NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Late-stage assessment

[GID-HTE10041] - Topical antimicrobial dressings for infected leg ulcers in people and 16 and over

Addendum

Produced by: York Health Economics Consortium (YHEC)

Authors:

Hayden Holmes, Associate Director, YHEC

Lavinia Ferrante di Ruffano, Project Director, YHEC

Laura Kelly, Senior Research Consultant, YHEC

Mary Edwards, Senior Research Consultant, YHEC

Angel Varghese, Senior Research Consultant, YHEC

Sarah Medland, Senior Research Consultant, YHEC

Mick Arber, Senior Information Specialist, YHEC

Emma Carr, Research Consultant, YHEC

Ben Hyde, Research Assistant, YHEC

Monica Garrett, Research Assistant, YHEC

Sam Woods, Research Assistant, YHEC

Correspondence to: Hayden Holmes, York Health Economics Consortium, Enterprise House, University of York, YORK, YO10 5NQ.

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1 Silver with antibiofilm mechanisms

Following submission of the external assessment report (EAR) on topical antimicrobial dressings for infected leg ulcers in people aged 16 and over, the EAG has developed this addendum to provide additional information using evidence which did not meet the evaluation scope but was raised by Convatec as relevant. We have taken a pragmatic approach to run this additional analysis in this instance because it may be beneficial to provide further context in light of the lack of appropriate data to inform the base case model for the silver sub-agent with antibiofilm mechanisms.

1.1 *EAG comment on suitability*

1.1.1 Harding et al (2016)

The clinical SR used data from Harding et al (2016) (Harding et al. 2016) to inform the the silver sub-agent with antibiofilm mechanisms. However, the EAG did not consider this appropriate evidence to use in the model. Harding et al (2016) conducted a prospective single-arm study of 42 people with venous leg ulcers enrolled at 6 study centers in the UK and Poland. Of these, a subset of 10 people had clinically infected venous leg ulcers.

People received treatment for 8 weeks, during which participants received treatment with 2 types of silver dressings. In the first 4 weeks, participants were prescribed Aquacel Ag+ dressings, which contains the sub-agent silver with antibiofilm mechanisms. In the subsequent 4 weeks, participants were prescribed Aquacel Ag+ dressings, which contains the sub-agent ‘silver salts and compounds’ without antibiofilm. The study reported the number of participants healed at 8 weeks.

The study’s sub-group of participants with infected venous leg ulcers adheres to the decision problem and is within scope. However, the key outcome (number healed) was reported at 8 weeks. Without outcome data at 4 weeks, the data is not reflective of ‘silver with antibiofilm mechanisms’, rather the healing rate when 2 different silver sub-agents are applied.

1.1.2 Convatec Clinical study report (CSR)

This open label RCT (ConvaTec Inc. 2024) compared Aquacel Ag+ Extra (agent subtype: ionic silver with antibiofilm agents, dressing category: alginate, gelling fibre, absorbent fibre) to Cutimed Sorbact (agent subtype: DACC, dressing category: wound contact layer) for 2 to 4 weeks in patients with chronic (>2 month) VLUs, followed by standard care wound management up to 12 weeks. Wound infection was not an inclusion criterion and only [redacted] patients (all in the Aquacel® Ag+ Extra arm) had infected wounds at baseline. For these reasons, the study was not considered eligible for including in the clinical review.

The trial was conducted across 20 study centers in Germany, Colombia and the UK in mixed care settings. Dressings were applied either by study staff or clinical providers on- or off-investigation site, or by subjects at home depending on the standard of care at each centre. The sample size calculations required [redacted] wounds to test for non-inferiority which was achieved in the full analysis population up to week 12 (Aquacel Ag+ Extra [redacted], Cutimed Sorbact [redacted]). Study authors reported a baseline [redacted]

The study reported [redacted]

The study population was [redacted] compared with the Harding et al (2016) study (n=10). Participants were treated with Aquacel Ag+ Extra exclusively, therefore, results will not be biased by the use of multiple silver sub-agents. However, the main concern with this study is that the population did not have a locally infected leg ulcer at study entry, ([redacted] did develop a local infection during the course of the study). Therefore, the population fell outside the scope for this research and the outcomes, if used in the model, may overestimate the benefits. In the colour-coding system used in the main report this study would therefore fall under the "orange" category that included studies of patients with non-infected wounds or wounds with an unclear infection status.

1.2 *Data to inform economic model*

1.2.1 Clinical efficacy data

In order to run a silver sub-agent analysis, clinical data was extracted from each study. These data are presented in Table 1.1 and Table 1.2.

Table 1.1 Data from Harding et al (2016)

Clinical parameter	Model input	EAG comment
Rate of infection resolution (per week)	0.069	This was not reported in the study, Therefore, this was derived using methods outlined in the EAR.
Healing rate from 0 to 4 weeks (per week)	0.018	At 8 weeks, 1 of 10 people had healed. Using multipliers derived from Guest et al (see EAR for methods), this was converted into a 4 week probability of healing of 7%. This was converted into a per week healing rate of 0.018 applicable for the first 4 weeks
Percentage discontinued	0%	Harding et al (2016) reported that one participant discontinued because of adverse events not related to the dressing. It was not stated whether the participant was in the clinically infected subgroup. Therefore, this was assumed to be 0.
Percentage with reoccurring infection	0%	Harding et al (2016) did not report the percentage with a reoccurring infection, therefore, this was assumed to be 0.

Table 1.2 Data from the Convatec RCT

Clinical parameter	Model input	EAG comment
Rate of infection resolution (per week)	[redacted]	This was not reported in the study, Therefore, this was derived using methods outlined in the EAR.
Healing rate from 0 to 4 weeks (per week)	[redacted]	At week 12, [redacted] of participants had healed leg ulcers. This gives a per week rate of [redacted]. Using multipliers derived from Guest et al (see EAR for methods), this was converted into a per week healing rate of [redacted] applicable for the first 4 weeks.
Percentage discontinued	[redacted]	[redacted] were discontinued prior to the end of study defined as all study wounds healed or attending Week 12 visit
Percentage with reoccurring infection	[redacted]	Table 50 (Summary of Adverse Events) in the Convatec CSR stated that [redacted] participants in the Aquacel Ag+ Extra group developed a wound infection.

1.2.2 Resource use and cost data

Harding et al (2016) did not report the frequency of dressing changes per week. The Convatec RCT reported an interquartile range of dressing changes every [redacted]. Therefore, it was assumed that in the 'infected unhealed wound' health state, [redacted] dressings were required per week, and in the 'non-infected unhealed wound' health state, [redacted] dressings were required per week.

1.3 *As per the EAR, the cost for silver with anti-biofilm mechanisms was £7.83. Silver sub-agent analysis*

This section summarises the results of the cost-effectiveness analysis of silver sub-agents. The data from the Convatec RCT and Harding et al (2016) for silver with anti-biofilm mechanisms, were compared with silver salts and compounds and elemental silver using data from the EAR. As per the principal results, PSA and DSA were run. Given that there a fully incremental analysis was done.

1.3.1 Convatec RCT

In the deterministic and average probabilistic results, silver with anti-biofilm mechanisms was cost-effective compared with both elemental silver and silver salts and compounds. This was indicated by the positive NMB (see Table 1.3 and Table 1.4).

Table 1.3: Deterministic pairwise analysis of silver sub-agents

	Silver with anti-biofilm mechanisms (Convatec)	Elemental silver	Silver salts and compounds
Total LYs	0.97	0.97	0.97
Total QALYs	[redacted]	0.69	0.69
Total cost GBP (£)	[redacted]	£7,385	£7,290
Incremental LYs	-	0.00	0.00
Incremental QALYs	-	[redacted]	[redacted]
Incremental costs	-	[redacted]	[redacted]
ICER	-	[redacted]	[redacted]
NMB	-	[redacted]	[redacted]

Abbreviations: GBP – Great British Pound; ICER – Incremental cost-effectiveness ratio; LY – Life years; NMB – Net monetary benefit; QALY – Quality-adjusted life year.

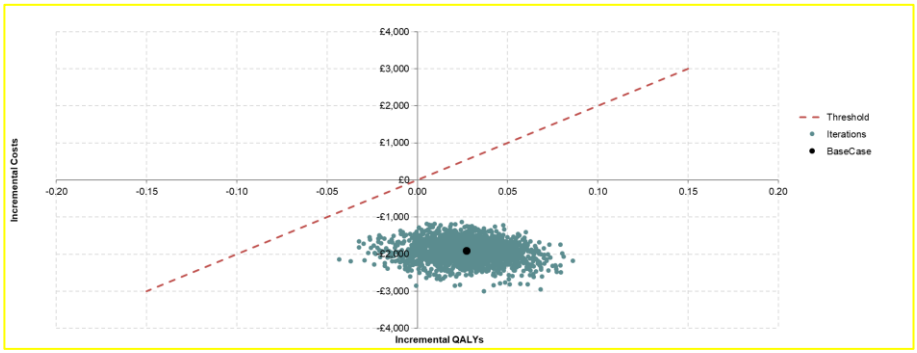
Table 1.4: Probabilistic pairwise analysis of silver sub-agents, mean (95% CI)

	Silver with anti-biofilm mechanisms (Convatec)	Elemental silver	Silver salts and compounds
Total LYs	0.97 (95% CI: 0.97 to 0.97)	0.97 (95% CI: 0.97 to 0.97)	0.97 (95% CI: 0.97 to 0.97)
Total QALYs	[redacted]	0.69 (95% CI: 0.63 to 0.76)	0.69 (95% CI: 0.63 to 0.76)
Total cost GBP (£)	[redacted]	£7,391 (95% CI: £6,623 to £8,159)	£7,326 (95% CI: £6,428 to £8,224)
Incremental QALYs	-	[redacted]	[redacted]
Incremental costs	-	[redacted]	[redacted]
ICER	-	[redacted]	[redacted]
Probability of cost-effectiveness		[redacted]	[redacted]
NMB	-	[redacted]	[redacted]

Abbreviations: CI – Confidence interval; GBP – Great British Pound; ICER – Incremental cost-effectiveness ratio; LY – Life years; NMB – Net monetary benefit; QALY – Quality-adjusted life year.

The cost-effectiveness planes (Figure 1.1) and Table 1.4 shows that the conclusions for the cost-effectiveness model are consistent for 100% of probabilistic runs. The vertical spread of costs is relatively small, compared with the spread of QALYs, suggesting there is less uncertainty in the costs. Furthermore, the costs never cross the x-axis, suggesting that, with the data reported in the Convatec RCT, silver with anti-biofilm mechanisms was cost saving compared with both elemental silver and silver salts and compounds. However, there is a wide horizonal spread, indicating uncertainty in the QALYs. A key outcome from the EAR was that the faster the cohort can progress to the healed health state the more likely it is that the outcome will be cost-effective because of a lower AMD cost, lower health state costs, and higher QALYs. Given that the available percent healed data for silver with anti-biofilm mechanisms from the Convatec RCT was from a population outside the scope, the per-week healing rate was numerically larger compared with elemental silver and silver salts and compounds. This indicates that the cohort progress to the healed health state quicker.

Figure 1.1: Cost-effectiveness plane for silver with anti-biofilm mechanisms (informed by the Convatec RCT) compared with elemental silver (left) and salts and compound (right)



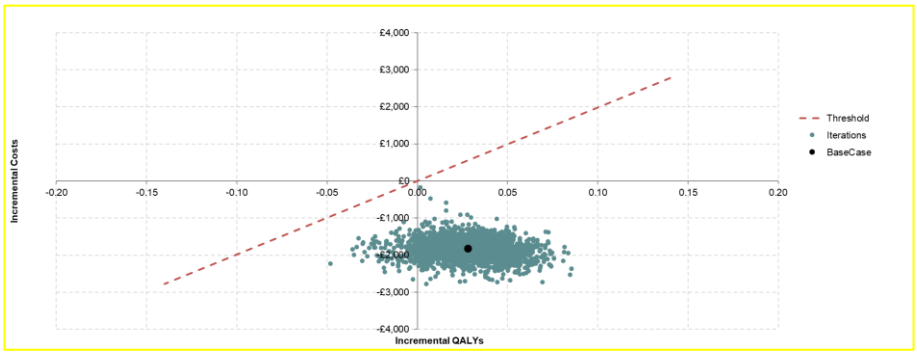
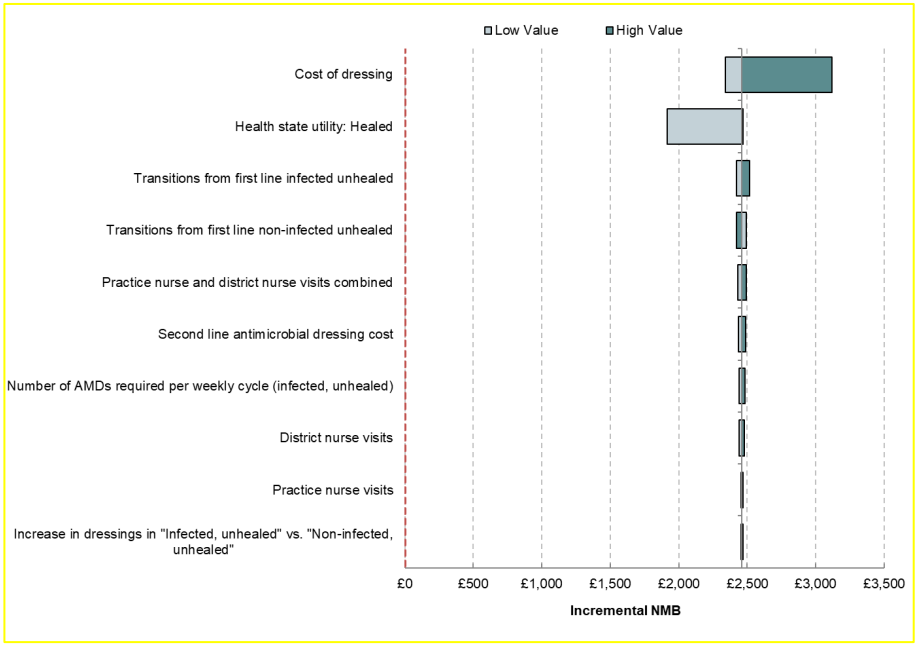
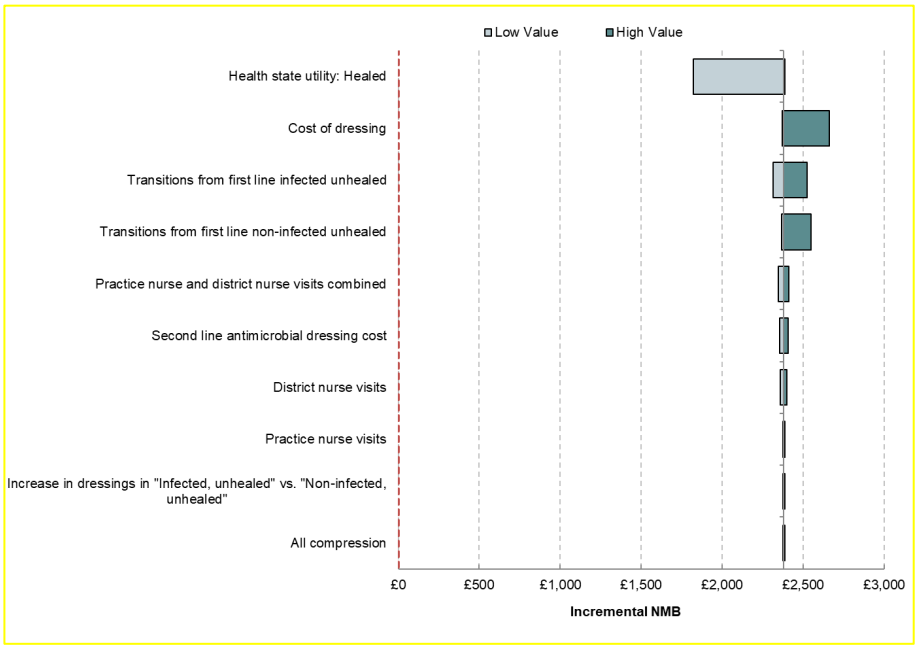


Figure 1.2: DSA tornado plot for silver with anti-biofilm mechanisms (informed by the Convatec RCT) compared with elemental silver (left) and salts and compound (right)




Low Value
High Value
Health state utility: Healed
Cost of dressing
Transitions from first line infected unhealed
Transitions from first line non-infected unhealed
Practice nurse and district nurse visits combined
Second line antimicrobial dressing cost
District nurse visits
Practice nurse visits
Increase in dressings in "Infected, unhealed" vs. "Non-infected, unhealed"
All compression
£0
£500
£1,000
£1,500
£2,000
£2,500
£3,000
Incremental NMB

Changes to the utility value of this health state had a substantial impact on the model. The findings from the cost-effectiveness plane are highlighted further in the DSA. Indeed, health state utilities were identified as one of the key drivers of cost-effectiveness, alongside use of extreme costs for AMDs and the efficacy data from first line infected, unhealed and first line non-infected, unhealed. No DSA scenarios changed the cost-effectiveness conclusion as observed by the bars in the tornado plot never crossing zero (Figure 1.2).

1.3.2 Harding et al (2016)

In contrast to Section 1.3.1, the average PSA and the deterministic results show that silver with anti-biofilm mechanisms was dominated by both elemental silver and silver salts and compounds, meaning it is less costly and less effective. This was indicated by the negative NMB (see Table 1.5 and Table 1.6).

Table 1.5: Deterministic pairwise analysis of silver sub-agents

	Silver with anti-biofilm mechanisms (Harding et al, 2016)	Elemental silver	Silver salts and compounds
Total LYs	0.97	0.97	0.97
Total QALYs	0.69	0.69	0.69
Total cost GBP (£)	£7,702	£7,385	£7,290
Incremental LYs	-	0.00	0.00
Incremental QALYs	-	-0.01	-0.01
Incremental costs	-	£317	£411
ICER	-	-£48,841	-£70,718
NMB	-	-£446	-£527

Abbreviations: GBP – Great British Pound; ICER – Incremental cost-effectiveness ratio; LY – Life years; NMB – Net monetary benefit; QALY – Quality-adjusted life year.

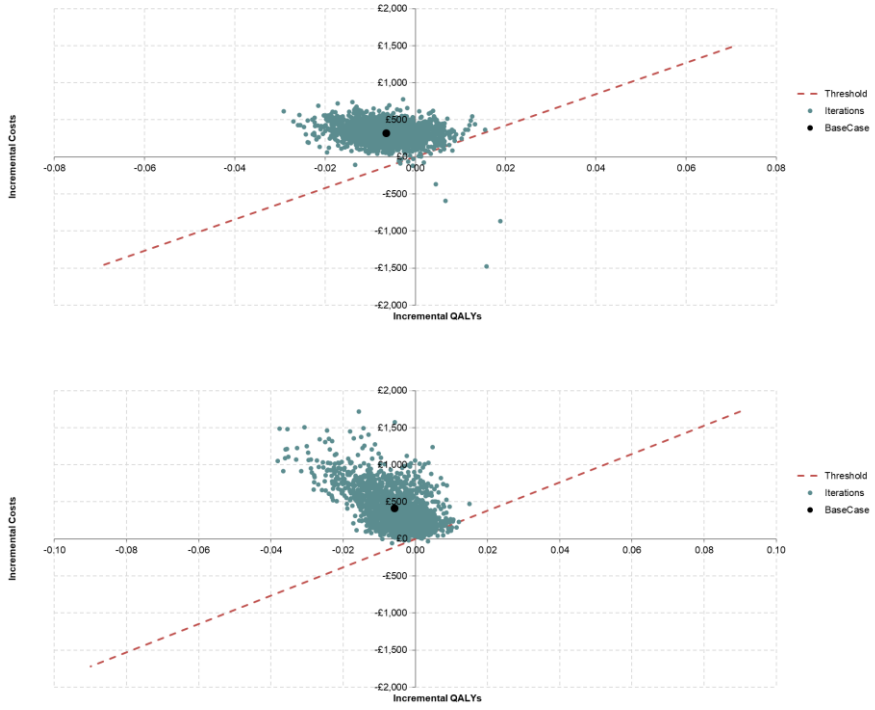
Table 1.6: Probabilistic pairwise analysis of silver sub-agents, mean (95% CI)

	Silver with anti-biofilm mechanisms (Harding et al, 2016)	Elemental silver	Silver salts and compounds
Total LYs	0.97 (95% CI: 0.97 to 0.97)	0.97 (95% CI: 0.97 to 0.97)	0.97 (95% CI: 0.97 to 0.97)
Total QALYs	0.69 (95% CI: 0.63 to 0.75)	0.69 (95% CI: 0.63 to 0.76)	0.69 (95% CI: 0.63 to 0.76)
Total cost GBP (£)	£7,712 (95% CI: £6,947 to £8,477)	£7,391 (95% CI: £6,623 to £8,159)	£7,326 (95% CI: £6,428 to £8,224)
Incremental QALYs	-	-0.01 (95% CI: -0.02 to 0.00)	-0.01 (95% CI: -0.02 to 0.00)
Incremental costs	-	£321 (95% CI: £139 to £503)	£386 (95% CI: £22 to £749)
ICER	-	-£49,629	-£71,423
Probability of cost-effectiveness		0.8%	1.2%
NMB	-	-£450 (95% CI: -£725 to -£176)	-£494 (95% CI: -£994 to £7)

Abbreviations: CI – Confidence interval; GBP – Great British Pound; ICER – Incremental cost-effectiveness ratio; LY – Life years; NMB – Net monetary benefit; QALY – Quality-adjusted life year.

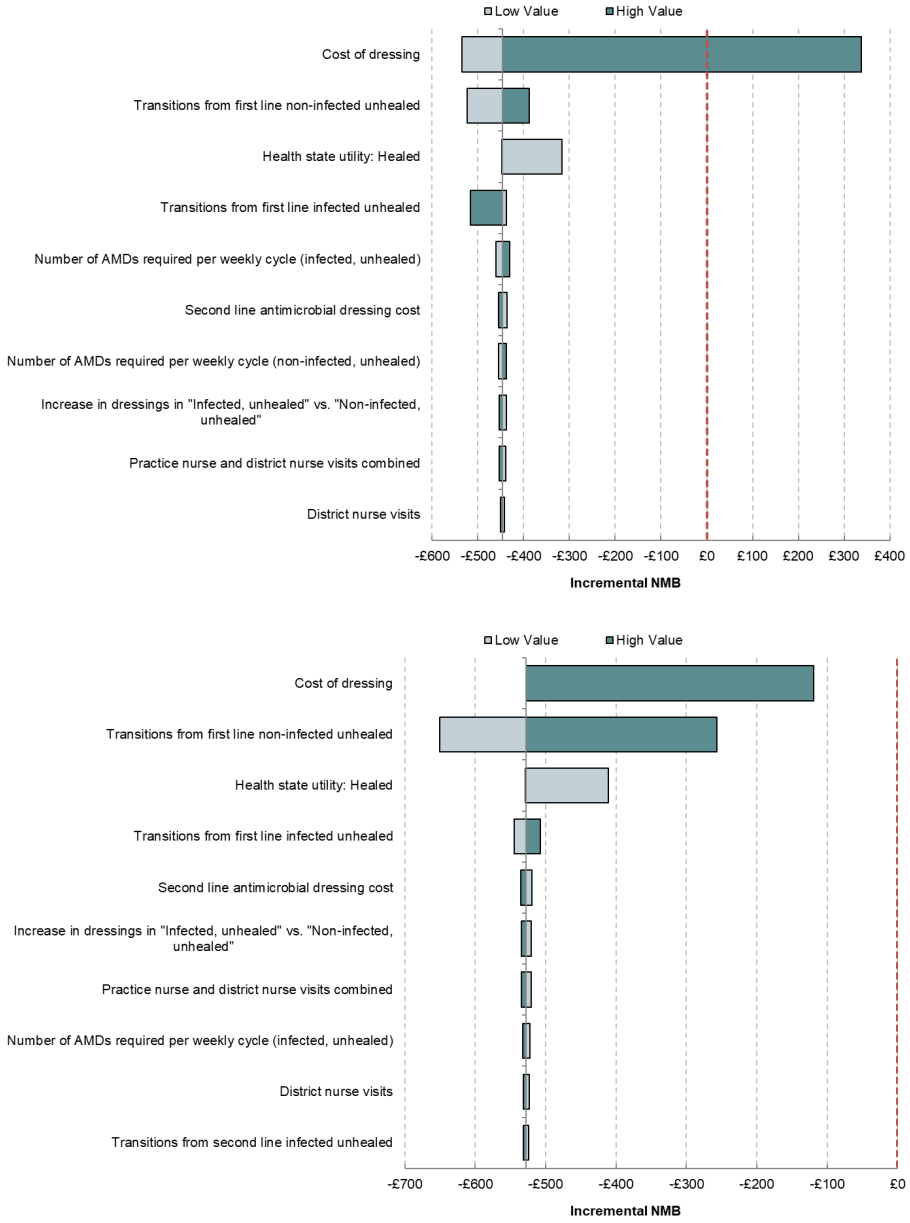
The cost-effectiveness planes (Figure 1.3) shows that there is only a 0.8% and 1.2% likelihood of silver with antibiofilm mechanisms being cost-effective at a threshold of £20,000 per QALY gained, compared with both elemental silver and silver salts and compounds, respectively. This is likely because the efficacy data from Harding et al (2016) was numerically lower than the efficacy data available to inform the other silver sub-agents. The points in the cost-effectiveness planes have a negative trajectory suggesting that as the intervention accrues more QALYs and that there is a decrease in costs. As per Section 1.3.1, the faster the cohort can progress to the healed health state, the more likely it is that the agent will be cost-effective.

Figure 1.3. Cost-effectiveness plane for silver with anti-biofilm mechanisms (informed by Harding et al, 2016) compared with elemental silver (left) and salts and compound (right)



The outcomes are more sensitive to changes in the cost of AMDs, compared with Section 1.3.1. Indeed, the cost of the AMD a key driver of cost effectiveness, above efficacy data and health state utility of the healed health state (Figure 1.4). When compared with elemental silver, which has a larger cost and resource use requirements, a use of the maximum AMD costs caused the conclusion to change.

Figure 1.4: DSA tornado plot for silver with anti-biofilm mechanisms (informed by Harding et al, 2016) compared with elemental silver (left) and salts and compound (right)



1.4 *Summary*

The conclusions from the two silver-sub analyses were contradictory. Indeed, when the Convatec RCT informed the model, silver with antibiofilm mechanisms was the dominant sub-agent compared with other silver subagents. Conversely, when the data from Harding et al (2016) informed the model, silver with antibiofilm mechanisms was dominated by the other silver subagents. Model outcomes with Harding et al (2016) predicted silver with antibiofilm mechanisms would cost [redacted] than when the Convatec RCT informed the model as well as accruing [redacted] QALYs.

Neither the Convatec RCT, nor the data from Harding et al (2016), was considered to be appropriate for use in the economic model to inform the EAR. This is because the participants of the Convatec RCT population did not adhere to the population specified in the scope, namely, people with leg ulcers with local infections. Furthermore, sub-agents used in Harding et al (2016) was a combination of silver salts and compounds and silver with antibiofilm mechanisms. The EAG acknowledge that there are key areas of uncertainty in the data and assumptions informing the economic model. However, data from Harding et al (2016) and the Convatec CSR were, and continue to be, inappropriate for use in the model. These results should not replace the existing silver sub-agent analysis, and they do not change the outcome from the principal analysis.

However, outcomes from both silver sub-agent analyses support those of the EAR, highlighting that, where there was a greater difference in efficacy, the cost savings and QALY gains associated with moving to the healed health state faster offset the additional AMD costs.

2 References

ConvaTec Inc. (2024) Clinical Sudy Report: a clinical study to compare the performance of Aquacel® Ag+ Extra™ and Cutimed® Sorbact® Dressing in the management of patients with venous leg ulcers over a 12-week period. London: Inc., C.

Harding KG, Szczepkowski M, Mikosinski J, et al. (2016) Safety and performance evaluation of a next-generation antimicrobial dressing in patients with chronic venous leg ulcers. International Wound Journal 13(4)**:** 442-8