386 - 0.441 (Beta distribution)	7.3.1 & 7.3.2
Proportion Mild JSS Degarelix	0.54	0.507 - 0.563 (Beta distribution)	7.3.1 & 7.3.2
Proportion Severe JSS Comparator	0.05	0.045 - 0.056 (Beta distribution)	7.3.1 & 7.3.2
Proportion Moderate JSS Comparator	0.41	0.386 - 0.441 (Beta distribution)	7.3.1 & 7.3.2
Proportion Mild JSS Comparator	0.54	0.507 - 0.563 (Beta distribution)	7.3.1 & 7.3.2
Proportion experiencing pain relief after 1 cycle	0.04	0.038 - 0.046 (Uniform distribution)	7.3.1 & 7.3.2
Proportion of patients with metastatic prostate cancer	0.25	0.238 - 0.268 (Beta distribution)	6.3.4
Adverse event-related parameters			
CV events with death			
CV events with death - Degarelix Weibull fit: intercept	2.22		7.3.1 & 7.3.2
CV events with death - Degarelix Weibull fit: scale	0.79		7.3.1 & 7.3.2
CV events with death - Degarelix exponential fit: intercept	0.06		7.3.1 & 7.3.2
CV events with death - LHRH Weibull fit: intercept	1.68		7.3.1 & 7.3.2
CV events with death - LHRH Weibull fit: scale	0.84		7.3.1 & 7.3.2
CV events with death - LHRH exponential fit: intercept	0.13		7.3.1 & 7.3.2
CV events without death			
CV events without death - Degarelix Weibull fit: intercept	3.26		7.3.1 & 7.3.2
CV events without death - Degarelix Weibull fit: scale	0.98		7.3.1 & 7.3.2
CV events without death - Degarelix exponential fit: intercept	0.04		7.3.1 & 7.3.2
CV events without death - LHRH	2.16		7.3.1 &

		Covariance matrix	
		Intercept	**Scale**
Weibull	Intercept	0.186	
	Scale	0.057	0.021
Exponential	Intercept	0.209	

(Multivariate normal distribution)

		Covariance matrix	
		Intercept	**Scale**
Weibull	Intercept	0.098	
	Scale	0.038	0.01
Exponential	Intercept	0.186	

(Multivariate normal distribution)

		Covariance matrix	
		Intercept	**Scale**
Weibull	Intercept	0.685	
	Scale	0.184	0.055
Exponential	Intercept	0.267	

(Multivariate normal distribution)

		Covariance matrix

Weibull fit: intercept				**Intercept**	**Scale**	7.3.2
CV events without death - LHRH Weibull fit: scale	0.89	**Weibull**	Intercept	0.236		7.3.1 & 7.3.2
			Scale	0.081	0.034	
CV events without death - LHRH exponential fit: intercept	0.09	**Exponential**	Intercept	0.230		7.3.1 & 7.3.2
		(Multivariate normal distribution)				
All MSEs						
All MSEs - Degarelix Weibull fit: intercept	2.84			**Covariance matrix**		7.3.1 & 7.3.2
				Intercept	**Scale**	
All MSEs - Degarelix Weibull fit: scale	1.31	**Weibull**	Intercept	0.082		7.3.1 & 7.3.2
			Scale	0.029	0.012	
All MSEs - Degarelix exponential fit: intercept	0.12	**Exponential**	Intercept	0.090		7.3.1 & 7.3.2
		(Multivariate normal distribution)				
All MSEs - LHRH Weibull fit: intercept	2.81			**Covariance matrix**		7.3.1 & 7.3.2
				Intercept	**Scale**	
All MSEs - LHRH Weibull fit: scale	1.45	**Weibull**	Intercept	0.114		7.3.1 & 7.3.2
			Scale	0.043	0.020	
All MSEs - LHRH exponential fit: intercept	0.15	**Exponential**	Intercept	0.105		7.3.1 & 7.3.2
		(Multivariate normal distribution)				
Fracture						
Fracture - Degarelix Weibull fit: intercept	7.05			**Covariance matrix**		7.3.1 & 7.3.2
				Intercept	**Scale**	
Fracture - Degarelix Weibull fit: scale	1.52	**Weibull**	Intercept	4.581		7.3.1 & 7.3.2
			Scale	0.905	0.187	
Fracture - Degarelix exponential fit: intercept	0.01	**Exponential**	Intercept	0.302		7.3.1 & 7.3.2
		(Multivariate normal distribution)				
Fracture - LHRH Weibull fit: intercept	3.09			**Covariance matrix**		7.3.1 & 7.3.2
				Intercept	**Scale**	
Fracture - LHRH Weibull fit: scale	0.80	**Weibull**	Intercept	0.715		7.3.1 & 7.3.2
			Scale	0.167	0.042	
Fracture - LHRH exponential fit: intercept	0.02	**Exponential**	Intercept	0.277		7.3.1 & 7.3.2
		(Multivariate normal distribution)				
Joint related signs and symptoms						
Joint related signs and symptoms - Degarelix Weibull fit: intercept	3.89			**Covariance matrix**		7.3.1 & 7.3.2
				Intercept	**Scale**	
Joint related signs and symptoms - Degarelix Weibull fit: scale	1.32	**Weibull**	Intercept	0.295		7.3.1 & 7.3.2
			Scale	0.084	0.026	
Joint related signs and symptoms - Degarelix exponential fit: intercept	0.06	**Exponential**	Intercept	0.132		7.3.1 & 7.3.2
		(Multivariate normal distribution)				
Joint related signs and symptoms - LHRH Weibull fit: intercept	3.43			**Covariance matrix**		7.3.1 & 7.3.2
				Intercept	**Scale**	
Joint related signs and symptoms - LHRH Weibull fit: scale	1.39	**Weibull**	Intercept	0.249		7.3.1 & 7.3.2
			Scale	0.082	0.031	
Joint related signs and symptoms - LHRH exponential fit: intercept	0.09	**Exponential**	Intercept	0.135		7.3.1 & 7.3.2
		(Multivariate normal distribution)				
Baseline health state utility values						
First-line treatment utility	0.887	0.879 - 0.894 (Uniform distribution)				7.4.4 & 7.4.9
Anti-androgen addition utility	0.753	0.697 - 0.806 (Uniform distribution)				7.4.6 & 7.4.9
Anti-androgen withdrawal utility	0.753	0.697 - 0.806 (Uniform distribution)				7.4.6 & 7.4.9
Chemotherapy and abiraterone utility	0.689	0.686 - 0.692 (Uniform distribution)				7.4.6 & 7.4.9
Supportive and palliative care utility	0.554	0.527 - 0.580 (Uniform distribution)				7.4.6 & 7.4.9
CV event utility values						
Utility for non-fatal serious CV events	0.801	0.649 - 0.917 (Uniform distribution)				7.4.4 & 7.4.9
MSE utility values						
Metastatic prostate cancer with mild SCC - First-line	0.370	0.27 - 0.47 (Uniform distribution)				7.4.6 & 7.4.9
Metastatic prostate cancer with severe SCC - First-line	0.195	0 - 0.39 (Uniform distribution)				7.4.6 & 7.4.9
Metastatic prostate cancer with severe JSS - First-line	0.781	0.706 - 0.848 (Uniform distribution)				7.4.4 & 7.4.9
Metastatic prostate cancer with severe fracture - First-line	0.270	0.031 - 0.643 (Uniform distribution)				7.4.4 & 7.4.9

Metastatic prostate cancer with moderate JSS - First-line, utility decrement	0.066	0.015 - 0.153 (Uniform distribution)	7.4.4 & 7.4.9
Metastatic prostate cancer with moderate fracture - First-line, utility decrement	0.387	0.317 - 0.460 (Uniform distribution)	7.4.4 & 7.4.9
Metastatic prostate cancer with mild JSS - First-line, utility decrement	0.053	0.007 - 0.143 (Uniform distribution)	7.4.4 & 7.4.9
Metastatic prostate cancer with mild fracture - First-line, utility decrement	0.310	0.241 - 0.384 (Uniform distribution)	7.4.4 & 7.4.9
Drug costs			
Degarelix drug cost: first cycle	260.00	No uncertainty	7.5.5 & 7.5.6
Degarelix drug cost: subsequent cycles	129.37	No uncertainty	7.5.5 & 7.5.6
Comparator drug cost: first cycle	81.40	No uncertainty	7.5.5 & 7.5.6
Comparator drug cost: subsequent cycles	78.33	No uncertainty	7.5.5 & 7.5.6
Drug cost: anti-androgen for 2nd line hormonal therapy	6.59	3.446 - 11.400 (Log-normal)	7.5.5 & 7.5.6
Drug cost: abiraterone per cycle	2,735.19	No uncertainty	7.5.5 & 7.5.6
Total drugs costs for all chemotherapy cycles	405.13	96.32 - 1,439.82 (Log-normal based upon standard error for drug costs. Uniform distribution ±30% for number of sessions)	7.5.5 & 7.5.6
Total administration and side effect costs for all chemotherapy cycles	3021.74	1,813.12 - 4,489.29 (Uniform distribution ±30%)	7.5.5 & 7.5.6
Degarelix - First-line administration cost - first cycle	269.63	188.74 - 350.51 (Uniform distribution)	7.5.5 & 7.5.6
Degarelix - First-line administration cost - subsequent cycle	28.32	19.82 - 36.81 (Uniform distribution)	7.5.5 & 7.5.6
Degarelix - AA addition administration cost - first cycle	269.63	188.74 - 350.51 (Uniform distribution)	7.5.5 & 7.5.6
Degarelix - AA addition administration cost - subsequent cycle	44.49	31.14 - 57.84 (Uniform distribution)	7.5.5 & 7.5.6
Degarelix - AA withdrawal administration cost - first cycle	269.63	188.74 - 350.51 (Uniform distribution)	7.5.5 & 7.5.6
Degarelix - AA withdrawal administration cost - subsequent cycle	44.49	31.14 - 57.84 (Uniform distribution)	7.5.5 & 7.5.6
Comparator - First-line administration cost - first cycle	269.63	188.74 - 350.51 (Uniform distribution)	7.5.5 & 7.5.6
Comparator - First-line administration cost - subsequent cycle	20.22	14.15 - 26.29 (Uniform distribution)	7.5.5 & 7.5.6
Comparator - AA addition administration cost - first cycle	269.63	188.74 - 350.51 (Uniform distribution)	7.5.5 & 7.5.6
Comparator - AA addition administration cost - subsequent cycle	36.40	25.48 - 47.31 (Uniform distribution)	7.5.5 & 7.5.6
Comparator - AA withdrawal administration cost - first cycle	269.63	188.74 - 350.51 (Uniform distribution)	7.5.5 & 7.5.6
Comparator - AA withdrawal administration cost - subsequent cycle	36.40	25.48 - 47.31 (Uniform distribution)	7.5.5 & 7.5.6
Abiraterone administration and concomitant medication costs - first cycle	845.16	591.61 - 1098.70 (Uniform distribution)	7.5.5 & 7.5.6
Abiraterone administration and concomitant medication costs - subsequent cycle	220.51	154.35 - 286.66 (Uniform distribution)	7.5.5 & 7.5.6
Cost of follow-on treatment after abiraterone	1,754.00	1227.80 - 2280.20 (Uniform distribution)	7.5.5 & 7.5.6
Cost of supportive care each cycle	132.38	92.67 - 172.09	7.5.5 &

before palliative care		(Uniform distribution)	7.5.6
Cost of palliative care	4,182.51	2927.76 - 5437.26 (Uniform distribution)	7.5.5 & 7.5.6
Initial cost of a serious non-fatal CV event cost	1,504.77	1053.34 - 1956.20 (Uniform distribution)	7.5.5 & 7.5.7
Cost of a fatal CV event	1,704.41	1193.09 - 2215.73 (Uniform distribution)	7.5.5 & 7.5.7
Long-term cost of a serious non-fatal CV event	52.73	36.91 - 68.55 (Uniform distribution)	7.5.5 & 7.5.7
Costs for RT per patient	1,459.95	1021.967 - 1897.938 (Uniform distribution)	7.5.5 & 7.5.7
Costs for surgery per patient	12,153.69	8507.581 - 15799.793 (Uniform distribution)	7.5.5 & 7.5.7
Total daily cost of care for ambulant patients (mild SCC)	104.08	72.855 - 135.301 (Uniform distribution)	7.5.5 & 7.5.7
Daily cost of care for non-ambulant patients (severe SCC)	1,096.82	767.776 - 1425.869 (Uniform distribution)	7.5.5 & 7.5.7
Metastatic prostate cancer with severe fracture - event cost	8,493.52	5945.465 - 11041.579 (Uniform distribution)	7.5.5 & 7.5.7
Metastatic prostate cancer with moderate fracture - event cost	1,419.96	993.974 - 1845.952 (Uniform distribution)	7.5.5 & 7.5.7
Metastatic prostate cancer with mild fracture - event cost	375.05	262.534 - 487.563 (Uniform distribution)	7.5.5 & 7.5.7
Metastatic prostate cancer with severe fracture - continuous cost	14.02	9.812 - 18.222 (Uniform distribution)	7.5.5 & 7.5.7
Metastatic prostate cancer with moderate fracture - continuous cost	6.08	4.256 - 7.905 (Uniform distribution)	7.5.5 & 7.5.7
Metastatic prostate cancer with severe MSE - event cost	905.87	634.110 - 1177.632 (Uniform distribution)	7.5.5 & 7.5.7
Metastatic prostate cancer with moderate MSE - event cost	1,008.47	705.926 - 1311.005 (Uniform distribution)	7.5.5 & 7.5.7
Metastatic prostate cancer with mild MSE - event cost	86.00	60.200 - 111.800 (Uniform distribution)	7.5.5 & 7.5.7
Metastatic prostate cancer with severe MSE - continuous cost	42.14	29.499 - 54.784 (Uniform distribution)	7.5.5 & 7.5.7
Metastatic prostate cancer with moderate MSE - continuous cost	36.60	25.622 - 47.583 (Uniform distribution)	7.5.5 & 7.5.7

Key: AA = anti-androgen; CV = cardiovascular; ITT = intention-to-treat; JSS = joint-related symptoms and signs; LHRH = luteinising hormone-releasing hormone; MSE = musculoskeletal events; PSA = prostate-specific antigen; RT = radiotherapy; SCC = spinal cord compression

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Costs and clinical outcomes are extrapolated beyond the follow-up periods. The methods used to extrapolate outcomes beyond the clinical trial period are outlined in Sections 7.3.1 and 7.3.2. Section 7.3.2 also contains the parametric curves used to extrapolate the outcomes beyond the trial period, along with the Kaplan–Meier plots they were fitted to. A scenario is explored, in which the estimated difference in efficacy between degarelix and the LHRH agonists is conservatively not assumed to continue beyond the one-year period for which comparative data are available (this scenario is described in greater detail in Section 7.6.1.[10]

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table 33. Assumptions in the de novo economic model

Assumption	Justification
Differential efficacy continues after the trial	The Kaplan–Meier Curves from CS21 show no indication of moving towards convergence. Sensitivity of the model to this assumption is tested in a scenario analysis
The efficacy across the doses of LHRH agonists is equal	The clinical literature available shows no statistically significant clinical difference between leuprorelin 3.75 mg and leuprorelin 7.5 mg. It therefore seems valid to assume that for leuprorelin there is no clinical difference between the doses[121,136-142,158]
The efficacy of goserelin and triptorelin, are equal to leuprorelin	The MTC reported in Section 6.7 and meta-analyses undertaken by Seidenfeld *et al* and Hemels *et al* indicate that there is no significant difference in progression or mortality-related outcomes for patients on a variety of LHRH agonists[120,121]
The efficacy of an LHRH in combination with anti-androgen flare cover is equal to the efficacy of treatment with LHRH alone.	This test could only be undertaken on a small number of patients, as anti-androgens are provided only for flare cover it is not clinically likely that PSA progression is affected by its provision. Additionally, Oh *et al* conducted an analysis of 1,566 patients, which concluded that anti-androgen therapy before LHRH agonists in metastatic prostate cancer was not associated with differences in fractures, SCC, BOO, or narcotic prescriptions.[78] The trial data not only supports the equivalency of the efficacy between those patients receiving anti-androgen flare cover and those who do not; it also supports that degarelix has enhanced efficacy versus those who have flare cover as well as the population that predominantly does not (CS21). Pooled analysis from CS21 and CS35 degarelix trials showed that the PSA PFS failure rate (adjusted for baseline PSA, PCa stage and Gleason score) was significantly lower with degarelix than with LHRH agonists + anti-androgen flare protection for all patients (HR=0.490, p=0.0028); and that patients receiving LHRH agonists + anti-androgen flare protection still experienced testosterone surge.[116]
Patients who initially have mild SCC who improve have the same utility as those whose problems were resolved	The publication by Lu *et al* only gave utilities for three SCC outcomes (cured, ambulant or non-ambulant). The most reasonable assumption seemed to be that those who were improved from mild SCC had the same utility as those who were cured.[144] This assumption is likely to favour the LHRH agonists rather than degarelix as the risk of SCC is associated with treatment with LHRH agonists – reducing the disutility associated with SCC therefore reduces the benefit of treatment with degarelix. A scenario analysis is undertaken where SCC, fractures and joint-related signs and symptoms are not included in the model.
Patients who initially have severe SCC who improve have the same utility as those who have mild SCC	The publication by Lu *et al* only gave utilities for three SCC outcomes (cured, ambulant or non-ambulant).[144] The most reasonable assumption seemed to be that those who were improved from severe SCC but not cured had the same utility as those who were ambulant (mild SCC). This assumption is likely to favour the LHRH agonists rather than Degarelix as the risk of SCC is associated with treatment with LHRH agonists – reducing the disutility associated with SCC therefore reduces the benefit of treatment with degarelix. A scenario analysis is undertaken where SCC, fractures and joint-related signs and symptoms are not included in the model.
Metastatic patients who progress from first-line treatment have an increased risk of mortality	This assumption is supported by the evidence reported in Hussain *et al.*[107] Sensitivity of the model to this assumption is tested in a scenario analysis.

Assumption	Justification
Patients who have a non-fatal cardiovascular event do not experience additional disutility from 28 days after the event	This assumption was incorporated to avoid undue complexity in the model. It is conservative from the perspective of the cost effectiveness of degarelix because the trial data indicate that patients treated with degarelix experience fewer non-fatal cardiovascular events. A scenario analysis is undertaken where the costs, mortality and disutility associated from fatal and non-fatal cardiovascular events are not included.
Rates of adverse events (MSEs and cardiovascular events) are not dependent on the dose of degarelix given	This assumption is supported by the data from the six pooled trials. Adverse events were only incorporated when there was a statistically significant difference in their distribution between patients on degarelix and those on leuprorelin and when they were not dose dependent. Some MSEs were excluded due to evidence of dose dependency – these events happened less frequently in those patients treated with degarelix so the exclusion of these events is conservative. A scenario analysis is undertaken where the cost and HRQL implications of SCC, fractures and joint-related signs and symptoms are not incorporated into the cost-effectiveness calculation.
Treatment pathway & stopping rule	Supported by the licensed indication. A scenario analysis is undertaken where patients remain on degarelix and LHRH agonists until death as certain clinical experts suggested this occurred as regular practice.[7]

Key: BOO = bladder outlet obstruction; HR = hazard ratio; HRQL = health-related quality of life; LHRH = luteinising hormone-releasing hormone; MSEs = musculoskeletal events; MTC = mixed treatment comparison; PFS = progression-free survival; PSA = prostate-specific antigen; SCC = spinal cord compression

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Patients' quality of life is adversely affected by both disease progression and the side-effects of current hormonal treatments.

The literature reviewed in Section 7.4.5 indicates that as patients progress to later lines of treatment, their HRQL decreases. This may, in part, be related to the aggressiveness of chemotherapy.[159] However, it is also likely to be related to the pain associated with bone metastases, loss of mobility and independence and the worsening of the patient's general condition and emotional well-being as the disease progresses.[160-162] Pain due to bone metastases is often a symptom of advanced prostate cancer, and older men are often reluctant to take pain medications or dosages adequate to alleviate their pain.[163]

The side-effects of hormonal therapies can be particularly distressing for otherwise asymptomatic men. These side-effects include: hot flushes, osteoporosis, anaemia, fatigue, sarcopenia, gynaecomastia, loss of libido, erectile dysfunction, risk of diabetes, risk of cardiovascular disease and fatal cardiac events, as well as possible emotional distress.[162,163] These side-effects have led some oncologists to use intermittent hormonal therapy to decrease the morbidity of the therapy.[163] Anxiety tends to be the most commonly experienced psychiatric symptom for men with prostate cancer.[163]

Hot flushes are caused by many hormonal therapies. Symptoms include: diaphoresis, feelings of intense heat and chills, similar to symptoms that women have during the menopause. At times, hormonal therapy must be stopped because of the drenching sweats and discomfort caused by hot flushes, especially when sleep is disturbed.[163]

Symptoms of fatigue are particularly upsetting to men who have led active and independent lives. These symptoms usually result in increased dependence on family or friends and are further reminders of the contrast with how they were before

the cancer. Fatigue and lack of motivation can be caused by the illness, hormonal therapy, pain medication, steroids, chemotherapy and other factors.[163]

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

As a patient progresses through the different treatment lines for prostate cancer, their HRQL is likely to fall. First, their disease will progress, adversely affecting the general health and vitality of the patient. Second, the disease will spread, increasing the likelihood of bone metastases, which are associated with higher levels of pain.[160,163] Third, when patients are no longer sensitive to hormone-based treatments they will typically move on to chemotherapy, which is more aggressive and, therefore, associated with a lower HRQL.[159]

The utility values shown in Table 41, which are sourced from the trial HRQL data and the systematic literature review, reflect the expected trend. The CS21 clinical trial data indicate a lower HRQL for patients who have experienced PSA progression compared with those who do not experience PSA progression (Section 7.4.4).[10] The literature consistently shows lower utility values for those who have progressed to requiring treatment with chemotherapy[159,164,165] compared with those who are being treated with LHRH, whether in combination with an anti-androgen or after the anti-androgen has been withdrawn.[161,166,167]

In addition, as treatment continues, there is a continued risk of suffering from an AE. Data from the pooled degarelix versus leuprorelin trials indicate that, over time, patients are statistically significantly more likely to suffer a fracture, JSS or a cardiovascular event when treated with leuprorelin.[110] These treatment-related AEs are likely to further increase the patient's burden of morbidity, leading to a fall in their HRQL.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

EQ-5D values were not collected in CS21. HRQL data in the study were collected using the Short Form 12 version 2 (SF-12 v2) and the European Organization for

Research and Treatment of Cancer, Quality of Life Questionnaire-C 30 (EORTC QLQ-C30) tools at five points during the study period (at Days 0, 28, 84, 168 and 364). These data are not consistent with the reference case and can only be used in cost-effectiveness analysis after mappings have been applied.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Both SF12v2 and EORTC QLQ-C30 data were collected in CS21. Both of these instruments have been mapped to the EQ-5D and, additionally, the EORTC QLQ-C30 has been mapped to the EORTC-8D.

The mapping from EORTC QLQ-C30 data into preference-based EORTC-8D utilities, which was carried out using an algorithm published by Rowen *et al* in 2011,[168] has also been included in the model, although it does not result in utilities derived using the EQ-5D. It is not in accordance with the reference guide, which recommends using EQ-5D-derived utilities if they are available[148], but is reported for completeness.

Two methods were used to map EORTC QLQ-C30 quality of life data into preference-based EQ-5D utilities. First, the algorithm published by Kontodimopoulos *et al,* which is based on three EORTC QLQ-C30 summary scales and is shown in Equation 3.

Equation 3

$$\mathrm{U} = -0.18143 + 0.00508\mathrm{xPF} + 0.00313\mathrm{xEF} + 0.00546\mathrm{xGH}$$

Second, the algorithm published by McKenzie and van der Pol, which is based on all fifteen EORTC QLQ-C30 summary scales, and is shown in Table 34.

Table 34. Summary scale coefficients used in mapping algorithm

EORTC QLQ-C30 summary scale	Coefficient
Global health status	0.0016
Physical functioning	0.0004
Role functioning	0.0022
Emotional functioning	0.0028
Cognitive functioning	0.0009
Social functioning	0.0002
Fatigue	–0.0021
Nausea/vomiting	–0.0005
Pain	–0.0024
Dyspnoea	0.0004
Insomnia	0.00004
Appetite loss	0.0003
Constipation	0.0001
Diarrhoea	–0.0003
Financial problems	–0.0006
Constant	0.2376

Key: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-C 30

The SF-12 v2 was mapped using an algorithm written by the Health Economics Research Centre, using the same methodology as the SF-36 to EQ-5D mapping algorithm published by Gray *et al*.[169]

Table 35. Mapping study descriptions

	SF-12v2 [169]	**EORTC-8D**[168]	**Kontodimo-poulos**[170]	**McKenzie and van der Pol**[171]
Source	SF-12v2	EORTC-QLQ C30	EORTC QLQ-C30	EORTC QLQ-C30
Country	England	Dataset: International Valuation study: UK	Greece	Scotland
Dataset for original mapping	General population: Health Survey for England	Patients newly diagnosed with multiple myeloma	Gastric cancer patients, split into equal subgroups by age, sex and chemotherapy scheme	Patients with inoperable oesophageal cancer, on palliative therapy
Techniques for original mapping	First, a regression analysis was conducted, mapping individual SF-12 items onto individual EQ-5D domains and multinomial logistic regression was used to predict the probability of each response level for the five questions. The utility on the EQ-5D was then calculated from the simulation domain scores.	First a factor analysis was applied to 27 of the 30 items to determine 5 factors, using 24 items. Then Rasch and other psychometric analyses were used to select items and dimension to represent each factor. This led to a classification system of 8 dimensions, using 10 items. For validation, these steps were repeated in another time period. Then a sample of health states were valued by interviewing a sample of the general population, using TTO. Finally, TTO values were modelled for all health states defined by the classification system. Five models were compared, choosing the best performing one.	Patients were interviewed using a survey including QLQ-C30, SF-36, EQ-5D and 15D. Model predictive ability and explanatory power were assessed by RMSE and adjusted R^2 values, respectively. Three validation samples were created to test the modelling equations generated by the full sample. Three scales were significant predictors of EQ-5D indices. A stepwise regression model of these scales can be used to create an equation to predict EQ-5D utility score.	EORTC QLQ-C30 and EQ-5D data were collected at a range between 1- and 3-weekly intervals from baseline to 90 weeks. Then EQ-5D values are modelled as a function of the EORTC QLQ-C30 data. To assess goodness of fit, R^2 is used for the OLS regression. Also EQ-5D values were estimated from a separate data set: a trial on radiotherapy after breast cancer surgery for low-risk elderly women. Regression analysis was done for all the 15 scales of EORTC QLQ-C30, and those values are used to create an equation to predict EQ-5D utility score.

	SF-12v2 [169]	EORTC-8D[168]	Kontodimo-poulos[170]	McKenzie and van der Pol[171]
MAE and other goodness of fit stats	No information	MAE: 0.046 MAE>0.05: 41 (2710 observations) MAE>-0.10: 132710 observations)	RMSE = 0.192 MID >0.03 in one of three samples	MCID < 0.03 Relative prediction error: 1.84%
Info in original mapping on severity bias	No information	Does not capture shortness of breath and cognitive function.	Exceeds unity at the upper end (1.186)	No information

Key: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-C 30; EQ-5D = EuroQol five-dimensions; MAE, mean absolute error; MCID, minimal clinically important difference; MID, minimally important difference: OLS, ordinary least square; RMSE, root mean square error; SF = Short Form; TTO, time trade-off

All utilities were summarised by treatment group, progression status and defined AEs, as shown in Table 36 toTable 39.

Table 36. HRQL analysis treatment

	SF-12 v2 mapped to EQ-5D[169]		EORTC QLQ-C30	EORTC-8D[168]	EQ-5D Kontodimopoulos[170]	EQ-5D McKenzie + van der Pol[171]
	n	**Utility (sd)**	**n**	**Utility (sd)**	**Utility (sd)**	**Utility (sd)**
Degarelix 240/160 mg	913	0.743 (0.135)	904	0.865 (0.116)	0.876 (0.193)	0.794 (0.204)
Degarelix 240/80 mg	935	0.740 (0.134)	923	0.871 (0.110)	0.888 (0.199)	0.814 (0.184)
Leuprorelin 7.5 mg	914	0.740 (0.129)	899	0.862 (0.113)	0.886 (0.199)	0.791 (0.204)

Key: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-C 30; EQ-5D = EuroQol five-dimensions; HRQL = health-related quality of life; SF-12 = Short Form 12

Table 37. HRQL analysis by progression status

	SF-12 v2 mapped to EQ-5D[169]		EORTC QLQ-C30	EORTC-8D[168]	EQ-5D Kontodimopoulos[170]	EQ-5D McKenzie + van der Pol[171]
	n	**Utility (sd)**	**n**	**Utility (sd)**	**Utility (sd)**	**Utility (sd)**
No PSA progression	2689	0.743 (0.132)	2653	0.868 (0.112)	0.887 (0.195)	0.803 (0.195)
PSA progression	73	0.673 (0.150)	72	0.806 (0.127)	0.753 (0.238)	0.682 (0.250)

Key: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-C 30; EQ-5D = EuroQol five-dimensions; HRQL = health-related quality of life; PSA = prostate-specific antigen; SF-12 = Short Form 12

Table 38. HRQL analysis by AE status (patients who had not progressed)

	SF-12v2 mapped to EQ-5D[169]		EORTC QLQ-C30	EORTC-8D[168]	EQ-5D Kontodi-mopoulos[170]	EQ-5D McKenzie and van der Pol[171]
	n	**Utility (sd)**	**n**	**Utility (sd)**	**Utility (sd)**	**Utility (sd)**
No AEs	2522	0.745 (0.132)	2488	0.871 (0.109)	0.891 (0.189)	0.808 (0.189)
Fracture	6	0.593 (0.257)	6	0.596 (0.251)	0.533 (0.434)	0.434 (0.391)
JSS	59	0.707 (0.076)	57	0.820 (0.142)	0.826 (0.277)	0.726 (0.261)
CV SAE	10	0.732 (0.105)	9	0.803 (0.120)	0.801 (0.211)	0.692 (0.232)

Key: AE = adverse event; CV SAE, cardiovascular serious adverse event; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-C 30; EQ-5D = EuroQol five-dimensions; HRQL = health-related quality of life; JSS, joint-related signs and symptoms; SF-12 = Short Form 12

Table 39. HRQL analysis by disease progression status and treatment

	SF-12 mapped to EQ-5D[169]		EORTC QLQ-C30	EORTC-8D[168]	EQ-5D Kontodi-mopoulos[170]	EQ-5D McKenzie and van der Pol[171]
	n	**Utility (sd)**	**n**	**Utility (sd)**	**Utility (sd)**	**Utility (sd)**
Degarelix 240/160 mg						
No PSA progression	891	0.743 (0.135)	882	0.867 (0.116)	0.878 (0.193)	0.796 (0.203)
PSA progression	22	0.689 (0.141)	22	0.815 (0.112)	0.772 (0.188)	0.696 (0.213)
Degarelix 240/80 mg						
No PSA progression	919	0.741 (0.134)	907	0.872 (0.109)	0.889 (0.198)	0.815 (0.182)
PSA progression	16	0.701 (0.103)	16	0.832 (0.151)	0.872 (0.245)	0.759 (0.246)
Leuprorelin 7.5 mg						
No PSA progression	879	0.743 (0.126)	864	0.865 (0.112)	0.894 (0.193)	0.797 (0.198)
PSA progression	35	0.651 (0.173)	35	0.789 (0.125)	0.707 (0.259)	0.638 (0.269)

Key: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-C 30; EQ-5D = EuroQol five-dimensions; HRQL = health-related quality of life; PSA = prostate-specific antigen; SF-12 = Short Form 12

The four mapping algorithms provide relatively similar results. The SF-12 v2 algorithm, however, provides consistently lower results than the algorithms based on the EORTC QLQ-C30.

PSA progression has a significant effect on quality of life ($p<0.001$ using all mapping algorithms). When a patient progresses, the utility value drops by approximately 0.1, which is consistent with the available literature (Section 7.4.6).

The effect of treatment on utility differs when using the two algorithms. When using the Kontodimopoulos algorithm,[170] the difference between the two treatment arms is not significant (p=0.27); however, the difference is significant when using the McKenzie and van der Pol algorithm[171] (p=0.03), with utility being higher for patients on degarelix.

Of the AEs tested, fractures influence utility the most, with a drop in utility of 0.358 and 0.374, followed by cardiovascular events, with a drop of 0.090 and 0.117 for the Kontodimopoulos and McKenzie and van der Pol algorithms, respectively. The HRQL effects of JSS (0.064 and 0.082) are lower.

Where possible, the results from the algorithm developed by Kontodimopoulos were incorporated into the model base case. The algorithms based on the EORTC QLQ-C30 were chosen, as the results were consistent across algorithms and similar to the literature values found. The Kontodimopoulos study was chosen, as it was derived from patient data that comes from a less severe condition, which is, therefore, more comparable to that of the patients with advanced hormone-dependent prostate cancer enrolled in CS21. A scenario analysis was undertaken, in which the sensitivity of the results to the choice of algorithm used was explored (the scenarios are outlined in greater detail in Section 7.6.1.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A broad systematic review was conducted in March 2013 to identify HRQL studies for advanced prostate cancer patients. A precise search strategy was utilised, incorporating terms for prostate cancer and quality of life. In order to ensure the published literature was comprehensively reviewed, a wide range of databases were searched, these included:

- Medline and Medline in Process & Other Non-Indexed citations
- EMBASE
- Cochrane CDSR
- Cochrane CCRT
- Cochrane DARE
- Cochrane NHS EED
- Cochrane HTA
- CINAHL
- EconLit
- Science Citation Index
- Conference Proceedings index (Science)

Appendix 10 describes the search strategy used to search the databases. The structure of the search is described by providing the structure and the terms used to search the Medline database. Having identified studies of potential relevance from a wide range of databases, the titles and abstracts were reviewed in greater detail to assess their relevance for informing the overall decision problem.

Table 71 in Appendix 12 outlines the eligibility criteria employed for assessing the relevance of the different studies.

In previous UK submissions, the HRQL values for the disease states were informed by a study investigating the cost-effectiveness of androgen suppression therapies in advanced prostate cancer.[166] However, this study was not a primary study investigating the HRQL of patients with prostate cancer using the EQ-5D. As outlined below, the systematic search aimed to identify studies with a primary aim to investigate HRQL (and therefore did not rely on values sourced from the literature), which used the EQ-5D to measure the HRQL. A scenario analysis, outlined in Section 7.6.1 explored the sensitivity of the results to the incorporation of the values reported in Bayoumi *et al.*[166]

The papers that appeared to meet the inclusion criteria after a detailed review of the title and abstract were obtained for a secondary review. In this secondary review, the entire article was assessed according to the criteria outlined in Table 71. The studies that were assessed to have met the inclusion criteria after a secondary review are reviewed below.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

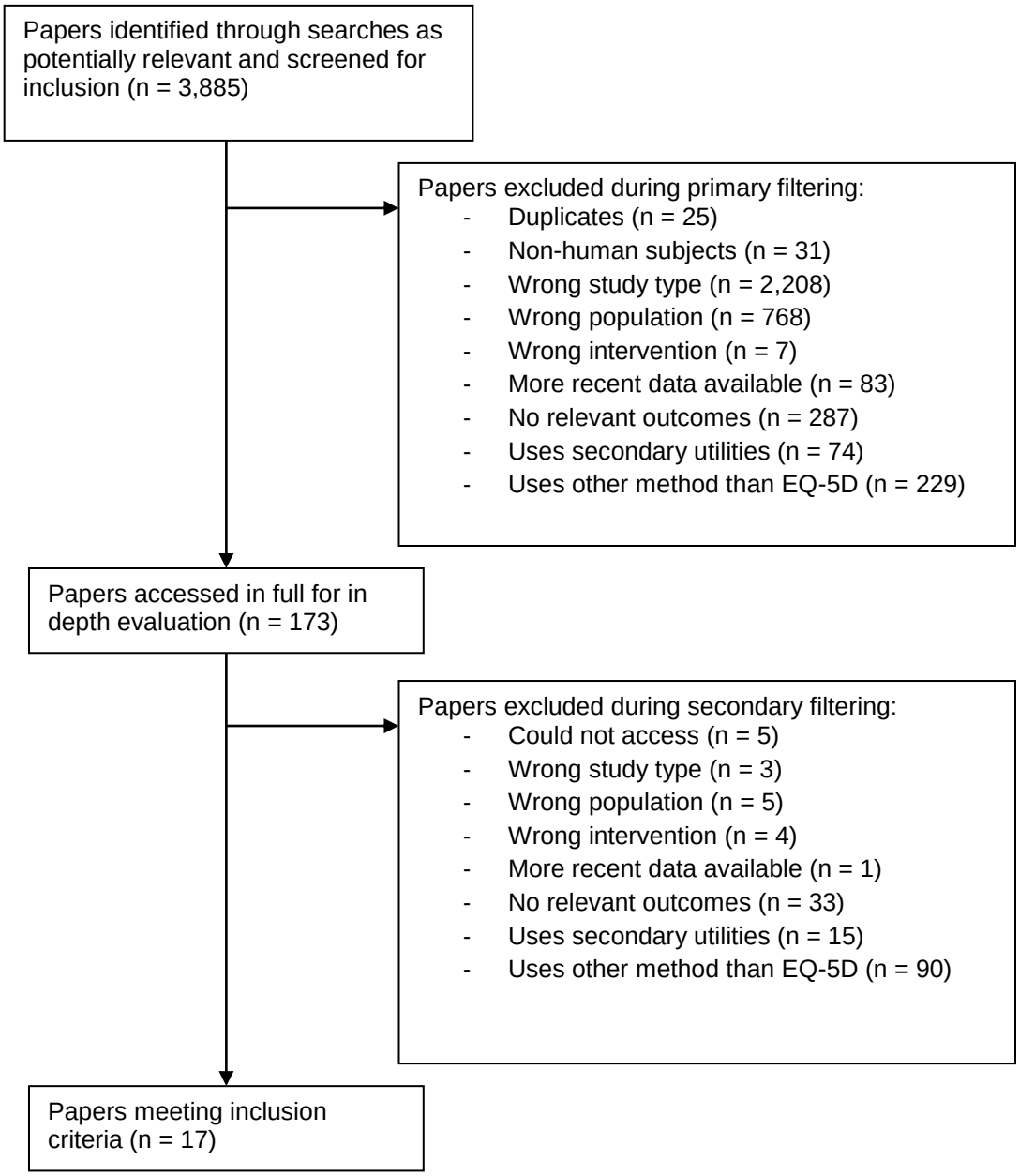
Identification of relevant studies

As illustrated in Figure 33 below, the majority of papers initially identified failed to meet the inclusion criteria discussed in Section 7.4.5. The reason for the exclusion of 2,208 of 3,712 studies excluded in primary filtering was that they were the wrong study type.

Additionally, a considerable number of studies (768) were measured in the wrong population. In most of these, quality of life was measured in patients with localised prostate cancer rather than advanced prostate cancer. Because a large number of studies measuring quality of life in the target population were identified, studies not using EQ-5D were also excluded in line with the inclusion/exclusion criteria.

In secondary filtering, most studies were again excluded for not using EQ-5D utilities as an outcome measure. Seventeen studies remained after primary and secondary filtering that met all the inclusion criteria. These studies are reviewed below.

Figure 33. Identification of HRQL studies of relevance to the decision problem



Overview of the relevant studies

Seventeen studies of relevance were identified, of which 14 captured utilities solely within advanced prostate cancer patients.

Three studies report utilities in prostate cancer patients without specifying the disease stage. Sandblom *et al* (2004) measured utilities for prostate cancer patients in the last year before death, split by men that died from prostate cancer and by men that died from other causes.[172] The study by Sennfalt *et al* (2004) provides utilities for men with or without pain.[161] The results are separated for different pain states, for stage of cancer (localised or advanced) and for type of treatment (life expectancy, palliative and curative treatment). Shimizu *et al* (2008) provided utilities for different subgroups of prostate cancer patients.[173] Results are summarised according to age, index of co-existent disease (ICED), sexual, urinary and hormonal function, having bowel problems and having lower urinary tract symptoms (LUTS).

Fernandez-Arjona *et al* (2012), Namiki *et al* (2008) and Reed *et al* (2011) provide utilities for advanced prostate cancer patients.[167,174,175] The report by Fernandez-Arjona *et al* is a validation of the Prostate Cancer Specific Quality of Life Instrument (PROSQOLI) in Spain. This includes a comparison with EQ-5D outcomes. EQ-5D utilities are given for a group of disseminated or locally advanced prostate cancer patients. Namiki *et al* report utilities for men diagnosed with stage C or D advanced prostate cancer. Utilities for patients treated with a one-month depot preparation of goserelin were compared with those for patients treated with a three-month depot preparation of goserelin. Measurements were made at baseline and at Month 3, 6, 9 and 12. Reed *at al* gave utilities at different moments before and after first occurrence of a skeletal-related event (SRE) in patients with advanced prostate cancer. Weinfurt *et al* (2005) report quality of life of patients with metastatic prostate cancer having experienced an SRE.[176]

The abstract by Hechmati *et al* compares utilities for patients with castration-resistant prostate cancer (CRPC) at risk for developing bone metastases to those that have already developed bone metastases.[160]

Five studies report specifically on metastatic CRPC (mCRPC). The abstract by Bahl *et al* 2013 gives utilities for patients treated with carbazitaxel plus prednisolone.[164] Measurements were performed at baseline, after every other cycle of therapy and post-treatment. The abstract by Diels *et al* reports a study designed to find an algorithm to map Functional Assessment of Cancer Therapy-Prostate (FACT-P) to EQ-5D utilities.[165] The EQ-5D utility measured in mCRPC patients is provided. The abstract by James *et al* (2011) provides the utility for mCRPC patients having progressed during or after first-line docetaxel chemotherapy.[177] The abstract by Wolff *et al* shows the quality of life of mCRPC patients, split into three groups: no past chemotherapy, with past chemotherapy and with ongoing chemotherapy.[159] The study by Wu *et al* 2008[178] is the only study in this group that is a full article, rather than an abstract. This study aimed to find an algorithm to map FACT-P and EORTC QLQ-C30 to EQ-5D. An EQ-5D measurement was performed for mCRPC patients.

Three studies measure quality of life in several types of cancer. Closs *et al* (2009) measures utilities in a group of younger and a group of older cancer patients with at least moderate intensity pain living at home.[179] Younger patients were aged 60 years or younger; older patients were aged 75 years and over. The abstract by Fehlings *et al* (2012) reports on quality of life measured before and three and six months after surgery for metastatic epidural SCC.[180] The study by Miksad *et al* (2011) measures quality of life in cancer patients using bisphosphonates who have osteonecrosis of the jaw compared with those who do not have osteonecrosis of the jaw.[181]

The study by Coyne *et al* (2008) reports utilities for men and women with overactive bladder or urinary incontinence.[182]

Glazener *et al* (2011) report utilities in patients with urinary incontinence after prostate cancer surgery, treated with either conservative treatment or standard management.[183]

Results

Table 40 includes a summary of the utilities by health state; Table D2 in Appendix D includes the results of the 17 included studies as well as information on methods used.

Table 40. Summary of utilities by health state

Health state		n	Mean	SD
Advanced prostate cancer, using 1-month depot goserelin[167]	Baseline		0.87	0.2
	3 months		0.92	0.1
	6 months		0.85	0.2
	9 months		0.88	0.1
	12 months		0.93	0.1
Advanced prostate cancer, using 3-month depot goserelin[167]	Baseline		0.83	0.2
	3 months		0.83	0.1
	6 months		0.88	0.1
	9 months		0.80	0.1
	12 months		0.88	0.1
Advanced prostate cancer, wait-and-see[161]	Pain-scale 1	20	0.874	
	Pain-scale 2	31	0.665	
	Pain-scale 3	2	0.090	
Advanced prostate cancer, palliative therapy[161]	Pain-scale 1	64	0.828	
	Pain-scale 2	123	0.646	
	Pain-scale 3	10	-0.004	
Advanced prostate cancer, curative therapy[161]	Pain-scale 1	17	0.910	
	Pain-scale 2	20	0.701	
	Pain-scale 3	3	0.173	
Advanced prostate cancer: disseminated symptomatic or locally advanced[174]			0.785	0.201
CRPC[160]	At high-risk for bone metastases	36	0.77	
	With bone metastases	165	0.59	
mCRPC[184]		276	0.635	0.309
mCRPC[159]	All patients		0.72	0.30
	No chemotherapy		0.81	0.27
	Past chemotherapy		0.66	0.30
	Ongoing chemotherapy		0.64	0.31
mCRPC treated with carbazitaxel 25 mg/m^2 every 3 weeks and oral prednisolone 10 mg daily[164]	Baseline	100	0.698	
	After cycle 2	97	0.730	
	After cycle 4	74	0.765	
	After cycle 6	63	0.761	
	After cycle 8	37	0.781	
	After cycle 10	28	0.81	
	Post-treatment	62	0.695	
mCRPC with disease progression[165]			0.67	
mCRPC with progression during or after first-line docetaxel treatment[177]	All patients		0.63	0.26
	ECOG-PS 0-1		0.38	
Metastatic prostate cancer, with SRE[176]	Zoledronic acid every 3 weeks		0.70	0.20

Health state		n	Mean	SD
Prostate cancer, using zoledronic acid[175]	90 days before SRE		0.694	
	60 days before SRE		0.692	
	30 days before SRE		0.289	
	30 days after SRE		0.615	
	60 days after SRE		0.628	
	90 days after SRE		0.644	
Prostate cancer, year before death[172]	Dead from PC	66	0.538	0.077
	Dead from other cause	100	0.564	0.067
Prostate cancer, > 1 year before death[172]		1076	0.77	0.015
Prostate cancer[173]		323	0.90	0.15
Prostate cancer, age[173]	51-59	7	0.77	0.14
	60-69	112	0.92	0.12
	70-79	172	0.91	0.15
	80-89	32	0.85	0.23
Prostate cancer, ICED[173]	0	60	0.93	0.14
	1	173	0.90	0.12
	2	74	0.89	0.15
	3	16	0.90	0.23
Prostate cancer, Sexual function[173]	16-85	80	0.94	0.11
	4-16	57	0.91	0.15
	3	35	0.91	0.14
	0	149	0.84	0.16
Prostate cancer, Urinary function[173]	100	170	0.94	0.11
	75-95	73	0.88	0.17
	11-74	80	0.84	0.17
Prostate cancer, Bowel problem[173]	100	134	0.94	0.12
	93-95	47	0.91	0.15
	81-92	62	0.92	0.13
	0-80	80	0.84	0.17
Prostate cancer, Hormonal function[173]	100	155	0.93	0.14
	95	26	0.91	0.12
	85-90	71	0.92	0.12
	35-80	71	0.84	0.17
Prostate cancer, LUTS[173]	0-7	168	0.93	0.12
	8-19	116	0.89	0.16
	20-35	38	0.83	0.19
Cancer, using bisphosphonate[181]	No ONJ		0.82	
	ONJ stage 1		0.78	
	ONJ stage 2		0.55	
	ONJ stage 3		0.32	
Metastatic epidural spinal cord compression[180]	Baseline		0.39	0.26
	6 months after surgery		0.55	0.30
Overactive bladder[182]		2851	0.85	0.2
	Continent	440	0.9	0.0
	Incontinent	263	0.9	0.0
	Postmicturition	162	0.9	0.0
	Voiding	287	0.8	0.0

Health state		n	Mean	SD
	Postmicturition + voiding	281	0.8	0.0
Urinary incontinence from PC surgery Conservative treatment	Baseline	200	0.797	0.216
	6 months	184	0.884	0.205
	12 months	187	0.879	0.209
Standard Management[183]	Baseline	206	0.782	0.225
	6 months	189	0.875	0.189
	12 months	189	0.887	0.176

Key: CRPC = castration-resistant prostate cancer; ICED = index of co-existant disease; mCRPC = metatstatic CRPC; ONJ = osteonecrosis of the jaw; SD = standard deviation; SRE = skeletal-related events

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Three of the reviewed studies provide utilities specifically for advanced prostate cancer. The outcomes reported by Namiki *et al*[167] are similar to the outcomes of the CS21 study, mapped using the EORTC-8D and the Kontodimopoulos algorithm.[170] The outcomes by Fernandez-Arjona[174] are similar to those mapped using the McKenzie and van der Pol algorithm.[171]

The Reed *et al* study[185] measures SREs. The utility value of 0.78 falls between the CS21 trial utilities for fractures and JSS using the Kontodimopoulos algorithm and is higher than both of those utilities when using the McKenzie and van der Pol algorithm.

The effects of using alternative sources for utilities are explored in the scenario analyses. In the base case, where possible, the utilities are sourced from the clinical trial data using the mapping algorithm by Kontodimopoulos *et al* (2009). For the model states that go beyond the trial data, the HRQL values are sourced from the literature. Preference is given to studies that include UK patients (European studies are also favoured to non-European studies) and are based on data from a large number of patients.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

In line with the approach outlined in Section 7.4.4, HRQL data have, where possible, been taken from the clinical trial using the algorithm by Kontodimopolous *et al*.[170] For mild and severe SCC, it was not possible to estimate HRQL using the trial data. To be consistent in the approach for modelling this AE (outlined in Section 7.3.1), the values used are the same as those used by Lu *et al*.[144]

To retain consistency with the approach used by Lu *et al*,[144] the model tracks patients who have experienced either: SCC or a severe fracture or severe JSS. The lower utility value associated with these events is applied for the duration of the patient's

lifetime while the patient remains in pain. For more minor AEs, the decrement is only applied for the first cycle in which the event occurs.

In accordance with the approach adopted by Lu *et al*,[144] the HRQL decrement in later lines of treatment is applied multiplicatively rather than additively; for example, as shown in Table 41, a patient on first-line treatment with severe SCC has a utility of 0.195. If they had not experienced an AE, their utility would be 0.887. If a patient in the chemotherapy disease states had not suffered SCC, their utility would be 0.67. If a patient in the chemotherapy disease states had severe SCC, their utility would be 0.151 (0.195*(0.67/0.887). This same approach is used to estimate the HRQL for the other AEs in the disease states later in the treatment pathway.

The utility value of patients who experience a non-fatal cardiovascular event is also estimated using the trial data, and the utility in later lines of therapy uses a multiplicative approach. However, as discussed in Section 7.3.1, in contrast to the approach taken for SCC, fractures and JSS, patients experiencing a non-fatal cardiovascular event are not tracked for the purpose of utility calculations as the available literature suggests only slight decrements in long-term utility for the majority of cardiovascular events. The model, therefore, only applies the lower utility value for one cycle. This approach was adopted to avoid unnecessary complexity. This simplifying step is conservative, as more patients have a non-fatal cardiovascular event when treated with LHRH agonists.

Utility decrements are not included for any other AEs, including injection site reactions, as the clinical trial data indicate that the quality of life of patients receiving degarelix is either higher or the same as for those receiving LHRH agonists, indicating that injection site reactions are not impacting quality of life in any meaningful way.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table 41. Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
First-line treatment	0.887	(0.879–0.894)	7.4.4	Mapping algorithm produces an EQ-5D based utility in line with the reference case
Anti-androgen addition	0.753	(0.697–0.806)	7.4.4	Mapping algorithm produces an EQ-5D based utility in line with the reference case
Anti-androgen withdrawal	0.753	(0.697–0.806)	7.4.4	Assumed the same as for anti-androgen addition based upon Bayoumi *et al*[166]
First-line chemotherapy	0.689	(0.686–0.692)	7.4.5	Study using the EQ-5D identified using the literature search. Study by Bahl *et al*[164] chosen as included UK patients and had a large number of patients.
Palliative care	0.551	(0.527–0.580)	7.4.5	Study using the EQ-5D identified using the literature search. Study by Sanbolm *et al*[172] chosen as included European patients.
*Adverse events**				
Severe SCC	0.195	(0–0.390)	7.4.8	Used by Lu *et al*[144] in earlier analysis
Mild SCC	0.370	(0.270–0.470)	7.4.8	Used by Lu *et al* in earlier analysis
Fracture	0.533	(0.19–0.88)	7.4.4	Mapping algorithm produces an EQ-5D based utility in line with the reference case
Joint-related signs and symptom	0.816	(0.75–0.90)	7.4.4	Mapping algorithm produces an EQ-5D based utility in line with the reference case
Non-fatal CV event	0.803	(0.66–0.94)	7.4.4	Mapping algorithm produces an EQ-5D based utility in line with the reference case

Key: CV cardiovascular; EQ-5D = EuroQol five-dimensions; HRQL = health-related quality of life; SCC = spinal cord compression

* The value shown for the adverse events is the utility value when on first-line treatment. In later lines of treatment the value is calculated by taking the given adverse event value in first line and multiplying it by the ratio between the HRQL value in the first line of treatment and the HRQL value in the line of treatment the patient is in (e.g. HRQL of a patient with severe SCC when on chemotherapy = 0.2*(0.67/0.887))

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Advisory board details have been previously described in Section 7.3.5.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

As outlined in Section 7.4.8, HRQL is reduced by an individual experiencing an AE. This reduction happens for the duration of the patient's lifetime if they suffer severe SCC, mild SCC, and while they remain in pain if they suffer a severe fracture or severe JSS. It is applied for only one cycle if they experience a non-fatal cardiovascular event, or mild or moderate fracture or JSS. If a patient does not suffer an AE, they experience the HRQL value associated with the model state. These values are reported in the first five rows of Table 41.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

As discussed in Section 7.4.8, the health effect associated with a non-fatal cardiovascular event is not fully included. This has been conservatively excluded to maintain simplicity in the model.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

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[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

N/A – quality of life is tracked via the model health states.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

As described in Section 7.4.2, HRQL is assumed to worsen as a patient's disease progresses and they, therefore, move through the model states. This assumption is supported by the literature reviewed in Section 7.4.5. The utilities associated with the different disease states are shown in Table 41. Section 7.4.8 outlines how an individual's utility changes over time if they have an AE.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

N/A

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

No specific Healthcare Resource Groups (HRG) or tariff currently exist for the costing of treatment of hormone-dependent advanced prostate cancer. The HRG likely to cover this are:

- LB06D Kidney, Urinary Tract or Prostate Neoplasms, with length of stay 2 days or more, with Major CC
- LB06E Kidney, Urinary Tract or Prostate Neoplasms, with length of stay 2 days or more, with Intermediate CC
- LB06F Kidney, Urinary Tract or Prostate Neoplasms, with length of stay 2 days or more, without CC
- LB06G Kidney, Urinary Tract or Prostate Neoplasms, with length of stay 1 day or less.

The relevant payment by results (PbR) tariff for 2012/13 and NHS Reference Cost for 2011/12 may be found on the Department of Health website.[186,187] In practice, coding may vary between providers.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The intervention being appraised (degarelix) does not have a specific PbR tariff associated with it; therefore, a PbR costing approach has not been used. Costs related to the monitoring of patients and management of AEs have been estimated using NHS Reference Costs, the Personal and Social Services Research Unit (PSSRU) and literature.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy

used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

Search strategy

A broad systematic review was conducted in March 2013 to identify cost and resource use studies for advanced prostate cancer patients. A precise search strategy was utilised, incorporating terms for prostate cancer and costs and resource use. To ensure the published literature was comprehensively reviewed, a wide range of databases were searched (see Appendix 10, Section 10.10).

Appendix 10 describes the search strategy used to search the databases. Having identified studies of potential relevance from a wide range of databases, the titles and abstracts were reviewed in greater detail to assess their relevance for informing the overall decision problem. The eligibility criteria employed for assessing the relevance of the different studies are shown in Appendix 10.3.6.

Identification of relevant studies

The papers that appeared to meet the inclusion criteria after a detailed review of the title and abstract were obtained for a secondary review. In this secondary review the entire article was assessed according to the criteria outlined in Appendix 10.3.6.

As illustrated in Figure 34, the majority of papers initially identified failed to meet the inclusion criteria. The reason for the exclusion of 1,814 of 4,095 studies excluded was that they were the wrong study type, while 1,408 were excluded because they were not from the UK.

In secondary filtering, most studies were excluded for not being UK-based. Eleven studies remained that met all the inclusion criteria, both after primary and secondary filtering.

Results

Table 42 provides a summary of the costs by health state,[144,183,188-193] and Table D3 in Appendix D includes the results of the 11 studies as well as information on methods used.[144,183,188-196]

Table 42. Identification of cost and resource use studies of relevance

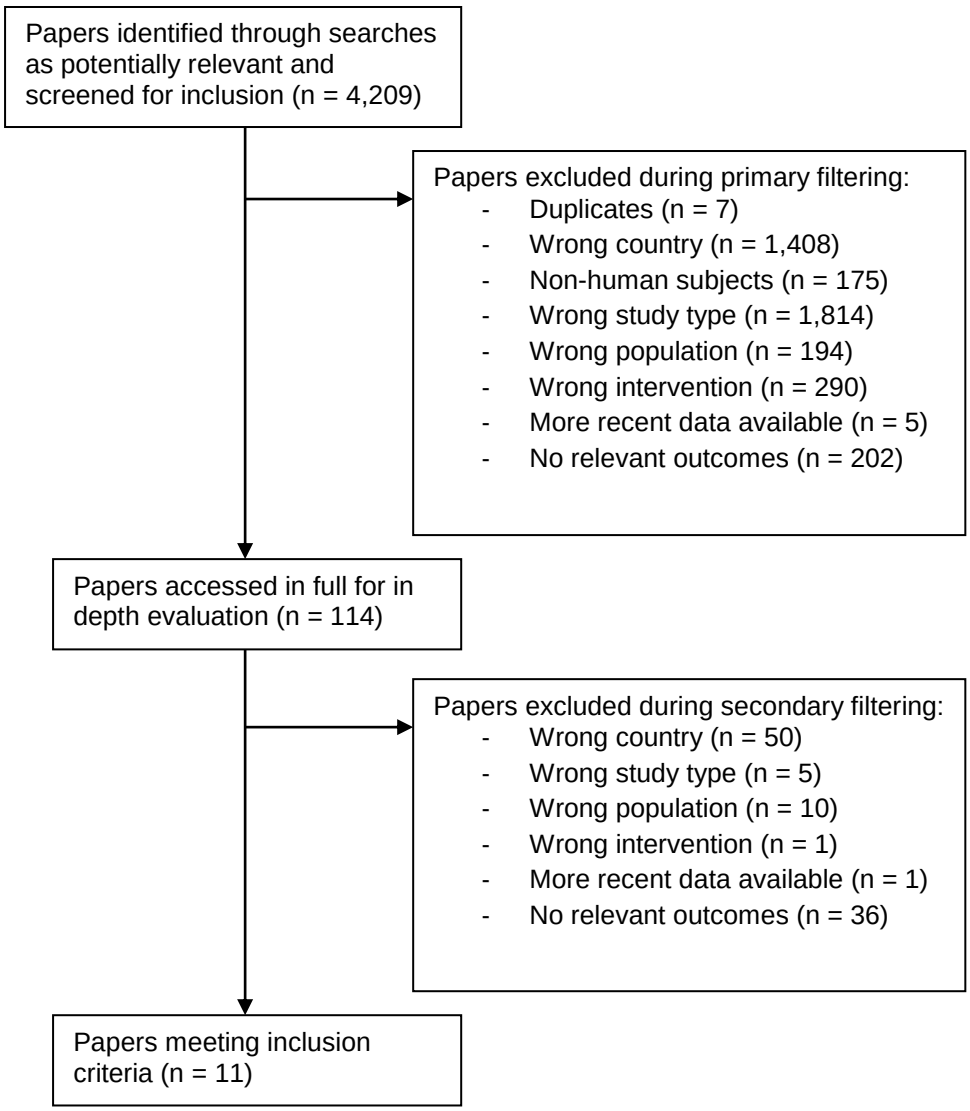
Health state		Cost	Source
LHRH analogue + steroidal anti-androgen	Per month	£151-222	Chamberlain *et al*[188]
LHRH analogue + non-steroidial anti-androgen	Per month	£232-253	Chamberlain *et al*[188]
Total cost of treatment	Docetaxel	£8,329	Collins *et al*[189]
	Mitoxantrone	£1,695	Collins *et al*[189]
Follow-up cost	Docetaxel	£7,438	Collins *et al*[189]
	Mitoxantrone	£8,016	Collins *et al*[189]
Costs in first year after diagnosis*	Diagnostic intervention	€578 (£457)	Fourcade *et al*[190]
	Surgery	€316 (£250)	Fourcade *et al*[190]
	Chemotherapy	€78 (£62)	Fourcade *et al*[190]
	Radiotherapy	€1,598 (£1,262)	Fourcade *et al*[190]
	Hormonal therapy	€601 (£475)	Fourcade *et al*[190]
	Total	€3,171 (£2,505)	Fourcade *et al*[190]
Urinary incontinence after PC	NHS	£389.82	Glazener *et al*[183]
	Patient	£1,669.31	Glazener *et al*[183]
	Participant travel and companion travel and time-off-work	£305.53	Glazener *et al*[183]
Palliative care		£3,765.10	Guest *et al*[191]
Metastatic PC	Hormonally responsive	£2,302	Hummel *et al*, 2003[195]
	Hormonally refractive	£2,169	Hummel *et al*, 2003[195]
Radiotherapy for localised or locally advanced PC	PSA failure (annual)	£670.67	Hummel *et al,* 2010[196]
	Hormone therapy	£1,324.11	Hummel *et al,* 2010[196]
Late gastrointestinal effects of RT	Monitoring grade 2	£265	Hummel *et al,* 2010[196]
	Monitoring grade 3	£530	Hummel *et al,* 2010[196]
	Treatment grade 2	£1,525	Hummel *et al,* 2010[196]
	Treatment grade 3	£3,858	Hummel *et al,* 2010[196]
Monitoring	Pre-PSA-fail	£47.26	Hummel *et al*, 2012[192]
	Post-PSA-fail	£670.67	Hummel *et al*, 2012[192]
Hormone therapy		£1,324	Hummel *et al*, 2012[192]
Treatment of late GI effects	Grade 2	£264.99	Hummel *et al*, 2012[192]
	Grade 3	£529.98	Hummel *et al*, 2012[192]
Maintenance therapy	Leuprorelin 3-month depot (L3)	£1,656	Lloyd *et al*[193]

Health state		Cost	Source
	Goserelin 12-week depot (G48)	£1,507	Lloyd *et al*[193]
	Leuprorelin 1-month depot (L1)	£1,949	Lloyd *et al*[193]
	Goserelin 28-day depot (G28)	£2,121	Lloyd *et al*[193]
	Leuprorelin 6-month depot (L6) (based on daily cost of L3)	£1,580	Lloyd *et al*[193]
	L6 based on daily cost G28	£1,169	Lloyd *et al*[193]
	L6 based on daily cost G48	£1,235	Lloyd *et al*[193]
Ambulant patient, cared at home	Per day	£13	Lu *et al*[144]
Non-ambulant patient cared at home or in nursing home	Per day	£137	Lu *et al*[144]
TURP	Per patient	£4,133	Lu *et al*[144]
Catheterisation	Per patient	£1,331	Lu *et al*[144]

Key: GI = gastro-intestinal; PC=prostate cancer, GI = gastro-intestinal; RT = radiotherapy; TURP = transurethral resection of the prostate

* Exchange rate of £0.79 = €1 as per the source paper

Figure 34. Identification of cost and resource use studies of relevance to the decision problem



7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Advisory board details have been previously described in Section 7.3.5.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The costs of treatment with degarelix or LHRH agonists are shown in Table 43 below. Treatment costs have been calculated using the *British National Formulary (BNF)*[6] and eMIT.[104] It is assumed, in line with UK practice, that flare cover is provided with bicalutamide 50 mg using a 28-tablet pack for all LHRH agonists. The actual dose of bicalutamide administered varies between regions, with some hospitals recommending longer cover times than others; however, as packs are not split, the cost of a full pack is included for all patients.

As different UK regions administer degarelix and LHRH agonists in different settings (primary or secondary care), the model base case assumes that 50% of administrations of degarelix and LHRH are carried out by a practice nurse in a GP surgery and 50% by a nurse in a hospital, with frequency depending on whether the drug is administered monthly, three-monthly or six-monthly. The impact of location of care is tested in sensitivity analysis. The time taken to administer has been assumed to be the average appointment length for a

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

practice nurse (15.5 minutes) to include all paperwork and other requirements. In reality, administration times for degarelix and LHRH agonists are shorter (degarelix typically takes a few minutes for reconstitution).

Treatment initiation costs are assumed to consist of a CT and bone scan, a PSA test and a urologist outpatient appointment (initial prescription). Following the initial prescription, follow-up appointments with a urologist are assumed to occur every six months, at which time a PSA test is administered,

The costs of later lines of treatment and AEs are described in Sections 7.5.6 and 7.5.7.

Table 43. Unit costs associated with the technology in the economic model

Items	Degarelix	Ref. in submission	Leuprorelin 3-monthly	Leuprorelin monthly	Goserelin 3-monthly	Goserelin monthly: Zoladex	Goserelin monthly: Novgos	Triptorelin 3-monthly	Triptorelin monthly: Decapeptyl	Triptorelin monthly: Gonapeptyl	Triptorelin 6-monthly
Technology cost	£260 for starter injections £129.37 for monthly maintenance injection	1.10 Cost of LHRH agonists and degarelix: BNF[6] Cost of bicalutamide flare cover: eMIT 2013[104]	£225.72 for 3 monthly injection £3.07 for flare cover for 28 days	£75.24 for monthly injection £3.07 for flare cover for 28 days	£235 for 3-monthly injection £3.07 for flare cover for 28 days	£65 for monthly injection £3.07 for flare cover for 28 days	£58.50 for monthly injection £3.07 for flare cover for 28 days	£207 for 3-monthly injection £3.07 for flare cover for 28 days	£69 for monthly injection £3.07 for flare cover for 28 days	£81.69 for 3-monthly injection £3.07 for flare cover for 28 days	£414 for 6-monthly injection £3.07 for flare cover for 28 days
Mean cost of technology treatment	£260 first 28 days £129.37 per 28 days thereafter		£78.31 first 28 days £75.24 per 28 days thereafter	£78.31 first 28 days £75.24 per 28 days thereafter	£81.40 first 28 days £78.33 per 28 days thereafter	£68.07 first 28 days £65.00 per 28 days thereafter	£61.57 first 28 days £58.50 per 28 days thereafter	£72.07 first 28 days £69 per 28 days thereafter	£72.07 first 28 days £69 per 28 days thereafter	£84.76 first 28 days £81.69 per 28 days thereafter	£72.07 first 28 days £69 per 28 days thereafter
Administration cost	£12.14 per 28 days	Average of cost of a practice nurse visit (15.5 minutes) and cost of a nurse on a day ward for 15.5 minutes[103]	£12.14 per 84 days	£12.14 per 28 days	£12.14 per 84 days	£12.14 per 28 days	£12.14 per 28 days	£12.14 per 84 days	£12.14 per 28 days	£12.14 per 28 days	£12.14 per 168 days
Monitoring cost	On initiation:, £93.96 for an outpatient urologist consultation Thereafter: consultation every 6 months	OPATT code 101. CLFUSFF[186]	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix

Items	Degarelix	Ref. in submission	Leuprorelin 3-monthly	Leuprorelin monthly	Goserelin 3-monthly	Goserelin monthly: Zoladex	Goserelin monthly: Novgos	Triptorelin 3-monthly	Triptorelin monthly: Decapeptyl	Triptorelin monthly: Gonapeptyl	Triptorelin 6-monthly
Tests	On initiation: £67.14 for a bone scan, £105.45 for a CT scan, £3.09 for a PSA test Thereafter: PSA test once every 6 months	RA15Z DIAGIM_OP[186] RA09A DIAGIM_OP (19 years and older) [186] DAP823 Total other currencies[186]	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix	Same as degarelix
Total	£529.63 on initiation £157.69 per 28 days thereafter		£347.94 on initiation £95.46 per 28 days thereafter	£347.94 on initiation £103.56 per 28 days thereafter	£351.03 on initiation £98.55 per 28 days thereafter	£337.70 on initiation £93.32 per 28 days thereafter	£331.20 on initiation £86.82 per 28 days thereafter	£341.70 on initiation £89.22 per 28 days thereafter	£341.70 on initiation £97.32 per 28 days thereafter	£354.39 on initiation £110.01 per 28 days thereafter	£341.70 on initiation £87.20 per 28 days thereafter

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Table 44 below provides a summary of the costs associated with each of the health states in the model. Treatment costs are sourced from eMIT and *BNF* and all other costs are sourced from NHS Reference Costs, the PSSRU or the published literature. The costs and resource use assumptions presented in the table were validated by UK clinicians (see Section 7.5.4).

Table 44. List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
First-line treatment	Technology	Degarelix: £260 first 28 days £129.37 per 28 days thereafter Goserelin 3 monthly: £81.40 first 28 days £78.33 per 28 days thereafter	7.5.5
	Staff	£12.14 per 28 days, 56 or 84 days depending on treatment regime On initiation: £93.96 and 6-monthly thereafter	7.5.5
	Tests	On initiation: £67.14 + £105.45 + £3.09 6 monthly: £3.09	7.5.5
	Total	Degarelix: £529.63 on initiation £157.69 per 28 days thereafter Goserelin 3 monthly: £351.03 on initiation £98.55 per 28 days thereafter	
Anti-androgen addition	Technology	Degarelix: £135.96 per 28 days Goserelin 3 monthly: £84.92 per 28 days	Cost of degarelix or goserelin maintenance therapy + 150 mg bicalutamide at £0.24 per day (eMIT 2013)[104]
	Staff	£12.14 per 28 days, 56 or 84 days depending on treatment regime On initiation: £93.96 and 3-monthly thereafter	7.5.5
	Tests	On initiation: £67.14 + £105.45 + £3.09 3 monthly: £3.09	7.5.5

Health states	Items	Value	Reference in submission
	Total	Degarelix: £399 on initiation £173.86 per 28 days thereafter Goserelin 3-monthly: £347.96 on initiation £114.73 per 28 days thereafter	
Anti-androgen withdrawal	Technology	Degarelix: £135.96 per 28 days Goserelin 3-monthly: £84.92 per 28 days	7.5.5
	Staff	£12.14 per 28 days, 56 or 84 days depending on treatment regime On initiation: £93.96 and 3-monthly thereafter	7.5.5
	Tests	On initiation: £67.14 + £105.45 + £3.09 3 monthly: £3.09	7.5.5
	Total	Degarelix: £399 on initiation £173.86 per 28 days thereafter Goserelin 3-monthly: £347.96 on initiation £114.73 per 28 days thereafter	

Health states	Items	Value	Reference in submission
First-line chemotherapy	Technology	Per 3 weekly session: 75 mg/m2 docetaxel Mean body surface area 1.8m2 1.7 x 80 mg vials at £32.40 per vial Total docetaxel: £54.68 12 x 2 mg tablets of dexamethasone at £0.04 per tablet Total docetaxel: £0.43 42 x 5 mg tablets of prednisolone per day at £0.01 per tablet Total prednisolone: £1.51 Total of 7.3 sessions on average per course[97] Total drug cost per course: £405.13	eMIT[104]
	Staff	£113.17 oncologist visit per 3 weekly session £826.14 per course	OPATT code 800. CLFUSFF[186]
	Tests	On initiation & withdrawal: £89.52 bone scan £140.59 CT scan £192.68 MRI On initiation: £3.09 blood test £637.28 per course	RA15Z DIAGIM_OP RA09A DIAGIM_OP (19 years and older) RA01A DIAGIM_OP (19 years and older) DAP823 Total other currencies[186]
	Adverse events and concomitant medication	Blood, bisphosphonates, epoetin and G-CSF: £683.17 per course	NICE submission for docetaxel: TA101 prices inflated to 2011/2012[97]
	Total	£3,426.87 per course	
Second line chemotherapy	Technology	4 x 250mg tablets abiraterone per day at £24.42 per tablet 2 x 5 mg prednisolone tablets per day at £0.01 per tablet £2,735.19 per 28 days	BNF[6]

Health states	Items	Value	Reference in submission
	Staff	£113.17 oncologist every 3 weeks	OPATT code 800. CLFUSFF[186] Every 2 weeks for 3 months and monthly thereafter. Costed every 3 weeks given average duration of treatment of approx 6 months
	Tests	On initiation & withdrawal and every 6 weeks for 5% of patients[147]: £89.52 bone scan £140.59 CT scan £192.68 MRI On initiation and once every 6 weeks: £3.09 blood test	RA15Z DIAGIM_OP RA09A DIAGIM_OP (19 years and older) RA01A DIAGIM_OP (19 years and older) DAP823 Total other currencies[186]
	Adverse events and concomitant medication	Bisphosphonates and G-CSF: £56.98 per 28 days Due to high level of censorship in the abiraterone submission adverse event costs could not be included	Abiraterone submission[147], duration of events taken from cabazitaxel submission[197] as abiraterone submission was censored
	Total	£788.17 on initiation + £2,955.69 per 28 days	
Supportive Care	Total	£1,754 for follow-on treatment after failing abiraterone + £132.38 per 28 days for supportive care	Cabazitaxel submission [197] (ACD slides, Slide 9)[198] using the cost from the cabazitaxel arm Abiraterone submission[147]
Palliative Care	Total	£4,182.51 for 3 months prior to death – applied on death	Abiraterone submission[147]

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The cost-effectiveness analysis includes the costs of all AEs related to disease progression or treatment that could be associated with anything more than a minimal cost. The costs of injection site reactions and hot flushes associated with degarelix are not included, as it is unlikely additional costs would be incurred.

The following AEs are included within the model (the modelling approach to the AEs is outlined in Sections 7.3.1and 7.3.2):

- Cardiovascular events – as these are a reported complication of LHRH agonist treatment (see Section 6.9.2). Both fatal and non-fatal events are included within the model.
- MSEs – disease progression can result in musculoskeletal complications such as SCC, fracture and JSS (see Section 6.9.2). Based on the modelling carried out by Lu *et al*, the costs associated with SCC have been included in the model.[144] Additionally, costs associated with fracture and JSS are included in the model because pooled analysis showed a significant difference between degarelix and LHRH agonists for these MSEs.

The costs of AEs have been calculated, based on NHS Reference Costs and PSSRU costs; they were validated by UK clinicians (see Section 7.5.4).

The cost of cardiovascular events has been calculated using the weighted mean NHS Reference Cost for the five types of cardiovascular events experienced within the trial and weighted according to the proportion of patients experiencing each type of event in the trial (pooled across both arms as the types of events were similar in both arms of the trial).[110] Table 49 shows the calculation of acute cardiovascular event costs. Long-term follow-up costs have been taken from the published literature (see Table 50).

The cost of fractures has been calculated, based on published literature and dependent on the severity of the event (see Table 45): The proportion of patients experiencing each type of event in the trial was pooled across both arms as the severity of events was similar in both arms of the trial.[110]

Table 45. Calculation of fracture costs

Cost of fractures			Initial event cost	% of events
Severe	Hip fracture	Stevenson 2004[199], inflated to 2011/2012 costs using PSSRU Follow-up costs captured below	£8,493.52	30%
Moderate	Humerus fracture	Stevenson 2004, inflated to 2011/2012 costs using PSSRU Follow-up: 1 GP visit + follow-up costs as per vertebral fracture from Stevenson *et al* for 1 year for the 12.5% of patients with spinal, vertebral or femoral neck fractures from CS21	£1,419.96	56%
Mild	Wrist fracture	Stevenson 2004, inflated to 2011/2012 costs using PSSRU Follow up: 1 GP visit	£375.05	15%

The cost of JSS has been calculated, based on NHS Reference Cost codes dependent on the severity of the event (see Table 46). The proportion of patients experiencing each type of event in the trial was pooled across both arms as the severity of events was similar in both arms of the trial.

Table 46. Calculation of joint-related signs and symptoms costs

Cost of fractures			Event cost	% of events
Severe	HD39A	Initial inpatient: Inflammatory Spine, Joint or Connective Tissue Disorders weighted average of HD23A, HD23B and HD23C Follow up costs captured below	£1,352.05	5%
Moderate	HD39B	Initial day case: Inflammatory Spine, Joint or Connective Tissue Disorders weighted average of HD23A, HD23B and HD23C +2 GP visits + 6 visits to the physio + 1 visit to a consultant + 0.5 MRI scans	£923.27	38%
Mild		Initial GP visit +1 GP visit for follow-up	£86.00	45%

The costs of long-term follow-up after a severe MSE were also calculated and applied to patients remaining in pain each cycle (see Table 47). These follow-up costs were applied to both fractures and JSS.

Table 47. Calculation of long-term follow up costs for musculoskeletal events

Severity	Visits to GP	Visit to physiotherapist*	Visits to consultant**	MRI	Other	Total cost per year
Severe fracture	2				⅓* vertebral fracture follow-up[199]	£182.85
Severe JSS	2	6	1	1		£549.72
* £37.35 per session NCLFUSFF 650: OPATT ** £95.14 per appointment CLFUSFF 110N: Trauma and Orthopaedics: Non-trauma						

The costs of SCC are calculated, as shown in Table 48, and based on the same methodology as reported by Lu *et al*.[144] Initially, patients either receive the cost of radiotherapy or surgery, based on the proportions shown in Table D1 in Appendix D. After patients receive rescue therapy and are discharged from hospital (length of stay assumed to be ten days),[200] they receive supportive care, which is ongoing for the rest of the patients' lifetime. Patients who are ambulant receive a daily cost for home care and patients who are non-ambulant receive a daily cost for either home care or care in a nursing home. The proportion of patients who are ambulant versus non-ambulant can be found in Table D1 in Appendix D.

Table 48. Calculation of the costs of spinal cord compression

Description	*Cost*	*Source*
Costs for RT per patient	£1,459.95	CG75[200] (pp81) £1276.50 (06-07) Inflated using PSSRU indices
Costs for surgery per patient	£25,293.83	CG75 (pp81) £9,350 (06-07) plus RT. Inflated using PSSRU indices
Total daily cost per patient cared at home (ambulant)	£34.00	PSSRU 2012 average cost for an hour of care (the assumed amount per week)
Total weekly cost per patient cared at home or in a nursing home (non-ambulant). Assumption taken from Lu *et al*[144]	£158.00	PSSRU 2012 average cost for a week in accommodation

Table 49 shows the calculation of acute cardiovascular event costs, and the long-term follow-up costs are shown in Table 50.

Table 49. Calculation of cardiovascular adverse event costs

Cost of cardiovascular events		Cost	Prop*	Proportion of non fatal CV events	Proportion of fatal CV events
Ischaemic cerebrovascular conditions					
AA22A	Non-transient stroke or cerebrovascular accident, nervous system infections or encephalopathy, with CC	£2,771.00	77%	**14.29%**	**23.08%**
AA22B	Non-transient stroke or cerebrovascular accident, nervous system infections or encephalopathy, without CC	£1,673.00	5%		
AA29A	Transient ischaemic attack with CC	£931.00	17%		
AA29B	Transient ischaemic attack without CC	£559.00	1%		
Total cost for ischaemic cerebrovascular conditions		**£2,375.58**	**100%**		
Myocardial Infarction					
EB10Z	Actual or suspected myocardial infarction	£1,582.00	100%	**20.41%**	**25.96%**
Total cost for myocardial infarction		**£1,582.00**	**100%**		
Other Ischaemic Heart Disease		-	-		
PA22Z	Chest pain	£542.00	100%	**26.53%**	**29.81%**
Total cost for other ischaemic heart disease		**£542.00**	**100%**		
Haemorrhagic cerebrovascular conditions		-	-		
AA23A	Haemorrhagic cerebrovascular disorders with CC	£2,858.00	93%	**8.16%**	**21.15%**
AA23B	Haemorrhagic cerebrovascular disorders without CC	£1,507.00	7%		
Total cost for haemorrhagic cerebrovascular conditions		**£2,760.39**	**100%**		
Embolic and thrombotic events, arterial		-	-		
DZ09A	Pulmonary embolus with major CC	£1,930.00	45%	**30.61%**	**0.00%**
DZ09B	Pulmonary embolus with intermediate CC	£1,374.00	40%		
DZ09C	Pulmonary embolus without CC	£884.00	16%		
Total cost for embolic and thrombotic events, arterial		**£1,546.47**	**100%**		
Total cost of a non-fatal CV event		**£1,504.77**			
Total cost of a fatal CV event		**£1,704.41**			

Key: CC = Complications or Comorbidities; CV = cardiovascular

*Proportion of events experienced of that type within NHS Reference Costs (calculated using activity levels

Table 50. Calculation of cardiovascular long-term follow-up costs

Annual cost following serious CV events	Cost per year	Reference
Ischaemic cerebrovascular conditions	£2,396.60	Youman 2003[201] five year cost inflated to 2011/2012 prices using PSSRU[103]
Myocardial infarction	£668.46	2006 analysis for pharmacological update to the guideline that the costs post-MI were £500 per year inflated from 2002/2003 to 2011/2012
Other ischaemic heart disease	£50.73	NICE guidance for Stable Angina (2012)[202] Sublingual tablets, glyceryl trinitrate: 500micrograms once weekly £1.11 per year[102] Calcium channel blocker (Verapamil): 80mg 3 times daily £14.35 per year[102] Once yearly GP consultation: £43 per year[103]
Haemorrhagic cerebrovascular conditions	£2,396.60	Youman 2003[201] five year cost inflated to 2011/2012 prices using PSSRU[103]
Embolic and thrombotic events, arterial	£0.00	Assumed 0
Weighted average annual cost	**£687.89**	
Weighted average per cycle cost	**£52.73**	

Key: CV = cardiovascular; PSSRU = Personal Social Services Research Unit

Table 51 shows a summary of the AE costs included in the model.

Table 51. List of adverse events and summary of costs included in the economic model

Adverse events	Items	Value	Reference section
CV event	Technology	Not included	
	Staff	Not included	
	Hospital costs	£1,504.77 for a non-fatal event + £52.73 follow-up per year £1,704.41 for a fatal event	7.5.7
	Total	£1,504.77 for a non-fatal event + £52.73 follow-up per year £1,704.41 for a fatal event	
Fracture	Technology	Not included	
	Staff	Not included	
	Hospital costs	£375.05 for a mild fracture £1,419.96 for a moderate fracture £8,493.52 for a severe fracture + £182.85 per year follow-on costs while in pain	7.5.7
	Total	£3,471.08 for a fracture on average	
Joint-related signs and symptoms	Technology	Not included	
	Staff	Not included	
	Hospital costs	£86 for a mild case £923.27 for a moderate case £1,352.05 for a severe case + £549.72 per year follow-on costs while in pain	7.5.7
	Total	£496.64 on average	
Spinal cord compression	Technology	Not included	
	Staff	Not included	
	Hospital costs	£1,459.95 for radiotherapy £25,293.83 for surgery £34 per day for home care £158 per week in a nursing home	7.5.7

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

All costs used within the model have been included in the sections above.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The uncertainty around the following structural assumptions has been included within the model:

- **Comparator:** sensitivity analysis comparing degarelix to the cheapest and most expensive LHRH agonists currently used in the UK is presented.[100] The sensitivity analysis conducted assumes equal efficacy between LHRH agonists as the mixed treatment comparison presented in Section 6.7 and literature evidence support the assumption of a class effect.[136-142] Therefore, the only variation between comparator treatments is in the cost of drugs and resource use.
- **Modelling of treatment efficacy:** within the model base case, the long-term efficacy of degarelix in terms of PSA progression is based on extrapolation from the clinical trial data. Within sensitivity analysis, the curve chosen for the extrapolation is tested along with the assumption that benefit continues long term. One scenario analysis investigates the impact of setting the efficacy of degarelix equal to LHRH after one year (that is, no sustained benefit following the end of CS21). Sensitivity analysis is also conducted to examine the impact of assuming no difference in PSA progression between the two treatments, in which case benefits are derived solely from preventing MSEs and cardiovascular events. This analysis presents a worst-case scenario.

- **Modelling of mortality:** within the base-case analysis, it is assumed that metastatic patients who progress experience a higher rate of mortality than those who do not, based on available literature.[107] The impact of assuming the same rate of mortality for progressed and non-progressed patients is tested. Additionally, the model includes the option to base mortality on general population life tables rather than prostate-cancer-specific estimates.
- **Treatment continuation:** within the base-case analysis, it is assumed that treatment continues until patients progress beyond advanced disease, in line with the licence for degarelix. In some UK centres, LHRH or degarelix treatment is actually continued until death. The impact of continuing treatment until death is modelled.
- **Setting of care:** the impact of assuming treatment is carried out by practice nurses or wholly in a hospital setting is tested.
- **Modelling of MSEs:** there is an option to include MSEs within the model structure or to remove them. Additionally, the curve choice for the time to MSEs is included in a sensitivity analysis as is the type of MSEs included (solely those that were significantly different between the treatments or all events). Within the base case model, the proportion of patients experiencing mild, moderate and severe events is set equal in both arms, sensitivity analysis is conducted using separate trial results for each arm.
- **Modelling of cardiovascular events:** within the base case, it is assumed that patients with a history of CVD have a higher risk of fatal and non-fatal cardiovascular events when receiving LHRH agonists than when not receiving LHRH agonists. The impact of assuming the same rate of cardiovascular events for both arms is tested in a sensitivity analysis, as is the curve choice used to model the time to events.
- **Utilities:** the model includes the option to use utilities derived primarily from the literature or from alternative utility mappings, using the SF-12 and EORTC QLQ C30 from the CS21 trial.[13,151,164,166,167,172,203,204]
- **Anti-androgen choice:** the model includes the option to analyse the effects of using cypterone acetate rather than bicalutamide for both flare cover and anti-androgen addition.
- **Abiraterone:** the impact of inclusion of abiraterone as second-line treatment following docetaxel chemotherapy is tested in sensitivity analysis.

In addition to the above, the model includes a subgroup analysis modelling only the effects of degarelix and LHRH agonists in the higher-risk PSA >20 ng/ml population.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The following variables were included in sensitivity analysis:

- Discount rates for costs and QALYs (0–6%, according to guidelines, used only in one-way sensitivity analysis)

- The cost of resource use and palliative care (uniform distribution: ±30%, as no other information was available)
- The cost of AEs (uniform distribution: ±30% as no other information was available)
- Utilities within each health state and utility decrements for AEs (beta distribution: based on either the published ranges or the standard errors from the trial data)
- The curve fit parameters for time to AEs and the severity of those events (multivariate normal distribution: 95% confidence interval [CI], based on trial data)
- The proportion of patients responding to treatments after first-line (uniform distribution: ±10% as no other information was available)
- The curve fit parameters for PSA progression for degarelix (multivariate normal distribution: 95% CI, based on trial data)
- The HR for degarelix efficacy compared with LHRH agonists (uniform distribution: 95% CI, based on trial data)
- The HR for mortality for progressed patients compared with non-progressed patients in the metastatic population (uniform distribution: 95% CI, based on the published paper)
- The relative risk of mortality for patients receiving abiraterone (uniform distribution: ±10%, as no other information was available)
- The proportion of patients experiencing SCC and the outcomes of SCC (uniform distribution: ranges taken from Lu *et al*).[144]

Deterministic sensitivity analysis was undertaken through the production of a tornado diagram (testing the sensitivity of the model to all parameters and ordering them by impact on the incremental net benefit).

In addition a threshold analysis was conducted, investigating the HR for degarelix efficacy for PSA progression.

Drug costs were not included within the sensitivity analysis, as the majority of these are taken from the *BNF* and, therefore, not subject to uncertainty.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analysis was undertaken with all parameters included, as stated in Section 7.3.6, except for the discount rate for costs and QALYs. A full list of the distributions used for each parameter can be found in Table 32.

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

As expected and as shown in Table 52, the results in the model are similar to those of the clinical trials.

Table 52. Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Degarelix: Percentage alive after 1 year	97.4% (CS21) 98.3%(pooled trials)	93.7%
LHRH agonist: Percentage alive after 1 year	95.1% (CS21) 96.7%(pooled trials)	93.5%
Degarelix: Percentage who have not had PSA progression after 1 year	91.1% (CS21)	91.0%
LHRH agonist: Percentage who have not had PSA progression after 1 year	85.9% (CS21)	85.2%
Degarelix: Percentage who have had a fracture after 1 year	0.9% (pooled trials)	0.9%
Leuprorelin: Percentage who have had a fracture after 1 year	2.1% (pooled trials)	1.8%
Degarelix: Percentage who have had a joint-related sign and symptom after 1 year	5.2% (pooled trials)	4.7%
Leuprorelin: Percentage who have had a joint-related sign and symptom after 1 year	8.3% (pooled trials)	7.7%
Degarelix: Percentage of those with cardiovascular risk at baseline who have a serious cardiovascular event after 1 year	5.4% (pooled trials)	6.2%
Leuprorelin: Percentage of those with cardiovascular risk at baseline who have had a serious cardiovascular event after 1 year	12.9% (pooled trials)	13.9%

Key: LHRH = luteinising hormone-releasing hormone; PSA = prostate-specific antigen

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Figure 35 and Figure 36 illustrate how patients move through the model states over time when treated with degarelix and goserelin, respectively. The diagrams illustrate that over the first few years, a large proportion of patients remains on first-line treatment but that after five years of treatment, the patients who remain alive are predominantly on supportive and palliative care. Comparing the diagrams, it is clear that the model estimates that patients remain on first-line treatment for longer when treated with degarelix. This is consistent with the trial data from CS21, which was used to estimate the time to PSA progression, as outlined in Sections 7.3.1and 7.3.2.

Figure 35. Markov trace diagram for patients treated with degarelix

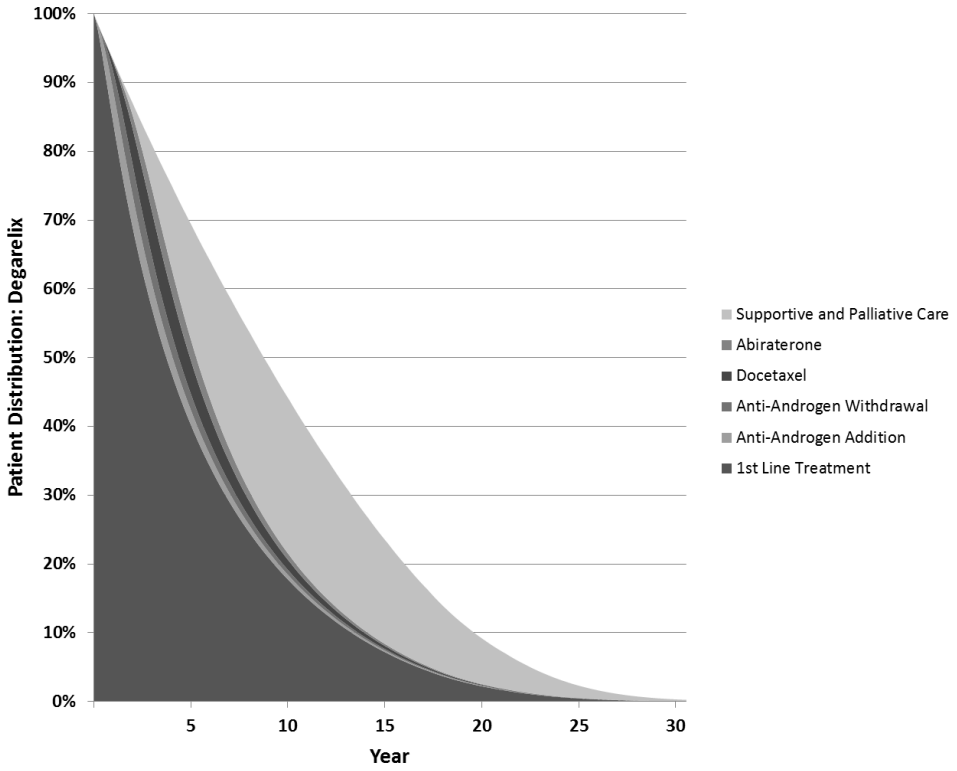
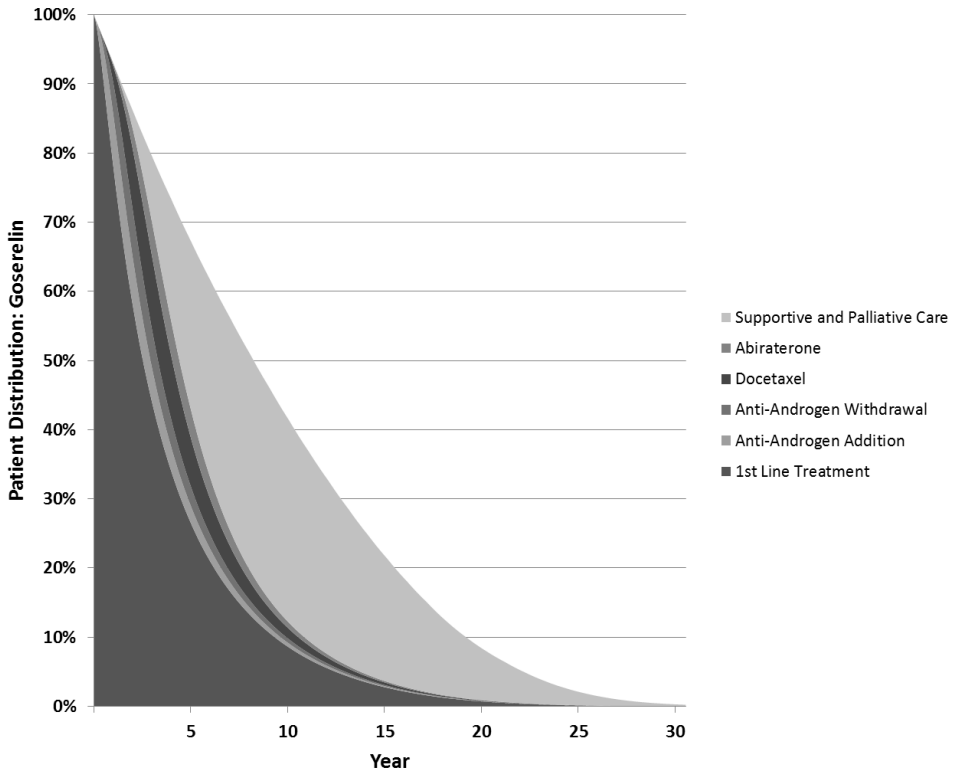


Figure 36. Markov trace diagram for patients treated with goserelin (10.8 mg)



7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Figure 37 and Figure 38 illustrate how QALYs are accumulated over time when patients are treated with degarelix and goserelin, respectively. As would be expected from Figure 35 and Figure 36, the QALYs are initially primarily accrued in the first-line model state; as time continues, the QALYs are increasingly accrued in the supportive and palliative care model state. When comparing Figure 37 and Figure 38, it is evident that the model predicts a greater number of total QALYS accrued when patients are treated with degarelix compared with goserelin. It is also evident that when patients are treated with degarelix, a relatively higher proportion of the total QALYs accumulated are in the first-line model state.

Figure 37. QALY accumulation over time – degarelix

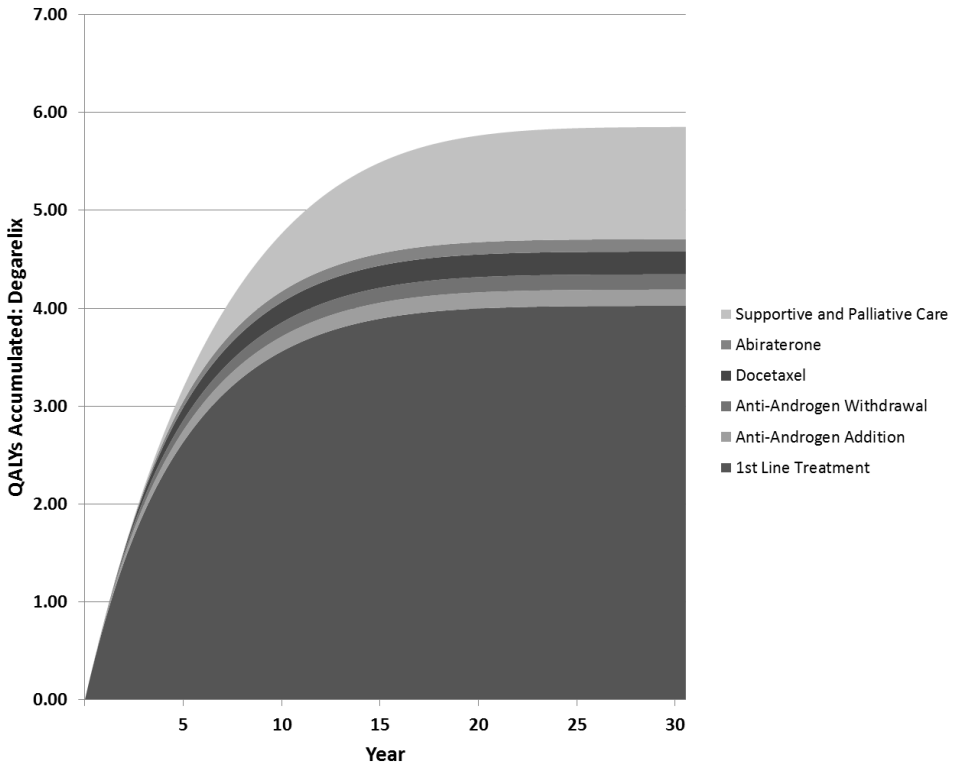
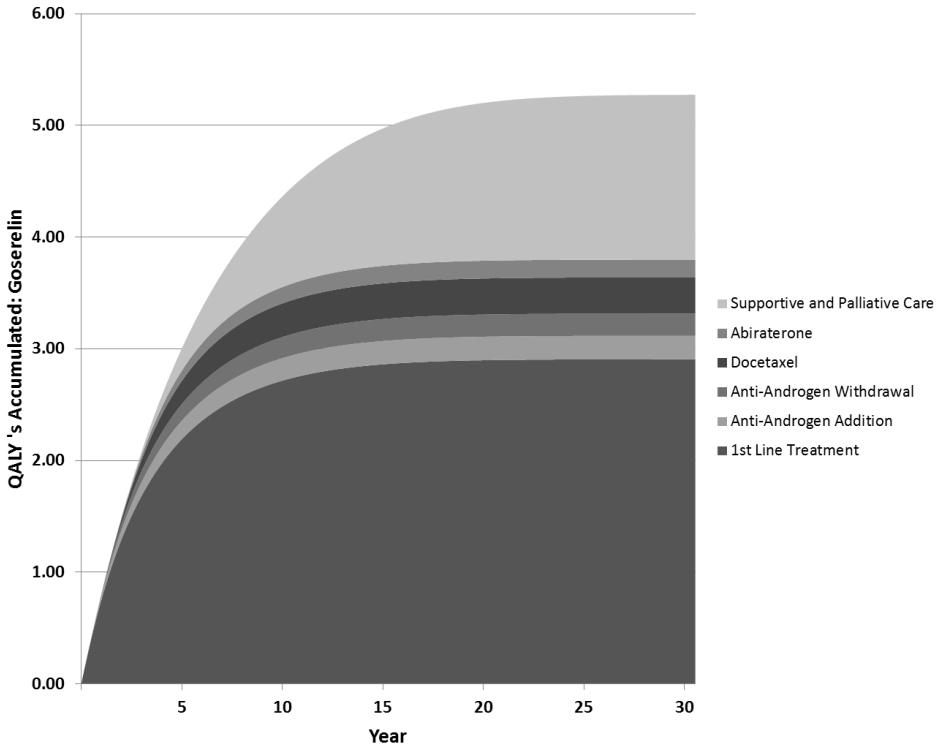


Figure 38. QALY accumulation over time – goserelin (10.8 mg)



7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table 53 and Table 54 below illustrate the life years, QALYs and costs by clinical outcome for patients treated with degarelix and goserelin, respectively. The tables illustrate that compared with patients on goserelin, patients treated with degarelix:

- Spend longer on first-line treatment and accumulate more costs and QALYs in this state,
- Spend less time in all other model states and accumulate lower costs in all except for the anti-androgen addition model state,
- Accumulate less cost as a result of AEs.

The reduced cost as a result of AEs is to be expected, given the results of the pooled clinical trial data reported in Section 6.9.

Table 53. Model outputs by clinical outcomes: degarelix

Outcome	LY	QALY	Cost (£)
First-line treatment	5.39	4.02	£9,720
Anti-androgen addition	0.26	0.17	£627
Anti-androgen withdrawal	0.25	0.16	£574
Chemotherapy	0.41	0.23	£1,464
Abiraterone	0.23	0.13	£7,326
Supportive and palliative care	3.05	1.15	£5,483
Adverse events			£901
Total	9.58	5.85	£26,095

Key: LY = life-years; QALY = quality-adjusted life-year

Table 54. Model outputs by clinical outcomes: goserelin (10.8 mg)

Outcome	LY	QALY	Cost (£)
First-line treatment	3.81	2.91	£4,543
Anti-androgen addition	0.32	0.21	£599
Anti-androgen withdrawal	0.31	0.20	£541
Chemotherapy	0.57	0.32	£1,899
Abiraterone	0.28	0.16	£9,380
Supportive and palliative care	3.92	1.48	£7,115
Adverse events			£3,559
Total	9.21	5.27	£27,636

Key: LY = life-years; QALY = quality-adjusted life-year

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 55 below shows the QALY gain by health state for degarelix and goserelin. As shown by Figure 37 and Figure 38, patients treated with degarelix accumulate a greater proportion of their total QALYs while on first-line treatment and accumulate proportionally fewer of their QALYs while treated with supportive and palliative care.

Table 56 illustrates the summary costs by health state and shows that, in total, treatment with degarelix is expected to cost approximately £400 more over a patient's lifetime than treatment with goserelin. While the costs accumulated in the first-line disease state are substantially higher when treated with degarelix, the costs incurred due to AEs, first-line chemotherapy, abiraterone, and supportive and palliative care are all substantially lower. This is supported by Table 57 below which shows predicted resource use by category of cost.

Table 55. Summary of QALY gain by health state

Health state	QALY degarelix	QALY goserelin (10.8 mg)	Increment	Absolute increment	% absolute increment
First-line treatment	4.02	2.91	1.12	1.12	193%
Anti-androgen addition	0.17	0.21	-0.04	0.04	8%
Anti-androgen withdrawal	0.16	0.20	-0.04	0.04	7%
Chemotherapy	0.23	0.32	-0.09	0.09	16%
Abiraterone	0.13	0.16	-0.03	0.03	6%
Supportive and palliative care	1.15	1.48	-0.33	0.33	57%
Total	5.85	5.27	0.58	0.58	100%

Key: QALY = quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee, 2008.

Table 56. Summary of costs by health state

Health state	Cost degarelix	Cost goserelin (10.8 mg)	Increment	Absolute increment	% absolute increment
First-line treatment	£9,720	£4,543	£5,177	£5,177	-336%
Anti-androgen addition*	£627	£599	£28	£28	-2%
Anti-androgen withdrawal	£574	£541	£33	£33	-2%
Chemotherapy	£1,464	£1,899	-£435	£435	-28%
Abiraterone	£7,326	£9,380	-£2,054	£2,054	-133%
Supportive and palliative care	£5,483	£7,115	-£1,632	£1,632	-106%
Adverse Events	£901	£3,559	-£2,658	£2,658	-172%
Total	£26,095	£27,636	-£1,541	-£1,541	100%

Key: QALY = quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee, 2008.

* This refers to second-line treatment, whereby an anti-androgen is added as an adjuvant to current LHRH agonist/GnRH antagonist therapy, as opposed to anti-androgen addition for flare protection.

Table 57. Summary of predicted resource use by category of cost

Item	Cost degarelix	Cost goserelin (10.8 mg)	Increment	Absolute increment	% absolute increment
Drug cost: flare cover	£0	£3	-£3	£3	0%
Drug cost: agonist or antagonist	£8,524	£3,978	£4,545	£4,545	-295%
Administration cost during first-line treatment	£1,919	£1,128	£790	£790	-51%
Drug cost: anti-androgens (anti-androgen addition)	£19	£25	-£6	£6	0%
Administration cost during anti-androgen addition	£237	£283	-£47	£47	-3%
Administration cost during anti-androgen withdrawal	£223	£265	-£42	£42	-3%
Drug cost: chemotherapy	£173	£224	-£51	£51	-3%

Item	Cost degarelix	Cost goserelin (10.8 mg)	Increment	Absolute increment	% absolute increment
Administration and side-effect cost during first-line chemo-therapy	£1,291	£1,674	-£383	£383	-25%
Drug cost: abiraterone	£6,561	£8,401	-£1,840	£1,840	-119%
Administration and concomitant medications cost during treatment with abiraterone	£765	£979	-£214	£214	-14%
Cost of follow-on treatment after abiraterone	£625	£801	-£176	£176	-11%
Cost of supportive care	£3,582	£4,673	-£1,091	£1,091	-71%
Cost of palliative care	£1,276	£1,641	-£365	£365	-24%
Cost of SCC	£0	£1,836	-£1,836	£1,836	-119%
Cost of fractures	£120	£993	-£873	£873	-57%
Cost of joint-related signs and symptoms	£124	£179	-£56	£56	-4%
Cost of cardiovascular events	£657	£551	£107	£107	-7%
Total	£26,095	£27,636	-£1,541	-£1,541	100%

Key: SCC = spinal cord compression

Adapted from Pharmaceutical Benefits Advisory Committee Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee, 2008.

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 58 below illustrates the base case model results. Due to delayed progression to later lines of therapy and reduced AEs, patients treated with degarelix are estimated to live for longer and experience improved HRQL. The improved efficacy and safety profile of degarelix also results in large cost offsets, resulting in degarelix being dominant; that is, both more effective and cost saving compared with goserelin.

Table 58. Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Goserelin (10.8 mg)	£27,636	9.21	5.27				
Degarelix	£26,095	9.58	5.85	-£1,541	0.37	0.58	Dominating

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Figure 39 below presents a tornado diagram, illustrating the effect on the net benefit of treatment with degarelix of varying the ten most influential parameters between their upper and lower bounds. The assumed willingness to pay for a QALY used in the net benefit calculation is £20,000.

The model is most sensitive to the HR for PSA progression. The lower bound value for the HR of PSA progression is 1.01. This is the lowest value in the 95% CI. Figure 40 illustrates the threshold analysis undertaken to investigate the effect of varying the HR of PSA progression on net benefit.

In all cases, the net benefit at £20,000 remains positive, which means that for all one-way variation in parameters, degarelix remains cost-effective at a threshold of £20,000 per QALY.

For degarelix to no longer be cost-effective at a threshold of £20,000 per QALY, the HR for PSA progression must be less than 1 (approximately 0.96). This is unlikely, as it falls outside of the CIs calculated from the trial.

Figure 39 Tornado diagram containing 10 most influential parameters

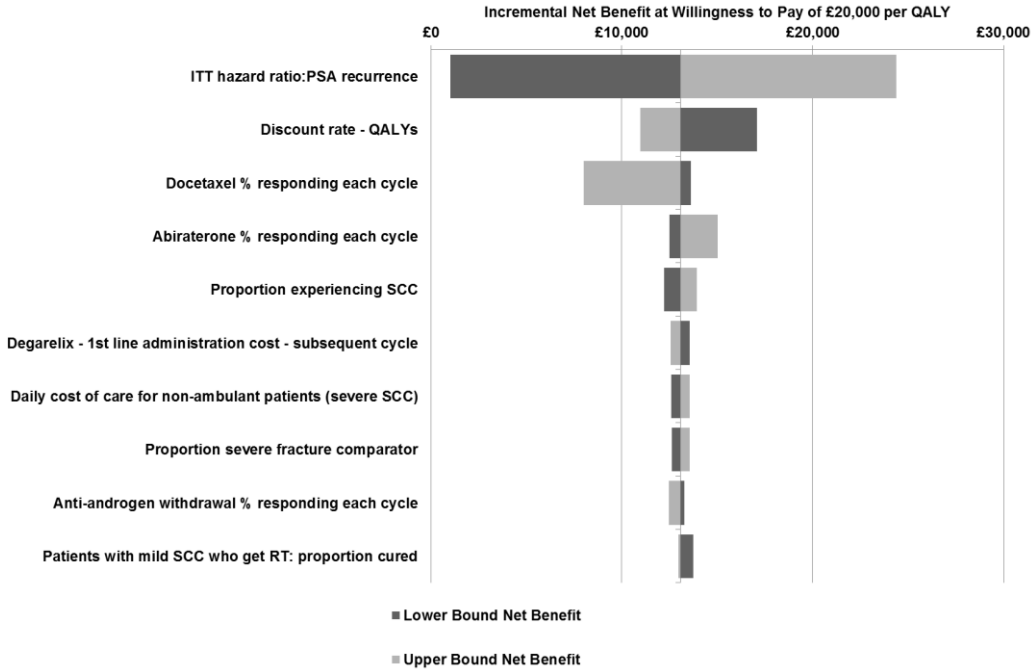
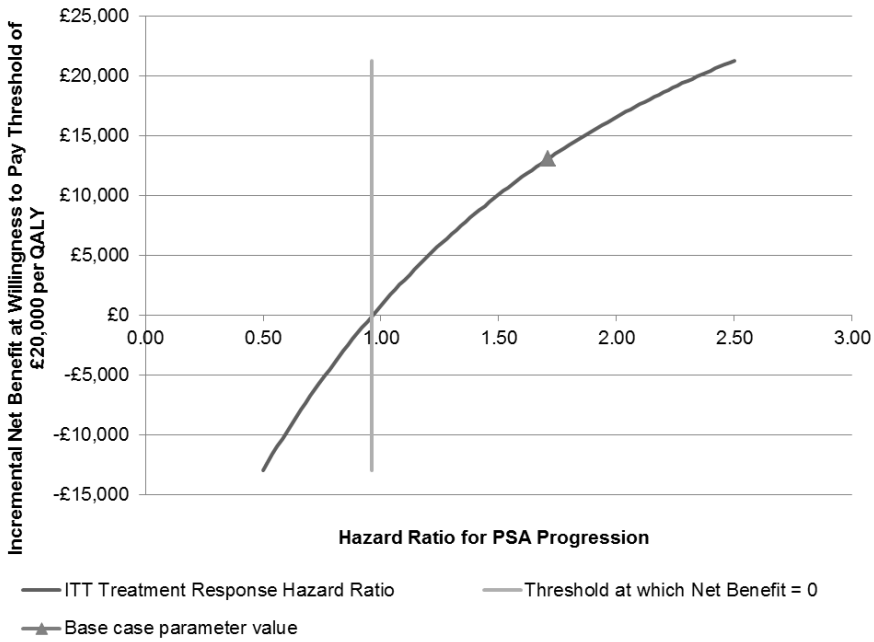


Figure 40. Threshold Analysis investigating the effect of varying the hazard ratio for time to PSA progression



7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Figure 41 below is an ICER scatter plot containing the result of 5,000 runs of the probabilistic sensitivity analysis. As can be seen, the majority are substantially below the line representing the £20,000 threshold. Figure 42 below shows the cost-

effectiveness acceptability curve (CEAC) for treatment with degarelix; there is a 99.5% chance that degarelix is cost saving at a willingness-to-pay threshold of £20,000 per QALY, and a 100% chance at a willingness-to-pay threshold of £30,000 per QALY.

Figure 41. PSA scatter plot

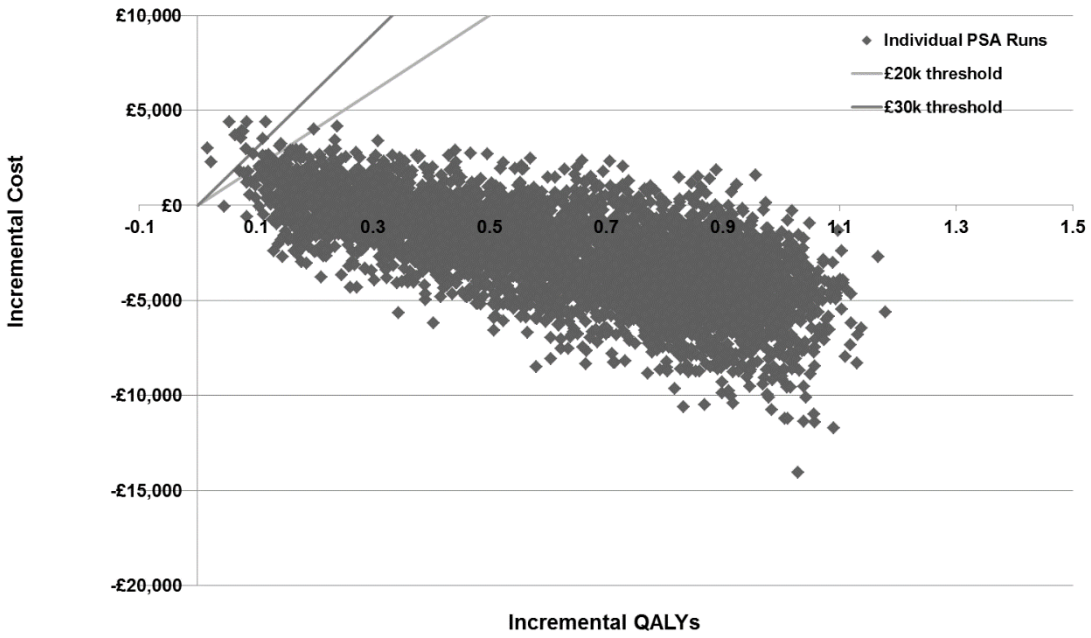
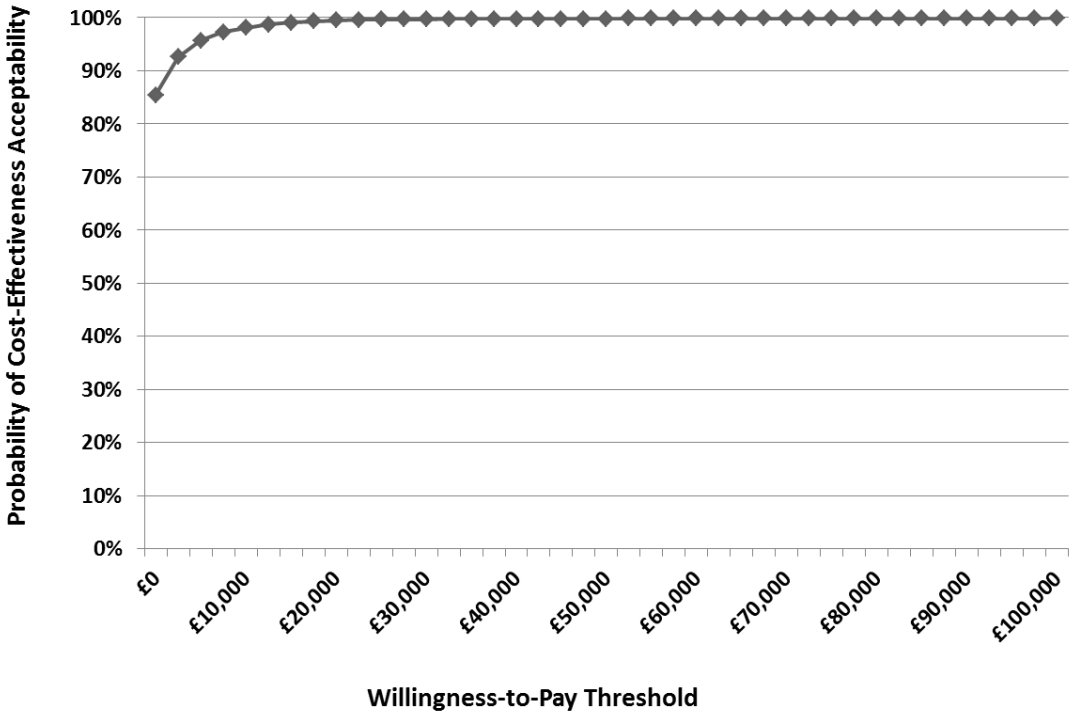


Figure 42. Cost-effectiveness acceptability curve



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table 59 below reports the results of the scenario analyses. For the scenarios for which treatment with degarelix results in lower costs and higher QALYs, the cells in the right column contain the word 'Dominating'. As can be seen from the results of the scenario analyses, the cost-effectiveness of degarelix is relatively insensitive to changes in the structural assumptions. The least favourable ICER is £12,987 (when no differential efficacy is assumed for PSA progression), which is still substantially below conventional cost-effectiveness thresholds, even in a scenario that goes against the weight of clinical evidence.

Table 59. Results of the scenario analyses

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Base case	N/A	N/A	Dominating	£13,068
Varying the comparator				
First-line LHRH agonist	Goserelin 10.8mg (Zoladex)	Goserelin 3.6 mg (Novgos) *lowest-cost comparator*	Dominating	£12,454
		Triptorelin 3.75 mg (Gonapeptyl) *highest-cost*	Dominating	£13,632

		comparator		
Varying treatment efficacy assumptions				
Variation of the parametric curve chosen				
Curve choice for first-line time to PSA progression	Log-normal	Log-logistic	Dominating	£12,907
		Gompertz	Dominating	£13,024
		Exponential	Dominating	£12,554
		Weibull	Dominating	£12,093
Variation in the duration of differential efficacy				
Duration for which hazard ratio applied	For the duration patients remain on first-line therapy	Efficacy of degarelix and LHRH agonists assumed to be equal	£12,987	£804
		For one year; the duration for which there is comparative trial data	£3,751	£3,933
Varying the approach to modelling mortality				
Mortality	i) Increased hazard of mortality post-progression for metastatic patients	No increased hazard of mortality post-progression for metastatic patients	Dominating	£11,542
	ii) Prostate cancer specific mortality incorporated	i) No increased hazard of mortality post-progression for metastatic patients ii) General population mortality incorporated	Dominating	£16,870
Varying the approach to modelling Musculoskeletal Adverse Events				
Inclusion/ exclusion of MSE's from the model structure				
MSE's incorporated	Fractures, joint-related signs and symptoms and spinal cord compression incorporated in the model	Include no MSEs	£2,484	£8,625
		Include all MSEs[a]	Dominating	£12,887
Variation in the parametric curve used to model MSEs over time				
Parametric curve for MSEs	Weibull	Exponential	Dominating	£13,143
Variation of proportion of mild, moderate and severe MSEs across both arms				
Proportion of Mild, Moderate and Severe MSEs	Equal across both arms	Proportions as seen in trial	Dominating	£13,158
Varying the approach to modelling cardiovascular (CV) adverse events				
Inclusion/exclusion of CV events from the model structure	CV events incorporated	CV events not incorporated	Dominating	£12,804
Curve choice for CV event	Exponential	Weibull	Dominating	£13,159
Varying the source used for utilities				
Utility values	i) Kontodimopoulos Algorithm[b]	i) McKenzie Algorithm[c]	Dominating	£11,242

i) First-line utilities ii) Post-progression utilities iii) Chemotherapy, abiraterone and palliative care utilities iv) Adverse event utilities	ii) Kontodimopoulos Algorithm[b] iii) Sourced from systematic search iv) Kontodimopoulos Algorithm[b]	ii) McKenzie Algorithm[c] iii) Sourced from systematic search iv) McKenzie Algorithm[c]		
		i) Gray Algorithm[d] ii) Gray Algorithm[4] iii) Sourced from systematic search iv) Gray Algorithm[d]	Dominating	£9,083
		i) Rowen Algorithm[e] ii) Rowen Algorithm[e] iii) Sourced from systematic search iv) Rowen Algorithm[e]	Dominating	£12,230
		i) Bayoumi *et al*. ii) Bayoumi *et al*. iii) Bayoumi *et al*. iv) Predominantly sourced from literature used by Lu *et al*. (MSEs) and NICE clinical guideline (CV events)	Dominating	£14,971
Variation in treatment and administration practice				
Treatment used for flare cover and anti-androgen addition	Bicalutamide	Cyproterone acetate	Dominating	£13,102
Treatment with LHRH and degarelix takes place in	50% primary care; 50% secondary care	All treated in primary care	Dominating	£12,996
		All treated in secondary care	Dominating	£13,141
Incorporation of abiraterone	Incorporated in the treatment pathway	Not incorporated	£2,072	£10,658
Stopping rule	Stop treatment on degarelix/ LHRH agonist when castrate/ resistant, in line with the licensed indication	Don't stop treatment until death	Dominating	£12,030
Varying the time horizon				
Time horizon	30 Years	5 years	Dominating	£4,882
		10 Years	Dominating	£9,800
		20 Years	Dominating	£12,968

[a] Including those not incorporated in the base-case as not statistically significant different between treatment arms in the pooled trials or because of evidence of dose-dependency.
[b] EORTC-C30 to EQ-5D using data from gastric cancer patients
[c] EORTC-C30 to EQ-5D using data from inoperable oesophageal cancer patients
[d] SF-36 to EQ-5D using data from the general UK population
[e] EORTC-C30 to EORTC-8D using data from patients with newly diagnosed with multiple myeloma

7.7.10 What were the main findings of each of the sensitivity analyses?

The main finding of the deterministic sensitivity analysis reported in Section 7.7.7 is that the model is most sensitive to the HR for time to PSA progression. However, the threshold analysis undertaken showed that for all of the values within the 95% CI of the HR, degarelix remains a cost-effective use of healthcare resources, at a threshold of £20,000 per QALY gained.

The probabilistic sensitivity analysis indicated that simultaneous variation in the parameter values did not affect the result that degarelix was cost-effective. This is illustrated by Figure 42, which shows that the model estimates degarelix to have a 100% probability of being cost-effective at a willingness-to-pay threshold of £30,000 per QALY and 85% probability of being cost saving.

The scenario analyses indicated that the cost-effectiveness of degarelix is not sensitive to structural uncertainty. A number of variations were made to the base-case specification; none resulted in an ICER higher than £13,000 per QALY.

7.7.11 What are the key drivers of the cost-effectiveness results?

The key driver of the cost-effectiveness results is the enhanced efficacy and safety profile of degarelix.

The enhanced efficacy profile increases time to PSA progression, which results in: higher patient HRQL, reduced hazard of mortality, and reduced time on abiraterone (with the resulting offsets in medication costs).

The enhanced safety profile results in: higher patient HRQL, reduced mortality from cardiovascular events, and cost-offsets due to the avoidance of costs associated with managing AEs.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Several methods were used to validate and quality-assure the model. First, the outcomes of the model were compared with those from the clinical trials that informed the model. As outlined previously in Table 52, the outcomes of the model over one year closely match the trial outcomes for:

- Percentage who have not experienced PSA progression
- Percentage who have had a fracture or a JSS
- Percentage who have had a serious cardiovascular event.

Second, model outputs were compared with relevant literature not used in the construction of the model. The outcomes of this comparison are presented below.

As discussed in Section 7.3.1, the mortality risk in the model is primarily based on the general population mortality rate[155] and the prostate-specific mortality rates.[156] The relative mortality rate predicted by the model over five years for current standard of care was compared to the results outlined in a draft clinical guideline.[205] The relative mortality rates over five years for individuals with Stage 3 and Stage 4 prostate cancer that were provided by the guidelines were weighted by the proportion of individuals in CS21 who were in Stage 4 and the proportion who were not. The calculated relative mortality rate was 82.4% over four years. The model estimates a relative mortality rate of 80.5% for patients treated with goserelin, defined as current standard of care. The similarity in the relative mortality rates indicates that the model provides a viable estimate of the rate of mortality over time.

In addition, the model's estimates for the proportion of individuals dying from a serious cardiovascular event seem viable, given external sources. Two literature reviews were identified, which included studies reporting the risk of cardiovascular death for prostate cancer patients treated with hormonal therapy.[150,206] Of the studies which were suitable, as the patients enrolled were all treated with hormonal therapies, the median percentage of deaths reported to have been caused by a cardiovascular event was 20.4% of the total deaths (the studies ranged from reporting 16.4% to 35.1% of deaths being caused by a cardiovascular event). The model estimates that for current standard of care, 18.9% of individuals die as a result of a serious cardiovascular event.

Of the costing and resource use studies reviewed in Section 7.5.3, few were suitable for assessing the model's validity for estimating costs. The study by Hummel *et al* (2003) estimated the annual cost of treatment with goserelin to be £2,302. This coincides with the model's estimated undiscounted cost over a one-year time horizon of £2,183 for patients treated with goserelin.

Third, to further validate the resource use in the model, the model resource use estimates were validated by leading healthcare professionals, as outlined in Section 7.5.4. Given the viability of the model's predictions of disease progression and the likelihood of AEs the model's estimates of cost should be accurate if the resource use estimates, given disease stage and AE status, are accurate.

The healthcare professionals not only reviewed the resource use estimates within the model. In addition they reviewed the viability of:

- The model structure
- The HRQL estimates
- The model's extrapolation of time to PSA progression beyond the clinical trial period.

Finally, the model was also quality-assured by internal processes at the company who built the economic model. In these processes, an economist not involved in the model's construction reviewed the model for coding errors, inconsistencies and the plausibility of inputs.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

As discussed in Section 7.2.1 and in line with the decision problem, analysis was undertaken for the subgroup of patients who had a PSA levels >20 ng/ml at baseline. This subgroup was selected as they are a higher-risk subgroup of the ITT population who are more reflective of the population treated with hormonal therapy in the UK.[8]

7.9.2 Please clearly define the characteristics of patients in the subgroup.

The patients had a PSA reading >20 ng/ml at baseline.

7.9.3 Please describe how the statistical analysis was undertaken.

Separate parametric curves were fitted for the time to progression for this subgroup. The log-logistic curves again provided the best fit to the data, as they had the lowest AIC scores. The analysis estimated the HR for PSA progression to be 1.74, slightly higher than the value of 1.71 for the ITT population as a whole. The approach to the analysis is outlined in greater detail in Section 7.3.1.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Table 60 below presents the results for the subgroup. Treatment with degarelix is cost saving.

Table 60. Results for the PSA >20 ng/ml population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Goserelin (10.8 mg)	£29,794	4.77	8.78				
Degarelix	£28,306	5.36	9.22	-£1,489	0.58	0.44	Dominating

Key: ICER =incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life-years

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

The following additional subgroups were considered in line with the decision problem:

- Patients with spinal metastases with impending or actual SCC
- Patients with high tumour volume with impending or actual urinary outflow obstruction
- Patients with bony metastases associated with intractable pain
- Patients for whom standard anti-androgen treatment is contraindicated
- Patients at risk of evolving cardiovascular comorbidity.

There was not enough evidence available for these subgroups to accurately estimate the cost-effectiveness of degarelix; therefore, these subgroups were not included in the model.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results in this economic evaluation are consistent with two of the three published studies outlined in Section 7.1. The results are not consistent with the study published by Lu *et al*.[144] The result of the study by Lu *et al* was that treatment with degarelix was not cost-effective; however, the authors did not have access to all of the information that is now available.

First, the authors did not have access to the five-year safety study (CS21A) or the pooled analysis for AEs; as such, they were not able to incorporate the differential hazard of serious cardiovascular events between degarelix and the LHRH agonists. Nor was the study able to incorporate the increased ongoing risk of fractures and JSS.

Second, the authors did not appear to have consulted with clinicians familiar with recent research in prostate cancer or wider UK clinical practice. The clinicians consulted by Lu *et al* did not support the link between PSA progression and progression to a subsequent line of treatment.

In contrast, three advisory boards, undertaken by Ferring in Scotland, Wales and England (with leading clinicians from a range of locations across these countries), have all strongly supported the link between PSA progression and progression to second-line treatments. The omission of this link by Lu *et al* caused the study to omit the differential efficacy profile of degarelix compared with LHRH agonists reported in CS21.[10] Omitting the differential in the efficacy profile of the two treatments is the central cause of the difference in results. The validity of the link between PSA progression and treatment progression, combined with the evidence provided by CS21, is the central reason why the results of the analysis reported above should be given credence instead of the results reported by Lu *et al*.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strengths of the evaluation are that it is based on UK clinical practice and populated by the long-term efficacy and safety data of patients treated with degarelix. In particular, the length of follow-up and amount of follow-up data should be stressed. These include multiple RCTs, including a large number of patients and HRQL data measured through a generic and disease specific metric.

The main weakness of the model is that the trial data available only contain comparative data over a one-year period. However, this weakness is not critical. As shown in Table 59, when the differential efficacy is assumed to last only for the duration of the comparative data, degarelix remains a cost-effective use of healthcare resources.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Due to the level of certainty in the results demonstrated both clinically (six RCTs), and in the economic evaluation (100% chance of cost-effectiveness at £30,000 per QALY, no one way sensitivity analysis above £13,000/QALY), it is unlikely that further studies would result in a change in decision. Indeed the only plausible item missing from this submission are directly measured EQ-5D values, with HRQL instead measured by the SF-12v2 and EORTC QLQ C-30.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The eligible population numbers have been estimated by first calculating the incidence for prostate cancer in 2013:

- The 2011 incidence was calculated by combining the annual incidence of prostate cancer in England and Wales for 2011[84,85]
- The annual rate of increase in incidence, which was calculated using the average percentage increase in incidence between 2009 and 2011, was applied.[85,96,155]

The number of patients eligible for treatment with degarelix was calculated by multiplying this incidence for overall prostate cancer by the proportion of incident prostate cancer patients who are treated with hormonal therapy without radiation or prostatectomy.[95]

The estimated patient numbers for the PSA >20 ng/ml subgroup have been estimated by multiplying the expected number of patients treated with hormonal therapy by the percentage of patients in the CS21 trial who had a PSA >20 ng/ml (48%).

The total numbers of eligible patients from Year 1 to Year 5 (2013–17) are shown in Table 61.

Table 61. Eligible population in England and Wales

	Year 1	Year 2	Year 3	Year 4	Year 5
Expected number of newly diagnosed prostate cancer patients	39,376	3,9877	40,383	40,896	41,416
Expected number treated with hormonal therapy	15,458	15,655	15,854	16,055	16,259
Expected number treated with hormonal therapy PSA >20 ng/ml subgroup	7,425	7,519	7,615	7,712	7,810

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

It was assumed that goserelin 10.8 mg, the most commonly prescribed LHRH agonist in England and Wales, would be displaced by patients who were treated with degarelix.

8.3 What assumption(s) were made about market share (when relevant)?

The assumption was made that the market share of degarelix would increase from [redacted] over the next five years, resulting in the following numbers of new patients starting treatment (Table 62).

Table 62. Treated population in England and Wales

	Year 1	Year 2	Year 3	Year 4	Year 5
Expected number treated with hormonal therapy	15,458	15,655	15,854	16,055	16,259
Expected number treated with hormonal therapy: PSA>20 subgroup	7,425	7,519	7,615	7,712	7,810
Estimated Degarelix Market Share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated number of new Degarelix patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated number of new Degarelix patients: PSA>20 subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In addition to the new patients receiving degarelix treatment in Year 1, there are currently 554 patients treated with degarelix in England and Wales.[207] The model estimates that 22.24% of these 554 patients will have failed on this treatment within a year in the ITT population, therefore leaving an additional 431 patients (207 for PSA

>20 ng/ml subgroup) who continue to receive degarelix in the following year and are added to the estimated number of new patients starting in 2014 (the penultimate row of Table 62).

Table 63 shows the treatment of patients over time through the budget impact model for the ITT population. The first column matches the number of patients in the penultimate row of Table 62. The second cell in the first row of Table 63 shows the number of patients entering the model who have previously been treated with degarelix.

Table 63. Patient flow in the budget impact model: whole licensed indication population

		Patients (years on treatment)					
		1	**2**	**3**	**4**	**5**	**6**
Year	**1**	[redacted]	[redacted]				
	2	[redacted]	[redacted]	[redacted]			
	3	[redacted]	[redacted]	[redacted]	[redacted]		
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 64 illustrates the estimated progression of patients over time through the budget impact model for the PSA >20 ng/ml population.

Table 64. Patient flow in the budget impact model: PSA > 20 ng/ml population

		Patients (years on treatment)					
		1	**2**	**3**	**4**	**5**	**6**
Year	**1**	[redacted]	[redacted]				
	2	[redacted]	[redacted]	[redacted]			
	3	[redacted]	[redacted]	[redacted]	[redacted]		
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The budget impact was estimated across a range of categories. The categories considered were the same as those reported in
Table 57.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on

national reference costs or the PbR tariff, which HRGs reflected activity?

The same unit costs were applied as were applied in the cost-effectiveness model (reported in Sections 7.5.5–7.5.7)

8.6 Were there any estimates of resource savings? If so, what were they?

The resource savings estimates were derived from the cost-effectiveness model on a yearly basis (taking account of the changing cost profile over time) and multiplied over the population estimated to be treated with degarelix over the next five years.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated budget impact for the entire licensed indication population and the PSA >20 ng/ml are shown in Table 65 and Table 66, respectively. The estimated budget impact peaks in Year 1 for the whole licensed indication population, at approximately £68,000 with cost savings starting in Year 3. For the PSA >20 ng/ml population, use of degarelix leads to a cost saving from Year 2 onwards. By Year 5, the annual saving is approximately £932,000 for the entire licensed indication population and approximately £968,000 for the PSA >20 ng/ml population.

Table 65. Estimated budget impact for the whole licensed indication population

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5
Drug cost: flare cover	-£1,663	-£2,576	-£4,444	-£6,066	-£7,431
Drug cost: agonist or antagonist	£678,200	£1,216,301	£2,147,628	£3,341,854	£4,718,760
Administration cost during first-line treatment	£97,063	£179,852	£319,902	£509,213	£735,077
Drug cost: anti-androgens (anti-androgen addition)	-£1,790	-£3,114	-£5,210	-£8,075	-£11,171
Administration cost during anti-androgen addition	-£20,376	-£33,882	-£56,480	-£85,090	-£114,154
Administration cost during anti-androgen withdrawal	-£14,384	-£25,829	-£42,916	-£67,252	-£94,143
Drug cost: chemotherapy	-£11,097	-£22,237	-£37,632	-£60,960	-£89,006
Administration and side-effect cost during first-line chemotherapy	-£82,773	-£165,858	-£280,690	-£454,685	-£663,871
Drug cost: abiraterone	-£88,893	-£326,885	-£690,120	-£1,219,424	-£1,976,148
Administration and concomitant medications cost during treatment with abiraterone	-£12,650	-£42,365	-£86,361	-£150,856	-£241,982
Cost of follow-on treatment after abiraterone	-£7,259	-£28,888	-£62,649	-£111,633	-£182,232
Cost of supportive care	-£2,783	-£19,074	-£60,023	-£135,207	-£259,058
Cost of palliative care	-£7,950	-£23,462	-£48,784	-£89,930	-£150,194
Cost of spinal cord compression	-£255,798	-£455,548	-£804,807	-£1,248,369	-£1,758,415
Cost of fractures	-£53,776	-£110,276	-£203,616	-£342,442	-£522,882
Cost of joint-related signs and symptoms	-£12,599	-£21,371	-£37,045	-£55,665	-£75,560
Cost of cardiovascular events	-£38,713	-£66,719	-£114,651	-£174,608	-£239,379
Total	**£162,759**	**£48,070**	**-£67,899**	**-£359,195**	**-£931,788**

Table 66. Estimated budget impact for the PSA >20 ng/ml population

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5
Drug cost: flare cover	-£797	-£1,235	-£2,131	-£2,909	-£3,564
Drug cost: agonist or antagonist	£305,567	£560,743	£998,039	£1,551,489	£2,177,292
Administration cost during first-line treatment	£44,052	£83,552	£149,695	£237,656	£340,045
Drug cost: anti-androgens (anti-androgen addition)	-£1,203	-£2,034	-£3,370	-£5,036	-£6,621
Administration cost during anti-androgen addition	-£13,371	-£21,382	-£35,304	-£50,616	-£63,696
Administration cost during anti-androgen withdrawal	-£9,506	-£16,365	-£26,643	-£40,148	-£52,940
Drug cost: chemotherapy	-£7,449	-£14,431	-£23,953	-£37,907	-£52,998
Administration and side-effect cost during first-line chemotherapy	-£55,559	-£107,636	-£178,659	-£282,734	-£395,294
Drug cost: abiraterone	-£61,720	-£213,037	-£435,173	-£753,729	-£1,189,558
Administration and concomitant medications cost during treatment with abiraterone	-£8,703	-£27,483	-£54,295	-£93,024	-£145,097
Cost of follow-on treatment after abiraterone	-£5,077	-£18,872	-£39,538	-£69,017	-£109,824
Cost of supportive care	-£2,007	-£12,836	-£38,893	-£85,484	-£160,473
Cost of palliative care	-£5,633	-£16,089	-£32,780	-£59,373	-£96,678
Cost of spinal cord compression	-£115,186	-£210,510	-£376,719	-£586,841	-£827,228
Cost of fractures	-£23,131	-£49,493	-£93,329	-£158,459	-£242,786
Cost of joint-related signs and symptoms	-£5,710	-£9,913	-£17,354	-£26,124	-£35,420
Cost of cardiovascular events	-£16,822	-£29,333	-£50,576	-£76,361	-£103,085
Total	**£17,743**	**-£106,353**	**-£260,984**	**-£538,618**	**-£967,926**

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

N/A

9 References

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10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following databases were searched, with no date restrictions, for relevant clinical trials of degarelix:

- Bibliographic databases: MEDLINE®, MEDLINE In-Process, Embase, Web of Science, and the Cochrane Library
- References of retrieved articles and reports
- Ferring Pharmaceuticals Ltd:
  - List of sponsored studies
  - Clinical study reports of completed studies (when available, clinical study reports from Ferring were used as the main data source)
- Clinical trial registries: WHO International Clinical Trials Registry Platform (ICTRP).

10.2.2 The date on which the search was conducted.

Searches were conducted on 25 March 2013.

10.2.3 The date span of the search.

No date limitations were applied to the search – for example, MEDLINE was searched from 1946 to the date of the search and Embase from 1974 to the date of the search.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

#1: degarelix OR Firmagon OR abarelix OR Plenaxis
#2: (luteinising OR luteinizing OR LHRH OR gonadotrop* OR GNRH) AND (agonist* OR antagonist* OR blocker*)
#3: androgen deprivation OR ADT OR androgen suppression
#4: goserelin OR Zoladex OR Novgos OR Eulexin OR leuprorelin OR leuprolide OR Prostap OR Lupron OR Eligard OR Carcinil OR Depo-Eligard Enanton OR Enantone OR Ginecrin OR Leuplin OR Lucrin OR Procren OR Procrin OR Trenantone OR Uno-Enantone OR Viadur OR triptorelin OR Trelstar OR Decapeptyl OR Gonapeptyl OR salvacyl OR buserelin OR Suprefact OR suprecur OR Etilamide OR Bigonist OR Profact OR Receptal OR Flakon OR Cinnafact
#5: bicalutamide OR Casodex OR Cosudex OR Calutide OR Kalumid OR Bicalox
#6: #1 OR #2 OR #3 OR #4 OR #5
#7: (prostate OR prostatic) AND (cancer OR carcinoma OR adenocarcinoma OR tumour OR tumor OR neoplasm*)
#8: (spinal cord compression) OR musculoskeletal OR arthralgia OR fracture OR (back pain) OR (bone pain) OR (urinary tract) OR (bladder outlet obstruction) OR cardiovascular OR (myocardial infarction) OR ((ischaemic OR haemorrhagic) AND cerebrovascular) OR ((embolic OR thrombotic) AND events) OR (ischaemic heart disease)
#9: (adverse effect*) OR (adverse event*) OR (side effect*) OR side-effect*) OR safety
#10: #8 AND #9
#11: #7 OR #10
#12: (#6 AND #11)
#13: #12 Filters: Clinical Trial; Meta-analysis; Systematic Reviews
#14: #12 AND (cost OR cost-effective* OR resource*)
#15: #12 AND (utility OR quality of life OR QALY)

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Ferring Pharmaceuticals confirmed the list of publications that were identified and, in addition, provided the complete study reports for all relevant studies of degarelix.

10.2.6 The inclusion and exclusion criteria.

The systematic review included randomised controlled trials (RCTs) that compared degarelix with LHRH agonists alone or in combination with short-term anti-androgen treatment. The review also considered clinical trials of degarelix for the treatment of patients with prostate cancer, in which LHRH agonist or anti-androgen control was not used; these were considered to be non-RCTs and included degarelix dose-finding trials and extensions of completed RCTs. Pharmacokinetic (mostly Phase I) studies were not considered. The eligibility criteria for study selection are summarised in Table 8 in Section 6.2.1.

10.2.7 The data abstraction strategy.

Two independent reviewers scanned titles/abstracts of references from the bibliographic databases to identify potentially relevant studies and then assessed the full text of obtained articles or reports to determine whether the studies should be included. Any disagreements were resolved by discussion.

After the study selection process, which is shown in Figure 3 (in Section 6.2.2), six completed RCTs that compared degarelix and LHRH agonists (see Table 9 in Section 6.2.4),[9-18] six dose-finding trials (see Table B1 in Appendix B), and seven non-randomised studies (mostly the extension of completed RCTs) (see Table B1 in Appendix B) remained.[54-71]

The study included a search of the WHO ICTRP, which identified three ongoing RCTs that compared degarelix and LHRH agonists in patients with prostate cancer. Table 67 below shows the identified ongoing RCT studies.

Table 67. Ongoing relevant studies of degarelix

Study	Design
ClinicalTrials.gov: NCT01744366 (Ferring ID: 000006)[208]	An open label, multicentre, randomised, parallel-group trial, comparing efficacy and safety of a degarelix one-monthly dosing regimen with goserelin in Chinese patients with prostate cancer requiring androgen ablation therapy
ClinicalTrials.gov: NCT01674270[209]	Phase II randomised open label study of neo-adjuvant degarelix versus LHRH agonist in prostate cancer patients prior to radical prostatectomy
ClinicalTrials.gov: NCT01751451[210]	A Phase II, randomised, three-arm study of abiraterone acetate alone, abiraterone acetate plus degarelix, and degarelix alone for patients with prostate cancer with a rising PSA and nodal disease following definitive radical prostatectomy

Key: LHRH = luteinising hormone-releasing hormone, PSA = prostate-specific antigen

10.3 Appendix 3: Quality assessment of RCT(s) (Section 6.4)

Quality assessment results for the RCTs of degarelix are shown in Table B8 in Appendix B.

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process

The following databases were searched, with no date restrictions, for relevant clinical trials that include triptorelin and bicalutamide monotherapy:

- Bibliographic databases: MEDLINE®, MEDLINE In-Process, Embase, Web of Science, and the Cochrane Library
- References of retrieved articles and reports
- Ferring Pharmaceuticals Ltd:
  - List of sponsored studies
  - Clinical study reports of completed studies (when available, clinical study reports from Ferring were used as the main data source)
- Clinical trial registries: WHO ICTRP.

10.4.2 The date on which the search was conducted.

Searches were conducted on 25 March 2013.

10.4.3 The date span of the search.

No date limitations were applied to the search – for example, MEDLINE was searched from 1946 to the date of the search and Embase from 1974 to the date of the search.

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

For search terms see Section 10.2.4.

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Ferring Pharmaceuticals confirmed the list of publications that were identified.

10.4.6 The inclusion and exclusion criteria.

The literature search strategy used for the identification of RCTs involving degarelix (previously described) was also used to identify clinical trials that directly compared different LHRH agonists for patients with prostate cancer. Study inclusion for mixed treatment comparison (MTC) was conducted by a senior systematic reviewer (University of East Anglia).

10.4.7 The data abstraction strategy.

Data extraction for the MTC was conducted by a senior systematic reviewer (Univeristy of East Anglia). From the 2,002 records identified by the initial search of the literature databases (see Figure 3), ten trials that directly compared the relevant comparators specified in the NICE STA scope were identified.

Table 16 (in Section 6.7.1) shows details of these identified trials and the reasons for their inclusion in or exclusion from the MTC analysis. The network of trials involved in the MTC of degarelix and relevant comparators is shown in Figure 14 in Section 6.7.3. To improve the trial comparability and relevance, only degarelix data from the 240/80 mg group and only data from trials that compared one-monthly treatment regimens were used.[132,133]

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym: Heyns *et al,* 2003[124]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	No details.	Not clear
Was the concealment of treatment allocation adequate?	At enrolment, investigators and patients were unaware of the randomisation	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Patients were evenly distributed between treatment groups, in terms of baseline demographic and disease characteristics	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients were single-masked to treatment. Providers and outcome assessors were not blinded	Yes: patients No: care providers and outcome assessors
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	2.5% of patients (7 in total; 3 from the triptorelin and 4 from the leuprorelin group) were excluded from the intention-to-treat population because they had no primary efficacy data at 29 days	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Trial protocol was not available	Not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Intention-to-treat analysis was conducted, after excluding 7 patients without efficacy data	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study ID or acronym: Iversen *et al,* 1998[125]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	No details	Not clear
Was the concealment of treatment allocation adequate?	No details	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The baseline demographic characteristics were comparable between groups, and disease prognostic variables were balanced	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	An open design; providers, participants and outcome assessors were not blinded to treatment allocation. The assessment of quality of life may be biased, as it was assessed using a self-administered questionnaire.	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No details reported in the paper	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Trial protocol is not available. Clinically relevant outcome measures, objective progression and treatment failure, were clearly described	Not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Seven patients had protocol violations (stage T2 tumours and/or a prostate-specific antigen level less than 20 ng/ml), but are included in the intention-to-treat analyses	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following databases were searched, with no date restrictions, for relevant clinical trials of degarelix:

- Bibliographic databases: MEDLINE®, MEDLINE In-Process, Embase, Web of Science, and the Cochrane Library
- References of retrieved articles and reports
- Ferring Pharmaceuticals Ltd:
  - List of sponsored studies
  - Clinical study reports of completed studies (when available, clinical study reports from Ferring were used as the main data source)
- Clinical trial registries: WHO ICTRP.

10.6.2 The date on which the search was conducted.

Searches were conducted on 25 March 2013.

10.6.3 The date span of the search.

No date limitations were applied to the search – for example, MEDLINE was searched from 1946 to the date of the search and Embase from 1974 to the date of the search.

10.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 10.2.4 for search terms used.

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Ferring Pharmaceuticals confirmed the list of publications that were identified and, in addition, provided the complete study reports for all relevant studies of degarelix.

10.6.6 The inclusion and exclusion criteria.

The systematic review included randomised controlled trials (RCTs) that compared degarelix with LHRH agonists alone or in combination with short-term anti-androgen treatment. The review also considered clinical trials of degarelix for the treatment of patients with prostate cancer, in which LHRH agonist or anti-androgen control was not used; these were considered to be non-RCTs and included degarelix dose-finding trials and extensions of completed RCTs. Pharmacokinetic (mostly Phase I) studies were not considered. The eligibility criteria for study selection are summarised in Table 8 in Section 6.2.1.

10.6.7 The data abstraction strategy.

Two independent reviewers scanned titles/abstracts of references from the bibliographic databases to identify potentially relevant studies and then assessed the full text of obtained articles or reports to determine whether the studies should be included. Any disagreements were resolved by discussion.

After the study selection process, which is shown in Figure 3 (in Section 6.2.2), six completed RCTs that compared degarelix and LHRH agonists (see Table 9 in Section 6.2.4),[9-18] six dose-finding trials (see in Section 6.2.7),[39,41,43,44,46-49,52] and seven non-randomised studies (mostly the extension of completed RCTs)[54-71] (see Table B1 in Appendix B) remained

The study included a search of the WHO ICTRP, which identified three ongoing RCTs that compared degarelix and LHRH agonists in patients with prostate cancer. Table 67 shows the identified ongoing RCT studies.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

10.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Further quality assessment of these studies was not deemed appropriate, because relevant comparators (LHRH agonists) were not included in these studies and their results contributed minimally to clinical conclusions.

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following databases were searched, with no date restrictions, for relevant clinical trials of degarelix:

- Bibliographic databases: MEDLINE®, MEDLINE In-Process, Embase, Web of Science, and the Cochrane Library
- References of retrieved articles and reports
- Ferring Pharmaceuticals Ltd:
  - List of sponsored studies
  - Clinical study reports of completed studies (when available, clinical study reports from Ferring were used as the main data source)
- Clinical trial registries: WHO ICTRP.

10.8.2 The date on which the search was conducted.

Searches were conducted on 25 March 2013.

10.8.3 The date span of the search.

No date limitations were applied to the search – for example, MEDLINE was searched from 1946 to the date of the search and Embase from 1974 to the date of the search.

10.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 10.2.4 for search terms used.

10.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Ferring Pharmaceuticals confirmed the list of publications that were identified and, in addition, provided the complete study reports for all relevant studies of degarelix.

10.8.6 The inclusion and exclusion criteria.

The systematic review included randomised controlled trials (RCTs) that compared degarelix with LHRH agonists alone or in combination with short-term anti-androgen treatment. The review also considered clinical trials of degarelix for the treatment of patients with prostate cancer, in which LHRH agonist or anti-androgen control was not used; these were considered to be non-RCTs and included degarelix dose-finding trials and extensions of completed RCTs. Pharmacokinetic (mostly Phase I) studies were not considered. The eligibility criteria for study selection are summarised in Table 8 in Section 6.2.1.

10.8.7 The data abstraction strategy.

Two independent reviewers scanned titles/abstracts of references from the bibliographic databases to identify potentially relevant studies and then assessed the full text of obtained articles or reports to determine whether the studies should be included. Any disagreements were resolved by discussion.

After the study selection process, which is shown in Figure 3 (in Section 6.2.2), six completed RCTs that compared degarelix and LHRH agonists (see Table 9 in Section 6.2.4,[9-18] six dose-finding RCTs[39,41,43,44,46-49,52] (see Table B1 in Appendix B), and seven non-randomised studies (mostly the extension of completed RCTs) (see Table B1 in Appendix B) remained.[54-71]

The study included a search of the WHO ICTRP, which identified three ongoing RCTs that compared degarelix and LHRH agonists in patients with prostate cancer. Table 67 shows the identified ongoing RCT studies.

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

10.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Quality assessment results are shown in Table B8 in Appendix B.

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Databases Searched:

- Medline and Medline in Process & Other Non-Indexed citations
- EMBASE
- Cochrane CDSR
- Cochrane CCRT
- Cochrane DARE
- Cochrane NHS EED
- Cochrane HTA
- CINAHL
- EconLit
- Science Citation Index
- Conference Proceedings index (Science)

10.10.2 The date on which the search was conducted.

26th April – 6th May 2013.

10.10.3 The date span of the search.

The date span of the search was from database inception until 26/04/2013.

10.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

A precise search strategy was utilised, incorporating terms for degarelix and its comparators (1-15), together with terms for prostate cancer (16-18) and an economics filter (20-51), as reported on the Centre for Reviews and Dissemination (CRD) website.[143]

Search strategies

Medline search strategy (cost-effectiveness)

Please note that the Medline search strategies presented in this document were adapted in accordance with each of the databases searched.

1 (degarelix or Firmagon or abarelix or Plenaxis).ti,ab.
2 exp Gonadotropin-Releasing Hormone/ and exp Hormone Antagonists/
3 ((luteini?ing or LHRH or gonadotrop$ or GNRH) and (agonist$ or antagonist$ or blocker$)).ti,ab.
4 2 or 3
5 (androgen deprivation or ADT or androgen suppression).ti,ab.
6 exp Goserelin/
7 exp Leuprolide/
8 exp Triptorelin Pamoate/
9 exp Buserelin/
10 (goserelin or Zoladex or Novgos or Eulexin leuprorelin or leuprolide or Prostap or Lupron or Eligard or Carcinil or Depo-Eligard Enanton or Enantone or Ginecrin or Leuplin or Lucrin or Procren or Procrin or Trenantone or Uno-Enantone or Viadur or triptorelin or Trelstar or Decapeptyl or Gonapeptyl or salvacyl or buserelin or Suprefact or suprecur or Etilamide or Bigonist or Profact or Receptal or Flakon or Cinnafact).ti,ab.
11 or/6-10
12 exp Androgen Antagonists/
13 (Bicaloxbicalutamide or Casodex or Cosudex or Calutide or Kalumid or Bicalox).ti,ab.
14 or/12-13
15 1 and (4 or 5 or 11 or 14)
16 exp Prostatic Neoplasms/
17 (prostat$ and (cancer or carcinoma or adenocarcinoma or tumo?r$ or neoplasm$)).ti,ab.
18 16 or 17
19 15 and 18
20 Economics/
21 "costs and cost analysis"/
22 Cost-benefit analysis/
23 Cost control/
24 Cost savings/
25 Cost of illness/
26 Cost sharing/
27 "deductibles and coinsurance"/
28 Medical savings accounts/
29 Health care costs/
30 Direct service costs/
31 Drug costs/
32 Employer health costs/
33 Hospital costs/
34 Health expenditures/
35 Capital expenditures/
36 Value of life/
37 exp economics, hospital/
38 exp economics, medical/
39 Economics, nursing/
40 Economics, pharmaceutical/
41 exp "fees and charges"/
42 exp budgets/
43 (low adj cost).mp.
44 (high adj cost).mp.
45 (health?care adj cost$).mp.
46 (fiscal or funding or financial or finance).tw.
47 (cost adj estimate$).mp.
48 (cost adj variable).mp.
49 (unit adj cost$).mp.
50 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
51 or/20-50
52 19 and 51

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

Table 68. Quality assessment: Lu *et al*, 2011[144]

	Item	Yes	No	Not clear	Not appropriate
	Study design				
1	The research question is stated.	X			
2	The economic importance of the research question is stated.			X	
3	The viewpoint(s) of the analysis are clearly stated and justified.	X			
4	The rationale for choosing alternative programmes or interventions compared is stated.	X			
5	The alternatives being compared are clearly described.	X			
6	The form of economic evaluation used is stated.	X			
7	The choice of form of economic evaluation is justified in relation to the questions addressed.			X	
	Data collection				
8	The source(s) of effectiveness estimates used are stated.			X	
9	Details of the design and results of effectiveness study are given (if based on a single study).				X
10	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).				X
11	The primary outcome measure(s) for the economic evaluation are clearly stated.	X			
12	Methods to value benefits are stated.		X		
13	Details of the subjects from whom valuations were obtained were given.		X		
14	Productivity changes (if included) are reported separately.				X
15	The relevance of productivity changes to the study question is discussed.				X
16	Quantities of resource use are reported separately from their unit costs.	X			
17	Methods for the estimation of quantities and unit costs are described.		X		
18	Currency and price data are recorded.		X		
19	Details of currency of price adjustments for inflation or currency conversion are given.		X		
20	Details of any model used are given.	X			
21	The choice of model used and the key parameters on which it is based are justified.	X			
	Analysis and interpretation of results				
22	Time horizon of costs and benefits is stated.	X			
23	The discount rate(s) is stated.	X			
24	The choice of discount rate(s) is justified.	X			
25	An explanation is given if costs and benefits are not discounted.				X
26	Details of statistical tests and confidence intervals are given for stochastic data.		X		
27	The approach to sensitivity analysis is given.		X		
28	The choice of variables for sensitivity analysis is justified.		X		
29	The ranges over which the variables are varied are justified.		X		
30	Relevant alternatives are compared.	X			
31	Incremental analysis is reported.	X			
32	Major outcomes are presented in a disaggregated as well as aggregated form.	X			
33	The answer to the study question is given.	X			
34	Conclusions follow from the data reported.	X			
35	Conclusions are accompanied by the appropriate caveats.	X			

Table 69. Quality assessment: Lee *et al*, 2012[145] (Poster)

	Item	Yes	No	Not clear	Not appropriate
	Study design				
1	The research question is stated.	X			
2	The economic importance of the research question is stated.		X		
3	The viewpoint(s) of the analysis are clearly stated and justified.		X		
4	The rationale for choosing alternative programmes or interventions compared is stated.	X			
5	The alternatives being compared are clearly described.			X	
6	The form of economic evaluation used is stated.	X			
7	The choice of form of economic evaluation is justified in relation to the questions addressed.	X			
	Data collection				
8	The source(s) of effectiveness estimates used are stated.	X			
9	Details of the design and results of effectiveness study are given (if based on a single study).		X		
10	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).				X
11	The primary outcome measure(s) for the economic evaluation are clearly stated.	X			
12	Methods to value benefits are stated.		X		
13	Details of the subjects from whom valuations were obtained were given.		X		
14	Productivity changes (if included) are reported separately.		X		
15	The relevance of productivity changes to the study question is discussed.		X		
16	Quantities of resource use are reported separately from their unit costs.		X		
17	Methods for the estimation of quantities and unit costs are described.		X		
18	Currency and price data are recorded.	X			
19	Details of currency of price adjustments for inflation or currency conversion are given.		X		
20	Details of any model used are given.	X			
21	The choice of model used and the key parameters on which it is based are justified.	X			
22	Time horizon of costs and benefits is stated.	X			
23	The discount rate(s) is stated.	X			
24	The choice of discount rate(s) is justified.	X			
25	An explanation is given if costs and benefits are not discounted.				X
26	Details of statistical tests and confidence intervals are given for stochastic data.				X
27	The approach to sensitivity analysis is given.		X		
28	The choice of variables for sensitivity analysis is justified.		X		
29	The ranges over which the variables are varied are justified.		X		
30	Relevant alternatives are compared.	X			
31	Incremental analysis is reported.	X			
32	Major outcomes are presented in a disaggregated as well as aggregated form.	X			
33	The answer to the study question is given.	X			
34	Conclusions follow from the data reported.	X			
35	Conclusions are accompanied by the appropriate caveats.		X		

Table 70. Quality assessment: Hatoum *et al*, 2013[146]

	Item	Yes	No	Not clear	Not appropriate
	Study Design				
1	The research question is stated.	X			
2	The economic importance of the research question is stated.	X			
3	The viewpoint(s) of the analysis are clearly stated and justified.	X			
4	The rationale for choosing alternative programmes or interventions compared is stated.	X			
5	The alternatives being compared are clearly described.	X			
6	The form of economic evaluation used is stated.	X			
7	The choice of form of economic evaluation is justified in relation to the questions addressed.	X			
	Data collection				
8	The source(s) of effectiveness estimates used are stated.	X			
9	Details of the design and results of effectiveness study are given (if based on a single study).	X			
10	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).				X
11	The primary outcome measure(s) for the economic evaluation are clearly stated.	X			
12	Methods to value benefits are stated.	X			
13	Details of the subjects from whom valuations were obtained were given.			X	
14	Productivity changes (if included) are reported separately.				X
15	The relevance of productivity changes to the study question is discussed.				X
16	Quantities of resource use are reported separately from their unit costs.			X	
17	Methods for the estimation of quantities and unit costs are described.	X			
18	Currency and price data are recorded.	X			
19	Details of currency of price adjustments for inflation or currency conversion are given.		X		
20	Details of any model used are given.	X			
21	The choice of model used and the key parameters on which it is based are justified.	X			
	Analysis and interpretation of results				
22	Time horizon of costs and benefits is stated.	X			
23	The discount rate(s) is stated.	X			
24	The choice of discount rate(s) is justified.	X			
25	An explanation is given if costs and benefits are not discounted.				X
26	Details of statistical tests and confidence intervals are given for stochastic data.			X	
27	The approach to sensitivity analysis is given.	X			
28	The choice of variables for sensitivity analysis is justified.	X			
29	The ranges over which the variables are varied are justified.			X	
30	Relevant alternatives are compared.	X			
31	Incremental analysis is reported.	X			
32	Major outcomes are presented in a disaggregated as well as aggregated form.	X			
33	The answer to the study question is given.	X			
34	Conclusions follow from the data reported.	X			
35	Conclusions are accompanied by the appropriate caveats.	X			

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

Databases searched:

- Medline and Medline in Process & Other Non-Indexed citations
- EMBASE
- Cochrane CDSR
- Cochrane CCRT
- Cochrane DARE
- Cochrane NHS EED
- Cochrane HTA
- CINAHL
- EconLit
- Science Citation Index
- Conference Proceedings index (Science).

10.12.2 The date on which the search was conducted.

26th April – 6th May 2013.

10.12.3 The date span of the search.

The date span of the search was from database inception until 26/04/2013.

10.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search strategy

Medline search strategy (QoL)

Please note that the Medline search strategies presented in this document were adapted in accordance with each of the databases searched.

1 exp Prostatic Neoplasms/
2 (prostat$ and (cancer or carcinoma or adenocarcinoma or tumo?r$ or neoplasm$)).ti,ab.
3 1 or 2
4 health related quality of life.tw.
5 hrql.tw
6 hrqol.tw.
7 hql.tw.
8 sf 36.tw.
9 sf thirtysix.tw.
10 sf thirty six.tw.
11 short form 36.tw.
12 short form thirty six.tw.
13 short form thirtysix.tw.
14 shortform 36.tw.
15 shortform thirty six.tw.
16 sf36.tw.
17 medical outcomes survey.tw.
18 mos.tw.
19 euroqol.tw.
20 eq 5d.tw.
21 eq5d.tw.
22 qaly$.tw.
23 quality adjusted life years/
24 quality adjusted life year$.tw.
25 hye$.tw.
26 health$ year$ equivalent$.tw.
27 psychological general well being index.tw.
28 psychological general wellbeing index.tw.
29 pgwb$.tw.
30 health utilit$.tw.
31 hui.tw.
32 quality of wellbeing$.tw.
33 quality of well being.tw. (317)
34 qwb$.tw.
35 rosser.tw.
36 trade off$.tw.
37 standard gamble.tw.
38 tto.tw.
39 "Quality of Life"/
40 "Outcome Assessment (Health Care)"/
41 (preference$ or utilit$).tw. and (39 or 40)
42 ((preference$ or utilit$) and quality of life).tw.
43 (preference$ adj2 (elicit$ or patient$ or population$ or measure$ or based or cost$)).tw.
44 (utilit$ adj2 (elicit$ or patient$ or population$ or measure$ or based or cost$)).tw.
45 or/4-38,41-44
46 3 and 45

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A

10.12.6 The inclusion and exclusion criteria.

Table 71. Inclusion and exclusion criteria

Inclusion criteria		
Category	**Inclusion criteria**	**Rationale**
Population	Adults with advanced hormone-dependent prostate cancer (locally-advanced or metastatic, including biochemical relapse) in whom orchidectomy is not preferred. And patients with later stages of prostate cancer. If this population is only one of a few different populations the study is still eligible for inclusion.	This was the population identified by the draft pre-invite scope and is in accordance with the licenced indication for degarelix. Results for patients with later stages are required for modelling those states
Study type	Studies that assess HRQL	The aim of the review was to identify papers with relevant quality-of-life values
Outcomes	EQ-5D utilities	The aim of the review was to identify papers with relevant quality-of-life values and EQ-5D is most closely aligned to the NICE reference case. If sufficient studies containing EQ-5D were not identified this would have been expanded to include other measures of utility.
Intervention	The interventions of interest were degarelix, LHRH agonists, chemotherapy and palliative care (in line with the interventions within all lines of therapy within the model structure) Additionally relevant adverse events were searched for regardless of the intervention	This is in line with the model structure and designed to include evidence for all model health states
Exclusion criteria		
Category	**Exclusion criteria**	**Rationale**
Publication type	Letters; editorials; reviews of HRQL studies (although reference list of these would be hand-searched)	Primary study articles or relevant cost-effectiveness analyses citing utility values were required

10.12.7 The data abstraction strategy.

If a study met the inclusion/exclusion criteria the data from the study was extracted to fill a table. The headings for this table was in accordance with the

bullet points at the start of section 7.4.6 which requested the information deemed of relevance from each study.

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Databases searched:

- Medline and Medline in Process & Other Non-Indexed citations
- EMBASE
- Cochrane CDSR
- Cochrane CCRT
- Cochrane DARE
- Cochrane NHS EED
- Cochrane HTA
- CINAHL
- EconLit
- Science Citation Index
- Conference Proceedings index (Science)

10.13.2 The date on which the search was conducted.

26th April – 6th May 2013.

10.13.3 The date span of the search.

The date span of the search was from database inception until 26/04/2013.

10.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search strategy

Medline search strategy (Costing and Resource Use)

Please note that the Medline search strategies presented in this document were adapted in accordance with each of the databases searched.

1 *Prostatic Neoplasms/
2 (prostat$ adj2 (cancer or carcinoma or adenocarcinoma or tumo?r$ or neoplasm$)).ti.
3 1 or 2
4 cost$.mp.
5 cost benefit analys$.mp.
6 health care costs.mp.
7 (resource? adj1 (allocat$ or use$ or usage or utili$)).tw.
8 or/4-7
9 3 and 8

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A.

10.13.6 The inclusion and exclusion criteria.

Table 72. Inclusion and exclusion criteria

Inclusion criteria		
Category	**Inclusion criteria**	**Rationale**
Population	Adults with advanced hormone-dependent prostate cancer (locally-advanced or metastatic, including biochemical relapse) in whom orchidectomy is not preferred. And patients with later stages of prostate cancer	This was the population identified by the draft pre-invite scope and is in accordance with the licenced indication for degarelix. Results for patients with later stages are required for modelling those states
Study type	Costing studies, cost-effectiveness studies, studies that assess resource use	The aim of the review was to identify papers with relevant costs and figures about resource use
Outcomes	Costs and use of resources	The aim of the review was to identify papers with relevant costs and use of resources
Intervention	The interventions of interest were degarelix, LHRH agonists, chemotherapy and palliative care (in line with the interventions within all lines of therapy within the model structure) Additionally relevant adverse events were searched for regardless of the intervention	This is in line with the model structure and designed to include evidence for all model health states
Exclusion criteria		
Category	**Exclusion criteria**	**Rationale**
Publication type	Letters; editorials; reviews of HRQL studies (although reference list of these would be hand-searched)	Primary study articles or cost-effectiveness analyses were required
Country of study	UK	Costs and use of resources from a UK perspective were required

10.13.7 The data abstraction strategy.

If a study met the inclusion/exclusion criteria, the data from the study were extracted to fill a table. The headings for this table was in accordance with the bullet points at the start of Section 7.5.3 which requested the information deemed of relevance from each study.

11 Related procedures for evidence submission

11.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted

- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data

have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.