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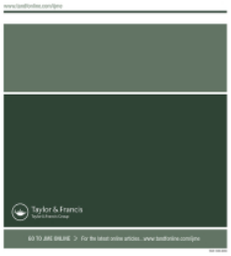

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Cost-effectiveness of 4 mg dibotermin alfa/absorbable collagen sponge versus iliac crest bone graft for lumbar degenerative disc disease in the United Kingdom

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Declaration of financial/other interests

MZ, AW and SE are employees of Medtronic and hold stock in Medtronic.

DC, FS and RT are all paid consultants for Medtronic.

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Author Contributions

DC, RT, FS and MZ led the study. FS undertook the meta-analysis of clinical studies, with input from DC, RT, AW and MZ. MZ and SE populated and ran the decision-analytic model, with methods and data informed by DC and RT. SE drafted the manuscript, and all authors reviewed and provided input. All authors approved the submitted version of the manuscript and agree to be accountable for all aspects of the work.

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Abstract

Aims: To develop a model to evaluate the cost-effectiveness of 4 mg dibotermin alfa/absorbable collagen sponge (ACS) versus iliac crest bone graft (ICBG) in patients with lumbar degenerative disc disease in the United Kingdom.

Materials & Methods: A Markov decision-analytic model was constructed to calculate costs and quality-adjusted life-years over a 4-year time horizon in each treatment group, from a

United Kingdom National Health Service perspective. An individual patient data meta-analysis was undertaken to synthesize data from four randomized controlled trials and two single-arm studies concerning health-related quality of life and procedural resource use. Current cost data from the United Kingdom were then applied to determine the overall mean cost per patient in each group. One-way and probabilistic sensitivity analyses were undertaken to explore the impact of parameter uncertainty.

Results: The model predicted 4-year discounted cost savings of £192 per patient treated with dibotermin alfa/ACS, compared with ICBG, and a gain of 0.0114 QALYs per patient over the same time period. Sensitivity analyses indicated that the results were most sensitive to variability in the differences in health-related quality of life and secondary surgery rate, with dibotermin alfa/ACS having a 60% probability of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained.

Limitations: There is uncertainty in the difference in cost and QALYs between the two groups. However, comprehensive sensitivity analyses were undertaken to explore this and present the results in a transparent manner.

Conclusions: Our results provide an economic case for the use of 4 mg dibotermin alfa/ACS versus iliac crest bone graft, with additional health benefits predicted at reduced overall cost.

Key words: Cost-effectiveness; quality of life; spinal fusion; health economics
JEL codes: I15; I1; I; I18

Short title: Cost-effectiveness of dibotermin alfa/absorbable collagen sponge

Introduction

Degenerative changes in the discs of the spine are a normal part of ageing. The pathological process leads to lumbar degenerative disc disease (LDDD) in which the water content becomes depleted. The degenerative process can cause instability, height loss, spinal stenosis, degenerative spondylolisthesis, herniated discs and end-plate changes. The development of LDDD can be related to biomechanical, traumatic, environmental and genetic factors. Symptoms as a result of the degenerative process include lower back pain, and if the nerve roots are compressed can cause neurological symptoms that can lead to leg pain, paresthesia, weakness and reduced mobility.

The annual incidence of LDDD in Europe has been reported at 8,586 new cases per 100,000 population [1], while prevalence has been reported to range from 40% to 90% and increases with age [2,3]. LDDD imposes a significant detrimental effect on various dimensions of quality of life, including a 40% decrement in physical functioning compared with an age- and gender-matched general population [4]. Low back pain resulting from LDDD is also associated with a substantial economic burden. In the United States, the cost of elective lumbar fusion surgery in 2015 was estimated at more than $10 billion, while work absenteeism and reduced productivity due to low back pain related to lumbar disc disorders also lead to a substantial societal cost [5]. A UK study concluded that the direct cost of back pain care in 1998 was £1.6 billion, with informal care and productivity losses related to back pain totaling more than £10 billion [6].

Management of pain resulting from LDDD may in some cases progress to surgical intervention if conservative approaches fail [7,8]. Current standard of care for eligible patients with LDDD is spinal fusion using iliac crest bone graft (ICBG) [9], which aims to

immobilize the painful segment and fuse two or more vertebrae together using bone graft harvested from the patient. However, complication rates of up to 20% have been reported after ICBG harvesting, including donor site pain, sensory loss, deep vein thrombosis and infection [10,11]. An alternative to ICBG is dibotermin alfa/absorbable collagen sponge (ACS), a powder containing the active substance recombinant human bone morphogenetic protein-2 (rhBMP-2). It aims to help new bone to develop when used in conjunction with an approved medical device for spinal fusion in LDDD [12]. One vial contains 4 mg or 12 mg dibotermin alfa and the required volume is determined by the intervertebral disc space and the size, shape and internal volume of the lumbar interbody fusion device(s) used. The efficacy of dibotermin alfa/ACS is supported by three meta-analyses of randomized controlled trials (RCTs), offering clinical outcomes similar to those of ICBG and a positive risk-benefit profile [13–16]. A recent UK health-economic study concluded that the 12 mg pack (with a dose of 4-8 mg delivered) was cost-effective compared with ICBG, with an incremental cost-effectiveness ratio of £13,523 per quality-adjusted life-year (QALY) gained [17].

To date, however, a specific economic analysis of the recently launched 4 mg pack, the dose most frequently used in licensing studies, has not been undertaken. We therefore undertook an individual patient data (IPD) meta-analysis of RCTs and single-arm studies for the 4 mg pack, and used the results to update the economic model and determine the cost-effectiveness of the dibotermin alfa/ACS 4 mg pack versus ICBG in patients with LDDD undergoing lumbar interbody spine fusion from a United Kingdom payer perspective. The objective was to develop evidence to allow payers and clinicians to make decisions regarding management of patients with LDDD. This study was reported in accordance with the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) [18].

Methods

Economic Model Description

The model structure and overall modelling approach has previously been described in detail [17]. Briefly, a two-state Markov structure was developed in Microsoft ® Excel to calculate costs and QALYs of dibotermin alfa/ACS versus ICBG from a UK National Health Service (NHS) and Personal Social Service perspective over a four-year period with a six-month cycle length and is therefore intended to be applicable to the UK setting. The two health states were used 'surgical success' (after one or more surgeries) and 'surgical failure'. The patient population considered patients who had at least six months of non-operative treatment and who required a lumbar fusion procedure. Operative time and post-operative length of stay in hospital, failure-related second surgery and the proportion of patients returning to work were all derived from the IPD meta-analysis and were used to determine incremental cost in the dibotermin alfa/ACS group (versus ICBG). The main health outcome measure was QALYs (thus capturing both survival time and quality of life), with the improvements in health utility for the first two years based on data collected using the Short-Form-36 (SF-36) and mapped to SF-6D utilities [19], with mean differences between the treatment groups estimated from the mixed-effects model. For the remaining two years of the model, the utility for patients treated with dibotermin alfa/ACS was assumed to remain constant; the utility difference between dibotermin alfa/ACS and ICBG was assumed to decline to zero over this latter two-year period ('utility offset').

Cost analysis included the acquisition of dibotermin alfa/ACS, the cost per day in hospital and per hour of operating time, repeat surgery cost, and mean salary per six months (societal perspective only). Since the model was built around the mean differences derived

from the meta-analysis, the model outputs consisted of the difference in costs and QALYs between the two treatment groups. Thus, the results presented below are the incremental values rather than treatment-specific values. Costs and QALYs were discounted at 3.5% per year, in accordance with recommendations from the National Institute for Health and Care Excellence (NICE) [20].

Model Inputs

A subset of analyses from the IPD meta-analysis was used as the basis for populating specific model inputs, including failure-related secondary surgery rates, utility weights over time, operative parameters (procedure duration and in-hospital length of stay), and the proportion of patients returning to work (which was used for sensitivity analysis). These parameter values are described in the following sections. Full details of the meta-analytic methods, covering endpoint definitions, included studies and statistical methods, are provided in the Supplement. Briefly, individual patient data were taken from four RCTs and two single-arm studies and meta-analyzed using multi-level, mixed-effects regression models to determine mean differences (for continuous variables) and odds ratios (for binary variables) for the model inputs described above. All model inputs are shown in Table 1 and are described in more detail in the following sections.

Failure-Related Secondary Surgery Rates

Table 1 shows the odds ratio for the difference in the proportion of patients requiring failure-related secondary surgery up to 24 months post-surgery, derived from the meta-analysis of included studies. Further details on the underlying number of patients in each

treatment group are given in the Supplement (Table S3). Thus, a higher proportion of patients in the ICBG group underwent a second surgery and incurred the corresponding cost.

Quality of Life Parameters

Table 1 also provides the mean between-group difference in the change from baseline in mean SF-6D utility, based on the meta-analysis and for several time points during trial follow-up. All utility weights were calculated by mapping the SF-36 to SF-6D utilities using a published algorithm [19]. Further details of the treatment-specific utility weights are given in the Supplement (Table S4).

Over 24 months, these mean differences led to a QALY gain of 0.0041 (95% CI: -0.049, 0.058) for patients receiving dibotermin alfa/ACS. In the subsequent two years of the model, this QALY gain was assumed to decline to zero in a linear fashion.

Procedural Resource Use Parameters

Table 1 shows the model inputs relating to procedure duration and post-operative length of hospital stay, each of which was based on the meta-analysis of individual patient data. For each outcome, the mean difference is presented together with the 95% confidence interval and p-value. Patients receiving dibotermin alfa/ACS were therefore modelled to spend less time in the operating room and to have a shorter stay in hospital. Further details of these parameters are given in the Supplement (Table S5).

Return-to-Work Parameters

Detailed data regarding return-to-work parameters are provided in the Supplement (Table S6).

Unit Cost Parameters

The unit cost of each element of resource use applied in the model is shown in Table 1 (with further details provided in Table S7 of the Supplement). The cost of dibotermin alfa/ACS was based on the average selling price (ASP) of the 4 mg pack in the UK per data extracted in June 2020. The cost per hospital bed day (to determine cost savings associated with a reduced length of stay) and the cost of failure-related second surgery were based on NHS Reference Costs [21], using a weighted mean of payments for inpatient spinal reconstruction procedures. The cost per hour of an operating theatre was based on data from a study by NHS Improvement [22]. Patient mean salary per 6 months was based on employee earnings data from the UK in 2019 [23]. All costs were based on 2019 prices.

Data Analyses

The base-case deterministic analysis was performed using a four-year time horizon to calculate mean costs and QALYs in the dibotermin alfa/ACS and ICBG groups. This horizon was considered sufficiently long to capture relevant costs and health outcomes, including secondary surgery and post-recovery quality of life. The incremental cost-effectiveness ratio (ICER) was calculated using the following formula:

$$ICER = \frac{Cost_{dibotermin\ alpha\ ACS} - Cost_{ICBG}}{QALYs_{dibotermin\ alpha\ ACS} - QALYs_{ICBG}}$$

A series of one-way sensitivity analyses (OWSA) was then conducted, varying individual input parameters within plausible ranges (or using alternative model settings) to identify inputs whose uncertainty had the most impact on the ICER. Finally, a full probabilistic sensitivity analysis (PSA) was performed to explore the impact on the ICER of the joint uncertainty in all model inputs. Statistical distributions were chosen for each input to be appropriate to the type of data (for example, gamma and beta distributions for cost and probability inputs, respectively). Ten thousand sets of input parameters were sampled with the resulting incremental costs and QALYs used to generate a cost-effectiveness scatter plot and acceptability curve. Full details of the distributions used for the PSA are given in the Supplement (Table S8).

Patient and Public Involvement

Neither patients nor the public were involved in our study. Our analysis simulated a hypothetical cohort of adult patients.

Results

Base-Case Analysis

Table 2 shows the incremental mean discounted cost and QALYs per patient over the 4-year horizon. As all clinical and safety parameters were estimated using a mixed-effects approach, the model calculated the incremental QALYs based on the mean between-group differences for each parameter rather than directly calculating total costs and QALYs in each treatment group. Thus, the table reports only the incremental values. Dibotermin alfa/ACS

was predicted to dominate ICBG in the deterministic analysis, with cost savings of £192 and a QALY gain of 0.0114 per patient.

Sensitivity Analyses

The results of the OWSA are shown in Figure 1 in the form of a tornado diagram (tabulated results are provided in the Supplement [Table S9]). The parameters whose uncertainty has most influence upon the ICER are shown towards the top of the diagram. To avoid the issue of computing negative ICERs, the results of each scenario are instead presented in the form of the incremental net benefit (INB) [24], for which positive and negative values indicate cost-effectiveness and cost-ineffectiveness of dibotermin alfa/ACS, respectively, at a threshold of £20,000 per QALY gained. The solid vertical line represents the INB for the base-case analysis (£420), and the values at the ends of each bar represent the range of values tested for the corresponding parameter. The dotted vertical line indicates an INB of £0 to separate cost-effective and cost-ineffective results.

The tornado diagram shows that dibotermin alfa/ACS remains cost-effective (a positive INB, with the horizontal bars positioned to the right of the dashed vertical line) in all but two scenarios, using the confidence interval for each parameter from the meta-analysis as the basis for the range used in each case. When the lower confidence interval value for the QALY gain at 2 years (-0.049) was used, the model predicted that dibotermin alfa/ACS was not cost-effective at a £20,000 per QALY threshold. Similarly, applying the lower limit of the confidence interval around the rate of failure-related secondary surgery on ICBG (7.1%) also led to a scenario in which dibotermin alfa/ACS was marginally cost ineffective (denoted by a INB below zero).

Figure 2 shows the scatter plot derived from the PSA, with incremental QALYs (x-axis) plotted against incremental costs (y-axis). Each light-coloured dot represents the incremental cost and QALYs predicted by one set of sampled input parameter values, while the dark dot denotes the deterministic result described previously. The 95% confidence interval around the ICER is shown via the ellipse. Dibotermin alfa/ACS was predicted to be less costly than ICBG in 66.4% of model replications (the proportion of dots below the x-axis) and more effective (in terms of QALYs) in 55.6% of replications (the proportion of dots to the right of the y-axis).

Figure 3 shows the corresponding cost-effectiveness acceptability curve (CEAC), which presents the probability of each intervention being cost-effective across a range of willingness-to-pay thresholds. At the current NICE threshold of £20,000 per QALY gained, the model predicted a 60% chance of dibotermin alfa/ACS being cost-effective compared with ICBG. The dibotermin alfa/ACS line intersects the y-axis at 66.4%, denoting the proportion of replications in which it was predicted to save money, and tends to a value of 55.6% which is the proportion of replications associated with QALY gains.

Discussion

This study sought to update an existing decision-analytic model to determine the cost-effectiveness of the 4 mg dose of dibotermin alfa/ACS compared with ICBG from a UK NHS perspective. Model inputs were updated using a revised meta-analysis of studies evaluating the 4 mg dose, including procedure duration, failure-related secondary surgery rate, QALY gain at 2 years and patient length of stay. The updated cost model predicted mean cost savings of £192 per patient and a mean QALY gain of 0.0114 for patients on dibotermin

alfa/ACS, and a 60% probability of cost-effectiveness at the current willingness-to-pay threshold.

A key strength of our analysis is that it combines data from multiple studies to inform the model inputs, thus providing more robust evidence than relying on data from a single study. The meta-analytic approach allows us to incorporate variation in surgical practice and capture different levels of surgeon skill. The 4 mg dose of dibotermin alfa/ACS is the most commonly used dose in licensing studies, and therefore represents the most appropriate formulation to compare against ICBG.

Our analysis has some limitations which warrant discussion. Firstly, the meta-analysis concluded that many of the clinical benefits of dibotermin alfa/ACS were not statistically significant, leading to uncertainty in the model projections. Nevertheless, the deterministic results show cost savings and marginal QALY gains for patients receiving dibotermin alfa/ACS when using the meta-analysis results as calculated, and the probabilistic analysis enables the reader to understand the impact of the uncertainty. Secondly, the model did not explicitly include procedure only-related adverse events; however, previous studies have reported similar complication rates for the two interventions [25], and many complications are related to surgical technique rather than the product used [26]. Thirdly, the model conservatively included only failure-related repeat surgeries, and thus some re-operations (such as those for harvest graft site reasons) were excluded. Finally, the analysis excluded the costs of pre-surgery visits for repeat surgeries; as re-operation was more common in the ICBG group, however, this assumption was conservative from the perspective of dibotermin alfa/ACS.

The most relevant results against which to compare our own are those from Svedbom et al [17], upon which our analysis is based but which did not focus on a particular dose of

dibotermin alfa/ACS. The two studies reached similar overall conclusions, with the previous analysis predicting incremental costs and QALYs of £737 and 0.055, respectively, and an ICER of £13,253 per QALY gained. That study performed a meta-analysis covering a broader range of doses and gave an overall estimate of the cost-effectiveness of dibotermin alfa/ACS. As a result of the wider set of studies included and greater sample size, there was more certainty in the meta-analysis outputs and thus in the cost-effectiveness results.

One aspect not accounted for in the model was surgeon and patient preference. Most surgeons will prefer to use a technique that reduces time, stress and associated morbidity, and the use of ICBG has reduced due to these factors. Dibotermin alfa/ACS provides a simpler, single procedure that avoids the bone graft procedure and the associated risks and potential for patient morbidity [10,11]. Further, the procedure time saved by using dibotermin alfa/ACS gives surgeons more available theatre time, allowing them to improve efficiency, and the reduced length of stay may also reduce overall bed capacity.

Further research would be beneficial to have greater certainty around the quality of life benefit of dibotermin alfa/ACS and the rate of failure-related secondary surgery in each group. The model used a relatively short time horizon (4 years), and so long-term data on quality of life and other outcomes would be helpful to confirm that the cost-effectiveness profile does not change with a longer time horizon.

Conclusions

In summary, this analysis indicates that the 4 mg dose of dibotermin alfa/ACS is cost-effective compared with ICBG and supports its wider uptake in spinal fusion procedures, consistent with previous research.

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Figure captions

Figure 1: Tornado diagram of one-way sensitivity analysis results (ACS: absorbable collagen sponge; ICBG: iliac crest bone graft; QALY: quality-adjusted life-years)

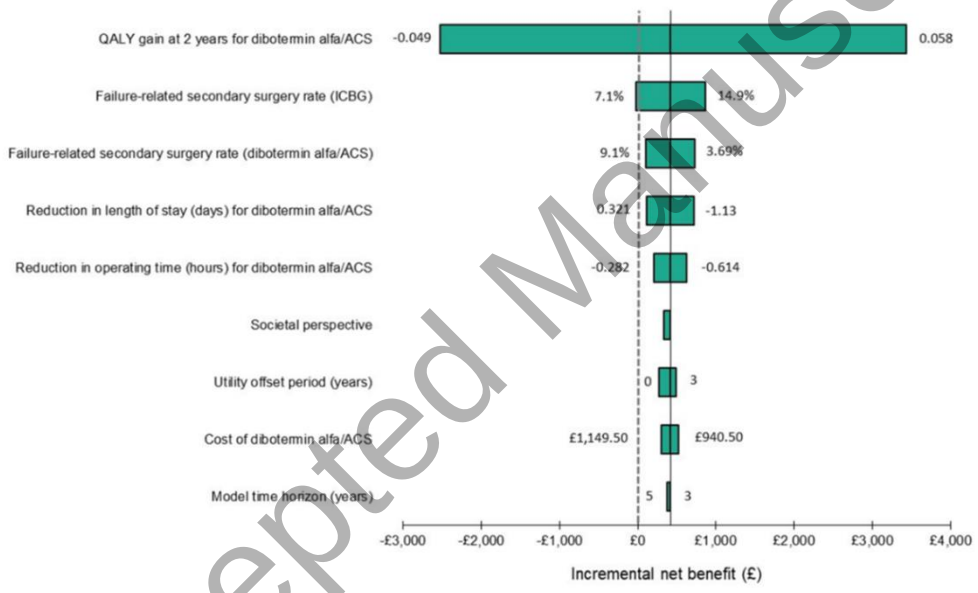
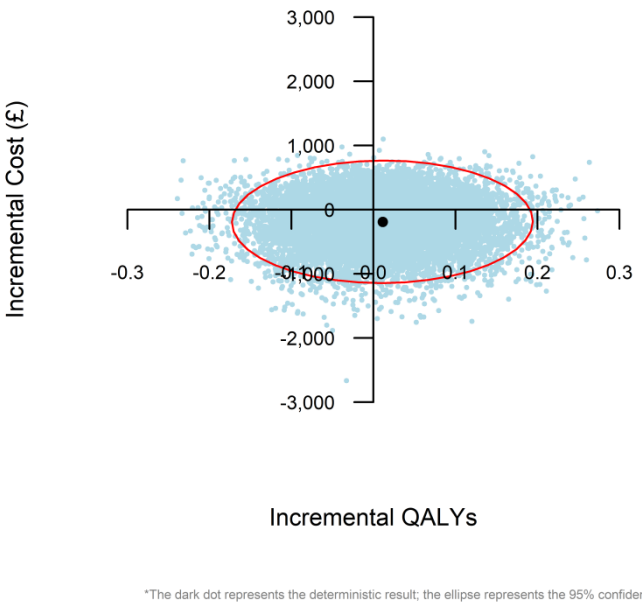


Figure 2: Cost-effectiveness scatter plot (QALYs: quality-adjusted life-years)



*The dark dot represents the deterministic result; the ellipse represents the 95% confidence interval

Figure 3: Cost-effectiveness acceptability curve (ACS: absorbable collagen sponge; ICBG: iliac crest bone graft)

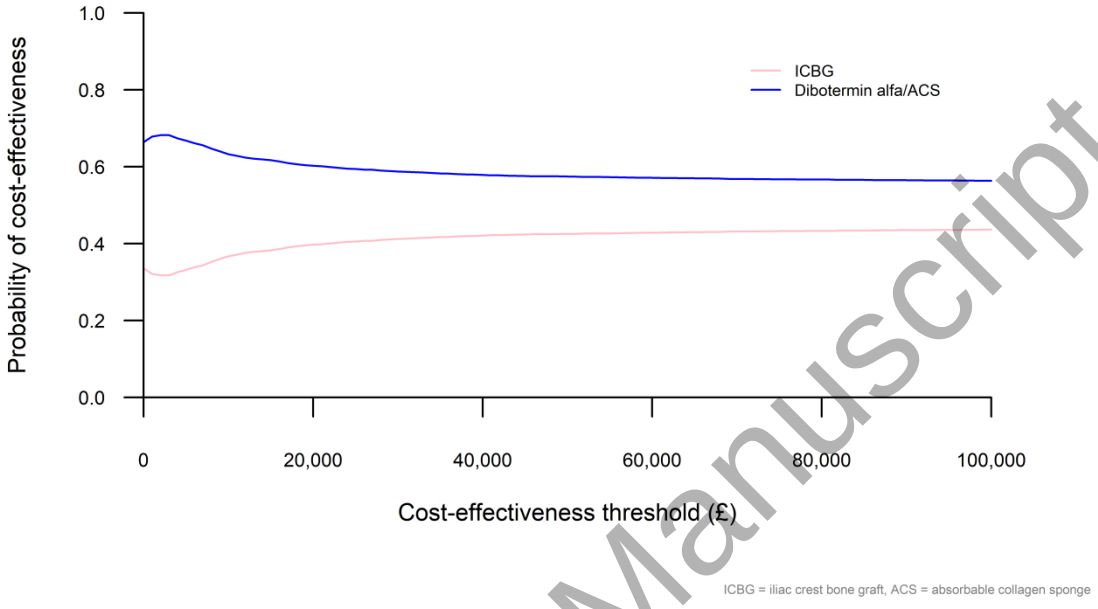


Table 1: Model input parameters and values

Parameter	Mean (95% CI)	p-value	Source
Mixed-effects odds ratio for difference in proportion of patients requiring failure-related secondary surgery	0.55 (0.30, 1.01)	0.055	IPD meta-analysis
Difference in change from baseline utility weight:			
1.5 months	0.001 (-0.024, 0.026)	0.936	IPD meta-analysis
3 months	0.014 (-0.013, 0.041)	0.319	IPD meta-analysis
6 months	0.004 (-0.024, 0.032)	0.804	IPD meta-analysis
12 months	-0.002 (-0.034, 0.03)	0.903	IPD meta-analysis
24 months	0.012 (-0.021, 0.046)	0.477	IPD meta-analysis
Difference in operating room time (hours)	-0.448 (-0.614, -0.282)	<0.001	IPD meta-analysis
Difference in hospital length of stay (days)	-0.404 (-1.13, 0.321)	0.275	IPD meta-analysis
Cost of dibotermin alfa/ACS – 4 mg pack	£1,045	-	Medtronic NHS acquisition cost
Cost per hospital bed day	£413	-	NHS Reference Costs 2017-18 [21]
Cost of failure-related second surgery	£12,224	-	NHS Reference Costs 2017-18 [21]
Cost of operating room use (per hour)	£1,220	-	NHS Improvement, 2019 [22]
Patient salary (per 6 months)	£15,210	-	Office for National Statistics [23]

All results from meta-analysis are for dibotermin alfa/ACS versus iliac crest bone graft. ACS: absorbable collagen sponge; CI: confidence interval; ICBG: Iliac crest bone graft; IPD: individual patient data; NHS: National Health Service.

Table 2: Deterministic cost-effectiveness results (discounted)

Incremental cost (£)	Incremental QALYs	ICER
-192	0.0114	Dibotermin alfa/ACS dominates

ACS: absorbable collagen sponge; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year