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## 1.0 Introduction

Surgical site infection (SSI) is the third most commonly reported type of hospital-acquired infection, and a major impediment to surgical wound healing [1]. SSIs can cause higher resource use (and hence higher healthcare costs), patient distress and poor physical, emotional or economic outcomes [2]. Thus, SSI prevention is an important perioperative care objective.

Negative pressure wound therapy (NPWT) was developed in the 1990s to aid wound healing [3] and is increasingly used prophylactically to prevent wound complications, including SSIs, particularly in obese patients or those with difficult-to-heal wounds [4]. This is despite a lack of understanding about the mechanisms by which NPWT aids wound healing (experimental evidence suggests several factors may be involved [3]) and limited evidence of efficacy [4]. There have been a number of reviews of NPWT [4-8], with some favouring NPWT over standard dressings [5, 6] and others failing to find convincing evidence of benefit [4, 7, 8]. The majority of these focus either primarily or entirely on studies of NPWT in the treatment setting [5-8], although a Cochrane review of NPWT for prophylactic postoperative use concluded that the evidence for effectiveness was unclear [4].

The cost-effectiveness of NPWT is also unclear. One study developed a decision model combining information from the literature with data from a small pilot study and professional assessments [9, 10]. The authors concluded that NPWT achieves lower overall costs and superior outcomes compared to standard treatment for severe pressure ulcers [9, 10]. Other researchers have concluded that NPWT is cost-effective compared to standard treatment in retrospective chart reviews [11] and comparative case-studies [12]. The results of these studies are highly uncertain and generalisability is limited by the heterogeneity of patients receiving NPWT [6]. Additionally, most cost-effectiveness studies have focused on the

treatment of chronic, difficult-to-heal wounds [6, 10, 11]. NPWT is increasingly used prophylactically following surgery for high-risk clean wounds [13], particularly in obese patients at greater risk of developing SSIs [14]. As obesity is a growing problem in Australia and other developed countries understanding the clinical effectiveness and cost-effectiveness of interventions for preventing SSIs in obese patients is important. Previous findings that NPWT may be cost-effective in the treatment of difficult-to-heal wounds do not necessarily support prophylactic use.

Given the increasing prophylactic use of NPWT despite limited evidence of benefit, a study of the clinical effectiveness and cost-effectiveness of prophylactic NPWT is urgently required. One previous study constructed a decision-analytic model of prophylactic NPWT following caesarean section and concluded that it was not cost-effective, however that study was not limited to overweight patients and did not consider quality of life (QoL) [15]. In this study, our aim was to evaluate whether NPWT is cost-effective compared to standard care for the prevention of SSIs in obese women undergoing elective caesarean section. Obese women are at greater risk of SSI following caesarean section compared to women who are not overweight [16].

## **2.0 Methods**

### **2.1 Study Design**

We estimate the cost-effectiveness of NPWT compared to standard care, based on data from a pilot study of NPWT use in obese women following elective caesarean section. Cost-effectiveness assessment was based on incremental cost (AU\$) per SSI prevented and per quality-adjusted life year (QALY) gained.

The design of the pilot study has been described in detail elsewhere [17]. The pilot study was a prospective, single site randomised controlled trial (RCT). Obese ( $BMI > 30 \text{ kg/m}^2$ ) women were recruited during the scheduled pre-operative visit before elective caesarean section booked prior to the commencement of labour. Informed consent was obtained from all patients. Randomisation occurred after recruitment and prior to surgery. Patients were allocated to two treatment arms in a 1:1 ratio using simple randomisation; NPWT PICO™ (disposable unit from Smith and Nephew, Hull, UK) (n=44) or standard care (n=43) which consisted of Comfeel Plus® dressing (Coloplast, Denmark). Data were collected on resource use, clinical outcomes and health-related QoL during the hospital stay and at weekly intervals for four weeks post-discharge. Total costs, SSI incidence and QALYs were compared across the two treatment arms and an incremental cost-effectiveness ratio (ICER) was calculated to describe the cost of additional QALYs gained by utilising NPWT for prophylaxis compared to standard care.

## **2.2 Setting and Perspective**

The perspective taken was that of the public health care provider. The setting was the obstetrics unit of a large Australian tertiary teaching hospital. A standard surgical technique was used for all procedures but the treating health professionals were able to administer antibiotics or other medicines at their discretion. Follow-up occurred daily while the women were in hospital and via telephone once per week for four weeks post-discharge. No discounting was applied to costs or outcomes due to the short time horizon.

## **2.3 Data Collection**

Data describing in-hospital resource use and clinical outcomes were collected by direct observation or chart audit by a research assistant (RA) using report forms specifically developed for the trial. Data describing post-discharge resource use, clinical outcomes and QoL were collected during the weekly post-discharge telephone follow-ups with patients.

The allocated dressings were applied by the operating obstetrician and their surgical assistant following wound closure.

## **2.4 Resource Unit Costs**

Resources were valued in Australian dollars (AU\$) at 2014 values (AU\$1~ US\$0.82 ~ €0.66 at 17 December 2014). Resources recorded and their unit costs are given in Table 1. The total cost per resource was calculated for each patient by multiplying the per-unit cost of the resource by the number of units used. Each individual's total cost of treatment was calculated as the sum of the individual's total costs per resource over all resources.

**Table 1: Unit Costs at 2014 Value**

<b>Resource</b>	<b>Unit Cost (AU\$)</b>	<b>Source</b>
<b>INTERVENTIONS</b>		
NPWT PICO™ Unit	180	Actual charge from Smith and Nephew
Comfeel Plus® Dressing	5	Hospital estimate
Nurse time to apply, change or remove NPWT or standard dressing (per hour)	35	Queensland Health [18]
<b>HOSPITAL CARE</b>		
Hospital stay for caesarean section without complications (per 6 day stay)	10,191	National Efficient Price Determination 2014-15 [19]
Hospital stay for caesarean section without complications (per marginal day) <sup>1</sup>	1,489	National Efficient Price Determination 2014-15 [19]
Adjustment for SSI treatment <sup>2</sup> (per episode)	380	National Efficient Price Determination 2014-15 [19]
<b>POST-DISCHARGE CARE</b>		
Hospital stay for wound treatment following readmission (per 4 day stay)	3,933	National Efficient Price Determination 2014-15 [19]
Hospital stay for wound treatment following readmission (per marginal day) <sup>3</sup>	780	National Efficient Price Determination 2014-15 [19]
General practitioner visit	37.50	Medicare Benefits Schedule 2014 [20]
Emergency department visit	288	National Efficient Price Determination 2014-15 [19]
Other health specialist visit	Varies	Medicare Benefits Schedule 2014 [20]
Medication	Varies	PBS Schedule 2014 [21]

<sup>1</sup> DRGv7.0 code O01C (caesarean delivery without catastrophic or serious complication/comorbidity). The NEPD 2014-15 provides inlier weights which apply to all lengths of stay between defined bounds (1-12 days in the case of O01C). For cost assignment we assumed that the full inlier weight applied to hospital stays of 6 days (the longest in our data set) and reduced the cost for shorter stays by the long-stay outlier per diem (assuming this to be the best estimate of the marginal cost of a day of hospitalisation).

<sup>2</sup> DRGv7.0 code O01B (caesarean delivery with serious complication/comorbidity). 1.5 days were subtracted at the long-stay outlier per diem weight to account for the longer average length of stay with a complication. The adjustment is the difference between the resulting cost and the O01C cost.

<sup>3</sup> DRGv7.0 code T61B (postoperative and post-trauma infection without catastrophic or serious complication/comorbidity). Calculated the same way as a day in hospital for caesarean section, with the full inlier weight assigned to a 4 day length of stay.

## **2.5 Outcome measures: SSI and Quality of Life**

SSI incidence measurement is described by REFERENCE REMOVED FOR BLINDING. [17]. Briefly, SSIs were assessed by an independent assessor blinded to treatment allocation in accordance with the Centres for Disease Control and Prevention definition [1]. Health related QoL data were collected using the SF-12v2® survey which is a multi-attribute health status classification system that assigns a single QoL index (utility weight) based on responses to 12 questions [22]. The SF-12v2® instrument was administered at baseline (prior to surgery) and at each of the four weekly post-discharge follow-ups.

## **2.6 Economic Analysis**

All patients had complete outcome (QALY) data and were included in the analysis. Descriptive statistics were used to describe resource use, costs and QoL. SF-12v2® QoL indices (utility weights) were calculated using the method of Brazier and Roberts [22]. QALYs were estimated from the utility weights using the standard area under the curve method. We assumed that the change from the baseline to the first post-discharge weight was linear and occurred over the period of hospitalisation, that the first post-discharge weight applied to the full first week following discharge and that the transition between post-discharge weights was linear. Additional days at the fourth post-discharge weight were added where necessary to ensure an equal number of days were considered for each patient, regardless of length of hospital stay. QALYs were adjusted for differences in baseline SF-12v2® indices using the regression-based adjustment of Manca, Hawkins and Sculpher [23]. Data analysis was conducted using IBM SPSS Statistics for Windows 22 (IBM Corp, USA) [24] and Stata Statistical Software 13 (StataCorp, USA) [25]. When testing differences between means we used a Shapiro-Wilk test for the normality of the two distributions followed by an independent *t*-test or Mann-Whitney U test as appropriate. A Chi-square test

or Fisher's exact test was used for proportions. The differences in mean costs and outcomes between the two arms were used to estimate the ICER. A non-parametric bootstrap with 1,000 replications was used to construct 95% percentile method confidence intervals (CIs) for the estimates.

## **2.7 Sensitivity Analysis**

The method chosen to construct QALYs from QoL weights for the base case analysis is described in 2.6. Arguably, the change in QoL over the hospital stay is too complex to be analysed with weights taken before and approximately 10 days after surgery. Consequently, it might be best to ignore the period of hospitalisation and consider only QALY differences between the two groups following discharge. Acknowledging this, we analysed only post-discharge QALYs as a sensitivity analysis.

## **3.0 Results**

### **3.1 Participant characteristics**

Table 2 shows summary statistics for the characteristics of the two treatment groups. As reported by REFERENCE REMOVED FOR BLINDING [17], patients receiving the standard treatment were more likely to smoke ( $p=0.032$ ) and had longer average surgery time ( $p=0.002$ ). They were also more likely to receive antibiotics post-surgery ( $p=0.021$ ), typically due to surgeon concerns about potential complications.



**Table 2: Summary of Descriptive Statistics for Treatment Groups**

Characteristic	NPWT	Standard Dressing
	(n=44)	(n=43)
	Mean $\pm$ SD	
Age (years)	30.61 $\pm$ 5.50	30.65 $\pm$ 5.00
Baseline BMI	35.75 $\pm$ 4.58	36.81 $\pm$ 5.85
Number of Previous CS	1.30 $\pm$ 0.95	1.26 $\pm$ 0.69
Number of Other Comorbidities	0.73 $\pm$ 0.97	0.65 $\pm$ 0.78
QoL Weight at Baseline	0.70 $\pm$ 0.13	0.70 $\pm$ 0.13
Surgery Time (minutes)*	47.16 $\pm$ 12.50	57.26 $\pm$ 19.73
	Number, %	
Patients who Smoke*	3, 7%	10, 23%
Patients with Diabetes	0, 0%	4, 9%
Patients with Gestational Diabetes	13, 30%	8, 19%
Patients Receiving Prophylactic Antibiotics	38, 86%	31, 72%
During Surgery		
Patients Receiving Antibiotics Post-Surgery in Hospital*	2, 5%	9, 21%
Patients Receiving NSAIDs Post-Surgery in Hospital	39, 89%	40, 93%

Note: Table presents mean  $\pm$  standard deviation, \* indicates statistically significant difference at 5% significance level

### 3.2 Comparative Cost and Effectiveness Results

Table 3 details the average resource use and costs for the treatment groups. For both groups, the cost of days in hospital accounted for the majority of the costs of treatment.

**Table 3: Average Resource Use and Costs (per person)**

Item	NPWT (n=44)		Standard Dressing (n=43)	
	Avg. Use	Avg. Cost (\$)	Avg. Use	Avg. Cost (\$)
<b>HOSPITAL CARE</b>				
Hospital days	2.84	5,487.10	2.86	5,516.22
Hospital readmission (events)	0.02	89.40	0.02	55.19
Hospital days following readmission	0.09		0.05	
PICO™ units	1.02	184.09	0	0
Comfeel Plus® dressing	0.02	0.11	1.12	5.60
In-hospital SSI treatment	0.23	86.37	0.28	106.06
Nurse labour for dressing change (minutes)	8.27	4.83	1.28	0.74
Nurse labour for dressing application (minutes)	5.25	3.06	0.53	0.31
<b>POST-DISCHARGE CARE</b>				
GP visits	0.25	9.38	0.74	27.91
Emergency department visits	0.02	6.55	0.05	13.40
Midwife visits	0	0	0.07	5.65
Post-discharge analgesics	-	14.51	-	19.49
Post-discharge antibiotics	-	1.81	-	3.48

REFERENCE REMOVED FOR BLINDING reported the effectiveness of NPWT based on median outcomes [17]. Table 4 presents analysis comparison of outcomes focusing on the *mean* values which better reflects the requirements of an economic analysis [26]. There was no significant difference in SSI incidence or QALY per patient between the NPWT and standard dressing groups at the 5% level (Table 4). Nevertheless, the point estimates for SSI incidence and QALY per patient suggests that a larger sample size might find a statistically significant result favouring NPWT.

**Table 4: Components of Cost-Effectiveness Analyses**

	NPWT (n=44)	Standard Dressing (n=43)	Incremental difference [95%CI]
Cost per Patient (mean $\pm$ SD) (AU\$)	5,887.21 $\pm$ 1,037.59	5,754.04 $\pm$ 1,483.93	133.17 [-397.07, 690.79]
SSI (proportion of patients)	11/44 (25%)	15/43 (34.89%)	9.88% [-10.78%, 28.38%]
QALYs per Patient (mean $\pm$ SD)	0.069 $\pm$ 0.010	0.066 $\pm$ 0.010	0.0031 [-0.00037, 0.0067]
ICER (AU\$ per unit outcome)	-	-	1,347.36 per SSI prevented [-17,666.06, 41,873.49]
	-	-	42,339.87 per QALY [-275,040.40, 884,018.60]

### 3.3 Cost-Effectiveness

Table 4 also presents the comparative total costs and benefits and consequent ICERs. The ICERs are estimated to be AU\$1,347 (95%CI dominant to \$17,666) per SSI prevented and \$42,340 (95%CI dominant to \$884,019) per QALY gained. However, the ICERs exhibit substantial uncertainty, as indicated by the very wide 95% CIs.

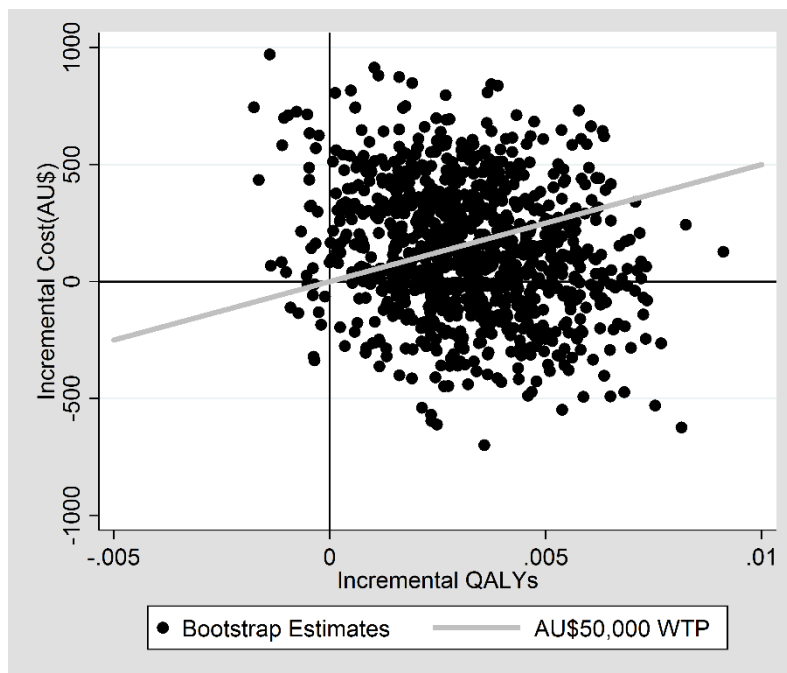
The point estimate for incremental QALY gain may be an underestimation because the apparent gap between mean utility weights for the two treatment groups (which was statistically significant at week 3) had not closed at the fourth post-discharge follow-up (Table 5). If this difference persisted beyond the fourth week then the QoL benefits of prophylactic NPWT may be greater than reported.

**Table 5: Utility Weights at Each Post-Discharge Follow-Up**

Post-Discharge Follow-Up (* indicates statistically significant difference at 5% significance level)	NPWT (n=44)	Standard Dressing (n=43)
1	0.70 ± 0.12	0.67 ± 0.13
2	0.74 ± 0.14	0.71 ± 0.14
3*	0.78 ± 0.12	0.72 ± 0.13
4	0.78 ± 0.13	0.74 ± 0.12

Note: Table presents mean ± standard deviation

The cost-effectiveness plane (Figure 1) shows the considerable uncertainty in the incremental cost and QALY estimates. Since the majority of points are to the right of the y-axis, NPWT is likely to improve QoL, even if only by a small amount. Most of the points lie in the upper right quadrant, suggesting that NPWT increases costs while improving outcomes. The points below the diagonal line suggest cost-effectiveness at a willingness-to-pay of AU\$50,000 per QALY.



**Figure 1: Individual bootstrap estimates of incremental cost and incremental effect with cost-effectiveness threshold of \$50,000/QALY**

### **3.5 Sensitivity Analysis**

The ICER estimated excluding hospitalisation QALYs is \$49,736 per QALY ( 95% CI - \$468,044 i.e. dominant to \$1,001,493]. The ICER point estimate and area of uncertainty is similar to the base case, suggesting that the inclusion or exclusion of the period of hospitalisation is not of great importance for the purpose of measuring incremental QALYs.

### **4.0 Discussion**

Our findings provide preliminary support for the hypothesis that NPWT is a cost-effective intervention for post-surgical wound management in obese women following elective caesarean section. The point estimates suggest NPWT may be more costly than standard treatment but may also offer improvements in QoL and prevention of SSIs. This is clinically promising, although the pilot study's small sample means the findings are statistically non-significant and therefore inconclusive. The point (best available) estimate of the ICER is below (but close to) the rule-of-thumb threshold of AU\$50,000 per QALY gained conventionally considered to represent good value for money in Australia [27]. The large confidence intervals highlight the small sample size and the challenges of assessing interventions with small changes in outcomes [28].

A larger study might strengthen the evidence of NPWT's cost effectiveness. Patients who developed SSIs in the pilot study had an average hospitalisation length of 2.96 days compared to 2.82 days for patients who did not develop SSIs ( $p=0.39$ ). Consequently the cost assigned to developing an SSI is quite low. Other studies have reported median increases in length of stay of several days and consequently assign high costs (exceeding \$3,000 in many

cases) to SSIs [29, 30]. If more severe SSIs requiring longer hospital stays are observed in a larger trial and NPWT proves effective at reducing SSI incidence then the cost-effectiveness results may be more convincing.

However, whilst there is a strong case for undertaking a full scale RCT to evaluate NPWT further and reduce the uncertainty around its clinical efficacy or cost, reducing the uncertainty around its cost-effectiveness will be hard to achieve. The pilot findings suggest NPWT may generate a very small QALY gain but for a small increased cost, with a lot of uncertainty in this small sample. The ratio of these two small numbers is giving an ICER near to the commonly adopted \$50,000 per QALY threshold. Whilst a change in QALY is desirable even if small, it can make it hard to show cost-effectiveness with an acceptable level of certainty, even in a larger trial.

Consequently, this pilot study provides important insights into the methods required to undertake a larger trial in this area. Using published guides on estimating sample size for cost-effectiveness analyses [31], it is possible to use the pilot findings to estimate the sample size required to show NPWT to be cost-effective under the assumption of a willingness to pay threshold of \$50,000 per QALY. A sample size of 175 participants would be needed per group to show a statistically significant difference of 0.003 QALYs (equivalent to 1.1 days in full health), and 1,386 per group to show a difference of \$133 in costs (80% power at the 95% confidence level). However, 109,190 participants would be needed per group to accept NPWT to be cost-effective with 95% confidence (power calculations assume expected correlation of -0.16 between difference in costs and difference in QALYs, standard deviation of \$1,250 and 0.01 QALY in each group [31]). This number reduces to 1,666 per group if we choose a more lenient threshold of \$100,000 per QALY. This estimate shows the difficulty in powering a study to reduce the uncertainty in cost-effectiveness (which is a ratio of two variables) rather than in just a single outcome measure, especially when the point estimate is

so close to the maximum acceptable cost-effectiveness threshold. Therefore, any future trial would need to carefully consider the capacity to more sensitively capture any cost offsets from avoidance of SSI or QoL benefits associated with NPWT, for example with longer follow up. If the true QALY gain were 50% greater and the incremental costs were half that associated with NPWT in this pilot (0.0045 QALY and \$66.50), the sample size reduces to 1,257 or 316 per group for a threshold of \$50,000 or \$100,000 per QALY respectively.

#### **4.1 Strengths and Limitations**

To our knowledge, this is the first RCT-based economic evaluation of prophylactic NPWT. Soares et al. [10] used data from a small pilot study; however, their evaluation was treatment focused as opposed to prophylactic. A previous pilot study reported some evidence of clinical effectiveness of prophylactic NPWT in obese women following caesarean section, however, that study used a weaker retrospective cohort design and did not evaluate cost-effectiveness [32]. A previous decision-analytic model of prophylactic NPWT following caesarean section concluded that prophylactic NPWT was not cost-effective [15]. That study considered only financial costs, which were also higher for NPWT in our study, and evaluated NPWT for all patients. The authors note that the greater risk of SSI in obese patients may mean prophylactic NPWT is cost-effective for that group.

A small sample of only 87 patients is the greatest shortcoming of our study and means that the findings, while promising, are too uncertain to inform practice. Although our study suggests that NPWT may be cost-effective in this setting, there clearly remains a need for large studies before the clinical and cost-effectiveness of NPWT can be established.

Similarly, the large confidence intervals around the estimates of incremental cost, effect and ICER emphasise that it is inappropriate to draw conclusions about cost-effectiveness from

our sample. Our current study is underpowered and larger studies will be necessary to determine whether NPWT is cost-effective.

There are a number of additional limitations, which should be considered in the design of a larger trial. Firstly, the 4 week follow-up period (which reflects the SSI definition) may have overlooked ongoing disparities in QoL (see Table 5). A further limitation is that the first post-surgery QoL data collected was at the first post-discharge follow-up. This may have prevented us from accurately describing the difference in QoL experienced during the hospital stay. Nevertheless, sensitivity analysis suggests that the complete exclusion of the time in hospital from the QALYs does not substantially change the result, so the precise treatment of QoL differences during the hospital stay may not be an issue of great importance.

As noted by REFERENCE REMOVED FOR BLINDING [17] and seen in Table 2, the two treatment groups may not be comparable. Patients receiving standard treatment were more likely to smoke, had longer average surgery times and were more likely to receive prophylactic antibiotics after surgery. This raises the possibility that patients receiving standard treatment may have had more complicated surgeries. Additionally, since smoking is a recognised risk factor for SSI [14] the data may overestimate the benefit from NPWT. Alternatively, the higher proportion of patients with standard treatment receiving antibiotics post-surgery might lead to underestimation of the benefits of NPWT. We did not assign costs for surgery duration or prophylactic antibiotic use as these were not directly linked to the treatment received. A larger trial should be able to overcome the effects of heterogeneity in these factors with satisfactory randomisation.



## 5.0 Conclusion

This pilot study suggests NPWT may be cost-effective at preventing SSIs and improving patient QoL in obese women after a planned caesarean section. However, the findings from this small pilot study are not conclusive as they do not reach statistical significance. The promising point estimates combined with the growing prophylactic use of NPWT in a clinical setting suggest that there may be value in conducting a larger study with greater power to evaluate the cost-effectiveness of NPWT in this setting. However, the point estimate ICER near the conventional threshold indicating value for money and the substantial uncertainty observed in this pilot suggest this might be challenging to achieve. This study provides important insights into methodological considerations for the larger trial in order to demonstrate cost-effectiveness.

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