DEGARELIX FOR TREATING ADVANCED HORMONE-DEPENDENT PROSTATE CANCER [ID590]

SPINAL CORD COMPRESSION ASSOCIATED WITH HORMONAL THERAPY IN MEN WITH HORMONE-DEPENDENT METASTATIC PROSTATE CANCER: A SYSTEMATIC REVIEW AND ECONOMIC ASSESSMENT

REPORT BY THE DECISION SUPPORT UNIT

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Duncan Chambers, Sophie Whyte, Ruth Wong

School of Health and Related Research, University of Sheffield

Decision Support Unit, ScHARR, University of Sheffield, Regent Court, 30 Regent Street
Sheffield, S1 4DA

Tel (+44) (0)114 222 0734
E-mail dsuadmin@sheffield.ac.uk
Website www.nicedsu.org.uk
Twitter @NICE_DSU

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EXECUTIVE SUMMARY

Background

Degarelix (Firmagon, Ferring Pharmaceuticals) is a selective gonadotrophin-releasing hormone (GnRH)/luteinising hormone-releasing hormone (LHRH) antagonist which holds a European marketing authorisation for the treatment of adult male patients with advanced hormone-dependent prostate cancer. Compared with its main comparators, the LHRH agonists, degarelix has the benefit of avoiding an initial 'testosterone flare' at the start of treatment; testosterone flare is thought to increase the risk of spinal cord compression (SCC). Degarelix was appraised by NICE under the Single Technology Appraisal (STA) process in 2014. Uncertainty remains regarding the cost-effectiveness of degarelix relative to LHRH agonists in subgroups of patients with different risks of SCC and whether the patients who would benefit most from treatment with degarelix can be reliably identified in clinical practice.

Objectives

The objectives of this project are:

1. To identify any relevant information on the rate of spinal cord compression (SCC) in people with metastatic hormone-dependent prostate cancer, or if possible, those with spinal metastases.
2. To explore the possibility of undertaking a subgroup analysis in people with spinal metastases and to perform an economic analysis if sufficient data are available to do so.

Methods

A rapid and focused systematic review was undertaken to identify any relevant evidence on rates of SCC in men with metastatic prostate cancer. Five databases and selected registries and websites were searched. Citation searches of included studies were also performed. Empirical studies of any design that reported on rates of SCC in men with metastatic hormone-dependent prostate cancer treated with an LHRH agonist or degarelix were eligible for inclusion in the review. Data were extracted from included studies and the quality of the evidence was critically appraised. The economic model developed for the degarelix STA was run for a range of values for the rate of SCC, using the appraisal committee's preferred assumptions and the ERG amended model.

Results

Systematic review

Four studies met the inclusion criteria for the systematic review. In two of these studies, SCC events occurred too late to be the result of a testosterone flare. A third study (Ahmann *et al.*[1]) reported that 2/33 patients with metastatic disease experienced SCC in the first week of therapy; however, this study was performed in the 1980s and patients did not receive anti-androgen therapy to reduce the risk of testosterone flare. The remaining study (Oh *et al.*[2]) reported a rate of 0.96% (15/1,566) for SCC occurring within the first 30 days of LHRH agonist therapy in men with metastatic disease. Limitations of this study include its observational design, reliance on administrative data collection methods and uncertain generalisability to current UK practice. No data were found for patients with known spinal metastases. No data were found to contradict the assumption that the rate of short-term SCC in patients receiving degarelix is expected to be zero.

Economic analysis

Sensitivity analyses demonstrated that the ICER for degarelix compared to LHRH agonists is sensitive to the rate of SCC. The ICER values compared to triptorelin were £342,984, £99,228, £39,163, and £11,974 for SCC rates of 0%, 1%, 2% and 3% respectively. At a SCC rate of 4% degarelix dominated triptorelin and degarelix dominated leuprorelin and goserelin at a SCC rate of 3.5%.

The best evidence available suggests that the rate of SCC in the metastatic subgroup is around 1%.[3] For the metastatic subgroup the economic model (run with appraisal committee's preferred assumptions) gives ICER values of £103,179, £86,335 and £82,277 per QALY gained for triptorelin, goserelin and leuprorelin, respectively.

Limited data were available on the relative sizes of the metastatic and spinal metastases subgroups compared to the scope population. An autopsy study identified during searching for the systematic review reported that approximately 70% of those with metastatic prostate cancer had spinal metastases.[4] Based on this study (the best available evidence) the rate of SCC in the subgroup with spinal metastases is likely to be greater than 1.35%. For the spinal metastases subgroup the economic model (run with appraisal committees preferred assumptions) suggests ICERs for degarelix versus triptorelin, goserelin and leuprorelin of less than £71,387, £57,821 and £54,552 per QALY gained, respectively. In the absence of data on

the population size of SCC rate for the spinal metastases subgroup it is not possible to accurately estimate the cost-effectiveness of degarelix for this subgroup. We also note that these analyses simply use model parameters and assumptions for the scope population for the subpopulations. This may be inappropriate in places hence the results are subject to considerable uncertainty.

Conclusions

Very limited evidence is available to assess the rate of SCC in men with metastatic hormone-dependent prostate cancer in the early stages of treatment with LHRH agonists or degarelix. The largest study located reported a rate of 0.96% (15/1,566) for SCC occurring within the first 30 days of LHRH agonist therapy in men with metastatic disease.

There is considerable uncertainty around the true rate of SCC in patients with metastatic hormone-dependent prostate cancer and in the subgroup with spinal metastases. Economic analyses undertaken using the appraisal committee's preferred assumptions suggest that degarelix is not cost-effective for the subgroup with metastatic disease. Economic analyses suggest that degarelix could be cost-effective for the subgroup with spinal metastases however there is insufficient data on the size of this subgroup or the rate of SCC in this subgroup to estimate an ICER. As economic model inputs and assumptions relate to the scope population rather than the subgroups, all analyses should be treated with caution.

CONTENTS

TABLES AND FIGURES

ABBREVIATIONS AND DEFINITIONS

AJCC	American Joint Committee on Cancer
DSU	Decision Support Unit
EG	Example
ERG	Evidence Review Group
FAD	Final appraisal determination
GnRH	Gonadotrophin releasing hormone
ICER	Incremental Cost Effectiveness Ratio
LHRH	Luteinising hormone releasing-hormone
MS	Manufacturer's submission
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
SCC	Spinal cord compression
STA	Single technology appraisal
TNM	Tumour Node Metastases

1. INTRODUCTION

1.1. BACKGROUND

Degarelix (Firmagon, Ferring Pharmaceuticals) is a selective gonadotrophin-releasing hormone (GnRH)/luteinising hormone-releasing hormone (LHRH) antagonist. Degarelix has a UK marketing authorisation for treatment of advanced hormone-dependent prostate cancer. Compared with its main comparators, the LHRH agonists, degarelix has the benefit of avoiding an initial 'testosterone flare' at the start of treatment, which is thought to increase the risk of spinal cord compression (SCC).

Degarelix was appraised by NICE under the Single Technology Appraisal (STA) process in 2014. In its initial draft guidance, the NICE Appraisal Committee recommended degarelix as an option for treating advanced hormone-dependent prostate cancer, only in people with spinal cord metastases who are at risk of impending SCC.[5]

This wording of the recommendation was revised in the final guidance to state that degarelix is recommended as an option for treating advanced hormone-dependent prostate cancer, only in adults with spinal metastases who present with signs or symptoms of SCC.[6]

Appeals were received stating that the change in the wording of the recommendations had led to a restriction in the population eligible for treatment with degarelix in the NHS without previous consultation. The Appeal Panel asked the NICE Appraisal Committee to reconsider the wording of the recommendation, stating that if degarelix is to be approved for a particular patient group, the definition of the group should be very clear, not reliant on different interpretations and capable of application in a routine clinical setting.[7]

At its third meeting, the NICE Appraisal Committee concluded that although a subgroup of people with spinal metastases who may develop SCC as a result of testosterone flare may exist in clinical practice, it cannot be reliably identified beyond those people with spinal metastases. The Committee expressed concern that if this subgroup cannot be clearly identified and defined in clinical practice, degarelix is likely to be used in all people with spinal metastases. It noted that the manufacturer had not presented a cost-effectiveness analysis for this group and that all the ICERs (incremental cost-effectiveness ratios) presented for the overall population of people with locally advanced or metastatic hormone-dependent

prostate cancer were outside the range normally considered to be a cost-effective use of NHS resources.

The DSU was therefore asked to undertake further work to identify any relevant information on the rate of SCC in people with metastatic hormone-dependent prostate cancer, or if possible, those with spinal metastases. The DSU was also asked to explore undertake a subgroup analysis in people with spinal metastases if sufficient data are available to do so. Section 2 presents the results of a rapid systematic review on rates of SCC in men with metastatic prostate cancer exposed to LHRH agonists. Section 3 presents the results of the economic analysis for the metastatic and spinal metastases subgroups.

2. SYSTEMATIC REVIEW

2.1. METHODS

2.1.1. Review question/objectives

The objective of the systematic review was to inform further economic modelling work by identifying and synthesising evidence on the rate of occurrence of SCC in men with metastatic hormone-dependent prostate cancer. Specifically, the review aimed to address the following questions:

- What is the rate of spinal cord compression in men with metastatic hormone-dependent prostate cancer who have received LHRH agonists or degarelix?
- What is the rate of spinal cord compression in men with spinal metastases of prostate cancer?

A specific objective was to use the results to inform an analysis of the cost-effectiveness of degarelix compared with LHRH agonists in the subgroup of men with spinal metastases of prostate cancer. A protocol was drawn up in advance and is provided in Appendix A1.

2.1.2. Inclusion and exclusion criteria

Population: Men with metastatic hormone-dependent prostate cancer. This relates to Stage IV disease according to the American Joint Committee on Cancer (AJCC) Tumour Node Metastases (TNM) system. Given that prostate cancer is normally hormone-dependent, it was

assumed that this is the case if hormone status was not reported. Studies of hormone-resistant or hormone-refractory prostate cancer were excluded from the review.

Intervention/exposure: The primary intervention or exposure of interest is treatment with degarelix or one of its comparators (LHRH agonists, namely goserelin, leuporelin, triptorelin or buserelin). The review aimed to locate reports of SCC within studies of patients being treated with these agents. Studies reporting data for men not treated with any of these agents, or where the treatment received was unclear, were excluded from the analysis.

Comparator: Data from comparative and non-comparative studies were included.

Outcomes: The outcome of interest is SCC. Cases of SCC occurring as a result of a testosterone flare shortly after starting treatment are most relevant to the decision problem. However, all data on rates of SCC in men treated with relevant drugs have been included in the review. Data on 'spinal cord symptoms' or 'skeletal-related events', where the reported events did not specifically relate to SCC, were excluded.

Study designs: Evidence from published empirical studies of any design and from UK and selected international cancer registries and association websites (see Section 2.1.3) was eligible for inclusion in the review.

2.1.3. Searching

To gauge the size of the evidence base, a scoping search was carried out by the DSU on 3 February 2015 in Medline, Embase and the Web of Science. Terms for the population (prostate cancer or spinal metastasis) combined with the adverse event (spinal cord compression) resulted in excess of 6,000 records. In light of the number of records and short timescales available for the review, the DSU considered that a pragmatic approach to searching was required and that terms for SCC would be combined with the named intervention degarelix and its drug comparator terms. This search resulted in a smaller set of records for assessment.

The following databases were searched on 9 February 2015:

- MEDLINE AND MEDLINE In-Process Citations: Ovid
- EMBASE: Ovid
- Cochrane Library: Wiley Online
- Science Citation Index Expanded: Web of Science.
- Science Citation Index and Conference Proceedings Index: Web of Science.

No study design filter was applied to the searches so that observational studies would be retrieved as well randomised and non-randomised controlled clinical trials. No date or language limits were applied in the searches. All search strategies are provided in Appendix A2.

Other levels of evidence using named drugs or conditions in the dataset were searched via UK and international cancer registries and association websites on 10 and 17 February 2015 respectively:

- Public Health England
- Scottish Cancer Registry
- Welsh Cancer Intelligence & Surveillance Unit (WCISU)
- National Cancer Registry, Ireland
- Australasian Association of Cancer Registries
- European Network of Cancer Registries (ENCR)
- International Agency for Research on Cancer (IARC)
- International Association of Cancer Registries (IACR)
- North American Association of Central Cancer Registries
- SEER (National Cancer Institute, USA)

The reference lists of included studies were checked and citation searches were carried out on 23 February 2015 in the Web of Science. All records from the electronic database and citations searches were imported using EndNote Bibliographic software (version X7.2.1, Thomson Reuters, Philadelphia, PA).

2.1.4. Study selection

Search results were stored in the reference management database. Selection of studies for inclusion was carried out by one reviewer, with input from other team members to resolve uncertainties.

2.1.5. Data extraction and quality assessment

Data extraction was undertaken by one reviewer, with input from other team members to resolve uncertainties. Standardised data extraction tables were developed in advance.

Data were extracted on key study characteristics and outcomes, including:

- study type and design
- details of the population
- setting
- rate of SCC in the population as a whole and (if reported) specifically in men with spinal metastases
- details of treatment with degarelix or LHRH agonists
- any data on when SCC occurred in relation to drug treatment
- details of any treatment (anti-androgen therapy) to mitigate the testosterone flare associated with LHRH agonist treatment, e.g. bicalutamide.

After consideration of the design of the included studies it was decided that the application of a formal quality assessment tool such as the Newcastle–Ottawa scale for observational studies may be inappropriate because of the absence of a control group for the exposure of interest. Instead the suitability of each included study was assessed in terms of relevance to the review question. Any obvious weaknesses of the study were highlighted, e.g. unknown temporal association between treatment and SCC events or uncertain generalisability to patients with metastatic prostate cancer in the UK. The assessment was carried out by one reviewer with input from other team members to resolve uncertainties.

2.1.6. Evidence synthesis

In view of the limited evidence retrieved, a narrative synthesis of evidence from studies reporting data on both occurrence of SCC and treatment with GnRH agonists or degarelix was carried out. This focused on assessing the reported rates of SCC during the initial

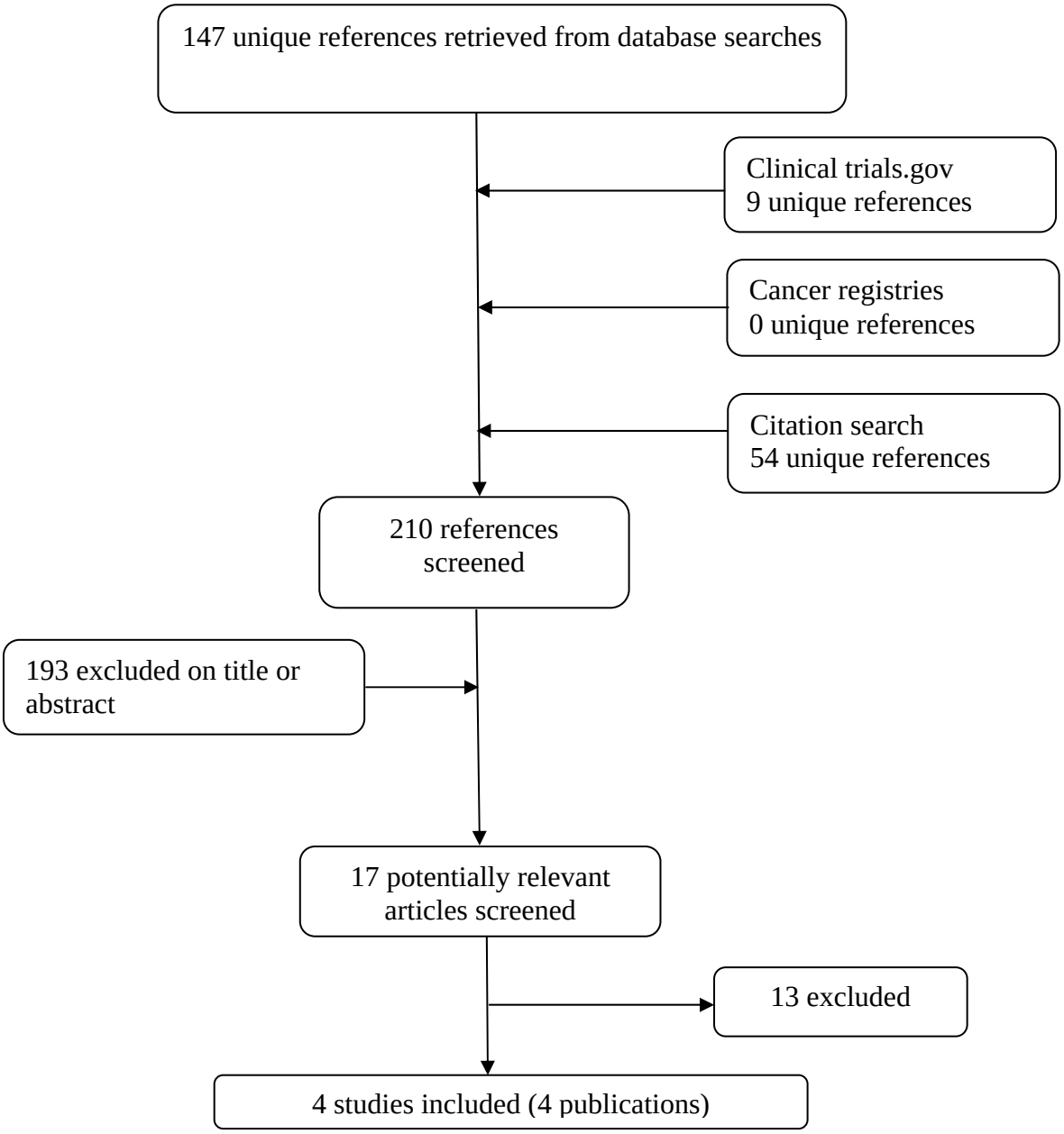
treatment period in relation to the methodological reliability of the studies and the applicability of the findings to patients who might be considered for treatment with GnRH agonists or degarelix in UK practice.

2.2. RESULTS

2.2.1. Study selection

The flow of studies through the review process is illustrated in Figure 1. 200 records were identified by database searching, resulting in 147 unique references. Four studies met the inclusion criteria and are discussed in detail below. Studies that were excluded from the review after examination of the full text are listed in Appendix A3, with reasons for rejection. One study[8] was identified from the reference list of a recent review of studies of disease flare associated with LHRH agonists,[9] which was itself identified by the citation search based on the four included studies.

Figure 1: Study flow diagram



2.2.2. Characteristics of included studies

Four studies met the inclusion criteria in terms of reporting data on rates of SCC in patients with metastatic cancer exposed to treatment with LHRH agonists (Table 1). However, only two studies by Ahmann *et al.*[1] and Oh *et al.*[2] reported events that may have occurred as a result of a testosterone flare, i.e. during the first few weeks of treatment. The analysis therefore concentrated on these studies, with the studies by Dawson *et al.*[10] and Nozawa *et al.*[11] being included for completeness in line with the review protocol.

Table 1: Main characteristics of included studies

Reference	Country/Setting	Study design	Population	Duration of study
Ahmann *et al*1987[1]	USA; hospital oncology departments	Multi-centre trial with random assignment to dose of Zoladex (goserelin)	Men with stage B-2, C or D prostate cancer; indication for hormonal therapy; no previous endocrine treatment or chemotherapy (n=46)	3 months, with continued therapy for those thought to have benefitted; median follow-up of 41 weeks
Dawson *et al* 1992[10]	USA; specialist cancer centres	Single-arm study	Men with previously untreated metastatic prostate cancer (n=15)	Indefinite (median follow-up 42+ months, range 22 to 54 months)
Nozawa *et al* 2014[11]	Japan; hospital urology/oncology departments	Single-arm study	Men with previously untreated prostate cancer with bone metastases (n=52)	24 months
Oh *et al* 2010[2]	USA; Veterans Affairs (VA) hospital system	Comparative observational study using VA registry data and VA and Medicare administrative data	Men with newly diagnosed metastatic prostate cancer treated with LHRH agonists with or without prior anti-androgen therapy (n=1566)	Patients diagnosed or treated during 2001 to 2004 were followed up to death or the end of 2005

2.2.3. Rate of spinal cord compression

The rate of SCC occurring within 30 days of starting treatment with an LHRH agonist was 0.96% in Oh *et al*. and 6.1% in Ahmann *et al*. (Table 2). In the Ahmann *et al*. study, both SCC events occurred within seven days of starting treatment. In the study reported by Oh *et al*., rates of SCC did not differ markedly between subgroups with no anti-androgen use (3/312, 0.9%), anti-androgen use 0–6 days before LHRH agonist therapy (4/491, 0.8%) and anti-androgen use seven or more days before LHRH agonist therapy (8/754, 1.0%).[2]

Table 2: Drug exposure and occurrence of SCC

Reference	LHRH agonist/antagonist therapy	Anti-androgen therapy	Any other therapy	Occurrence of SCC	Data on people with known spinal metastases?	Relationship with LHRH agonist or antagonist reported?
Ahmann *et al*1987[1]	Goserelin 0.9 (n=15), 1.8 (n=13) or 3.6 (n=17) mg depot by subcutaneous injection every 28 days	None reported	None reported	2/33 patients with stage D disease (6.1%) (2/46 patients overall (4.3%))	Patients with clinical findings suggesting impending SCC were excluded	SCC developed within 1 week of starting therapy
Dawson *et al* 1992[10]	Leuporelin (leuprolide) 1 mg daily by subcutaneous injection	Flutamide 250 mg 3 times daily on days 4 to 25 of each 28 day cycle	Carboplatin given intravenously every 28 days preceded and followed for 3 days by androgen treatment with fluoxymesterone, during which time flutamide was discontinued	One patient developed SCC after 12 cycles of therapy but this was shown to be secondary to tumour progression	Patients with significant vertebral metastases underwent additional spinal CT scan to exclude impending SCC before entry to the study	Authors stated that there were no cases of SCC related to testosterone flare
Nozawa *et al* 2014[11]	Goserelin 10.8 mg by subcutaneous injection every 12 weeks	Bicalutamide 80 mg per day orally from day 1	Zoledronic acid 4 mg intravenously every 4 weeks	One patient developed SCC after >6 months of treatment (exact timing unclear)	Not reported	Not reported
Oh *et al* 2010[2]	Details not reported. Authors stated that LHRH agonists in use included goserelin and leuporelin (leuprolide acetate)	Patients prescribed bicalutamide, flutamide or nilutamide were considered to have been treated with an oral anti-androgen	None reported	SCC within 30 days of first LHRH agonist dose: No anti-androgen therapy 3/321 (0.9%); anti-androgen use 0 to 6 days prior 4/491 (0.8%); anti-androgen use 7 or more days prior 8/754 (1.0%); total 15/1566 (0.96%)	Not reported	SCC developed within 30 days of starting therapy

None of the included studies provided data on rates of SCC in trials where one group received degarelix. Furthermore, none of the studies reported data for the subgroup of patients with known spinal metastases. In the studies reported by Ahmann *et al*.[1] and Dawson *et al*.[10], patients considered to be at risk of impending SCC were excluded from entry into the study. An autopsy study cited in one of the papers examined[12] found that of 1,589 men with prostate cancer, 631 had evidence of lymphatic or haematogenous metastases, 501 had bone metastasis and 447 tumours had spine metastases.[4] The autopsy study was used as the best available data to estimate the proportion of patients with metastatic disease who have spinal metastases (Section 3). Although this study has limitation it was the best available as a systematic review of spinal metastases prevalence was not undertaken.

2.2.4. Summary and critique of the evidence base

The best evidence located for this review suggests that the rate of SCC associated with a possible short-term testosterone flare in men starting treatment with an LHRH agonist for metastatic prostate cancer is about 1%. This estimate is reliant on data from a single, relatively large, observational study by Oh *et al*.[2] The other study that reported this outcome[1] had a higher percentage rate of SCC (6.06 vs. 0.96%) but included a much smaller number of patients (33 patients with metastatic disease in Ahmann *et al.* vs. 1,566 in Oh *et al.*).

The evidence included in the review has some important limitations that may impact upon its reliability. The study reported by Oh *et al*. adopted an observational design and was dependent on the treatments given and data recorded in everyday clinical practice. There was no control group, hence it is impossible to determine how many SCC events would have occurred in the absence of LHRH agonist treatment. It appears that a variety of different LHRH agonists and anti-androgen therapies were used and details of doses and duration of treatment were not reported. The use of administrative data means that the study findings could be affected by any coding errors in the data collection system. The study was conducted in a US population of patients diagnosed between 2001 and 2004[2] so possible differences from current UK practice need to be considered. On the positive side, the use of administrative data allowed the authors to study a relatively large group of patients. As the patients were treated through the Veterans Affairs health system, they had good access to health care and the study authors stated that treatment decisions were unlikely to have been influenced by socio-economic factors.[2]

The Ahmann *et al*. study also has some important limitations for answering the review question.[1] The study was conducted in the 1980s and is therefore unlikely to reflect current clinical practice. In particular, anti-androgen therapy was not used and this may explain the higher rate of SCC in this study. Compared with Oh *et al*., Ahmann *et al*. has the advantage of being a prospective clinical trial with regular monitoring of study participants. Patients with clinical signs of impending SCC were not eligible for the study, potentially removing the subgroup who could benefit most from treatment with degarelix, although it is possible that more patients at risk of SCC could have been identified by additional scanning as was done by Dawson *et al*.[10]

SCC events reported in the other two studies identified appeared to reflect disease progression rather than a possible response to starting LHRH agonist therapy. In the study by Dawson *et al*., a case of SCC occurred after 12 cycles of therapy and was attributed by the authors to disease progression.[10] The timing of SCC in the study by Nozawa *et al*. was less clear because the study looked at all skeletal-related events as a group but no such events occurred in the first six months of the study.[11]

The use of anti-androgen therapy to mitigate the risk of a short-term flare when starting treatment with LHRH agonists is generally recommended. In the study by Oh *et al*., 79.5% of participants received anti-androgen therapy and there were marked differences between the treated and untreated groups. However, rates of SCC did not differ between the groups. A commentary on the study suggested that the rate of events associated with disease flare was particularly low in this study and suggested that a rate of around 10% was more normal.[13] Unfortunately, the author did not supply a reference to support this statement. A recent review concluded that there is a lack of compelling evidence for disease progression associated with a short-term testosterone flare at the start of LHRH agonist therapy.[9] Full investigation of this topic was, however, beyond the scope of the review.

2.2.5. Strengths and limitations of the review process

This review was performed using transparent methods with a protocol prepared in advance (Appendix A1). In order to ensure that the included data were relevant to the target population, the literature search focused on papers indexed with the names of the drugs of interest. A comprehensive review on SCC in metastatic prostate cancer would not be possible within the timescales available for this appraisal; this means that it is not possible to rule out

the possibility that some evidence relevant to the decision problem could have been missed by this review. To minimise the effects of possible publication bias, sources of 'grey literature' were searched to identify completed but not yet published trials and relevant data from cancer registries. Much of the work on study selection and data extraction was undertaken by a single reviewer, although oversight of the process by the wider review team provides some protection against reviewer errors or unconscious bias.

3. ECONOMIC ANALYSIS

3.1. BACKGROUND

The initial draft guidance released by NICE recommended degarelix for a patient subgroup: patients with spinal metastases who are at risk of impending spinal cord compression (SCC). The subsequent final appraisal determination (FAD) changed the definition of the subgroup to: adults with spinal metastases who present with signs or symptoms of SCC. At its third meeting, the NICE Appraisal Committee concluded that a subgroup of people with spinal metastases who may develop SCC as a result of testosterone flare cannot be reliably identified (beyond those patients with spinal metastases). The company had not presented a cost-effectiveness analysis for the metastatic or spinal metastases subgroups. From here on we will refer to the scope population as the patients with locally advanced or metastatic hormone dependent prostate cancer.

In this section, firstly data on the size and SCC event rates for the metastatic and spinal metastases subgroups will be considered. Secondly, the economic model for the scope population will be rerun using a range of rates for SCC events based on the literature identified by the review (Section 2). The model used for these analyses will be the ERG amended model with the Appraisal Committees preferred assumptions.

3.2. SUMMARY OF MODELLING OF SCC TAKEN FROM THE ORIGINAL ERG REPORT

The total discounted cost associated with SCC for the overall scope population was £1,836 in the original company submission. The expected discounted cost associated with treating one patient with SCC was estimated to be £182,647 (£1,836/0.0102).[3]

In the manufacturer's submission (MS), SCC events were assumed to occur as a result of the testosterone flare and therefore the rate of SCC in the degarelix arm was assumed to be zero. The ERG report noted that the majority of the trials included in the company's submission did not report on the rate of the SCC events. The Oh *et al.* study reports SCC rates of 3/321=0.9%, 4/491=0.8% and 8/754=1.0% for no anti-androgen use and anti-androgen use 0-six days prior and seven or more days prior respectively. The ERG report suggested that given the size of the Oh *et al.* study, it is a useful source of data for SCC rates.[3] For LHRH agonists, SCC rates were estimated to be 0.96%.[3] It was assumed that the proportion of persons who have another SCC event that will suffer another event within one year is 6.2%.[14] Taking into account this impact of relapse, the estimated SCC rate in the comparator arm was 1.02%.

Expert clinical advice received by the ERG suggested that the use of degarelix in the subgroups "patients with spinal metastases with impending or actual SCC" and "patients with high tumour volume with impending or actual urinary outflow obstruction" could potentially be appropriate. The original ERG report[3] undertook an exploratory analysis for "patients with spinal metastases with impending or actual SCC" which considered the circumstances under which degarelix may be cost-saving. An analysis was also undertaken in which the base case analysis was modified to exclude SCC adverse events; this analysis could be representative for a subgroup with no risk of SCC. As noted in Section 2, there are no data directly comparing the efficacy of degarelix versus LHRH agonists for this subgroup "patients with spinal metastases with impending or actual SCC". Instead, the ERG's exploratory analysis relied on two assumptions:

1. Patients receiving degarelix will not experience SCC events
2. The efficacy (in terms of prostate specific antigen [PSA] progression and overall survival [OS]) is (conservatively) assumed to be the same for degarelix and LHRH agonists.

As the rate of SCC in the subgroup of patients with spinal metastases with impending or actual SCC was not known, results for several values are presented. Details of the analysis undertaken in the original ERG report are reproduced in Table 3. This analysis only compares the incremental cost associated with treatment and administration (no other cost) with the average cost of treating SCC. Under the assumption of equal PSA progression and OS efficacy, the QALY gains associated with degarelix will be higher than with triptorelin (due

to a lower frequency of QALY decrements associated with SCC events). If the rate of SCC in the subgroup is greater than 3.5% then degarelix results in cost-savings, hence it will dominate.[3]

Table 3: Exploratory analysis for the subgroup 'patients with spinal metastases with impending or actual SCC' [reproduced from ERG report Table 45]

Subgroup with spinal metastases with impending or actual spinal cord compression			
SCC rate in the subgroup	5%	10%	50%
Average cost of treating one person with SCC	£182, 647	£182,647	£182,627
Average cost of treating SCC	£9,132	£18,265	£91,324
Incremental costs associated with treatment and administration with degarelix compared to triptorelin 3-monthly	£6,396	£6,396	£6,396
Cost saving associated with addition of degarelix (incorporating degarelix/LHRH agonist treatment costs and SCC treatment costs)	£2,737	£11,869	£84,928

3.3. ADDITIONAL ANALYSIS UNDERTAKEN BY THE DSU

3.3.1. Estimating the proportion of patients with any metastases, spinal metastases and SCC

What proportion of the scope population has metastatic disease or spinal metastases?

Within trial CS21,[15] only 20% patients (125 patients) had metastatic disease (see Table 4). Of those characterised with locally advanced or metastatic disease, as would be relevant to the scope population, 41% patients (125/303) had metastatic disease.

Table 4: Patient demographics and baseline characteristics (CS21, Klotz 2008)

Localised	191	31%
Locally advanced	178	29%
Metastatic	125	20%
Non-classifiable	116	19%
Total	610	100%

With respect to the prevalence of spinal metastases, the following advice was received by the DSU from Prof Noel Clarke (Professor of Urological Oncology, Christine NHS Foundation Trust).

"At first presentation, about 10% of prostate cancer patients will have bone metastases and a large proportion of these will be in the "axial skeleton" i.e. the pelvis and thoraco-lumbar spine. As the patients approach the last 6 months of life most of them (90%+) will have metastases in their spine. Many will have symptoms. About 3 or more percent will develop spinal cord compression." (email, 27 February 2015)

However it appears that this answer relates to all prostate cancer patients rather than the scope population (patients with locally advanced or metastatic disease).

The autopsy study identified as part of the systematic review presented in Section 2 (Bubendorf *et al.*)[4] found that bone metastases were predominantly present in the spine (90%). This study found that of the 631 patients with metastases, 501 had bone metastases. Of these patients, 447 had spinal metastases.[4] Hence, 71% of patients with metastases had spinal metastases. However, as this is an autopsy study and includes patients whose disease had become hormone resistant, it is likely that the autopsy population will have more severe disease than the scope population because by definition the disease has progressed to its maximum extent. Hence, it seems reasonable to assume that based on this study 71% is an upper bound for the proportion of patients with metastatic disease that have spinal metastases. Other data on the relative sizes of these subgroups would be useful but was not within the scope of the systematic review undertaken for this project.

What is the rate of SCC in the subgroup of patients with spinal metastases?

The best evidence identified by the systematic review in Section 2 suggests that the rate of SCC associated with a possible short-term testosterone flare in men starting treatment with an LHRH agonist for metastatic prostate cancer is 0.96%, based on Oh *et al*[2] (n=1,566). The population in the study reported by Oh *et al*. consists of patients with metastatic disease receiving LHRH agonists; it does not include patients with locally advanced disease. As such, the Oh *et al.* study provides an overestimate of the rate of SCC in the broader scope population. The other study that reported this outcome[1] had a higher percentage rate of SCC events (6.06%) but was based on a much smaller sample of patients (n=33).

If one assumes that (i) the upper bound on the proportion of metastatic prostate cancer patients that could have spinal metastases is 71% (based on Bubendorf *et al.*,[4] detailed above), (ii) the rate of SCC events in patients with metastatic disease is 0.96% (based on Oh

et al.[2]), and (iii) SCC is only possible in those with spinal metastases, the rate of SCC in patients with spinal metastases would be at least 1.35% (0.0096/0.71).

3.3.2. Sensitivity analysis on the rate of SCC events

The economic model which reflects the scope population (locally advanced or metastatic disease) was run for a range of values for the rate of SCC. This analysis assumes the repeated proportion of SCC within a year is 6.2% as in the MS. This analysis was implemented by varying the value of cell E171 on the parameters sheet (cell name: "pr_scc_c") from 0 to 4% and running the model deterministically.

This analysis was run for the Appraisal Committee's base case most plausible assumptions (as described in FAD 3.33) and uses the ERG amended model. These assumptions are:

- Treatment with degarelix and LHRH agonists would continue until death, in line with clinical practice and their licensed indications
- No differential treatment effect of degarelix compared with LHRH agonists in terms of PSA progression or death
- The proportion of patients receiving chemotherapy after PSA progression would be 70% and the proportion of patients receiving abiraterone would be 70%
- The same rate of fractures for people receiving degarelix and LHRH agonists
- The same rate of cardiovascular events for people receiving degarelix and LHRH agonists.

Under these assumptions degarelix provided an incremental cost of £5,453 and a QALY gain of 0.053 compared with triptorelin, resulting in an ICER of £103,179 per QALY gained (goserelin ICER versus goserelin and leuprorelin were £86,335 and £82,277 respectively).

Table 5 presents the results of running the model for the scope population for a range of values for the SCC event rate.

Table 5: Sensitivity analysis on the rate of SCC

SCC rate	Treatment Arm	Totals			Incrementals			Cost per QALY gained
		Costs	QALYs Gained	Life Years Gained	Costs	QALYs Gained	Life Years Gained	
0.0%	Degarelix	£27,766	5.78	9.55				
0.0%	Triptorelin 3 Monthly (Decapeptyl)	£20,421	5.76	9.55	£ 7,345	0.02	-	£ 342,984
0.5%	Triptorelin 3 Monthly (Decapeptyl)	£21,407	5.74	9.55	£ 6,360	0.04	-	£ 168,299
1.0%	Triptorelin 3 Monthly (Decapeptyl)	£22,392	5.72	9.55	£ 5,374	0.05	-	£ 99,228
1.5%	Triptorelin 3 Monthly (Decapeptyl)	£23,377	5.71	9.55	£ 4,389	0.07	-	£ 62,224
2.0%	Triptorelin 3 Monthly (Decapeptyl)	£24,363	5.69	9.55	£ 3,404	0.09	-	£ 39,163
2.5%	Triptorelin 3 Monthly (Decapeptyl)	£25,348	5.67	9.55	£ 2,418	0.10	-	£ 23,414
3.0%	Triptorelin 3 Monthly (Decapeptyl)	£26,334	5.66	9.55	£ 1,433	0.12	-	£ 11,974
3.5%	Triptorelin 3 Monthly (Decapeptyl)	£27,319	5.64	9.55	£ 447	0.14	-	£ 3,289
4.0%	Triptorelin 3 Monthly (Decapeptyl)	£28,304	5.63	9.55	-£ 538	0.15	-	Dominating
0.0%	Leuprorelin Monthly (Prostap)	£21,526	5.76	9.55	£ 6,240	0.02	-	£ 291,399
0.5%	Leuprorelin Monthly (Prostap)	£22,511	5.74	9.55	£ 5,255	0.04	-	£ 139,064
1.0%	Leuprorelin Monthly (Prostap)	£23,497	5.72	9.55	£ 4,270	0.05	-	£ 78,832
1.5%	Leuprorelin Monthly (Prostap)	£24,482	5.71	9.55	£ 3,284	0.07	-	£ 46,562
2.0%	Leuprorelin Monthly (Prostap)	£25,467	5.69	9.55	£ 2,299	0.09	-	£ 26,452
2.5%	Leuprorelin Monthly (Prostap)	£26,453	5.67	9.55	£ 1,313	0.10	-	£ 12,717
3.0%	Leuprorelin Monthly (Prostap)	£27,438	5.66	9.55	£ 328	0.12	-	£ 2,742
3.5%	Leuprorelin Monthly (Prostap)	£28,424	5.64	9.55	-£ 657	0.14	-	Dominating
4.0%	Leuprorelin Monthly (Prostap)	£29,409	5.63	9.55	-£ 1,643	0.15	-	Dominating
0.0%	Goserelin 3 Monthly (Zoladex)	£21,311	5.76	9.55	£ 6,455	0.02	-	£ 301,415
0.5%	Goserelin 3 Monthly (Zoladex)	£22,297	5.74	9.55	£ 5,470	0.04	-	£ 144,741
1.0%	Goserelin 3 Monthly (Zoladex)	£23,282	5.72	9.55	£ 4,484	0.05	-	£ 82,792
1.5%	Goserelin 3 Monthly (Zoladex)	£24,268	5.71	9.55	£ 3,499	0.07	-	£ 49,603
2.0%	Goserelin 3 Monthly (Zoladex)	£25,253	5.69	9.55	£ 2,513	0.09	-	£ 28,920
2.5%	Goserelin 3 Monthly (Zoladex)	£26,238	5.67	9.55	£ 1,528	0.10	-	£ 14,794
3.0%	Goserelin 3 Monthly (Zoladex)	£27,224	5.66	9.55	£ 543	0.12	-	£ 4,534
3.5%	Goserelin 3 Monthly (Zoladex)	£28,209	5.64	9.55	-£ 443	0.14	-	Dominating
4.0%	Goserelin 3 Monthly (Zoladex)	£29,195	5.63	9.55	-£ 1,428	0.15	-	Dominating

3.3.3. Exploratory analysis for population subgroups

Firstly it is important to consider the relevance of economic model to subgroups of the scope population. The company's model is based on data from the CS21[15] and CS21A (unpublished) clinical trials. The study population within these trials therefore reflects a population of patients with localised, locally advanced or metastatic disease and unclassifiable prostate cancer. The subgroups of patients with metastatic disease and spinal metastases are therefore likely to have significantly poorer survival than seen in the study populations. The relative efficacy of degarelix compared to LHRH agonists in the metastatic and spinal metastases subgroups is not known. However, if the assumption of no differential treatment effect of degarelix compared with LHRH agonists in terms of PSA progression or death is assumed to extend to the metastatic and spinal metastases subgroups then the model could be considered relevant for these subgroups. Table 6 presents ICER values for SCC

event rates which may be relevant for the metastatic and spinal metastases subgroups. These analyses simply use model parameters and assumptions for the scope population for the subpopulations. This may be inappropriate in places hence the results are subject to considerable uncertainty.

Table 6: Scenario analysis for different SCC rates relevant to subgroups

Population	Initial SCC event rate	ICER for degarelix vs. comparator		
		Triptorelin 3 monthly (decapeptyl)	Goserelin 3 monthly (zoladex)	Leuprorelin monthly (prostap)
No risk of SCC	0%	£342,984	£301,415	£291,399
Scope population: Locally advanced or metastatic	<0.96%	> £103,179	> £86,335	> £82,277
Metastatic Disease	0.96%	£103,179	£86,335	£82,277
Spinal metastases	>1.35%	< £71,387	< £57,821	< £54,552

3.4. CONCLUSIONS OF ECONOMIC ANALYSES

A sensitivity analyses was undertaken using the appraisal committees preferred assumptions and the ERG amended model. These analyses demonstrated that the ICER for degarelix compared to LHRH agonists is sensitive to the rate of SCC. The ICER values compared to triptorelin were £342,984, £99,228, £39,163, and £11,974 for SCC rates of 0%, 1%, 2% and 3% respectively. At a SCC rate of 4% degarelix dominated triptorelin and degarelix dominated leuprorelin and goserelin at a SCC rate of 3.5%.

The best evidence available suggests that the rate of SCC in the metastatic subgroup is around 1%.[3] For the metastatic subgroup the economic model (run with appraisal committees preferred assumptions) gives ICER values of £103,179, £86,335 and £82,277 per QALY gained for triptorelin, goserelin and leuprorelin, respectively.

Limited data were available on the relative sizes of the metastatic and spinal metastases subgroups compared to the scope population. An autopsy study identified during searching for the systematic review reported that approximately 70% of those with metastatic prostate cancer had spinal metastases.[4] Available evidence suggests that the rate of SCC in the subgroup with spinal metastases is likely to be greater than 1.35%. For the spinal metastases

subgroup the economic model (run with appraisal committees preferred assumptions) suggests ICERs for degarelix versus triptorelin, goserelin and leuprorelin of less than £71,387, £57,821 and £54,552 per QALY gained, respectively. In the absence of data on the population size of SCC rate for the spinal metastases subgroup it is not possible to accurately estimate the cost-effectiveness of degarelix for this subgroup. We also note that these analyses simply use model parameters and assumptions for the scope population for the subpopulations. This may be inappropriate in places hence the results are subject to considerable uncertainty.

4. CONCLUSIONS

Based on a rapid and focused systematic review, very limited evidence is available to assess the rate of SCC in men with metastatic hormone-dependent prostate cancer in the early stages of treatment with LHRH agonists or degarelix. Only four studies met the inclusion criteria and in two of these SCC events occurred too late to be the result of a testosterone flare. A third study reported that 2/33 patients with metastatic disease experienced SCC in the first week of therapy[1] but this study was performed in the 1980s and patients did not receive anti-androgen therapy to reduce the risk of testosterone flare. The remaining study was an observational study by Oh *et al*. of patients in the US Veterans Affairs health system, all of whom had metastatic disease.[2] This study reported a rate of 0.96% (15/1566) for SCC occurring within the first 30 days of LHRH agonist therapy. Limitations of this study include its observational design, reliance on administrative data and uncertain generalisability to current UK practice. No data were found for patients with known spinal metastases. No data were found to contradict the assumption that the rate of short-term SCC in patients receiving degarelix is effectively zero.

A sensitivity analyses was undertaken using the appraisal committees preferred assumptions and the ERG amended model. These analyses demonstrated that the ICER for degarelix compared to LHRH agonists is sensitive to the rate of SCC. The ICER values compared to triptorelin were £342,984, £99,228, £39,163, and £11,974 for SCC rates of 0%, 1%, 2% and 3% respectively. At a SCC rate of 4% degarelix dominated triptorelin and degarelix dominated leuprorelin and goserelin at a SCC rate of 3.5%.

The best evidence available suggests that the rate of SCC in the metastatic subgroup is around 1%.[3] For the metastatic subgroup the economic model (run with appraisal committees preferred assumptions) gives ICER values of £103,179, £86,335 and £82,277 per QALY gained for triptorelin, goserelin and leuprorelin, respectively.

Limited data were available on the relative sizes of the metastatic and spinal metastases subgroups compared to the scope population. An autopsy study identified during searching for the systematic review reported that approximately 70% of those with metastatic prostate cancer had spinal metastases.[4] Available evidence suggests that the rate of SCC in the subgroup with spinal metastases is likely to be greater than 1.35%. For the spinal metastases subgroup the economic model (run with appraisal committees preferred assumptions) suggests ICERs for degarelix versus triptorelin, goserelin and leuprorelin of less than £71,387, £57,821 and £54,552 per QALY gained, respectively. In the absence of data on the population size of SCC rate for the spinal metastases subgroup it is not possible to accurately estimate the cost-effectiveness of degarelix for this subgroup. It should be noted that these analyses simply use model parameters and assumptions for the scope population for the subpopulations. This may be inappropriate in places, hence the results are subject to considerable uncertainty.

5. REFERENCES

1. Ahmann FR, Citrin DL, deHaan HA, Guinan P, Jordan VC, Kreis W, *et al.* Zoladex: a sustained-release, monthly luteinizing hormone-releasing hormone analogue for the treatment of advanced prostate cancer. *Journal of Clinical Oncology* 1987;5:912-7.

2. Oh WK, Landrum MB, Lamont EB, McNeil BJ, Keating NL. Does oral antiandrogen use before leuteinizing hormone-releasing hormone therapy in patients with metastatic prostate cancer prevent clinical consequences of a testosterone flare? *Urology* 2010;75:642-7.

3. Uttley L, Whyte S, Gomersall T, Ren S, Wong R, Tappenden P, *et al. Evidence Review Group's Report: Degarelix for treating advanced hormone-dependent prostate cancer*. Sheffield: School of Health and Related Research (ScHARR), University of Sheffield; 2013.

4. Bubendorf L, Schopfer A, Wagner U, Sauter G, Moch H, Willi N, *et al.* Metastatic patterns of prostate cancer: An autopsy study of 1,589 patients. *Human Pathology* 2000;31:578-83.

5. National Institute for Health and Care Excellence. *Prostate cancer (advanced, hormone dependent) - degarelix depot: appraisal consultation document*. 2014. URL: http://www.nice.org.uk/guidance/gid-tag352/documents/prostate-cancer-advanced-hormone-dependent-degarelix-depot-appraisal-consultation-document (Accessed 1 April, 2015).

6. National Institute for Health and Care Excellence. *Final appraisal determination: Degarelix for treating advanced hormone-dependent prostate cancer*. 2014. URL: http://www.nice.org.uk/guidance/gid-tag352/documents/prostate-cancer-advanced-hormone-dependent-degarelix-depot-fad-document2 (Accessed 1 April, 2015).

7. National Institute for Health and Care Excellence. *Appeal hearing: Advice on Single Technology Appraisal of degarelix for treating advanced hormone-dependent prostate cancer [ID590]*. 2014. URL: http://www.nice.org.uk/guidance/gid-tag352/documents/prostate-cancer-advanced-hormone-dependent-degarelix-depot-appeal-decision2 (Accessed 1 April, 2015).

8. Peeling WB. Phase III studies to compare goserelin (Zoladex) with orchiectomy and with diethylstilbestrol in treatment of prostatic carcinoma. *Urology* 1989;33:45-52.

9. Vis AN, van der Sluis TM, Al-Itejawi HHM, van Moorselaar RJA, Meuleman EJH. Risk of disease flare with LHRH agonist therapy in men with prostate cancer: Myth or fact? *Urologic Oncology-Seminars and Original Investigations* 2015;33:7-15.

10. Dawson NA, Wilding G, Weiss RB, McLeod DG, Linehan WM, Frank JA, *et al.* A pilot trial of chemohormonal therapy for metastatic prostate carcinoma. *Cancer* 1992;69:213-8.

11. Nozawa M, Inagaki T, Nagao K, Nishioka T, Komura T, Esa A, *et al.* Phase II trial of zoledronic acid combined with androgen-deprivation therapy for treatment-naive prostate cancer with bone metastasis. *International Journal of Clinical Oncology* 2014;19:693-701.

12. Spencer BA, Shim JJ, Hershman DL, Zacharia BE, Lim EA, Benson MC, *et al.* Metastatic epidural spinal cord compression among elderly patients with advanced prostate cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2014;22:1549-55.

13. Pavone-Macaluso M. Words of wisdom. Re: Does oral antiandrogen use before leuteinizing hormone-releasing therapy in patients with metastatic prostate cancer prevent clinical consequences of a testosterone flare? Oh WK, Landrum MB, Lamont EB, et al. Urology 2010;75:642-7. *European Urology* 2010;58:314-5.

14. Rades D, Stalpers LJ, Veninga T, Schulte R, Hoskin PJ, Obralic N, *et al.* Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *J Clin Oncol* 2005;23:3366-75.

15. Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, *et al.* The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int* 2008;102:1531-8.

16. Alva A, Hussain M. Intermittent androgen deprivation therapy in advanced prostate cancer. *Current Treatment Options in Oncology* 2014;15:127-36.

17. Honnens De Lichtenberg M, Kvist E, Hjortberg P, Karle A. Adenocarcinoma of the prostate and metastatic medullary compression. A retrospective study of 22 patients. *Scandinavian Journal of Urology and Nephrology* 1992;26:25-8.

18. Kakpovi K, Oniankitan O, Houzou P, Fianyo E, Koffi-Tessio VES, Tagbor KC, *et al.* Profile of bone metastases of prostate cancer among rheumatology inpatients in Lome (Togo): A single center experience. *Egyptian Rheumatologist* 2014;36:35-9.

19. Koch M, Steidle C, Brosman S, Centeno A, Gaylis F, Campion M, *et al.* An open-label study of abarelix in men with symptomatic prostate cancer at risk of treatment with LHRH agonists. *Urology* 2003;62:877-82.

20. Nagata M, Ueda T, Komiya A, Suzuki H, Akakura K, Ishihara M, *et al.* Treatment and prognosis of patients with paraplegia or quadriplegia because of metastatic spinal cord compression in prostate cancer. *Prostate Cancer & Prostatic Diseases* 2003;6:169-73.

21. Sfakianos JP, Winer A, Hyacinthe LM, McNeil BK. What will happen if we don't screen for prostate cancer? A 10-year analysis of metastatic prostate cancer as an initial presentation in an underserved population. *Journal of Urology* 2012;1):e589.

22. Smith MR, Halabi S, Ryan CJ, Hussain A, Vogelzang N, Stadler W, *et al.* Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). *Journal of Clinical Oncology* 2014;32:1143-50.

23. Sugiono M, Winkler MH, Okeke AA, Benney M, Gillatt DA. Bicalutamide vs cyproterone acetate in preventing flare with LHRH analogue therapy for prostate cancer--a pilot study. *Prostate Cancer & Prostatic Diseases* 2005;8:91-4.

24. Winer AG, Sfakianos JP, Hyacinthe LM, McNeil BK. A 10-year analysis of metastatic prostate cancer as an initial presentation in an underserved population. *International Braz J Urol* 2014;40:316-21.

25. Yood MU, Zyczynski TM, Wells K, Casso D, Gutierrez B, Woodcroft KJ, *et al.* Incidence of skeletal-related events (SREs) among prostate cancer patients. *Journal of Clinical Oncology* 2013;1.

APPENDIX

A1 SYSTEMATIC REVIEW PROTOCOL

Protocol: systematic review of spinal cord compression rates in men with locally advanced or metastatic hormone-dependent prostate cancer

Background

Degarelix (Firmagon, Ferring Pharmaceuticals) is a selective gonadotrophin-releasing hormone (GnRH)/luteinising hormone-releasing hormone (LHRH) antagonist. Degarelix has a UK marketing authorisation for treatment of advanced hormone-dependent prostate cancer. Compared with its main comparators, the LHRH agonists, degarelix has the benefit of avoiding an initial 'testosterone flare' at the start of treatment, which is thought to increase the risk of spinal cord compression (SCC).

Degarelix was evaluated by NICE under the single technology appraisal (STA) process in 2014. In its initial draft guidance the NICE Appraisal Committee recommended degarelix as an option for treating advanced hormone-dependent prostate cancer, only in people with spinal cord metastases who are at risk of impending SCC.

This wording was revised in the final guidance to state that that degarelix is recommended as an option for treating advanced hormone-dependent prostate cancer, only in adults with spinal metastases who present with signs or symptoms of SCC.

Appeals were received stating that the change in the wording of the recommendations had led to a restriction n the population eligible for treatment with degarelix in the NHS without previous consultation. The appeal panel asked the Committee to reconsider the wording of the recommendation, stating that if degarelix is to be approved for a particular patient group, the definition of the group should be very clear, not reliant on different interpretations and capable of application in a routine clinical setting.

At its third meeting the Committee concluded that although a subgroup of people with spinal metastases who may develop SCC as a result of testosterone flare may exist in clinical practice, it cannot be reliably identified beyond those people with spinal metastases. The Committee expressed concern that if this subgroup cannot be clearly identified and defined in clinical practice, degarelix is likely to be used in all people with spinal metastases. It noted that the manufacturer had not presented a cost-effectiveness analysis for this group and that all the ICERs (incremental cost-effectiveness ratios) presented for the overall population of people with locally advanced or metastatic hormone-dependent prostate cancer were outside the range normally considered to be a cost-effective use of NHS resources.

The DSU was therefore asked to carry out further work to identify any relevant information on the rate of SCC in people with locally advanced or metastatic hormone-dependent prostate cancer, or if possible those with spinal metastases. It was asked to explore the possibility of subgroup analysis in people with spinal metastases and to carry this out if sufficient data are available to do so. This protocol sets out our approach to searching for and synthesising this evidence using systematic review methods.

Methods

Review question/objectives

The objective of the systematic review is to inform further economic modelling work by identifying and synthesising evidence on the rate of occurrence of spinal cord compression in men with locally advanced or metastatic hormone-dependent prostate cancer. Specifically, the review aims to address the following questions:

- What is the rate of spinal cord compression in men with metastatic hormone-dependent prostate cancer who have received LHRH agonists or degarelix?

- What is the rate of spinal cord compression in men with spinal metastases of prostate cancer?

If there are sufficient data available, the results will be used to inform an analysis of the cost-effectiveness of degarelix compared with LHRH agonists in the subgroup of men with spinal metastases of prostate cancer.

Inclusion and exclusion criteria

Population: Men with metastatic hormone-dependent prostate cancer. This means stage IV of the American Joint Committee on Cancer (AJCC) TNM system. Given that prostate cancer is normally hormone-dependent, we will assume that this is the case if hormone status is not reported. Studies of hormone-resistant or hormone-refractory prostate cancer will be excluded from the review.

Intervention/exposure: The primary intervention or exposure of interest is treatment with degarelix or one of its comparators (LHRH agonists, namely goserelin, leuporelin, triptorelin or buserelin). Our search will aim to locate studies of spinal cord compression associated with these agents. Studies reporting data for men not treated with any of these agents, or where treatment is unclear, will be excluded from the primary analysis.

Comparator: Data from comparative and non-comparative studies will be included.

Outcomes: The outcome of interest is spinal cord compression (SCC). Cases of SCC occurring as a result of a testosterone flare shortly after starting treatment are most relevant to the decision problem. However, all data on rates of SCC in men treated with relevant drugs will be included in the analysis. Data on ‘spinal cord symptoms’ or ‘skeletal-related events’, where rates of SCC cannot be determined, will be excluded.

Study designs: Evidence from published empirical studies of any design and from UK and selected international cancer registries and association websites (see the section on searching below) will be eligible for inclusion.

Searching

Scoping searches have been carried out recently by the DSU team in Medline, Embase and the Web of Science in order to gauge the size of the literature. Terms for the population (prostate cancer or spinal metastasis) combined with the adverse event (spinal cord compression) gave in excess of 6000 records.

In light of the above, the DSU considered that a pragmatic approach to searching is required and that terms for spinal cord compression would be combined with the named intervention degarelix and its drug comparator terms to give approximately 200 records. An Embase search strategy is provided at the end of this document.

The following databases will be searched:

- MEDLINE AND MEDLINE In-Process Citations: Ovid
- EMBASE: Ovid
- Cochrane Library: Wiley Online
- Science Citation Index Expanded: Web of Science.
- Science Citation Index and Conference Proceedings Index: Web of Science.

No study design filter will be applied to the searches in order to retrieve observational as well as randomised and non-randomised controlled clinical trials. No date or language limits will be applied in the searches.

Other levels of evidence will also be searched via UK and selected international cancer registries and association websites:

- Public Health England
- Scottish Cancer Registry
- Welsh Cancer Intelligence & Surveillance Unit (WCISU)
- National Cancer Registry, Ireland
- Australasian Association of Cancer Registries
- European Network of Cancer Registries (ENCR)
- International Agency for Research on Cancer (IARC)
- International Association of Cancer Registries (IACR)
- North American Association of Central Cancer Registries
- SEER (National Cancer Institute, USA)

Study selection
Search results will be stored in a reference management database. Selection of studies for inclusion will be carried out by one reviewer, with input from other team members to resolve uncertainties.

Data extraction and quality assessment
Data extraction will be carried out by one reviewer, with input from other team members to resolve uncertainties. Data extraction tables will be developed in advance.

Data to be extracted will include:

- study type and design
- details of the population
- setting
- rate of SCC in the population as a whole and (if reported) specifically in men with spinal metastases
- details of treatment with degarelix or LHRH agonists
- any data on when SCC occurred in relation to drug treatment
- details of any treatment to mitigate the testosterone flare associated with LHRH agonist treatment, e.g. bicalutamide.

Study quality (risk of bias) will be assessed by one reviewer with input from other team members to resolve uncertainties. A suitable quality assessment tool such as the Newcastle–Ottawa scale for observational studies will be applied if this appears meaningful; however, it should be noted that the overall risk of bias of the study may not be related to its suitability for addressing the review question. Any obvious weaknesses of the study for answering the review questions will be highlighted, e.g. unknown temporal association between treatment and SCC event or uncertain generalisability to UK population.

Evidence synthesis
The evidence synthesis will provide a summary of the range of possible rates of SCC in men with locally advanced or metastatic hormone-dependent prostate cancer and in the subgroup with spinal metastasis of prostate cancer. The primary analysis will focus on evidence from studies that provide data on both occurrence of SCC and treatment with GnRH agonists or degarelix. Strengths and limitations of the available evidence base will be clearly highlighted. Summary weighted means across groups of studies will be calculated if this appears meaningful and feasible. Studies without data on exposure to the drugs of interest will be analysed separately. It should be recognised that searching for such studies was not the primary aim of the review and coverage may be less comprehensive.

Proposed time line

Process	Start	Finish
Protocol development	5 February	12 February
Approval of protocol	13 February	18 February
Searching	19 February	24 February
Sifting and study selection	25 February	2 March
Data extraction	3 March	17 March
Analysis and report writing (including internal peer review)	18 March	1 April

Embase Search strategy
Embase:Ovid. 1974 to 2015 February 04
5th February 2015

1 spinal cord compression/ (12388)
2 (cord adj5 compress$).tw. (9764)
3 mscc.tw. (282)
4 or/1-3 (16018)
5 (degarelix or firmagon or abarelix or plenaxis).tw. (363)
6 degarelix/ (368)
7 abarelix/ (331)
8 exp gonadorelin/ (31918)
9 exp hormone antagonist/ (210052)
10 8 and 9 (4524)
11 ((luteinising or luteinizing or LHRH or gonadotrop$ or GNRH) and (agonist$ or antagonist$ or blocker$)).tw. (15742)
12 (androgen deprivation or ADT or androgen suppression).tw. (8393)
13 goserelin/ (5906)
14 leuprorelin/ (8893)
15 triptorelin/ (4132)
16 buserelin/ (4085)
17 buserelin acetate/ (914)
18 (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).tw. (10840)
19 bicalutamide/ (4355)
20 (bicalutamide or casodex or cosudex or calutide or kalumid or bicalox).tw. (2085)
21 or/5-7,10-20 (42215)
22 4 and 21 (137)

A2 DATABASE, REGISTRY AND WEBSITE SEARCH STRATEGIES

Medline and Medline In-Process & Other Non-Indexed Citations: Ovid. 1946 to Present 9th February2015

1. Spinal Cord Compression/
2. (cord adj5 compress$).tw.
3. (mscc or mescc).tw.
4. or/1-3
5. (degarelix or firmagon or abarelix or plenaxis).tw.
6. exp Gonadotropin-Releasing Hormone/
7. exp Hormone Antagonists/
8. 6 and 7
9. ((luteinising or luteinizing or LHRH or gonadotrop$ or GNRH) and (agonist$ or antagonist$ or blocker$)).tw.
10. (androgen deprivation or ADT or androgen suppression).tw.
11. Goserelin/
12. Leuprolide/
13. Triptorelin Pamoate/
14. Buserelin/
15. (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).tw.
16. (bicalutamide or casodex or cosudex or calutide or kalumid or bicalox).tw.
17. exp Androgen Antagonists/
18. or/5,8-17
19. 4 and 18

Embase:Ovid. 1974 to 2015 February 04 9th February2015

1. spinal cord compression/
2. (cord adj5 compress$).tw.
3. (mscc or mescc).tw.
4. or/1-3
5. (degarelix or firmagon or abarelix or plenaxis).tw.
6. degarelix/
7. abarelix/
8. exp gonadorelin/
9. exp hormone antagonist/
10. 8 and 9

11. ((luteinising or luteinizing or LHRH or gonadotrop$ or GNRH) and (agonist$ or antagonist$ or blocker$)).tw.
12. (androgen deprivation or ADT or androgen suppression).tw.
13. goserelin/
14. leuprorelin/
15. triptorelin/
16. buserelin/
17. buserelin acetate/
18. (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).tw.
19. bicalutamide/
20. (bicalutamide or casodex or cosudex or calutide or kalumid or bicalox).tw.
21. or/5-7,10-20
22. 4 and 21

Cochrane library
Cochrane Database of Systematic Reviews (CDR): Wiley Online.
Cochrane Central Register of Controlled Trials (CENTRAL): Wiley Online.
Health Technology Assessment Database (HTA): Wiley Online.
Database of Abstracts of Reviews of Effects (DARE)): Wiley Online. 1995-2014
NHS Economic Evaluation Database (NHS EED): Wiley Online. 1995-2014
9th February2015

#1	degarelix or firmagon or abarelix or plenaxis:ti,ab,kw (Word variations have been searched)
#2	MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees
#3	MeSH descriptor: [Hormone Antagonists] explode all trees
#4	#2 and #3
#5	(luteinising or luteinizing or LHRH or gonadotrop* or GNRH) and (agonist* or antagonist* or blocker*):ti,ab,kw
#6	(androgen deprivation or ADT or androgen suppression):ti,ab,kw
#7	MeSH descriptor: [Goserelin] this term only
#8	MeSH descriptor: [Leuprolide] this term only
#9	MeSH descriptor: [Triptorelin Pamoate] this term only
#10	MeSH descriptor: [Buserelin] this term only
#11	(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):ti,ab,kw
#12	(bicalutamide or Casodex or Cosudex or Calutide or Kalumid or Bicalox):ti,ab,kw
#13	MeSH descriptor: [Androgen Antagonists] explode all trees
#14	{or #1, #4-#13}
#15	MeSH descriptor: [Spinal Cord Compression] explode all trees
#16	(cord next/5 compress*):ti,ab,kw
#17	(mscc or mescc):ti,ab,kw

#18	#15 or #16 or #17
#19	#14 and #18

Science Citation Index Expanded: Web of Science. 1900-present
Science Citation Index and Conference Proceedings Index: Web of Science. 1990-present
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#11	#3 and #10
#10	#9 OR #8 OR #7 OR #6 OR #5 OR #4
#9	TOPIC: ((androgen antagonist*))
#8	TOPIC: ((bicalutamide or casodex or cosudex or calutide or kalumid or bicalox))
#7	TOPIC: ((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))
#6	TOPIC: ((androgen deprivation or ADT or androgen suppression))
#5	TOPIC: (((luteinising or luteinizing or LHRH or gonadotrop* or GNRH) and (agonist* or antagonist* or blocker*)))
#4	TOPIC: ((degarelix or firmagon or abarelix or plenaxis))
#3	#2 OR #1
#2	TOPIC: (mscc or mescc)
#1	TS=(((cord or spine or spinal) SAME/5 compress*))

Clinical trials.gov: NIH. https://clinicaltrials.gov/ [online]
11th February 2015

no studies found for: degarelix | spinal cord compression
no studies found for: firmagon | spinal cord compression
no studies found for: abarelix | spinal cord compression
no studies found for: plenaxis | spinal cord compression
no studies found for: goserelin | spinal cord compression
no studies found for: leuprorelin | spinal cord compression
no studies found for: triptorelin | spinal cord compression
no studies found for: buserelin | spinal cord compression
no studies found for: bicalutamide | spinal cord compression

CANCER REGISTRY AND ASSOCIATION SEARCH

Named drug search (10 February 2015) and dataset search (17 February 2015) in the following sites:

Public Health England

https://www.gov.uk/government/organisations/public-health-england
https://www.gov.uk/government/statistics

Scottish Cancer Registry
http://www.isdscotland.org/Health-Topics/Cancer/Scottish-Cancer-Registry/

Welsh Cancer Intelligence & Surveillance Unit WCISU
http://www.wcisu.wales.nhs.uk/home
http://www.wcisu.wales.nhs.uk/documentmap/

National Cancer Registry, Ireland
http://www.ncri.ie/

Australasian Association of Cancer Registries
http://www.aihw.gov.au/cancer/aacr/

European Network of Cancer Registries (ENCR)
http://www.encr.eu/

International Association of Cancer Registries (IACR)
http://www.iacr.com.fr/

North American Association of Central Cancer Registries
http://www.naaccr.org/

International Agency for Research on Cancer (IARC)
http://www.iarc.fr/

Surveillance, Epidemiology and End Results Program (SEER) (National Cancer Institute, USA) http://seer.cancer.gov/

Citation search of included studies
26 February 2015

Citations searches were carried out on 25 February 2015 in the Web of Science of four included publications:

- Ahmann FR, Citrin DL, deHaan HA, Guinan P, Jordan VC, Kreis W, et al. Zoladex: a sustained-release, monthly luteinizing hormone-releasing hormone analogue for the treatment of advanced prostate cancer. Journal of Clinical Oncology. 1987;5(6):912-7. **36 citations**

- Nozawa M, Inagaki T, Nagao K, Nishioka T, Komura T, Esa A, et al. Phase II trial of zoledronic acid combined with androgen-deprivation therapy for treatment-naive prostate cancer with bone metastasis. International Journal of Clinical Oncology. 2014;19(4):693-701. **2 citations**

- Oh WK, Landrum MB, Lamont EB, McNeil BJ, Keating NL. Does oral antiandrogen use before leuteinizing hormone-releasing hormone therapy in patients with metastatic prostate cancer prevent clinical consequences of a testosterone flare? Urology. 2010;75(3):642-7. **6 citations**

- Dawson NA, Wilding G, Weiss RB, McLeod DG, Linehan WM, Frank JA, et al. A pilot trial of chemohormonal therapy for metastatic prostate carcinoma. Cancer. 1992;69(1):213-8. **11 citations on 2nd March 2015.**

A3 STUDIES REJECTED AFTER FULL-TEXT EXAMINATION

Reference	**Reason for exclusion**
Alva 2014[16]	Review article, no data on SCC
Honnens de Lichtenberg 1992[17]	No data on LHRH agonist treatment
Kakpovi 2014[18]	No data on LHRH agonist treatment
Koch 2003[19]	Mixed population, abarelix not degarelix
Nagata 2003[20]	No data on LHRH agonist treatment
Pavone-Macaluso 2010[13]	Commentary on Oh et al., no original data
Peeling 1989[8]	Mixed population, unclear whether patients with SCC had metastatic disease.
Sfakianos 2012[21]	No data on LHRH agonist treatment.
Smith 2014[22]	No data on SCC (SREs only)
Soloway 1988	Mixed population, metastasis status of patients unclear
Sugiono 2005[23]	Mixed population, metastasis status of patients unclear
Winer 2014[24]	No data on LHRH agonist treatment (SCC present at first presentation)
Yood 2013[25]	No data relating SCC to LHRH agonist treatment