NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation:

PICO negative pressure wound dressings for closed surgical incisions

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Scope of evaluation** – the framework for assessing the technology. The scope is based on the sponsor's case for adoption.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
8. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

Title: PICO negative pressure wound therapy for closed surgical incision wounds

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Description of any pecuniary relationship with the company, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.
http://www.nice.org.uk/niceMedia/pdf/Guidanceondeclarationsofinterest.pdf

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Ms Pauline Whitehouse, Consultant General and Colorectal Surgeon, Worthing Hospital (Western Sussex Hospitals NHS Foundation Trust), has given lectures on behalf of Smith and Nephew Ltd with minimal fee and expenses covered.

Mr Thomas Pinkney, Senior Lecturer and Consultant Colorectal Surgeon, Academic Department of Surgery, University of Birmingham, is a Senior Chief investigator of the SUNRRISE Trial that will have the PICO devices provided by Smith and Nephew. This is an NIHR-funded and investigator-initiated trial, and the company have no involvement in the study other than to provide the intervention.

Dr Fania Pagnamenta, Nurse Consultant (Tissue Viability), Newcastle upon Tyne Hospitals NHS Foundation Trust, no conflict declared.

Ms Caryn Carr, Lead tissue viability nurse, Southern Health Foundation Trust, no conflict of interest declared.

Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

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ABBREVIATIONS

Term	Definition
ASA	American Society of Anesthesiologists
BMI	Body mass index
CABG	Coronary artery bypass grafting
C-section	Caesarean section
CI	Confidence interval
DH	Department of Health
EAC	External Assessment Centre
IQR	Interquartile range
LOS	Length of Stay
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MIB	Medical innovation briefing
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
NPWT	Negative-pressure wound therapy
PHE	Public Health England
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised Controlled Trial
SD	Standard deviation
SSC	Surgical site complication
SSI	Surgical site infection
SWD	Surgical wound complications
VAS	Visual Analogue Scale
vs	Versus
WHO	World health organisation
WUWHS	World Union of Wound Healing Societies

1 Executive Summary

The sponsor included in their submission 29 clinical studies (23 published in full text, 5 as conference abstracts and 1 unpublished). The EAC identified 2 more relevant conference abstracts Caswell 2015 and Luciani 2016. From the included studies, 13 were RCTs (Chaboyer 2014, Galiano 2018a, Gillespie 2015, Hyldig 2018a, Nordmeyer 2016, Karlakki 2016, O'Leary 2016, Svensson 2018, Tanaydin 2018, Tuuli 2017, Uchino 2016, Witt 2015, Zotes 2015). Five of the RCTs were adequately powered to detect a difference in the primary outcome (Galiano 2018a, Hyldig 2018a, Karlakki 2016, O'Leary 2016, Uchino 2016). The rest of the studies were non-randomised controlled studies.

The sponsor submitted a meta-analysis of all the included studies. The SSI rate analysis included 4473 participants reported in 19 full text publications (21 with conference abstracts included). Combining data from 8 RCTs including all medical specialties, provided evidence that use of PICO reduces the rate of SSIs (OR 0.49, 95%CI 0.33-0.72, p=0.0003). The pooled analysis of the 11 observational studies confirmed this result (OR 0.28, 95%CI 0.17-0.46, p <0.0001). The EAC ran additional meta-analyses based on the critical appraisal of the sponsor's analyses using a random effects model and conducting further sensitivity analyses on the results. The additional analyses confirmed the findings of the sponsor with small changes in the estimated ORs and 95%CIs for the pooled SSI rate. From the subgroup analyses, there is evidence to support the reduction of SSIs in obstetric and orthopaedic surgery, the latter mainly driven from the effect of non-randomised comparative studies. The reduction in seroma and dehiscence rates is also mainly driven by the effect of non-randomised controlled studies. The clinical experts' views and similar literature for the field of NPWT systems supports the transferability of the results in terms of the overall superiority of PICO vs. standard dressing among different surgical procedures. However, given the wide 95%CIs and the variability of risk factors in clinical practice, it is difficult to estimate the size of the effect for each surgical procedure separately.

The EAC finds considerable uncertainty in the likelihood that PICO is cost saving. This arises because the additional cost of using PICO is similar in magnitude to the savings generated from reductions in surgical complications. The EAC notes that the evidence of effectiveness of PICO indicates the likelihood of a health benefit which would suggest that the likelihood that PICO is cost-effective is higher than the likelihood that it is cost saving.

2 Background

2.1 Overview and critique of company's description of clinical context

The clinical context provided by the sponsor is considered appropriate, stating that the main use of PICO is with prophylactic intent, post-operatively, with immediate application in the theatre. The sponsor also reports that PICO can be utilised with a therapeutic intent in the community setting for the treatment of SSCs, however, no additional context is provided for that intent or setting. The PICO system can be applied by all healthcare professionals and can be removed by a lay user such as the patient or caregiver.

The sponsor provided a brief overview of SSCs in closed wounds, including incidence and prevalence data from the UK and the US. Potential risk factors were also described. The sponsor describes rates of SSI according to the NICE guideline on preventing and treating surgical site infections. However, the sponsor did not use as a source the PHE annual audit on SSI rates in the NHS. The EAC agrees with the sponsor that the rate of SSCs, especially SSIs, varies widely due to different approaches to data capture, follow-up and definitions and reasons intrinsic to the surgical procedure and patient related characteristics. The wide variation in the SSI rates was confirmed by the views expressed by the clinical experts.

The sponsor, notes in section 3.5 that risk stratification should be done prior to surgery, and based on the WUWHS guideline. Patients with 1 major risk factor or multiple moderate risk factors should be considered as candidates for PICO. A brief description of the main international and national guidelines for the role of NPWT devices and the risk stratification were also given.

The sponsor states that the care pathway would not need to change apart from the replacement of conventional post-surgical wound dressings with PICO. According to the clinical experts the pathway is shaped by the national and international guidelines, however, local variation is observed especially concerning risk-stratification (see more details below). The EAC concurs that no significant additional interventions or facilities are required.

Relevant guidance

NICE has published a PICO negative pressure wound therapy for closed surgical incision wounds (MIB149) advice that describes the potential use of the PICO system in people with closed surgical incisions at high-risk for developing SSCs. The advice states that in cases that dehiscence occurs and

a deep infection is ruled out, sometimes a NPWT may be used to manage the wound to promote healing by secondary intention.

According to guidance on surgical site infections: prevention and treatment (CG74), surgical incisions should be covered with an appropriate interactive[1] dressing at the end of the operation using aseptic techniques. Wound cleaning should be done with sterile saline for up to 48 hours and cleaning with tap water afterwards and antibiotics should be used, if an SSI is suspected. Debridement can be used to remove the dead tissue if dead or infected tissues seem to be slowing down the healing process.

The sponsor highlights WHO guideline on the prevention of surgical site infections that conditionally recommend the use of prophylactic NPWT in adult patients on primarily closed surgical incisions in high-risk wounds, for the purpose of the prevention of SSI, while taking resources into account. The guideline provides examples of high-risk wounds such as poor tissue perfusion due to surrounding soft tissue/skin damage, decreased blood flow, bleeding/hematoma, dead space, and intraoperative contamination. The WHO notes that the evidence level for this recommendation is low. Due to the lack of evidence, no recommendations are made on the optimal level of pressure or duration of NPWT application. Finally, the guidance identifies blisters or maceration as possible side effects from the use of NPWT.

The sponsor outlines 2 World Union of Wound Healing Societies (WUWHS) Consensus documents. One describes the role of NPWT devices in closed surgical incisions, and provides a framework for risk stratifying patients. According with the guidance, the risk for surgical site complications is dependent on a large number of factors, patient-related and/or surgical procedure-related. Use of NPWT is recommended in patients with major patient-related factors[2] or in surgical procedures that have higher incidence and/or higher consequences of SSCs[3].

The second on improving prevention and outcomes on surgical wound dehiscence, describes the impact of surgical wound dehiscence. The sponsor mentions as part of this description that “PICO plays an important role in the prevention of SWD and is recommended for prophylactic use on patients where patient or surgical risk factors are present”, however the EAC could not find specific recommendations for PICO in this document. The document does describe the WHO recommendation (as above), and recent recommendations

[1] An interactive dressing is defined as a modern (post-1980) dressing material. Designed to promote the wound healing process through the creation and maintenance of a local, warm, moist environment underneath the chosen dressing, when left in place for a period indicated through a continuous assessment process.
[2] BMI≥40 kg/m^2 or ≤18 kg/m^2, uncontrolled insulin-dependent diabetes mellitus, renal dialysis.
[3] Table 5, page 13 of the guidance.

on the use of NPWT that state that NPWT should be used only as an adjunctive treatment in the management of wound infection. The document states that NPWT is particularly suitable for highly exuding, deep, or complex dehisced wounds. In relation to closed wounds specifically, the document notes that the use of NPWT over closed surgical incisions has been shown to reduce rates of SSI, seroma/haematoma and dehiscence, and to improve scar quality.

In the UK, PHE has reported in the annual audit on surveillance of SSIs in the NHS that main risk factors associated with high-risk for SSIs are age (>65 years), ASA score (≥3), duration of operation (>75th percentile), BMI (≥30), revision orthopaedic surgery.

According to the clinical experts, in the UK, guidance on the management of closed surgical incisions is provided by the above outlined guidelines, however, there is local variations especially about categorising patients as high-risk or the frequency of dressing change. For example, one expert advisor noted that Trusts have local policies that can vary for each specialty, for example, their Trust uses established risk factors as used by PHE to assign risk to patients. For their local audit the risk factors and grading system was taken from Stannard (2009).

2.2 Critique of company's definition of the decision problem

Table 1: Critique of the decision problem

Decision problem	Company submission	Matches decision problem? (Y/N/partially)	EAC comment
Population	Scope: "Patients having closed surgical incisions with low to moderate levels of exudate who are considered to be at high risk of developing a surgical site complication particularly SSI and dehiscence" Submission: The submission included 28 studies from different surgical specialities as follows: • 5 breast surgery studies • 2 cardiothoracic surgery studies • 4 studies on people undergoing colorectal surgery	Partially	Most of the evidence submitted meets the definition of a high-risk population for developing SSCs as defined by the WUWHS consensus document. However, the definition of a high-risk population varies not only at a national level in the UK but also locally on an NHS Trust level (please see section 2). However, in 8 of the included studies the presence of 1 or more risk factors constitutes part of the exclusion criteria (Adogwa 2014, Chaboyer 2014, Dingemans 2018, Galiano 2018a, Karlakki 2016, O'Leary 2016, Tanaydin 2018, Uchino 2016). Only one study (Tan 2017) reported the use of an objective assessment of pre-surgical estimation of SSI risk, ensuring that a 100% representative population was included.

	• 5 studies on people undergoing obstetrics surgery • 7 orthopaedic surgery • 1 study on each of the following ileostomy, laparotomy, lower limp bypass, and inguinal vascular surgery. All the included studies were on an adult population. The most relevant study(s) to the UK practice are the 5 studies conducted in a UK setting (Hackney 2017, Hester 2015, Holt 2015, Irwin 2018, Karlakki 2016).		
Intervention	Scope: 'PICO single-use negative pressure wound therapy system'' Submission: All included evidence used the PICO NPWT system.	Partially	There are 3 CE marked versions of PICO. The newest versions PICO 7 and PICO 7Y were CE marked in 2018 and none of the included evidence has used them. The 7 and 7Y versions also include a system change indicator so that dressing is not changed unnecessarily. It is not known how this may impact the frequency of changing the dressing in comparison with the evidence included in this report.

			All of the evidence included are for the prophylactic use of PICO and not for the therapeutic intent. The sponsor provided proof of CE marking compliance according with the Medical Device Regulation.
Comparator(s)	Scope: 'Conventional post-surgical wound dressings' Submission: All of the included evidence were comparative evidence. The majority of the evidence did not record the comparator used and reported it as standard care or conventional dressing. From the 4 studies that named the comparator dressing, 2 used Comfeel Plus, 1 used Mepore, and 1 used Vitri Pad.	Yes	Four of the studies (Galiano 2018a, Holt 2015, Tanaydin 2018, Svensson-Bjork 2018), used within patient comparison. Seven studies used a historic control as the comparator (Adogwa 2014, Dingemans 2018, Hester 2015, Hickson 2015, Kawakita 2018, Matsumoto 2015, Van der Valk 2017). Nine studies were comparative non-randomised (Caswell 2015, Fleming 2018, Hackney 2017, Pellino 2014a, Pellino 2014b, Selvaggi 2014, Irwin 2018, Selvaggi 2014, Tan 2017,) and 11 were standard randomised controlled trials (Chaboyer 2014, Gillespie 2015, Karlakki 2016, Luciani 2016, Nordmeyer 2016, O'Leary 2016, Stannard unpublished, Tuuli 2017, Uchino 2016, Witt 2015, Zotes 2015).

Outcomes	Scope: "The outcome measures to consider include: – rate of post-surgical wound complications (SSI, dehiscence, seroma, hematoma, delayed healing and abnormal scarring) – length of hospital stay as a result of surgical complications – time to heal – number of dressing changes – staff time to apply device – amount of wound exudate – rates of re-operation for wound complications – ease of use of the device by the patient – device-related adverse events	Yes	The most common primary outcome was SSI (13 studies), followed by SSCs (11 studies). One study looked at scar quality (Svensson 2018), 1 study time to wound healing (Uchino 2016), 1 length of stay (Karlakki 2016), 1 exudate volume (Nordemeyer 2016), 1 dehiscence (Holt 2015), 1 pain (Luciani 2016), and 1 wound healing (Witt 2015). There was variation in the definitions of SSIs (mostly on the follow-up time for reporting) and most studies did not report adequate information of how the outcomes were measured (if for example it was based on clinical judgement only or based on international criteria). Three RCTs (Chaboyer 2014, Gillespie 2015, Hyldig 2018a) and 4 observational studies (Dingemans 2018, Kawakita 2018, Matsumoto 2015, Pellino 2013) reported deep and superficial SSIs separately. The studies reported a variety of secondary outcomes, including ease of use, time taken to apply the devise and measuring the quantity of wound exudate.

	Details on outcomes reported from each study were included in table B9 for both the published and unpublished evidence.		
Cost analysis	Scope: Comparator(s): Costs will be considered from an NHS and personal social services perspective. Hospital and community settings should be considered. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	Partially	The analysis has been undertaken from an NHS and personal social services perspective. The time horizon is sufficient and appropriate sensitivity analysis has been undertaken in general. However, the sponsor has not addressed uncertainty in the number of PICO devices used per patient.
Subgroups	– individual surgical specialities* – wounds with low to moderate exudate – hard to heal wounds	Partially	The majority of studies did not include subgroup analyses. Selvaggi 2014 reported a subgroup analysis of patients receiving steroids at surgery. In addition, Pellino 2014a reported a subgroup analysis of patients over 65 years. Both analyses were post-hoc and not adequately powered. Galiano 2018a stratified their results on dehiscence based on BMI and reported that PICO performed

	* including but not limited to obstetric, colorectal, abdominal, orthopaedic, cardiothoracic, gynaecology etc. The submission included the following studies for each specialty: breast surgery, cardiothoracic surgery, colorectal surgery, obstetrics surgery, orthopaedic surgery, ileostomy, laparotomy, lower limp bypass, and inguinal vascular surgery (for more information see the Population section above).		better with increasing BMI. Karlakki 2016 included patients that had undergone either a total knee or a total hip arthroplasty. There were no studies providing subgroup analyses based on the level of exudate or on hard to heal wounds. The sponsor did not address the latter as the focus of the submission was closed surgical wounds.

Special considerations, including issues related to equality

The sponsor reports that the device may be of benefit to people with increased risk of surgical complications, however, no equality issues were identified in their submission (see section 6).

A number of population groups are identified by the scope as having potential special considerations for equality. More specifically, the scope reports that ‘’the device may be beneficial to women who have had obstetric, gynaecology and breast surgery. Certain ethnic groups are more prone to poor wound healing due to increased risk of diabetes or keloid formation. Older people are also more at risk of poor wound healing. Sex, race, and age are protected characteristics under the equality act 2010.’’

The EAC did not identify further equality issues.

3 Clinical evidence

3.1 Critique of and revisions to the company's search strategy

The EAC consider the sponsor's search strategy was too simple and that additional databases should have been searched. Using text from the studies included in the sponsor's submission the EAC employed text analysis software (http://textalyser.net/) to identify additional search terms.

The EAC devised a more sensitive strategy with additional free-text terms and keywords. As well as Embase, Cochrane (CDSR and CENTRAL) and PubMed, the EAC added Ovid Medline, Web of Science, CINAHL and grey literature sources. The searches were run so that only new records were uncovered by the new search strategy. Records were de-duplicated in EndNote X7.8.

The EAC's search located 11,346 records and following de-duplication 4847. Re-running the sponsor's search yielded 4133 records.

Following an initial review of the titles and abstracts of all the records by 3 independent reviewers, the EAC excluded 4797 records. The EAC reviewed the full-texts of 60 studies plus the 28 studies included by the sponsor. By re-running the sponsor's search, the EAC also identified 2 more eligible studies that were not included by the sponsor.

A PRISMA flow diagram and full details of the search strategies are included in Appendix A (Clinical evidence).

3.2 Critique of the company's study selection

The sponsor listed different inclusion and exclusion criteria for published and unpublished studies (tables B1 and B2 of sponsor's submission respectively). The sponsor's inclusion/exclusion criteria for published studies are listed in Table 2 below. The only difference in the criteria between published and unpublished evidence was the search dates set as studies published from 01/01/2011 to 01/08/2018 for the former and clinical trials registered on or after 01/01/2011 for the latter.

Although the sponsor's selection criteria states that the population is patients who were considered to be at high risk of developing a SSC their submission does not explicitly clarify what criteria were used to categorise the study populations as high-risk. In section 3.3 the sponsor states that *''Patients undergoing surgery should be risk stratified based on intrinsic patient factors such as high BMI, poor physical status (ASA score), Diabetes Mellitus. In addition to this a patient might also be considered to be at risk if they have emergency procedures, particularly relating to cardiac or colorectal surgery''*, however, it should be noted that there is significant variability between international and national guidelines with regards to the applied thresholds for most of these factors. For example the WUWHS criteria list as a major risk factor a BMI> 40 whilst the analysis of the PHE audit on SSI rates has been carried out using a BMI> 30.

Because of the above, the EAC requested from the sponsor to clarify how they defined high-risk populations in the included studies. More details were requested specifically for the following studies: Hackney 2017, Holt 2015, Irwin 2018, Matsumoto 2015, Pellino 2014a, and Tanaydin 2018. According to the sponsor, their search strategy captured studies that included high-risk patients. It also identified relevant studies where the underlying patient population had a large proportion of participants at high risk of wound complications, without having explicit inclusion/exclusion criteria to pre-select these patients. The sponsor provided further details for the above studies listed in Table 3. The EAC accepted the sponsor's reasons for including the studies by Hackney 2017, Holt 2015, Irwin 2018, Matsumoto 2015, Pellino 2014a, and Tanaydin 2018. The sponsor claimed that the inclusion of a proportion of patients without identifiable risk factors for SSCs in some of these studies would only dilute the positive benefit seen with PICO compared to conventional treatment. The EAC disagrees with this claim, it is currently unknown if the inclusion of a proportion of people without high risk factors will dilute or enhance the PICO safety or effectiveness profile. This is accepted as a limitation of the included evidence since all publications report summary statistics and not individual patient data.

The EAC considered the rest of the inclusion/exclusion criteria to be appropriate.

Table 2: Sponsor's inclusion/exclusion criteria for study selection

Inclusion criteria	
Population	*Patients having closed surgical incisions who were considered to be at high risk of developing a surgical site complication*
Interventions	*PICO single-use negative pressure wound therapy system*
Outcomes	*All clinical outcomes were considered but outcomes of particular interest were:* • *Surgical site infection* • *Dehiscence* • *Seroma* • *Haematoma* • *Delayed healing* • *Abnormal scarring* • *Skin/fat necrosis* • *Ease of use* • *Readmission rates* • *Reoperation rates* • *Length of hospital stay* • *Time to heal* • *Number of dressing changes* • *Staff time to apply* • *Amount of wound exudate* • *Adverse events*
Study design	*Comparative studies: randomised controlled trials or retrospective/prospective observational studies with at least 10 patients in each treatment arm*
Language restrictions	*English*
Search dates	*Studies published from 01/01/2011 to 01/08/2018*
Exclusion criteria	
Population	*Patients with open surgical incisions or any non-surgical wound*
Interventions	*Other forms of NPWT, such as traditional NPWT or non-disposable devices, were excluded*
Outcomes	*N/A*

Study design	*Non-comparative studies: case reports, case-series, studies with less than 10 patients in each treatment arm. Non-clinical studies: letters, commentaries, notes, reviews and editorials*
Language restrictions	*Not in English*
Search dates	*Studies published before 2011*

Table 3: Clinical risk factors deemed to place patients at higher risk for wound complications for studies highlighted.

Publication	**Clinical Risk Factors Deemed to Place a Patient at Higher Risk of Wound Complications**
Holt and Murphy 2015	• Oncological diagnosis requiring surgical intervention • Mean patient BMI >30 • The authors stated that they considered all these patients as being at high risk of complications
Matsumoto *et al* 2015	• Mean patient BMI >30 • The use of metal implants • A high proportion of patients had comorbidities • A high proportion of patients had a previous incision
Pellino *et al* 2014a	• Colorectal surgery • Long-time duration of surgery • Sub-analysis of older patients
Hackney *et al* 2017	• Colorectal surgery • All cases were open surgery • Some patients underwent emergency surgery
Tanaydin *et al* 2018	• Large length of incision • Large area of dissection/mass of dissection • Mean patient BMI > 25
Irwin *et al* 2018	• The use of implants

3.3 Included and excluded studies

Table 4: List of included studies identified by the sponsor and the EAC

Primary study number	Primary study reference	Sponsor inclusion	EAC inclusion	Reason for disagreement
1.	Adogwa 2014	Yes	Yes	NA
2.	Chaboyer 2014	Yes	Yes	NA
3.	Dingemans 2018	Yes	Yes	NA
4.	Fleming 2018	Yes	Yes	NA
5.	Galiano 2018a	Yes	Yes	NA
6.	Gillespie 2015	Yes	Yes	NA
7.	Hester 2015	Yes	Yes	NA
8.	Hickson 2015	Yes	Yes	NA
9.	Holt 2015	Yes	Yes	NA
10.	Hyldig 2018a	Yes	Yes	NA
11.	Karlakki 2016	Yes	Yes	NA
12.	Matsumoto 2015	Yes	Yes	NA
13.	Nordmeyer 2016	Yes	Yes	NA
14.	O'Leary 2016	Yes	Yes	NA
15.	Pellino 2014a	Yes	Yes	NA
16.	Pellino 2014b	Yes	Yes	NA
17.	Selvaggi 2014	Yes	Yes	NA
18.	Svensson 2018	Yes	Yes	NA
19.	Tan 2017	Yes	Yes	NA
20.	Tanaydin 2018	Yes	Yes	NA
21.	Uchino 2016	Yes	Yes	NA
22.	Van der Valk 2017	Yes	Yes	NA

23.	Witt 2015	Yes	Yes	NA
Conference abstracts				
24.	Hackney 2017	Yes	Yes	NA
25.	Irwin 2018	Yes	Yes	NA
26.	Kawakita 2018	Yes	Yes	NA
27.	Tuuli 2017	Yes	Yes	NA
28.	Zotes 2015	Yes	Yes	NA
29.	Luciani 2016	No	Yes	Retrieved by the EAC only
30.	Caswell 2015	No	Yes	Retrieved by the EAC only
Unpublished				
31.	Stannard unpublished - NCT02064270	Yes	Yes	NA

Included studies

The EAC included the following studies

RCTs (n=14)

Full text publications (n=11)

Chaboyer et al (2014) - ACTRN12612000171819

This pilot RCT compared PICO to standard dressing (Comfell Plus) in 92 elective caesarean section patients (randomised 1:1) in a single centre in Australia. Main risk factors were a pre-pregnancy BMI ≥30, and ASA score ≥2. Emergency procedures were excluded. The planned dressing change date was on day 4 post-operatively. Follow-up was 4 weeks for the primary outcome measure the rate of SSIs. Most of the baseline characteristics were similar between the two groups, with the exception of the length of surgery that was longer in the control group and this group had more smokers. SSI rates (superficial, deep or organ space) were not significantly different between the groups. In the PICO group, 36% women required at least 1 dressing change, as compared to 12% in the control group (p=0.006). Other wound complications, 28-day readmission rates, and length of stay were not significantly different between the groups.

Critical appraisal:

Patients were adequately randomised and although the study was non-blinded to clinicians and participants, SSI was assessed independently by someone blinded to the treatment allocation. The patient population was homogeneous and the treatment was consistent between the groups, suggesting a low risk of selection or performance bias. BMI was 36.8 in the PICO group and 35.7 in the standard dressing group; and 1 or more comorbidities in 69.8% and 68.2% respectively. A post hoc sample size calculation (using this study's SSI outcome, 22.7% vs. 27.9%) showed that 392 patients, per group, would be needed for the study to be adequately powered (alpha 0.05, beta 0.9); the small drop out of 5 patients and the lack of intention-to-treat analysis are irrelevant given the study is a pilot and under-powered. The follow-up may not have been long enough to detect deep SSIs (though superficial, deep and organ space all occurred). There were no conflicts of interest declared.

Gillespie et al (2015) - ACTRN12612000550808

This pilot open label, single-centre RCT compared PICO to a standard hydrocolloid dressing (Comfeel Plus) in 70 elective primary hip arthroplasty

patients, randomised 1:1 in a single centre in Australia. Main risk factors were BMI and ASA score. Patients were followed for 6 weeks, and the PICO dressing was changed on day 5 in most patients. The primary endpoint was the rate of SSIs. Overall, the mean age was 63.2-years (37 female patients) and follow-up was 6 weeks. There were no significant differences between the groups at baseline. There were no significant differences in SSIs or SSI indicator (swelling, erythema, purulence, leakage), although bleeding was significantly higher in the PICO group (8 vs. 1 patients, p=0.04), as were complications (24 vs. 15 patients, p=0.04), and patients requiring dressing change on or before day 5 (35 vs. 15 patients, p=0.0001).

Critical appraisal:

The study is non-blinded, however, SSIs were assessed by 2 independent clinicians: inter-rater reliability was measured for assessment of SSI (kappa of 0.48, moderate agreement). There is a risk of performance bias as the PICO group had their dressings changed to standard dressings prior to discharge, while the standard dressing group did not have their dressings changed at this point. The groups were well matched in terms of risk factors (PICO: mean BMI 29.9, ASA II-III 94.3%, 1-3 comorbidities in 77.1%; standard dressing: mean BMI 29.8, ASA II-III 94.3%, 1-3 comorbidities in 74.3%). The authors performed intention-to-treat analysis to allow for attrition bias. Two patients allocated to the PICO group ended up having standard dressings. There was no sample size calculation; 70 patients were recruited due to budget and time constraints. The 6-week follow-up period is likely to have been long enough to detect superficial SSI. There were no conflicts of interest declared.

Galiano 2018a

This open-label, multi-centre RCT compared PICO to standard dressing in 200 bilateral reduction mammoplasty patients in 6 centres in the USA (3), France, South Africa, and the Netherlands. Random allocation was applied within-patient (i.e. the left or right breast). Follow-up for the primary endpoint (SSCs: infection, dehiscence, or delayed healing[4]) was 21 days, 90 days for other complications and scar quality, and a subset of patients followed-up for scar quality only at 1-year postoperatively. At 21-days, wound complications were significantly lower in the PICO group (56.8% vs. 61.8%, p=0.004). The significant effect was maintained but reduced following sensitivity analysis to account for data completeness issues for delayed healing (39.7% vs. 44.7%, p=0.033). Dehiscence was also significantly lower (16.2% vs. 26.4%, p<0.001) though infection rates were not significantly different between the groups (2% vs. 3%). Nine patients developed skin necrosis (7 on standard

[4] Completely epithelialized wound at 7 days (10 days under sensitivity analysis).

dressing side only vs. 2 on both sides, p=0.008). Other complications and adverse events were not significantly different between the groups.

Critical appraisal:

Although a sample size calculation was done, 197 patients, only 185 reached the 21-day follow-up for the primary endpoint. However, the study did report a significant outcome. Randomising the treatment allocation within-patient may increase the chance of selection bias though the inclusion/exclusion criteria are well defined. Overall, BMI was ≥ 30 in 40.2% and 70.9% of patients were classified ASA I (normal healthy patient). The mean age was 35.7-years. Treatment was not consistent across all of the centres with one of the centres applying NPWT for a median of 14 days rather than 7 days as in all the other centres. However, the authors applied further sensitivity analysis for dehiscence (removed that centre's results) and the significant effect was maintained albeit reduced (14.7% vs. 24%, p=0.005). Additionally, the study was non-blinded so there is an increased risk of performance bias. The study promises but does not report outcomes on scar quality. The study received funding from the manufacturer.

Hyldig 2018a – NCT01890720

This study is a multicentre, open-label, RCT comparing PICO with standard dressing in 876 obese women (BMI ≥ 30) who had undergone an emergency or elective caesarean section in 5 hospitals in Denmark. Main risk factors were the type of surgery and BMI. The women were randomised 1:1 and had a follow-up appointment at day 5-6, when the PICO dressing was removed, and then followed up by postal questionnaire. The primary outcome was the rate of SSIs requiring treatment with antibiotics within 30 days of surgery. A total of 827 women responded to the questionnaire (response rate 94.4%). There were no significant differences between the groups at baseline. The incidence of SSI requiring antibiotics was significantly lower in the PICO group compared with the standard dressing group (4.6% vs. 9.2%, RR 0.50, 95%CI 0.3-0.84; p = 0.007). The incidence of deep SSI requiring surgery was similar between groups (1.9% vs. 2.0%, p value not reported). Wound exudate within 30 days of post-surgery was significantly lower in the PICO group (22.4% vs. 32.9%, RR 0.91, CI 0.55 to 0.86; p = 0.001). There was no significant difference between groups for minor wound dehiscence within 30 days post-surgery.

Critical appraisal

The study was not blinded and although the authors report that an independent data monitoring committee was involved, they do not report if

they ascertained the study outcomes. The primary outcome was defined as an SSI that occurred at the incision site within 30 days of caesarean section and treated with antibiotics. The secondary outcomes were self-reported and the patient's judgment may have introduced bias. There were some cases of non-adherence to the protocol (including BMI ≤ 30). Though the intervention was evaluated in young women (BMI ≥ 30) in good health, women with a BMI over who are undergoing a caesarean section may be at a greater risk of SSI (Anderson et al. 2013). The authors note that results may differ for other populations. The study was adequately powered for the primary outcome. The study was partially funded by the sponsor.

Karlakki 2016

This is a single centre, open-label, RCT comparing PICO with conventional dressing (Mepore or Tegaderm) in 209 people (intention to treat = 220) undergoing elective, routine primary hip and knee arthroplasties in a UK hospital. Main risk factors were ASA score, BMI, and age. People were randomised 1:1 and were followed up 6 weeks post-surgery at the hospital, with dressing change scheduled to occur on day 7. The primary outcome was wound healing and its effect on the length of stay (LOS). There were no significant differences between groups apart from patients with BMI >35 (17% in PICO group, 8% in control group). LOS was not statistically different between the 2 groups, however, there was a significant reduction in patients with extreme values of LOS in the PICO group (p = 0.003). There was a 4-fold reduction in reported post-operative surgical wound complications, though this was not significant (2.0% PICO vs. 8.4%; p = 0.06). Post-surgical exudate was significantly lower in the PICO groups compared with the standard dressing group (p = 0.007, Fisher's exact test). There were significantly fewer dressing changes (mean difference 1.7, CI 0.8 to 2.5, p = 0.002).

Critical appraisal

This is a UK study, which may mean that results are more relevant to the NHS. Due to the nature of the intervention, the study was unblinded. The study included people with a mean age over 65 years; age is a risk factor in SSI. There were twice as many people with BMI >35 in the PICO group as in the standard dressing group. The incidence of surgical wound complications was self-reported at a 2-week telephone check and the patient's judgment may have introduced bias. ITT population was used to analyse length of stay, but per protocol population was used to analyse wound complications as these outcomes could not be collected for people who dropped out of the study. The wound closure methodology was not standardised between surgeons. The study was adequately powered to detect a difference in LOS of

0.6 days, however, it is unclear if this was adequate for other outcomes. The study was partially funded by the sponsor.

Nordmeyer 2016

An open-label RCT comparing PICO with standard wound dressing in 20 people with large surgical wounds after surgical stabilisation of spinal fractures in Germany. The primary outcome was volume of exudate. Nursing time for wound care and number of dressings used were recorded. Duration of follow-up was 10 days and wounds were assessed at 5 and 10 days post-operatively. The volume of exudate was significantly higher at 5 and 10 days in the standard care group than that in the PICO group (day 5: 1.9ml vs. 0ml; p = 0.0007; day 10: 1.6ml versus 0.5ml; p <0.024). People in the standard care group required statistically significant more nursing time with wound care over 10 days (31±10 minutes vs. 13.8±6minutes; p = 0.0005) and more compresses (35± 15 vs. 11± 3; p =0.0376).

Critical appraisal

The study had a small sample size with no power calculation. There was no analysis of whether there was a significant difference in population characteristics between PICO and standard care, which may have led to bias. The mean age was higher in the standard care group than in the PICO group (57.8 vs. 52.3). Age is a risk factor in wound healing. Spinal fracture surgery may be classed as a high risk surgery as SSIs may be catastrophic to patient outcome.

O'Leary 2017

This open-label, single-centre RCT compared PICO with standard dressing in 50 people undergoing elective or emergency open abdominal surgery via laparotomy in Ireland. Randomisation was performed on a 1:1 basis. Main risk factors were BMI, ASA score and type of surgery. Patients were followed for 4 weeks, and the PICO dressing was changed on day 4 in most patients. No patients were reported as lost to follow-up, however, 1 patient in the PICO group had their dressing removed on postoperative day 2 and was excluded from data analysis. The primary outcome was the rate of SSIs at 30 days. Intention-to-treat and per protocol analyses performed for the primary outcome. There was a lower incidence of SSI in the PICO group than in the standard dressing group (per protocol: 2 [8.3%] vs. 8 [32%], p = 0.043 (1-sided), p = 0.074 (2-sided); intention-to-treat: 12% vs. 32%). Length of stay was significantly lower in the PICO group (6.1 vs 14.7 days, p = 0.019 [2-

sided]). Cosmetic outcome and patient satisfaction was similar between the 2 groups.

Critical appraisal

A power analysis was carried out indicating that a sample size of 50 was required to assess the difference in SSI rate at 30 days at 80% power. The intention-to-treat sample size was adequately powered. There was no statistical difference in any of the patient, surgery, or wound characteristics between the control and treatment groups. Confidence intervals for the data were not reported. Intention-to-treat and per protocol analyses were performed for the primary outcome but no ITT analysis was performed for secondary outcomes. The main risk factors were the procedure, BMI, the large wound area and a median ASA score of 2, however, the study excluded patients with major risk factors as per the WUWHS criteria such as ASA>3 and BMI>40. PICO dressings for the study were provided by the sponsor.

Tanaydin 2018

This open label RCT compared PICO, with fixation strips in 32 women who underwent bilateral breast reduction mammoplasty. Patients, randomised 1:1, were followed for 1 year in a single centre in the Netherlands. The patients served as their own control, with both breasts included in the study. The primary outcome was the rate of SSCs within 21 days post-surgery. The total number of wound complications was statistically significantly lower (p=0.004) for the PICO-treated breasts.

Critical appraisal

The patient population provide an opportunity for case-matched comparisons within-patient, and all patients received the same surgery on both sides. However, it is uncertain to what extent the included study population fit the profile of a high risk population. A post-hoc sample size calculation confirmed that the study was powered to detect a difference between NPWT and standard care for the secondary outcome (scar quality) but not for the rate of SSCs. The study was funded by the sponsor.

Svensson 2018

This open label, mutli-centre RCT compared PICO, with a standard dressing (Vitri Pad) in 34 people who underwent bilateral inguinal vascular surgery. Main risk factors were current smoking, presence of cardiovascular disease and a relative elderly population (median age 71.3). Patients, randomised 1:1, were followed for a median of 808 days, reported as time between surgery and photography. The primary endpoint was assessment of scar quality using

3 tools (SBSES objective measure, NRS10 overall scar quality, and PSAS subjective measure) post-operatively (no fixed time point was defined). Both the objective and subjective scar evaluations showed no statistically significant difference between PICO and standard dressing.

Critical appraisal

The patient population provide an opportunity for case-matched comparisons within patient, and all patients received the same surgery on both sides. However, in 21.9% of the patients, surgical dissection was more extensive on one side. The authors used both objective and subjective outcomes to evaluate their primary outcome that minimizes the chance of detection bias. However, no sample size calculation was reported. The study had a high attrition rate with only 44% of the patients included in final analysis after randomization. The authors attributed that to the rather long time interval between surgery and scar evaluation (approximately 2 years).

Uchino 2016

This open label, mutli-centre RCT compared PICO with standard dressing in 59 adults with ulcerative colitis scheduled to elective undergo ileostomy closure in Japan. Main risk factors were history of ulcerative colitis, and an ASA score of 2. Patients, randomised 1:1, were followed for 8 weeks. The primary endpoint was complete wound healing. There were no significant differences between the groups at baseline. There was no statistically significant difference for the mean duration of wound healing between the 2 groups (37.6 days in the PSS-alone and 33.5 in the PPS+PICO group).

Critical appraisal

A power analysis was carried out indicating that a sample size of 36 was required to detect a reduction of 10 days in the time to complete wound healing between the 2 cohorts at 80% power. However, the authors did not do an intention to treat analysis as the patients who developed SSI during the follow-up periods were excluded from prophylactic NPWT and from assessing the primary outcome. This approach introduces bias to the calculation and most likely results in an underpowered study. There was no statistical difference in any of the patient, surgery, or wound characteristics between the control and treatment groups. Confidence intervals for the data were not reported. The main risk factors were underlying diagnosis of ulcerative colitis, immunosuppression before or during the procedure and ASA score. However, although ostomy closure wounds are classified as a class 3 wound, this surgery was classified as small bowel surgery that had lower SSI risk than

colonic or rectal surgery. The authors do not report any conflicts of interest or funding from the sponsor.

Witt 2015

An open label, single-centre RCT compared PICO with conventional wound dressing in 80 people undergoing coronary artery bypass grafting surgery. Main risk factors were BMI> 30, ASA score 2, and prolonged surgery >2 h. Patients, randomised 1:1, were followed for 6 weeks postoperatively. The primary endpoint was wound healing defined as absence of SSCs post-operatively. The PICO dressing was applied for 6 days after surgery (the dressing was changed at day 2-3). Apart from age (people included in the PICO cohort were older, mean 66.2 vs. 62.1, p=0.044), there were no other statistically significant differences between the groups at baseline. The majority of procedures (85%) were elective. The PICO group achieved higher statistically significant wound healing rates (92.5% vs. 75%, p=0.34).

Critical appraisal

Although this was an RCT, the authors provided no information on randomisation. However, there were no major difference between the baseline characteristics of the 2 groups with the exception of age. A sample size calculation was not reported. Confidence intervals for the data were reported. The main risk factors were underlying the procedure and the presence of comorbidities or smoking status in some of the patients. The authors do not provide any information about any conflicts of interest or funding from the sponsor.

Conference abstracts (n=3)

Luciani 2016

This blinded RCT, evaluate the effectiveness of PICO treatment compared with standard treatment in hip or knee replacement revision surgery in 100 people with knee or hip prosthesis loosening in Italy. Main risk factor was the type of surgery (revision). People were randomised 1:1. Seven days after surgery a blinded evaluation of the wound healing process through the Asepsis Score (AS) was performed. The number of wound dressing changes and patient comfort and satisfaction levels were recorded. Wound healing was assessed during dressing changes. All people in the PICO group versus 90% of people in the standard care group (n=45) had satisfactory healing according to the AS scale. The PICO group had significantly fewer blisters (p= 0.048) and dressing changes (p < 0.001). The PICO group reported lower

mean pain level during dressing changes than the standard care group (mean reported numeric rating scale (NRS) pain level of 2.84 vs. 5.14).

Critical appraisal

This is an abstract so there is limited information about the study methodology, for example, there is no information on follow-up time. There is limited information on study population characteristics. No power calculation was reported. Wound assessment was blinded, which may have reduced bias. It is unclear what the standard treatment was and when dressing changes were carried out. Statistical analyses were not reported for healing scores or pain level scores.

Tuuli 2017 - NCT02578745

A pilot open label, single-centre RCT compared PICO with standard dressing in 120 women undergoing C-section in USA. Main risk factors were pregnancy, the type of surgery and BMI (>30). Patients, randomised 1:1, were followed for 30 days postoperatively. The primary endpoint was the rate of SSCs within 30 days of surgery. There were no significant differences between the groups at baseline. The majority of women had an elective cesarean section. There was no statistically significant difference for the rate of SSCs between the 2 groups (8.3% vs. 5.0%; RR 1.67, 95%CI 0.42-6.67; p=0.72).

Critical appraisal

This is an abstract so there is limited information about the study methodology, for example, there is no information on baseline patient characteristics, randomization method and follow-up time. The study included obese women undergoing C-section that constitutes a high-risk cohort. No power calculation was reported. However, the authors report that they performed intention to treat analysis. No information is provided by the authors about conflicts of interest or funding received by the sponsor.

Zotes 2015

A pilot open label, single-centre RCT compared PICO with traditional wound care in 20 people undergoing thoracotomy for empyema. Main risk factors were diabetes, nutritional status, steroids therapy, prolonged surgery >2 h. Patients, randomised 1:1, were followed for 10 days postoperatively. The primary endpoint was the rate of SSCs within 10 days of surgery. No information was provided for the baseline characteristics between the two groups at baseline. Although the SSC rate was higher in the PICO group (50% vs 10%), the difference was not statistically significant.

Critical appraisal

This is an abstract so there is limited information about the study methodology, for example, there is no information on baseline patient characteristics or randomization method. The study included people with diabetes, poor nutritional status, steroids therapy, and prolonged surgery >2 h, however, it is not clear in what percentage these risk factors were represented in the 2 groups. No power calculation was reported. No information is provided by the authors about conflicts of interest or funding received by the sponsor.

Non-randomised comparative studies (n=16)

Full-text publications (n=12)

Adogwa 2014

This retrospective before-after study compared PICO (46) to standard dressing (114) in 160 patients undergoing thoracolumbar fusion for spinal deformity at a single centre in the USA. Patient records were reviewed from 2007 to 2013; in 2012, the standard dressing was replaced by PICO. Follow-up was 30 days for the primary outcome measure, SSI, which were also measured alongside other wound complications at 90 days. There were no differences in the baseline characteristics between the 2 groups. SSI was statistically significant lower in the PICO group (10.63% vs. 14.91%, p=0.04) as was dehiscence (6.38% vs. 12.28%, p=0.02). Length of stay, 30-day readmissions, and return to operating theatre rates were not significantly different between the groups.

Critical appraisal:

The patient population was well chosen and homogeneous: the groups were well matched in terms of baseline demographic data and in postoperative surgery-related complications and the inclusion/exclusion criteria are explicit. Mean BMI was 28.44 in the PICO group and 28.64 in the standard dressing group; other risk factors are documented though the proportion of patients with more than one risk factor for SSI is unclear. Although some of the perioperative data was collected post hoc, patients were treated consistently across the two cohorts. Three months follow-up is likely to be long enough to detect deep SSIs. The authors do not report the use of an independent assessor for the primary outcome. There were no conflicts of interest declared.

Dingemans 2018 - NCT02739191

This pilot study compared 60 patients (PICO, prospectively recruited) with historical case-matched controls (standard dressing, retrospective) who had undergone primary or secondary surgery for foot or ankle fracture in a single centre in the Netherlands. Procedures with an incision of 3cm or greater were eligible for inclusion. The primary outcome measure was SSI and patients were assessed at 30 days post-operatively. Seven patients in the PICO group did not complete the study and were excluded from further analyses. Ultimately, 47 matched pairs were analysed. SSI rates (superficial and deep) were not significantly different between the groups.

Critical appraisal:

The authors estimated that 50 patients would be needed, but a post hoc sample size calculation (using this study's SSI outcome, 4.3% vs. 14.9%) showed that 236 patients would be needed for the study to be adequately powered (alpha 0.05, beta 0.8). Patients were case matched 1:1 (from 343 historic controls) on incision type, gender, age, smoking, diabetes, and SSI from previous surgery. The patient population was heterogeneous (both foot and ankle surgery and primary surgery as well as reoperations/revisions). However, the inclusion/exclusion criteria are explicit, but may have resulted in few to no patients at high risk of SSI. Follow-up of 30 days may not be long enough to detect deep SSI, although deep SSI occurred in 2 cases (both primary surgery). The authors were unable to find a match in the control cohort for 2 of the cases of superficial SSI. Additionally, the matching cohort of 343 controls was drawn from a period of 16 years (compared to 10 months for the PICO cohort), which makes valid comparisons hard to draw. The study received funding from the manufacturer.

Fleming 2018

This retrospective observational study compared PICO (73 patients) to standard dressing (78 patients) in 151 peripheral vascular surgery patients with groin wounds, treated in a single centre in Ireland. Main risk factors were age, smoking status and diabetes. Patient follow-up was 6 weeks for the primary endpoint, SSCs (seroma, infection, haematoma, and dehiscence). There were significantly more smokers in the PICO group (45.2% vs. 29.5%, p=0.034) and femoral endarterectomy cases (65.8% vs. 33.3%, p=0.001). Overall, there were significantly fewer wound complications in the PICO group (8.2% vs. 19.2%, p=0.042), although within this infection and dehiscence were not significantly different between the groups. Mean time to full resolution of

wound complications was significantly shorter in the PICO group (52 vs. 96 days, p=0.015).

Critical appraisal:

The patient population comprised a variety of peripheral arterial procedures on the lower limbs (femoral endarterectomy, iliofemoral bypass, femoro-femoral crossover bypass, and above and below knee femoro-popliteal bypass) and there were more smokers in the PICO group. The stated inclusion criteria and demographic data provided are not enough information to ascertain risk status for SSI (mean BMI was 27.011 in the PICO group and 26.76 in the standard dressing group; diabetes in 24.7% and 20.5%, respectively). Follow-up of 6 weeks is likely to be sufficient to detect superficial SSI. There were no conflicts of interest declared.

Hester 2015

This retrospective observational study compared PICO with a standard dressing in 36 patients (18 per group) undergoing revision arthroplasty (9 hip, 27 knee) in a single centre in the UK. Main risk factors were the nature of the procedure (revision surgery), age, BMI, and ASA score. The primary outcome measure was SSI requiring further surgery or antibiotics, and the follow-up was 6 weeks. Baseline characteristics were well matched with the exception of greater median ASA score (3) in the PICO group. Overall, wound complications were not significantly different between the groups (3 standard dressing vs. 1 PICO). With one exception, complications were seen in patients with BMI of 37-48.

Critical appraisal:

Although patient selection was not prospective, all patients were treated by the same surgeon in the same setting and the sample is relevant to the patient population. Median BMI was similar between the groups (PICO 30.2 and 2 respectively; standard dressing 30 and 3). Nine patients in the control group and 7 in the PICO group did not have any risk factors with the exception of undergoing revision surgery. Patients were selected from an one-year period during which the choice of dressing changed from standard to PICO. Follow-up is likely to be long enough to detect superficial SSI and dehiscence. The sample size is small and no sample size calculation was

done to indicate whether the study is sufficiently powered to detect differences in wound complications. There were no conflicts of interest declared.

Hickson 2015

This before-after observational study compared PICO (n=964) with various standard dressing protocols (n=984) over a 6-year period in low- and high-risk patients undergoing a caesarean section in a single-centre in the USA. Between 2011 and 2012 the only change to the dressing protocol was the addition of PICO in place of standard dressings, which was implemented for high-risk patients only (BMI >35, or 2 of diabetes, steroid use, autoimmune disease, haematological disorders, immunosuppressant medication, hypertension, multiple C-sections, history of wound infections, pre-existing skin problems, or emergent birth). Patient follow-up was 6-weeks. Primary endpoint was the rate of SSIs. Overall (low and high risk), SSIs decreased from 0.61% in 2011 (6 of 984) to 0.10% in 2012 (1 of 964).

Critical appraisal:

This study does not report demographic data for any period and there is minimal information on the comparable cohort periods (those treated in 2011 and 2012). The patient population is relevant and data is reported for all patients, with no inclusion/exclusion criteria reported. Follow-up was long enough to detect deep SSIs. The authors used the NHSN definition for SSI. The study reports a significant reduction in SSI rates from 2007 to 2012 (2.13% vs. 0.1%, $p<0.0001$) but there were numerous changes to the dressing protocol during that time.

Holt 2015

In this retrospective, single-centre, comparative study, PICO was compared to a standard dressing in 24 patients undergoing oncoplastic breast surgery (therapeutic mammoplasty or skin-sparing mastectomy followed by immediate reconstruction with implant), treated in the UK. All patients received a symmetrising reduction on the breast contralateral to the therapeutic surgery. Treatment allocation was divided within patient (PICO on the therapeutic side, standard dressing on the symmetrising side). Patients were assessed at 6- (removal of PICO dressing) and 12-days postoperatively and followed-up until healing was complete. The primary endpoint was dehiscence. Overall, dehiscence occurred in 1 (4.2%) therapeutic breast (PICO) versus 4 (16.7%) symmetrising (standard dressing). One patient suffered delayed healing on both breasts which healed by day 18 on the therapeutic side but not until day

28 on the symmetrising side. Mean time to healing was shorter on the therapeutic (PICO) side (10.7 vs. 16.1 days).

Critical appraisal:

The patient population provide an opportunity for case-matched comparisons within-patient, but the treatment received on each breast was different. Additionally, the symmetrising side was tumour free in all cases, which limits the validity of comparisons. The patient population is otherwise coherent. Eleven of the 24 patients had a BMI ≥30 meaning these patients had an increased risk of developing SSI. Patients were followed-up until complete healing occurred and the authors do not report on the occurrence of SSIs. Statistical analysis is very limited with no significance values reported. The small sample size and heterogeneous cohort severely limit the transferability and generalisability of these outcomes.

Matsumoto 2015

A retrospective, before and after, observational, single-centre study comparing PICO with standard dressing (Tefla gauze and ABD pads) in 74 people who had undergone total ankle arthroplasty in a US hospital. Main risk factor is BMI> 30. Patients were followed-up at 1 week (when the dressing was removed), at 3 weeks, and every 4 weeks thereafter if they presented with complications (total follow-up time unknown). The primary outcome was SSCs as defined by the Centers for Disease Control and Prevention[5]. The secondary outcome was the rates of SSIs. There were no significant differences between the study groups. There were statistically significant fewer SSCs in the PICO group than the standard dressing group (1/37 [3%] vs. 9/37 [24%], p = 0.014). Multivariate analysis showed that the application of PICO was an independent predictor of not developing wound healing problem (odds ratio [OR], 0.10; CI 0.01-0.50; p = 0.004). An infection was found in 3 (8%) of 37 patients in the control group, and 1 (3%) of 37 patients in the iNPWT group (deep infection); the difference was not significant (p = 0.615).

Critical appraisal

The study was based on a retrospective survey comparing PICO with a historical cohort. To minimise selection bias, the authors used consecutive sampling for both groups. All procedures in this study were performed by one

[5] In brief, an infection occurring within 30 days after the surgery must be associated with at least 1 of the following: (1) purulent drainage from the incision; (2) organisms isolated from an aseptically obtained culture from the incisional fluid or tissue; (3) at least 1 of the following signs or symptoms: pain or tenderness, erythema, localised swelling, heat, superficial incision that is deliberately opened by surgeon, unless culture of incision is negative; or (4) a diagnosis of SSI by an attending clinician.

surgeon which would have controlled for differences in practises between surgeons. A power analysis carried out by the study authors indicated that 434 patients would be necessary for each group to detect a significant effect of PICO on infection. The study was not adequately powered to detect a difference in the reported outcomes.

Pellino 2014a

A prospective, open-label, controlled study comparing PICO with standard dressing in 100 people undergoing surgery with primary wound closure for breast (n=50: 25 PICO and 25 standard dressing) and colorectal diseases (n=50: 25 PICO and 25 standard dressing) in Italy. The primary outcome was the rate of SSIs. The dressing was changed on day 7, total follow-up was 3 months, and SSIs were evaluated on postoperative-days 3, 7 and 30. Main baseline characteristics were similar in the 2 groups. There was a significantly lower incidence of SSI in the PICO group compared with standard dressings in both breast and colorectal groups. Overall, similar benefits were observed in breast and colorectal patients. A subgroup analysis of patients over 65 years showed the rates of SSI were much lower with PICO, compared with younger patients, irrespective of the type of surgery.

Critical appraisal

It is unclear if there was randomisation to study group, but there were no significant differences between groups according to age, BMI, comorbidities, and ASA but only a minority of patients had these risk factors. There were no patients lost to follow-up. There was no power calculation to assess the adequacy of sample size. The main risk factor in the study was the subgroup of patients over 65 years.

Pellino 2014b

A prospective, non-randomised, controlled study to compare PICO (n=13) with standard dressing (n=17) in 30 people with Crohn's disease undergoing small bowel resection or strictureplasty. Main risk factors were ASA score, immunosuppression, and smoking status. SSI and SSCs were evaluated on postoperative days 3, 7 (scheduled to remove the dressing), and 30, and cosmetic results at 3 months follow-up. The primary outcome measure was incidence of SSI and SSCs. Study group allocation was based on patient ability and willingness to manage PICO. People in the PICO group experienced significantly fewer postoperative wound complications ($p = 0.001$) and SSIs ($p = 0.017$) compared with the standard dressing group. This resulted in shorter hospital stay ($p = 0.0007$). No significant differences in cosmetic results were found.

Critical appraisal

This study lacks randomisation and study group allocation was based on patient ability and willingness to manage PICO which may introduce selection bias. Despite this, there were no significant differences in characteristics between study groups. A power calculation was carried out indicating that 12 people were needed to detect a reduction of 50% in SSI rates with a power of 80%. Though the sample size is small, this would indicate the study was adequately powered for this outcome. The main risk factors were median ASA of 2, surgical procedure and steroid use for a chronic disease, however fewer than 50% of the study population were taking corticosteroids at time of surgery. PICO devices for the study were bought with funding from the sponsor.

Selvaggi 2014

A prospective, open-label, controlled study compared PICO with standard dressing in adults with Crohn's disease undergoing abdominal surgery. Main risk factors were the presence of Crohn's disease, smoking status, corticosteroids and ASA score 2-3. Twenty-five people were treated with PICO and 25 with the standard dressing. Patients were followed for 12 months postoperatively. The primary endpoint was the rate of SSCs. Patients treated with PICO had less SSC rates (OR 0.21, 95%CI 0.15-0.5, p=0.001) resulting in shorter hospital stay. At last follow-up, readmission rates were lower with PICO.

Critical appraisal

This study does not report randomisation and no information is provided on how patients were allocated to the 2 groups and it may therefore be subject to selection bias. Despite this, there were no significant differences in characteristics between study groups. No sample size calculation was reported. The main risk factors were the surgical procedure and the use of immunosuppression, however, it is not clear if the majority of the patients were taking immunosuppression at time of surgery. The authors did not report the source of funding for this study.

Van der Valk 2017

A single-centre, before-after study comparing PICO with a historical cohort that used conventional wound care in people undergoing abdominoperineal resection for rectal cancer. Main risk factors were the presence of neoadjuvant treatment such radiotherapy and chemotherapy, age, and ASA score. Ten people were treated with PICO and 10 with the conventional dressing. Patients were followed for a maximum of 34 weeks in the PICO

group and 24 weeks in the control group. Primary endpoint was the incidence of SSCs. At baseline, more patients in the PICO group had cardiovascular comorbidity and were current smokers. No statistically significant difference in the SSCs between the two groups was noted (70% vs. 60%, 95%CI not reported, p value not reported).

Critical appraisal

This study is subject to selection and performance bias as it is a before-after historical control comparison. There was an imbalance in terms of smoking and cardiovascular disease co-morbidity between the 2 groups in favour of the control group. No sample size calculation was reported. The authors do not any conflicts of interest or funding received by the sponsor for this study.

Tan 2017

A retrospective, single-centre study comparing PICO (n=14) with standard dressing (OpSite) n=28 in people undergoing lower limb bypass in Singapore. Main risk factors were emergency procedure, age, and ASA score. All patients had their SSI risk calculated using an independent risk classification system. Patients were followed for a maximum of 30 days. No information was provided for the duration of the wound dressing application. Primary endpoint was the rate of SSIs and the need for subsequent surgical debridement. There were no significant differences between the groups at baseline. Patients treated with PICO had 0% SSIs vs. 32% at the control group (p=0.019).

Critical appraisal

This study is subject to selection bias as the decision to use conventional wound therapy or NPWT depended on the surgeon's preference. Despite this, there were no significant differences in characteristics between study groups. No sample size calculation was reported. This is the only study that reports using an objective assessment of pre-surgical estimation of SSI risk, ensuring that a representative population was included. The authors do not any conflicts of interest or funding received by the sponsor for this study.

Abstracts (n=4)

Caswell 2015

This before-after observational study compared PICO to standard dressing in 221 patients undergoing emergency laparotomy for large bowel surgery. Standard dressing data was retrospectively gathered in 2013 (119 patients) and PICO data was gathered prospectively in 2014 (102 patients, of whom 27

actually received PICO). All patients were at high risk of wound complications (age >70-yrs, BMI>35, emergency operation, diabetes, immunosuppression or immune-comprised, consultant-based decision). Primary endpoint was the rate of SSIs and the authors estimated a 50% reduction with the use of PICO. Baseline characteristics between the 2 cohorts were not reported. There was a 75% relative reduction in the SSIs (incisional and deep) in the PICO period (1.96% vs. 7.69%, p=0.049), although in the PICO-only cohort SSI occurred in 3.7% (1 of 27 patients).

Critical appraisal:

This poster presentation presents some demographic data, but there is no analysis of whether or not the groups were well matched. The authors state that all patients were at high risk of developing wound complications and list the inclusion criteria, though it is unclear how many of these factors would constitute 'high risk'; all patients underwent emergency surgery implying high risk in all cases anyway. The authors present a significant reduction in SSIs between the cohorts though in fact in the "PICO" cohort only 27 (of 102) patients actually received PICO. Follow-up time is not reported.

Hackney 2017

This retrospective single-centre, observational study compared PICO (n=39) to a control group (n=32) in 71 patients undergoing emergency and elective open abdominal surgery in the UK. Wound complications, readmissions, and length of stay were not significantly different between the groups.

Critical appraisal:

This conference abstract presents limited data on the patient population with neither demographic data nor surgery or disease information reported. Inclusion criteria are not reported, although the inclusion of both emergency and elective surgery could increase the generalisability of the outcomes. A sample size calculation was not reported. Although the reported outcomes were not statistically significant, the authors highlight the fact that wound complications were reduced by 50% in the PICO group (7.6% vs. 15.6%) and suggested that a larger sample size may lead to a clearer outcome.

Irwin 2018

A prospective, single-centre, controlled audit comparing PICO (n=102) with standard care (n=152) in 254 breasts of 155 people undergoing implant-based breast reconstruction surgery in the UK. ASA classification, weight, or comorbidities were not significantly different between the groups. Dehiscence occurred in 9 people in the standard dressing group compared with no incidences in the PICO group. This difference was significant for wound dehiscence ($p = 0.01$).

Critical appraisal

This is a UK study, which may mean that results are more relevant to the NHS. The study did not explain why some patients received the PICO dressing and other received standard dressings. As this is an abstract, there was limited detail about the study methodology, for example patient randomisation and follow-up. Confidence intervals were not reported. There is limited information on study population characteristics.

Kawakita 2018

A retrospective, single-centre, cohort study comparing PICO with standard care in 759 women (BMI ≥ 40) who had undergone a caesarean section (167 women in PICO group) in the US. The primary outcome was the rate of SSCs. Using adjusted odds ratios, no difference was found between PICO and standard care for risk of SSCs, endometritis before or after discharge, deep wound infection, other severe infection, cellulitis, and haematoma/seroma or wound dehiscence.

Critical appraisal

The abstract did not report the allocation process and is therefore subject to selection bias. The PICO group was much smaller than the standard dressing group which may have allowed for bias. The follow up period was not stated. Scoring methods and timing of assessments were not recorded. The main risk factors are the interaction of the procedure and the study population (women BMI > 40). Tables 5, 6, 7, and 8 below provide detailed information on the patient and procedure characteristics and methodology for each of the included studies.

Table 5: Patient and procedure characteristics of included full-text RCTs

STUDY	Chaboyer 2014	Galiano 2018a	Tanaydin 2018	Gillespie 2015	Svensson 2018	Uchino 2016	Hyldig 2018a	Karlakki 2016	Nordmeyer 2016	O'Leary 2017	Witt 2015
Surgery	**C-section**	**Reduction mammoplasty**	**Reduction mammoplasty**	**Primary hip arthroplasty**	**Inguinal vascular surgery**	**Ileo-stomy closure**	**C-section**	**Hip or knee arthro-plasty**	**Spinal fracture stabili-sation**	**Laparo-tomy**	**CABG**
Patients	87	185	32	70	68	59	827	220	20	50	80
Mean age (years)	30.6	35.7	40.9	63.2	71.3	48.1	32	69	PICO 52.3; standard dressing 57.8	PICO 58; standard dressing 63	64.2
Male patients %	0.0	0.0	0.0	52.8	81.8	29.6	0.0	49.30	NR	27	78.8
Mean BMI (kg/m^2)	36.2	30	26.5	29.9	24.4/27.5	20	34.7†	30.1†	NR	35% with BMI ≥ 30*	29.2
Diabetic %	28.7	3.0	0	NR	24.2	NR	17.80	8.10	NR	12.20	25
Smoking %	14.9	5.0	6.25	NR	33.3	0.0	7.60	22	NR	18.40	33.8
ASA status	NR	I (70.9), II (25.6), III (3.5)	NR	I (5.7), II (55.7), III (38.6)	NR	II (95) III (5)	NR	I (22.5), II (62.2), III (10.5)	NR	Median 2	NR
Antibiotics during or post-surgery %	NR	NR**	NR	NR	NR	100.0	PICO 4.6 vs. standard dressing 9.2	100	NR	100	100
Emergent case %	0.0	0.0	0	0.0	0.0	0.0	47	0.00	NR	NR	15

STUDY	Chaboyer 2014	Galiano 2018a	Tanaydin 2018	Gillespie 2015	Svensson 2018	Uchino 2016	Hyldig 2018a	Karlakki 2016	Nordmeyer 2016	O'Leary 2017	Witt 2015
Surgeons involved	NR	NR	NR	NR	NR	NR	2	3	NR	4	NR
When overall mean was not reported results from the intervention cohort only were used †results from intervention cohort, overall not reported *mean not reported											

Table 6: Patient and procedure characteristics of included full-text observational studies

STUDY	Selvaggi 2014	Tan 2017	Van der Valk 2017	Dingemans 2018	Fleming 2018	Hester 2015	Hickson 2015	Holt 2015	Adogwa 2014	Matsumoto 2015	Pellino 2014a	Pellino 2014b
Surgery:	**Laparotomy Laparoscopy**	**Lower limb bypass**	**Laparoscopic abdominoperineal resection**	**Lower extremity fracture**	**Peripheral vascular**	**Revision hip or knee arthroplasty**	**C-section**	**Oncoplastic breast**	**Thoracolumbar spine**	**Ankle arthro-plasty**	**Breast or colorectal surgery**	**Crohn's disease stricturing (laparotomy)**
Patients	50	42	20	53	151	36	1948	24	160	74	100 (breast n = 50, colorectal n = 50)	30
Mean age (years)	36	66	65.4	43.1	70.8	72	28	55.8	63.87	58	Four groups, mean age range 49.7 to 52	32.3**

STUDY	Selvaggi 2014	Tan 2017	Van der Valk 2017	Dingemans 2018	Fleming 2018	Hester 2015	Hickson 2015	Holt 2015	Adogwa 2014	Matsumoto 2015	Pellino 2014a	Pellino 2014b
Male patients %	56.0	67.0	60.0	75.0	NR	55.5	0.0	0.0	29.6	48.60	Breast 0, colorectal 44	40
Mean BMI (kg/m^2)	24	NR	26.46	24.5	26.88	30.1	35	31.1	28.58	30.1**	Four groups, mean BMI range 21.2 to 22.7	23.4**
Diabetic %	16.0	93.0	NR	0.0	21.1	5.5	NR	NR	17.3	5.10	18	16.70
Smoking %	56.0	57.0	20.0	44.0	37.1	2.7	NR	4.1	NR	9.10	NR	56.70
ASA status	III (12%)	NR	II (median)	I (76%), II (19%), III (5%)	NR	(Median) III in control, II in PICO	NR	NR	NR	NR	13% (≥2)	I (33.3%), II (53.3%), III (13.3%)
Antibiotics during or post-surgery %	100.0%	100.0%	100.0%	7.5%	13.9%	100.0 %	NR	NR	100.0 %	100.00%	100.00%	100.00%
Emergent case %	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	NR	0.0%	0.0%	0.00%	NR	NR
Surgeons involved	NR	NR	NR	NR	2	1	NR	1	NR	1	NR	1 and 4***

** results from intervention group (overall not reported)
*** 1 surgeon carried out the surgeries, 4 surgeons applied or supervised the application of PICO

Table 7: Patient and procedure characteristics of included conference abstracts

STUDY	Caswell 2015‡	Hackney 2017	Zotes 2015	Tuuli 2017	Irwin 2018	Kawakita 2018	Luciani 2016
Surgery	**Laparotomy**	**Open abdominal**	**Thoracotomy**	**C-section**	**Breast reconstruction**	**C-section**	**Hip and knee revision**
Patients	27	71	20	120	155*	759	100 (knee n = 50, hip n = 50)
Mean age (years)	67.4	NR	47	NR	NR	NR	NR
Male patients %	48.1%	NR	75.0%	0.0%	NR	NR	NR
Mean BMI (kg/m^2)	25	NR	NR	NR†	NR	All BMI≥40	NR
Diabetic %	NR	NR	NR	NR	NR	NR	NR
Smoking %	NR	NR	NR	NR	NR	NR	NR
ASA status	I (7.4%), II (37%), III (14.8%), IV (40.7%)	NR	NR	NR	NR	NR	NR
Antibiotics during or post-surgery %	NR	NR	NR	NR	NR	NR	NR
Emergent case %	100.0%	NR	NR	NR	NR	NR	NR
Surgeons involved	NR	NR	NR	NR	NR	NR	NR

Table 8: Methodological characteristics of included studies

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Adogwa 2014	Retrospective, before-after, single-centre, observational study. PICO or standard dressing (control). All patients received antibiotics following surgery. ●	USA. 160 patients undergoing thoracolumbar fusion for spinal deformity (46 PICO and 114 standard dressing) Included: patients aged over 18, multilevel (more than four vertebral levels) posterior spinal fusion using pedicle screws and rod instrumentation. Excluded: history of infections at surgical site, severe coexistent pathology, history of immunosuppression or chronic systemic infection, and pregnancy. ●	30- and 90-day follow-up for wound dehiscence, SSI, length of stay, 30-day readmission, return to operating theatre rates ●	Wound dehiscence: PICO 6.38% vs. control 12.28% (p=0.02) SSI: PICO 10.63% vs. control 14.91% (p=0.04) Other outcomes not significantly different between the groups.	None reported.	Methodological quality is acceptable for an observational study. Majority of the patient population are not likely to be high risk for SSI. PICO superior to standard dressing in the primary outcome measures (dehiscence and SSI).
Caswell 2015	Retrospective, before-after, single-centre,	UK. 221 patients undergoing laparotomy for large bowel surgery (119 in control cohort vs.102 in	SSI (incisional and deep) ●	SSI: PICO 3.7% vs. control 7.69%.	None reported.	Poster presentation with limited reporting of a number of key variables. Patients are

	observational study. PICO or standard dressing (control). ●	study cohort, of whom 27 had PICO). Included: patients aged over 70, BMI>35, emergency operation, diabetes, immunosuppression or immunocompromised, or consultant-based decision. ●				described as being high risk for SSI. The poster reports a p-value for the comparison between the cohorts but not between PICO and standard dressing.
Chaboyer 2014	Pilot RCT, single centre. PICO or standard dressing (control). ●	Australia. 92 elective C-section patients (randomised 1:1). Included: pre-pregnancy BMI≥30, Excluded: emergency procedures. ●	SSI (incisional, deep and organ-space), dehiscence, haematoma, bleeding, seroma, blisters, length of stay, 28-day readmissions. ●	Outcomes were not significantly different between the groups.	5 patients, excluded from final analyses.	Methodological quality is acceptable for a pilot RCT. Post-hoc power calculation showed that 392 patients per group would be needed to show a significant outcome at this effect size (alpha 0.05, beta 0.9).
Dingemans 2018	Pilot before-after study, single centre. PICO (prospective) or standard dressing (retrospective control).	Netherlands. (60 patients) 47 matched pairs of foot or ankle fracture patients (primary or secondary surgery). Included: procedures with incision of ≥3cm.	SSI (superficial and deep), dehiscence/delayed closure without infection, patient satisfaction with PICO. ●	Outcomes were not significantly different between the groups.	13 patients not matched to historical control	The study is methodologically weak and numerous variables are not reported. The inclusion/exclusion criteria mean that the patient population is unlikely to be high risk for SSI.

		Excluded: percutaneous surgery, open fractures or active infections, concomitant antibiotics, immunodeficiency. 				Post-hoc power calculation showed that 236 patients would be needed to show a significant outcome at this effect size (alpha 0.05, beta 0.8).
Fleming 2018	Retrospective observational study, single centre. PICO or standard dressing (control). 	Ireland. 151 peripheral vascular surgery patients with groin wounds (73 PICO, 78 control). Included: patients aged over 18. 	Wound complications (seroma, infection, haematoma, or dehiscence). Requirement for antibiotic therapy, readmissions, length of stay, and time to resolution of wound complications. 	Wound complications: PICO 8.2% vs. control 19.2% (p=0.042); infection and dehiscence were not significantly different between the groups. Resolution of wound complications: PICO 52 days vs. control 96 days (p=0.015).	Not reported.	Methodological quality is acceptable for an observational study. Although there is not enough information to ascertain risk factors for SSI it is likely that a minority were high risk.
Galiano 2018a	Multi-centre open label RCT. PICO or standard dressing (control). 	USA (3), France, South Africa, and the Netherlands. 200 reduction mammoplasty patients recruited (randomised 1:1, within-patient) Included: patients age over 18, bilateral reductions with similar incision lengths on each breast.	Healing complications (infection (superficial or deep), dehiscence, delayed healing). Postsurgical complications: skin necrosis, nipple, and areola necrosis, cellulitis, abscess, suture abscess, or	Healing complications: PICO 56.8%, control 61.8% (p=0.004); dehiscence: PICO 16.2% control 26.4% (p<0.001). Skin necrosis: PICO 2, control 7 (p=0.008). Other outcomes were not significantly	15 patients withdrew and were excluded from analyses.	Study was powered at 197 patients, but only 185 completed the study. However, a significant outcome was found. Treatment was not consistent across all centres, but sensitivity analysis was applied to account for this and the significant effect size pertained.

		Excluded: pregnancy or lactation, steroids or immunomodulators, history of radiation therapy, tattoos, skin conditions, history of scar problems. Post-surgical active bleeding, incisions >30cm. 	hematoma occurring within 21, 42, and 90 days postoperatively. 	different between the groups.		The majority of the patient population is unlikely to be high risk for SSI.
Gillespie 2015	Pilot open label RCT, single centre. PICO or standard dressing (control). 	Australia. 70 elective primary hip arthroplasty patient (randomised 1:1). Majority (94.3%) were ASA grade II-III. Included: patients aged 18 or over. Excluded: existing infection. 	SSI (superficial, deep, organ space). Individual SSI indicators (erythema, swelling, leakage, purulence), wound complications (dehiscence, haematoma, seroma, bleeding), dressing replaced before day 5, length of stay, and readmissions. 	Bleeding: PICO 8 patients, control 1 (p=0.04). Complications: PICO 24 patients, control 15 (p=0.04). Dressing replaced before day 5: PICO 35, control 15 (p=0.0001). Other outcomes were not significantly different between the groups.	None reported.	Methodological quality is acceptable for a pilot RCT, though the PICO group was treated slightly differently prior to discharge than the control group. The majority of patients are likely to be high risk for SSI.
Hackney 2017	Retrospective observational study, single centre.	UK. 71 open abdominal surgery patients (39 PICO, 32 control). Included: emergency and elective.	Wound complications (unspecified), readmissions, length of stay.	Wound complications: PICO 7.6%, control 15.6%. Length of stay: PICO 14.49, control 13.9.	None reported.	Conference abstract. The study is extremely poorly reported with no demographic data and no statistical significance tests

	PICO or unspecified control. 					performed. It is not possible to ascertain risk status for SSI.
Hester 2015	Retrospective observational study, single centre. PICO or standard dressing (control). 	UK. 36 revision arthroplasty patients (18 PICO, 18 control). 9 hip, 27 knee. 	Wound infection requiring further surgery or antibiotics. Dressing related complications. 	Outcomes were not significantly different between the groups.	None reported.	The study is poorly reported and can be considered methodologically weak for an observational study. Inclusion/exclusion criteria are vague, but the age, BMI, and ASA class indicate that the majority of patients are high risk for SSI.
Hickson 2015	Before-after retrospective observational study, single centre. PICO or standard dressing (control). 	USA. 1948 C-section patients (964 PICO, 984 control). High risk patients (BMI >35, or 2 of diabetes, steroid use, autoimmune disease, haematological disorders, immunosuppressant medication, hypertension, multiple C-sections, history of wound infections, pre-existing skin problems, or emergent birth)	SSI. 	SSI: PICO 0.1%, control 0.61%.	None reported.	The study is methodologically weak and does not report demographic variables very well. The inclusion criteria mean that the population is likely to be high risk for SSI. The authors do not report a significant reduction between the control and the PICO cohorts.

Holt 2015	Retrospective observational study, single centre. PICO or standard dressing (control).	UK. 24 oncoplastic breast surgery patients (within-patient comparison). Therapeutic mammoplasty or skin-sparing mastectomy and immediate reconstruction with inferior dermal flap and implant. Contralateral side had symmetrising reduction.	Delayed healing, wound breakdown (dehiscence), fat necrosis, days to adjuvant healing.	Dehiscence: PICO 4.2%, control 16.7%. Mean time to healing: PICO 10.7 days, control 16.1 days.	None reported.	Methodologically weak and poorly reported for numerous variables. It is not clear what proportion of patients are high risk for SSI, though it is likely to be a minority. Statistical analysis is very limited, with no significance values reported.
Hyldig 2018a	Multicentre RCT PICO or standard dressing (control).	Denmark. 827 women undergoing caesarean section (1:1 allocation to PICO or standard dressing) Included: pregnant women undergoing elective or emergency caesarean section, aged ≥18 years, who had a pre-pregnancy BMI ≥30, and could read and understand Danish Excluded: subsequent vaginal delivery	SSI within 30 days of surgery Wound exudate, dehiscence, and health-related quality of life	SSI:PICO 4.6% vs. control 9.2% (p=0.007) Wound exudate: PICO 22.4% vs. control 32.9% (p=0.001) Minor dehiscence: PICO 15.1% vs. control 16.6% (p=0.66) The health-related quality of life did not differ between the	None reported.	Methodological quality is acceptable for an RCT. Women with BMI ≥30 undergoing a C-section are at higher risk of SSI. PICO superior to standard dressing in the primary outcome measure. The study was funded by the sponsor.

				PICO and the control arm.		
Irwin 2018	Prospective database audit, single centre PICO or standard dressing (control).	UK. 155 people (254 breasts) undergoing prepectoral implant-based reconstruction procedures (102 PICO and 152 standard dressing) Included: Not reported. Excluded: Not reported.	Wound dehiscence, reconstructive failure.	Wound dehiscence: PICO 0 cases vs. 9 cases standard dressing (p=0.01) Reconstructive failure: PICO 0 cases vs. 6 cases (p=0.08)	None reported.	Abstract. No inclusion criteria are reported therefore risk profile of population is unclear. PICO superior to standard dressing in the primary outcome measure. UK study, results may be more relevant to the NHS.
Karlakki 2016	Non-blinded single centre RCT. PICO or standard dressing (control). All patients received antibiotics following surgery.	UK. 220 people undergoing hip and knee arthroplasty (102 PICO and 107 standard dressing) Included: people undergoing elective hip or knee arthroplasty (for any indication) Excluded: people who had known allergies to dressings, were undergoing revision joint surgery, were unwilling to attend additional clinics, and those on warfarin.	Wound complications, length of stay, level of exudate, dressing changes	LOS (mean days): PICO 3.8 days vs. 4.7 standard dressing p=0.07 Wound complications: PICO 2.0% vs. standard dressing 8.4% p = 0.06 Post-surgical exudate: PICO 4% had grade 4 exudate as compared with 16% in the control group p = 0.007	N=3 in PICO group	Methodological quality is acceptable for an RCT. PICO not significantly to standard dressing for LOS and wound complication outcomes, though this was of borderline significance Post-surgical exudate was significantly lower in the PICO group and there were fewer dressing changes.

				Dressing changes (mean): PICO 2.5 vs. 4.2 p = 0.002		UK study, results may be more relevant to the NHS. The study was partially funded by the sponsor.
Kawakita 2018	Single centre, retrospective cohort study. PICO or standard dressing (control). 	US. 759 women undergoing caesarean section (PICO 176 and 583 standard dressing) Included: women with BMI ≥ 40 undergoing a caesarean section Excluded: Unclear 	Wound complication, endometritis before discharge, endometritis after discharge, deep wound infection, other severe infection, cellulitis, hematoma/seroma, and wound dehiscence. 	Wound complication: (standard dressing 7.9% vs. PICO 9.6%; OR 1.02, not significant) Endometritis before discharge (standard dressing 1.7% vs. PICO 1.2%; OR 0.22, not significant) Endometritis after discharge (standard dressing 1.2% vs. PICO 0.6%; OR 1.21, not significant) Deep wound infection (standard dressing 0.7% vs. PICO 2.4%); OR 7.34, not significant) Other severe infection (standard dressing 1.0% vs. PICO 1.2%; OR not available)	None reported	Abstract with limited reporting of a number of key variables. No difference was found between PICO and standard dressing for any outcome. Large difference between study groups may have led to bias.

				Cellulitis (standard dressing 3.7% vs. PICO 3.0%; OR 0.86, not significant) Haematoma/seroma (standard dressing 2.0% vs. PICO 3.6%; OR 3.07, not significant) Wound dehiscence (standard dressing 2.4% vs. 7.8%; OR 2.35, not significant)		
Luciani 2016	Blinded RCT PICO or standard dressing (control). ●	Italy. 100 people undergoing hip or knee replacement revision surgery (PICO 50 and 50 standard dressing) Included: people with diagnosis of hip prosthesis aseptic loosening or knee prosthesis aseptic loosening Excluded: Unclear ●	Asepsis Score (AS) to assess wound healing, number of wound dressing changes, patient comfort and satisfaction ●	All people in the PICO group versus 90% of people in the standard care group (n=45) had satisfactory healing according to the AS scale. People in the PICO group reported lower levels of pain that in the standard care group (VAS score 2.6 in the PICO group vs. 4.8 in standard care). The PICO group had significantly fewer blisters (p= 0.048) and dressing changes	None reported	Abstract with limited reporting of a number of key variables. There is limited information on study population characteristics, therefore the risk profile is unclear. The authors state that the wounds had a high infection risk. Wound assessment was blinded, which may have reduced bias.

				(p < 0.001). The PICO group reported lower mean pain level during dressing changes than the standard care group (mean reported numeric rating scale (NRS) pain level of 2.84 vs. 5.14).		PICO was superior for preventing and for reducing dressing changes. Though scores for healing scores or pain level scores appear superior for PICO, no statistical analyses were reported
Matsumoto 2015	Before-after retrospective observational study, single centre. PICO or standard dressing (control). ●	USA. 74 total ankle arthroplasty patients (37 PICO, 37 control). Excluded: revision surgeries. ●	Wound healing problems (dehiscence, eschar, drainage), SSIs. ●	Wound healing problems: PICO 3%, control 24% (p=0.014). SSIs not significantly different between the groups.	No dropouts in either group.	Methodological quality is acceptable for an observational study. However, from the data reported, it is not possible to ascertain risk status for SSI. Post-hoc power calculation showed that 434 patients per group would be needed (alpha 0.05, beta 0.8).
Nordmeyer 2016	Unblinded single centre RCT. PICO or standard dressing (control). ●	Germany. 20 internal fixation of spinal fracture patients (randomised 1:1). Included: open reduction surgery. ●	Volume of wound exudate at 5- and 10-days. Nursing time, number of dressings (compresses) used. ●	Volume of exudate at 5-days: PICO 0ml, control 1.9ml (p=0.0007). At 10-days: PICO 0.5ml, control 1.6ml (p<0.024). Mean nursing time: PICO 13.8 minutes,	No dropouts in either group.	Methodologically very weak for an RCT. The study does not report inclusion/exclusion criteria or demographic variables. It is not possible to ascertain risk status for SSI. It is one of only a few studies that reports

				control 31 minutes (p=0.0005). Compresses: PICO 11, control 35 (p=0.0376).		outcomes for wound exudate and dressing changes.
O'Leary 2017	Unblinded single centre RCT. PICO or standard dressing (control), antibiotic prophylaxis in all patients. ●	Ireland. 50 laparotomy for open abdominal surgery patients (randomised 1:1). Included: patients aged between 18 and 80, emergency and elective, class I, II and III wounds. Excluded: class IV wounds, BMI≥40, ASA>3. ●	SSI, length of stay, VAS, POSAS wound score. ●	SSI (ITT analysis 2-sided test): PICO 12%, control 32% (p=0.095). Length of stay: PICO 6.1 days, control 14.7 days (p=0.019). Other outcomes were not significantly different between the groups.	1 patient excluded from PICO group.	Methodological quality is questionable for this RCT. Although the authors report that the study was powered to detect its primary outcome, the sample size was substantially lower than in other sample size calculations. It is not clear that all patients were at high risk for SSI, though it is probable that a majority were.
Pellino 2013 (2014b in submission)	Pilot RCT, single centre. PICO or standard dressing (control). ●	Italy. 30 small bowel resection patients with Crohn's disease (13 PICO, 17 control). Included: patients aged 18 or over, established Crohn's, structuring Crohn's with symptomatic stenosis, converted or	SSI, operative time, length of stay, length of antibiotic administration, global ASEPSIS score, major/minor complications, seroma. ●	SSI: PICO 7.7%, control 47% (p=0.041). Length of stay: PICO 7.5 days, control 10.3 days (p=0.0007). ASEPSIS score: PICO 13.5, control 27.2 (p=0.001).	None reported.	Methodologically acceptable for a pilot RCT. However, Although the sample size was substantially lower than in other sample size calculations, the outcome was statistically significant.

		hand-assisted laparoscopy. Excluded: unconverted laparoscopy, explorative laparotomy, penetrating disease, massive bowel resection. ●				The type of surgery indicates this patient population is likely to be high risk for SSI.
Pellino 2014 (2014a in submission)	Prospective non-randomised comparative study. PICO or standard dressing (control). ●	Italy. 100 patients (50 breast surgery, 50 colorectal surgery). PICO and control allocated 1:1. Inclusion: no more than 12 patients with malignancy per group. ●	Infectious surgical site events (SSIs), length of stay, seroma, global ASEPSIS scores.	SSI (breast): PICO 8%, control 36% (p=0.04); (colorectal) PICO 8%. control 44% (p=0.008). ASEPSIS (breast): PICO 12, control 18.2 (p=0.03); (colorectal) PICO 14.6, control 25.3 (p=0.01). Length of stay (colorectal): PICO 7.1 days, control 12 days (p=0.001). Seroma (colorectal): PICO 8%, control 40% (p=0.02). Other outcomes were not significantly different between the groups.	None reported.	Methodologically weak for a prospective study. A number of important variables are not reported and some results are reported for both colorectal and breast surgery patients, combined. The inclusion/exclusion criteria are not reported so it is not possible to ascertain risk status for SSI.

Selvaggi 2014	Unblinded single centre observational. PICO or standard dressing (control), antibiotic prophylaxis in all patients. 	Italy. 50 adults with Crohn's disease undergoing abdominal surgery. Included: ≥18-year-old, established Crohn's disease, symptomatic Crohn's disease not amenable for medical treatment, laparotomy, converted-laparoscopy, or hand-assisted laparoscopy (HAL) with bowel resection/s or strictureplasty/ies, primary wound closure, adherence to periodical follow-up Excluded: Unconverted laparoscopy, explorative laparotomy/laparoscopy without bowel opening, massive bowel resections (less than 30% of anatomical length preserved) 	SSI, re-admission rates, length of stay, usability	SSI (PP analysis 2-sided test): PICO 8%, control 48% (p=0.004). Re-admission rates: PICO 0%, control 24% days (p=0.02). Length of stay: PICO 7 days, control 12 days (p=0.0001). Seroma: PICO 2 (8%) vs. SC 11 (44%), p = 0.008. 2 patients reported issues with using PICO. Both were adequately resolved.	No dropouts in either group	Adequate methodological quality for an observational study. There were no significant differences in characteristics between study groups. No sample size calculation was reported. Most patients were likely high risk for SSIs because of underlying Crohn's disease and concomitant immunosuppression.
Svensson 2018	Open label, multi-centre, within-patient, RCT.	Sweden. 34 people who underwent bilateral inguinal vascular surgery (randomised 1:1).	Assessment of scar quality using 3 tools: SBSES objective measure, NRS10 overall scar quality, PSAS subjective	Both the objective and subjective scar evaluations showed no statistically significant difference	Low attendance rate (44%) after randomisation	Study underpowered to detect an effect. The patient population provide an opportunity for case-matched

	PICO or standard dressing (control), antibiotic prophylaxis in all patients. ●	Included: Elective vascular surgery with inguinal incisions Excluded: Non-SSI wound complication, presence of SSI, advanced terminal disease, non-completed NPWT device usage, advanced dementia ●	measure, post-operatively (no fixed time point was defined).	between PICO and standard dressing.		comparisons within patient, and all patients received the same surgery on both sides. However, in 21.9% of the patients, surgical dissection was more extensive on one side. The study had a high attrition rate with only 44% of the patients included in final analysis after randomization. High-risk procedure and patient population with comorbidities.
Tan 2017	Retrospective, single-centre observational study. PICO or standard dressing (OpSite, control), antibiotic prophylaxis in all patients. ●	Singapore. 42 people undergoing lower limb bypass. (PICO: n=14, control: n=28) Included: Patients who underwent lower limb arterial bypass with reversed great saphenous vein Excluded: Not reported ●	SSI, surgical debridement, length of stay, re-admission rates	SSIs PICO = 0% vs. 32% at the control group (p=0.019).	No dropouts in either group	This study is subject to selection bias as the decision to use conventional wound therapy or NPWT depended on the surgeon's preference. Despite this, there were no significant differences in characteristics between study groups. No sample size calculation was reported.

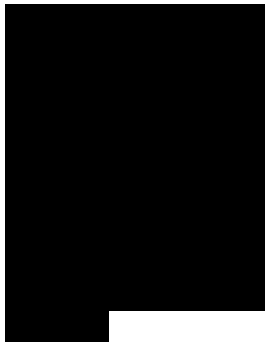
						This is the only study that reports using an objective assessment of pre-surgical estimation of SSI risk, ensuring that a representative population was included.
Tanaydin 2018	Open label, single-centre, within-patient, RCT PICO or fixation strips (control), antibiotic prophylaxis not reported. 	Netherlands. 32 women who underwent bilateral breast reduction mammoplasty (randomised 1:1) Included: Women aged >18 years, bilateral superomedial pedicle Wise-pattern breast reduction mammoplasty, postsurgical incisions of similar length on each breast Excluded: pregnancy, lactation, using steroids or other immune modulators, history of radiation of the breast, tattoos in the area of incision, skin conditions resulting in poor healing or widened scars, patients with a known history of scar problems, known allergies to product	SSCs, Scar quality	SSCs lower in PICO group (p=0.004). Scar quality not statistically significant in the long-term follow-up.	No dropouts reported	Poorly reported RCT. The patient population provide an opportunity for case-matched comparisons within-patient, and all patients received the same surgery on both sides. Population overlap with Galiano 2018. A post-hoc sample size calculation confirmed that the study was powered to detect a difference between NPWT and standard care for the secondary outcome (scar quality) but not for the rate of SSCs. It is uncertain to what extent the included

		components, incision still actively bleeding, exposure of blood vessels, organs, bone or tendon at the base of the reference wound, incisions > 30cm maximum dimension 🟡				study population fit the profile of a high risk population.
Tuuli 2017	A pilot open label, single-centre RCT. PICO or standard dressing (control), antibiotic prophylaxis not reported. 🟢	USA. 120 women undergoing C-section (randomised 1:1). Included: Obese women (BMI≥30), C-section Excluded: - Non-availability for postoperative follow-up, contraindication to NPWT, pre-existing infection around incision site, bleeding disorder, therapeutic anticoagulation, allergy to any component of the dressing 🟢	SSC, pain score, adverse skin reactions	SSCs: PICO: 8.3% vs. 5.0%, RR 1.67, 95%CI 0.42-6.67; p=0.72. Pain score: PICO 0 (0-1) vs. control 1 (0-3), p=0.02. Adverse skin reactions: PICO 2 (3.3) vs control 0 (0), p=0.50	No dropouts in either group reported	This is an abstract so there is limited information about the study methodology, for example, there is no information on baseline patient characteristics, randomization method, power calculation, and follow-up time. The study included obese women undergoing C-section that constitutes a high-risk cohort.

Uchino 2016	Open label, multi-centre RCT. PICO+PSS vs. PSS alone (control). All patients received 100% prophylactic antibiotics. 	Japan. 59 adults with ulcerative colitis scheduled to elective undergo ileostomy closure (randomised 1:1). Included: ≥18 years old, established ulcerative colitis, scheduled to undergo elective closure of ileostomy - including a restorative proctocolectomy with ileal pouch anal anastomosis Excluded: Death, dirty/infected wound, urgent/emergency surgery, separated double-barrel ileostomy, patients whose incision was extended due to adhesions during surgery, patients displaying complicated dermatitis due to adhesives, patients with SSIs during follow-up periods were excluded from prophylactic NPWT and from comparison of wound-healing duration as NPWT was terminated after SSI diagnosis 	Complete wound healing.	There was no statistically significant difference for the mean duration of wound healing between the 2 groups (37.6 days in the PSS-alone and 33.5 in the PPS+PICO group).	2 patients reported as lost to follow-up, 1 from each group. Patients excluded from wound healing duration analysis, due to SSIs were n=3 for PSS+PICO and n=1 for PSS alone	A power analysis was carried out indicating that a sample size of 36 was required to detect a reduction of 10 days in the time to complete wound healing between the 2 cohorts at 80% power. However, the authors did not do an intention to treat analysis as the patients who developed SSI during the follow-up periods were excluded from prophylactic NPWT and from assessing the primary outcome. This approach introduces bias to the calculation and most likely results in an underpowered study. Main risk factors were underlying diagnosis of ulcerative colitis, immunosuppression before or during the procedure and ASA score. However, the authors excluded patients with well-known risk factors such as dirty wounds

						and emergency procedures.
Van der Valk 2017	Single-centre, before-after, observational study. PICO vs. a historical cohort that used conventional wound care (control). Prophylactic antibiotic use not reported. 🟡	Netherlands. 20 people undergoing abdominoperineal resection for rectal cancer. Included: Patients undergoing laparoscopic abdominoperineal resection for rectal cancer. Excluded: Patients undergoing extralevator APR or treated with a perineal subcutaneous drain. 🟢	SSC, time to wound healing	SSC (PP analysis): No statistically significant difference in the SSCs between the two groups was noted (70% vs. 40%, 95%CI not reported, p value not reported). Time to wound healing: PICO = 8.5 (mean 10.4, range 0-34) vs. control = 13 (mean 11.4, range 0-24), p=0.87	None reported.	Small underpowered study. This study is subject to selection and performance bias as it is a before-after historical control comparison. There was an imbalance in terms of smoking and cardiovascular disease co-morbidity between the 2 groups in favour of the control group.
Witt 2015	Open label, single-centre RCT. PICO vs. conventional wound dressing (control). All patients received prophylactic antibiotics.	Poland. 80 people undergoing coronary artery bypass grafting surgery (randomised 1:1) Included: Not reported Excluded: Not reported 🟡	Wound healing defined as absence of SSCs post-operatively.	The PICO group achieved higher statistically significant wound healing rates (92.5% vs. 75%, p=0.034).	No dropouts reported.	Underpowered and not adequately reported RCT. There were no major difference between the baseline characteristics of the 2 groups with the exception of age. The main risk factors were underlying the procedure and the presence of

						comorbidities or smoking status in some of the patients.
Zotes 2015	Pilot open label, single-centre RCT. PICO vs. standard dressing (control). No information on prophylactic use of antibiotics reported.	Mexico. 20 people undergoing thoracotomy for empyema (randomised 1:1). Included: Not reported Excluded: Not reported	SSC	Although the SSC rate was higher in the PICO group (50% vs 10%), the difference was not statistically significant.	Not reported.	Small underpowered RCT. This is an abstract so there is limited information about the study methodology, for example, there is no information on baseline patient characteristics or randomization method. The study included people with diabetes, poor nutritional status, steroids therapy, and prolonged surgery >2 h, however, it is not clear in what % these risk factors were represented in the 2 groups.
Stannard unpublished - NCT02064270	Multi-centre, RCT	USA. [redacted] undergoing primary	Incision appearance, SSC	[redacted]	Not reported	This is an unpublished draft. According to the sponsor's submission, a blinded assessor

	PICO vs. standard dressing (control). Use of prophylactic antibiotics not reported. ●	or revision knee or hip arthroplasty. Included: adults, primary or revision total hip or knee arthroplasty, patients able to have an advanced technology device capable of digital photography Excluded: Pregnancy, history of poor compliance with medical treatment, allergy to silicone adhesives or polyurethane films, unwillingness to participate in a RCT ●				evaluated the wound healing outcome. No information is provided on sample size calculation.
(Green, amber or red colour coding indicates whether the study matches the scope fully, partially, or not at all: ●●●)						

3.4 Overview of methodologies of all included studies

- Three of the studies (Galiano 2018a, Tanaydin 2018, Svensson-Bjork 2018), used within patient comparison. Six studies used a historic control as the comparator (Adogwa 2014, Dingemans 2018, Hester 2015, Hickson 2015, Kawakita 2018, Matsumoto 2015, Van der Valk 2017). Eleven studies were comparative non-randomised (Caswell 2015, Fleming 2018, Hackney 2017, Holt 2015, Pellino 2014a, Pellino 2014b, Selvaggi 2014, Irwin 2018, Selvaggi 2014, Tan 2017, Witt 2015) and 10 were standard randomised controlled trials (Chaboyer 2014, Gillespie 2015, Karlakki 2016, Luciani 2016, Nordmeyer 2016, O'Leary 2016, Stannard unpublished, Tuuli 2017, Uchino 2016, Zotes 2015). All studies used the standard PICO version.

- Seven of the included studies (Caswell 2015, Hackney 2017, Irwin 2018, Kawakita 2018, Luciani 2016, Tuuli 2017, Zotes 2015) were abstracts and the rest were full text publications.

- All of the included studies were single-centre with the exception of Svensoon 2018 and Uchino 2016 that were multi-centre. Five studies were conducted in a UK setting (Hackney 2017, Hester 2015, Holt 2015, Irwin 2018, Karlakki 2016).

- The submission included 29 studies from different surgical specialities, all including adults, as follows:
    - 8 orthopaedic surgery
    - 5 studies on people undergoing obstetrics surgery
    - 5 breast surgery studies
    - 4 studies on people undergoing colorectal surgery
    - 2 cardiothoracic surgery studies
    - and 1 study on each of the following ileostomy, laparotomy, lower limp bypass and inguinal vascular surgery
    - The EAC identified 2 more studies, 1 in orthopaedic and 1 in colorectal surgery.

- Due to the nature of the intervention, most studies were open-label. However, 4 studies (Chaboyer 2014, Gillespie 2015, Luciani 2016, Stannard unpublished) used independent assessors to evaluate all or part of the clinical outcomes. One study (Hyldig 2018a) reports that an independent data monitoring committee was involved, however, it is unclear if they ascertained the study outcomes. The majority of the included studies did not report an imbalance between the baseline patient characteristics, with the exception of Karlakki 2016 and Witt 2015.

- The mean follow up durations for most of the included studies ranged between 4-6 weeks. A high range of follow-up was noted from 2 weeks (Holt 2015, Luciani 2016, Nordmeyer 2016) to approximately 2 years (Svensson 2018).

- The most common primary outcome was SSI (13 studies), followed by SSCs (11 studies). One study looked at scar quality (Svensson 2018), 1 study time to wound healing (Uchino 2016), 1 length of stay (Karlakki 2016), 1 exudate volume (Nordemeyer 2016), 1 dehiscence (Holt 2015), 1 pain (Luciani 2016) and 1 wound healing (Witt 2015). There was variation in the definitions of SSIs (mostly on the follow-up time for reporting) and most studies did not report adequate information of how the outcomes were measured (if for example it was based on clinical judgement only or based on international criteria).

- Three RCTs (Chaboyer 2014, Gillespie 2015, Hyldig 2018a) reported deep and superficial SSIs separately. The studies reported a variety of secondary outcomes, including ease of use, time taken to apply the devise and measuring the quantity of wound exudate.

- Quality of life was studied as a secondary outcome using EQ-5D in 1 of the included RCTs (Hyldig 2018a). There was no difference in outcomes between the 2 cohorts. Three studies (Galiano 2018a, Hester 2015, Karlakki 2016) reported adverse events associated with the use of PICO.

- Four studies reported subgroup analyses as follows:

    - Selvaggi 2014 reported a subgroup analysis of patients receiving steroids at surgery. There was a significant reduction in SSI rates with PICO compared with control ($p = 0.001$).

    - Pellino 2014a reported a subgroup analysis of patients over 65 years. There was no statistically significant difference between the 2 subgroups.

    - Galiano 2018a stratified their results on dehiscence based on BMI and reported that PICO performed better with increasing BMI. It is not clear if the difference was statistically significant.

    - Karlakki 2016 included patients that had undergone either a total knee or a total hip arthroplasty. More SSCs were noted in the knee cohort. Only this study had pre-planned subgroup analyses the rest were post-hoc.

3.5 Overview and critique of the company's critical appraisal

The sponsor used the checklist proposed by NICE for the critical appraisal included into their submission. For RCTs, they followed the "CRD's guidance for undertaking reviews in health care" from the Centre for Reviews and Dissemination, University of York, 2008 (Chapter 1, section 1.3.4.). For the observational studies, they used the CASP guidelines.

The EAC carried out a separate quality appraisal of the 28 full text publications included in the assessment report. The checklist proposed by NICE's guidelines manual (Appendix C of the manual) was used. For the non-comparative studies, the CASP guidelines were used. A copy of the EACs methodological quality appraisal checklist is included in appendix B. The EAC requested advice from the clinical experts on a) the definition of high-risk patient and procedure characteristics based on international and national standards, b) the definition of an adequate follow-up time and c) the importance of clinical outcomes.

According to the experts, risk factors associated with higher risk for SSCs are either due to patient-related risk factors (for example, ASA≥3, increased BMI, older age, diabetes, current smoker) or procedure-related risk factors (for example, vascular surgery, revision orthopaedic surgery, c- sections, emergency dirty procedures such as bladder and bowel, heart operations). For the primary outcome, the majority of the clinical experts reported SSIs. Finally, for follow-up they reported that the time for an SSI to occur would depend on the surgical procedure. For example, it may take years to occur in knee and hip replacement. However, 6 weeks follow-up will be an adequate follow-up time in many cases. Appropriate capture of SSCs within that follow-up time will also depend on how often the patient is being reviewed and if the follow-up is in the community, which may result in underreported numbers of SSIs. According to the PHE audit on SSIs, patients are followed-up to identify SSIs for 30 days after surgery for non-implant procedures and 1 year for prosthetic implant procedures. From the 7 studies included in the assessment report involving orthopaedic procedures with implants, the majority had total follow-up time of 6 weeks, with only 1 study having a maximum follow-up time of 3 months (Adogwa 2014).

From a total of 28 studies included in the sponsor's submission, 12 had as a primary outcome the rate of SSIs, however, only 3 (Hyldig 2018a, O'Leary 2016, Pellino 2014b) were adequately powered to detect a significant difference for the effect. Three more studies were adequately powered to detect a difference for other primary outcomes. These were Galiano 2018a (SSC), Karlakki 2016 (length of stay), and Uchino 2016 (time to wound healing).

Finally, only some of the included evidence submitted meets the definition of a high-risk population of developing SSCs as defined by the WUWHS consensus document. The EAC notes that based on feedback received by the clinical experts, the definition of a high-risk population varies not only at a national level in the UK but also locally on an NHS Trust level (please see section 2). Only one study (Tan 2017) reported the use of an objective assessment of pre-surgical estimation of SSI risk, ensuring that a representative population was included. In 8 of the included studies, the presence of 1 or more risk factors constitutes part of the exclusion criteria (Adogwa 2014, Chaboyer 2014, Dingemans 2018, Galiano 2018a, Karlakki 2016, O'Leary 2016, Tanaydin 2018, Uchino 2016). For the rest of the included studies the distribution rates of high-risk factors among the study participants were unclear.

Tables 9-12 show the methodological quality assessment undertaken by the EAC.

Table 9 Overview of methodological quality (full text RCTs)

STUDY	Chaboyer 2014	Galiano 2018a	Tanaydin 2018	Gillespie 2015	Svensson 2018	Uchino 2016	Hyldig 2018a	Karlakki 2016	Nordmeyer 2016	O'Leary 2017	Witt 2015
Selection Bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Performance Bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
Attrition Bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Detection Bias	Low risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias	Unclear risk of bias	Low risk of bias
Other (conflicts of interest, power, endpoint)	Unclear risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias

Table 10 Overview of methodological quality (full text observational studies)

STUDY	Selvagi 2014	Tan 2017	Van der Valk 2017	Dingemans 2018	Fleming 2018	Hester 2015	Hickson 2015	Holt 2015	Adogwa 2014	Matsumoto 2015	Pellino 2014a	Pellino 2014b	Caswell 2015*	Hackney 2017*	Irwin 2018*	Kawakita 2018*
Is the study based on a representative sample selected from a relevant population?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Are criteria for inclusion explicit?	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	No	No	No	Yes
Did all individuals enter the study at a similar point in their disease progression?	Yes	No	No	No	No	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes

STUDY	Selvagi 2014	Tan 2017	Van der Valk 2017	Dingemans 2018	Fleming 2018	Hester 2015	Hickson 2015	Holt 2015	Adogwa 2014	Matsumoto 2015	Pellino 2014a	Pellino 2014b	Caswell 2015*	Hackney 2017*	Irwin 2018*	Kawakita 2018*
Was follow up long enough for important events to occur?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No
Were outcomes assessed using objective criteria or was blinding used?	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes
If comparisons of sub-series are being made, was there sufficient description of the series and the distributio	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	N/A	N/A	Yes	N/A	N/A	N/A	N/A	N/A

STUDY	Selvagi 2014	Tan 2017	Van der Valk 2017	Dingemans 2018	Fleming 2018	Hester 2015	Hickson 2015	Holt 2015	Adogwa 2014	Matsumoto 2015	Pellino 2014a	Pellino 2014b	Caswell 2015*	Hackney 2017*	Irwin 2018*	Kawakita 2018*
n of prognostic factors?																

Table 11 Overview of methodological quality (abstract RCTs)

STUDY	Luciani 2016	Tuuli 2017	Zotes 2015
Selection Bias	Unclear risk of bias	Unclear risk of bias	High risk of bias
Performance Bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias
Attrition Bias	Unclear risk of bias	Low risk of bias	Unclear risk of bias
Detection Bias	Low risk of bias	Low risk of bias	Low risk of bias
Other (conflicts of interest, power, endpoint)	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias

Table 12 Overview of methodological quality (abstract observational studies)

STUDY	Caswell 2015	Hackney 2017	Irwin 2018	Kawakita 2018
Is the study based on a representative sample selected from a relevant population?	Yes	Yes	Yes	Yes
Are criteria for inclusion explicit?	No	No	No	Yes
Did all individuals enter the study at a similar point in their disease progression?	No	No	Yes	Yes
Was follow up long enough for important events to occur?	No	No	No	No

Were outcomes assessed using objective criteria or was blinding used?	No	No	No	Yes
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	N/A	N/A	N/A	N/A

3.6 Results

A total of 31 studies (29 studies identified by the sponsor and 2 by the EAC) were included in this assessment report. The results from these studies are included in Table 13 below.

Table 13: Included studies SSI and SSC rates

References, trial name & patient group.	**SSI (%)**	**Dehiscence (%)**
Adogwa 2014	PICO 10.63% vs. control 14.91% (p=0.04)	PICO 6.38% vs. control 12.28% (p=0.02)
Caswell 2015	PICO 3.7% vs. control 7.69% (significance not reported)	NR
Chaboyer 2014	PICO 22.7%, control 27.9% (p=0.579)	PICO 0%, control 0% (p=NS)
Dingemans 2018	PICO 4.3%, control 14.9% (p=0.29)	NR
Fleming 2018	PICO 2.7%, control 6.4% (p=0.249)	PICO 1.4%, control 1.3% (p=0.735)
Galiano 2018a	PICO 2%, control 3% (p=0.532)	PICO 16.2% control 26.4% (p=0.01)
Gillespie 2015	PICO 5.7%, control 8.6% (p=0.65)	PICO 2.9%, control 2.9% (p=0.75)

Hackney 2017	NR (wound complications: PICO 7.6%, control 15.6%, significance not reported)	NR
Hester 2015	NR (wound complications: PICO 5.5%, control 16.6%, p=0.14)	NR
Hickson 2015	PICO 0.1%, control 0.61% (significance not reported)	NR
Holt 2015	NR	PICO 4.2%, control 16.7 (significance not reported)
Hyldig 2018a	PICO 4.6% vs. control 9.2% (p=0.007)	PICO 15.1% vs. control 16.6% (p=0.66)
Irwin 2018	NR	PICO 0% vs. control 5.9% (p=0.01)
Karlakki 2016	NR (wound complications: PICO 2.0% vs. standard dressing 8.4% p = 0.06)	NR
Kawakita 2018	NR (wound complication: standard dressing 7.9% vs. PICO 9.6%; OR 1.02, not significant)	PICO 7.8% vs. standard dressing 2.4%; OR 2.35, not significant
Luciani 2016	NR	NR
Matsumoto 2015	PICO 3% vs. control 8% (p=0.615)	NR
Nordmeyer 2015	NR	NR
O'Leary 2017	PICO 12%, control 32% (p=0.095)	NR
Pellino 2013 (2014b in submission)	SSI: PICO 7.7%, control 47% (p=0.041)	NR
Pellino 2014 (2014a in submission)	(breast): PICO 8%, control 36% (p=0.04), (colorectal) PICO 8%. control 44% (p=0.008)	NR
Searle 2017	PICO 9%.	NR

Selvaggi 2014	PICO 8%, control 48% (p=0.004)	NR
Svensson-Bjork 2018	PICO 0%, control 0% (p=1.0)	NR
Tan 2017	PICO 0%, control 32%, (p=0.019)	NR
Tanaydin 2018	NR	NR
Timmons 2013	PICO 0%.	NR
Tuuli 2017	NR (wound complications: PICO 8.3%, control 5.0% p=0.72)	NR
Uchino 2016	PICO 10.7%, control 3.2% (p=0.76)	NR
van der Valk 2017	NR (wound complications: PICO 70%, control 40%)	NR
Witt 2015	PICO 2.5%, control 17.5% (p=0.0245)	PICO 2.5%, control 2.5% (p=1.0)
Zotes 2015	NR	PICO 10%, control 20% (significance not reported)

3.7 Description of the adverse events

The EAC found the sponsor's reporting of adverse events to be acceptable. The EAC re-ran the searches of the MHRA and FDA MAUDE databases (to cover the period following the sponsor's search) and found one additional record relating to a device malfunction in which the patient came to no harm (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=7818135&pc=OMP).

[redacted]

The WUWHS guidance identifies blisters or maceration as possible side effects from the use of NPWT. The MAUDE search result confirmed this finding as the most frequent adverse events reported were maceration and

blisters (see Appendix C for more details). From the studies included in this report, Hester 2015 reported that neither group experienced any dressing related complications, such as blistering, maceration, or skin tearing. Galiano 2018a reported that none of the observed adverse events was found to be associated with the use of PICO. Karlakki 2016 reported a higher rate of blisters in the PICO group (11%) vs. the control group (1%). Blisters were minor (< 1cm), seen around the composite/adhesive junction of the dressing, and were mainly developed in knee arthroplasties. They also noted that there was a high variability in the incidence of blisters between the 3 surgeons participating in the study and the highest incidence was observed in cases were a trainee applied the dressing.

3.8 Description and critique of evidence synthesis and meta-analysis

3.8.1 Sponsor's meta-analysis

The sponsor submitted a meta-analysis of all included full text publications. Conference abstracts were excluded as they lack methodological details and often contain incomplete data not suitable for meta-analyses. The results from abstracts were used as part of the sensitivity analysis. The unpublished study by Stannard was also excluded from the main analysis because it did not contain all necessary data. The submitted meta-analysis was compared with the published systematic review and meta-analysis by Strugala 2017 that reported the impact of PICO on SSCs. Based on the included studies, the sponsor's meta-analysis provided an update analysis of Strugala 2017.

A total of 4473 participants reported in 19 full text publications were included in the analysis (21 with conference abstracts included). Combining data from all medical specialties, among 8 RCTs, there was a significant reduction in SSIs with PICO (OR 0.49, 95%CI 0.33-0.72, p = 0.0003). The pooled analysis of the 11 observational studies confirmed this result (OR 0.28, 95%CI 0.17-0.46, p <0.0001). Non-randomised controlled studies often involve selection bias and publication bias, and therefore, overestimate the reported effect as evident by the lower OR in the current analysis. Combining all 19 studies, there was a significant reduction in SSIs with PICO (OR 0.39, 95%CI 0.29-0.52, p<0.0001).

The sponsor's approach to synthesize the results from different surgical specialties is supported by the views of clinical experts. When the latter were asked by the EAC transferable are the results between different specialties, the majority of the experts expressed the view that they are in cases where people with high-risk characteristics are included. This approach is also supported by the wider literature on NPWT systems. A recently published meta-analysis looking at the prophylactic use of NPWT systems in closed

incisions also pooled data from different medical specialties (De Vries 2016) supports this view and the findings of the sponsor's meta-analysis. The authors (De Vries 2016) reported a statistically significant reduction in SSIs from both RCTs (n=6) and observational studies (n=15). Their results are similar to the sponsor's and EAC's findings (observational studies, OR, 0.56, 95%CI, 0.32-0.96 and RCTs, OR, 0.30; 95% CI, 0.22-0.42, respectively).

In the sponsor's meta-analysis, there was variation in protocols used in the included studies, such as for example the duration of application for PICO and the standard dressing, follow-up times and frequency of follow-up. There was also significant variation in the SSI definitions and high variability in the risk profiles of the included populations with some of the studies as previously noted reporting high-risk factors as part of their exclusion criteria. Therefore, clinical heterogeneity is expected to be higher than statistical heterogeneity and the final analysis should have been reported using a random effects model at least for the overall pooled results[6].

Subgroup analysis

The sub-group analysis based on the type of surgery confirmed significant effects for orthopaedic surgery (0.43, 0.21-0.86, p=0.02), vascular (0.22, 0.05-0.87, p=0.03), obstetric surgery (0.47, 0.29-0.74, p=0.001), and plastic/breast (0.36, 0.14-0.97, p=0.04).

Orthopaedic surgery

The results of the meta-analysis showed significant effect for SSIs in favour of PICO (0.43, 0.21-0.86, p=0.02). It should be noted however, that Karlakki 2016 (the only adequately powered RCT analysing orthopaedic surgery outcomes, did not report reduction in LOS with the use of PICO (difference 0.9 days, 95%CI -0.2 to 2.5, p = 0.07) or SSCs (2.0% PICO vs. 8.4%; p = 0.06) in comparison with standard dressing in patients undergoing elective primary knee or hip arthroplasty.

Obstetric surgery

The results of the meta-analysis confirmed the findings of the pivotal study by Hyldig 2018a that the use of PICO results in fewer SSIs, in comparison with standard dressing (4.6% vs. 9.2%, RR 0.50, 95%CI 0.3-0.84; p = 0.007). The meta-analysis reported similar OR and 95%CIs for obstetric surgery overall (0.47, 0.29-0.74, p=0.001). It should be noted however, that the results from Hyldig 2018a were only statistically significant for superficial SSIs. The

[6] The inclusion of studies (RCTs and observational) with only a small number of patients, will also have resulted in large confidence intervals within each study. Therefore the statistical heterogeneity would be artificially deflated.

incidence of deep SSI requiring surgery was similar between groups (1.9% vs. 2.0%, p value not reported). O'Leary 2017 although reported results in a mixed population (colorectal and obstetrics patients) provided some evidence that PICO reduces the rate of SSIs in people undergoing elective or emergency laparotomy (per protocol: 8.3% vs. 32%, p = 0.043, intention-to-treat: 12% vs. 32%, p=0.073).

Plastic – Breast

Using a fixed effect model, the sponsor reported superiority of PICO vs. standard treatment for plastic/breast surgery (OR, 0.36, 0.14-0.97, p=0.04). The results of the EAC meta-analysis showed that when using a random effects model, there was no statistically significant difference in the rate of SSIs between PICO and standard dressing in patients undergoing breast surgery (OR, 0.35, 0.09-1.45, p=0.15). The results are in agreement with the pivotal RCT by Galiano 2018a that reported a reduction in the rate of SSCs (56.8% vs. 61.8%, p=0.004) and dehiscence (16.2% vs. 26.4%, p<0.001) with PICO in women undergoing reduction mammoplasty, however, SSIs were not significantly different between the 2 groups (2% vs. 3%).

3.8.2 EAC meta-analysis

The EAC ran additional meta-analyses based on the critical appraisal of the sponsor's analyses listed in section 3.8.1. First, a random effects model was used instead of a fixed model. The results are presented below in Table 14. In 2 subgroup analyses (plastic/breast and vascular surgery) the application of a random effects model changed the result to not statistically significant.

Second, the EAC performed leave-one-out analysis to test the influence of each individual study on the overall pooled SSI rate. Using a random effects model, all 19 studies were sequentially excluded. With the exception of Hyldig 2018a, none of the other studies had any significant effect on the results (Table 15). Removing Hyldig 2018a from the analysis resulted in a non-statistically significant result for the RCT SSI combined analysis. However, removing of Hyldig 2018a from the meta-analysis of the RCTs SSI combined analysis did not changed the point estimate (OR=0.51 in both cases) nor did it affect the heterogeneity estimate (I^2=0.14, p=0.32 vs. I^2=0.26, p=0.23 with and without Hyldig 2018a respectively). Since Hyldig 2018a represents approximately half the population (876 from 1804) included in the RCT SSI pooled estimate the loss of significance is attributed to its sample size.

Hyldig 2018a was the only study adequately powered to detect an effect in the SSI rates in obese women undergoing a C-section. Two more studies O'Leary 2016 (RCT) and Pellino 2014b (observational) were adequately powered to detect a difference in the SSI rates between the intervention and the control

group. Pooling the SSI rates of these 3 studies resulted in a statistically significant difference in the SSI rates between PICO and the control group (Table 16). The calculated OR and 95%CIs were similar to the pooled effect of all 19 studies included in the original analysis (0.33, 0.14-0.76 vs. 0.37, 0.24-0.57).

Table 14: Comparison of sponsor's and EAC's meta-analyses

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	EAC's estimate†	Statistical significance
Surgical Site Infection	19	4473	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.29, 0.52]	0.37 [0.24, 0.57]	P<0.0001
RCT SSI combined	8	1804	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.33, 0.72]	0.51 [0.31, 0.82]	P=0.006
Observational SSI combined	11	2669	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.17, 0.46]	0.27 [0.14, 0.53]	P=0.0001
Subgroup analysis based on surgical specialty						
Orthopaedic surgery SSI	5	607	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.21, 0.86]	0.45 [0.22, 0.91]	P=0.03
Orthopaedic RCT SSI	2	279	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.08, 1.24]	0.36 [0.09, 1.46]	P=0.15
Orthopaedic Observational SSI	3	328	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.21, 1.08]	0.48 [0.21, 1.11]	P=0.09
Colorectal SSI	5	209	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.21, 0.99]	0.39 [0.07, 2.11]	P=0.28
Colorectal RCT SSI	1	59	Odds Ratio (M-H, Fixed, 95% CI)	3.60 [0.35, 36.80]	3.60 [0.35, 36.80]	P=0.28
Colorectal Observational SSI‡	4	150	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.13, 0.77]	0.24 [0.04, 1.37]	P=0.11
Obstetric surgery SSI	3	2911	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.29, 0.74]	0.48 [0.30, 0.76]	P=0.002
Obstetric RCT SSI	2	963	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.31, 0.80]	0.50 [0.31, 0.81]	P=0.005
Obstetric Observational SSI	1	1948	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.41]	0.17 [0.02, 1.41]	P=0.10
Plastics/Breast surgery SSI	2	420	Odds Ratio (M-H, Fixed, 95% CI)	0.36, 0.14-0.97,	0.35 [0.09, 1.45]	P=0.15*
Plastics RCT SSI	1	370	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.18, 2.38]	0.66 [0.18, 2.38]	P=0.52
Plastics Observational SSI	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.03, 0.81]	0.15 [0.03, 0.81]	P=0.03

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	EAC's estimate†	Statistical significance
Vascular surgery SSI	2	193	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 0.87]	0.25 [0.05, 1.25]	P=0.09*
Vascular Observational	2	193	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 0.87]	0.25 [0.05, 1.25]	P=0.09
Cardiothoracic surgery SSI	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 1.03]	0.12 [0.01, 1.03]	P=0.05
Cardiothoracic RCT SSI	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 1.03]	0.12 [0.01, 1.03]	P=0.05
Mixed surgery SSI	1	49	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 1.03]	0.19 [0.04, 1.03]	P=0.05
Mixed surgery RCT SSI	1	49	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 1.03]	0.19 [0.04, 1.03]	P=0.05
Subgroup analyses based on SSCs						
Dehiscence	8	1753	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.57, 0.99]	0.76 [0.57, 1.01]	P=0.06
RCT dehiscence combined	4	1374	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.59, 1.05]	0.77 [0.53, 1.11]	P=0.16
Seroma	7	771	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.11, 0.45]	0.19 [0.08, 0.47]	P=0.0003
RCT seroma combined	2	440	Odds Ratio (M-H, Fixed, 95% CI)	2.03 [0.37, 11.14]	1.68 [0.08, 36.72]	P=0.74
Observational seroma combined	5	331	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.05, 0.31]	0.13 [0.05, 0.30]	P<0.00001
Haematoma	3	591	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.29, 2.65]	0.86 [0.26, 2.88]	P=0.80
Haematoma RCT	2	440	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.25, 4.07]	1.01 [0.11, 9.37]	P=0.99
Haematoma Observational	1	151	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.11, 4.34]	0.70 [0.11, 4.34]	P=0.71
Time to healing	3	259	Mean Difference (IV, Fixed, 95% CI)	-3.28 [-6.55, -0.02]	-10.83 [-22.91, 1.25]	P=0.08
Time to healing RCT	1	59	Mean Difference (IV, Fixed, 95% CI)	-4.10 [-9.64, 1.44]	-4.10 [-9.64, 1.44]	P=0.15

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	EAC's estimate†	Statistical significance
Time to healing Observational	2	200	Mean Difference (IV, Fixed, 95% CI)	-2.85 [-6.89, 1.19]	-21.07 [-62.49, 20.36]	P=0.32
Delayed healing	3	627	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.51, 1.16]	0.77 [0.51, 1.17]	P=0.22
Delayed healing RCT	2	579	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.50, 1.16]	0.77 [0.51, 1.17]	P=0.22
Delayed healing Observational	1	48	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 16.97]	1.00 [0.06, 16.97]	P=1.0
Necrosis	2	443	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.01, 4.27]	NA	P=0.27
Necrosis RCT	2	443	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.01, 4.27]	NA	P=0.27
Abnormal scarring	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.09, 1.60]	0.38 [0.09, 1.60]	P=0.19
Observational dehiscence combined	4	379	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.21, 1.30]	0.54 [0.21, 1.38]	P=0.2
Subgroup analyses based on hospital outcomes						
Length of Stay	11	948	Mean Difference (IV, Random, 95% CI)	-1.75 [-2.69, -0.81]	NA	P=0.0002
RCT LOS combined	4	415	Mean Difference (IV, Random, 95% CI)	-0.51 [-1.23, 0.21]	NA	P=0.16
Observational LOS combined	7	533	Mean Difference (IV, Random, 95% CI)	-2.78 [-4.90, -0.67]	NA	P=0.01
Readmission combined	9	966	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.38]	0.86 [0.49, 1.51]	P=0.59*
Readmission RCT	3	513	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [0.50, 8.12]	1.56 [0.22, 11.17]	P=0.66
Readmission Observational	6	453	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.39, 1.24]	0.79 [0.44, 1.45]	P=0.45
Reoperation combined	9	1427	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.52, 1.46]	0.91 [0.54, 1.54]	P=0.73
Reoperation for wound complications	6	1257	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.50, 1.77]	1.00 [0.53, 1.90]	P=1.0

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	EAC's estimate†	Statistical significance
Reoperation other	4	170	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.30, 1.81]	0.75 [0.30, 1.89]	P=0.55
*Result changed to not statistically significant after applying random effects model for the analysis. †A random effects model was used. ‡ We added in the non-randomised studies the subgroup by Pellino 2014 analysing colorectal patients.						

Table 15: Leave-one-out analysis, using a random effects model.

Excluded Study	Participants	Pooled OR, 95%CIs	Statistical significance
Chayboyer 2014	4386	0.34 [0.22, 0.55]	P<0.00001
Galiano 2018a	4103	0.35 [0.22, 0.56]	P<0.00001
Gillespie 2015	4403	0.36 [0.23, 0.56]	P<0.00001
Hyldig 2018a	3597	0.35 [0.21, 0.58]	P<0.0001
Karlakki 2016	4264	0.38 [0.24, 0.60]	P<0.0001
O'Leary 2016	4424	0.38 [0.25, 0.60]	P<0.0001
Uchino 2016	4410	0.36 [0.24, 0.54]	P<0.00001
Witt 2015	4393	0.39 [0.25, 0.60]	P<0.0001
Adogwa 2014	4313	0.35 [0.22, 0.55]	P<0.00001
Dingemans 2018	4379	0.38 [0.24, 0.60]	P<0.0001
Fleming 2017	4322	0.37 [0.23, 0.58]	P<0.0001
Hickson 2015	2525	0.38 [0.24, 0.60]	P<0.0001
Matsumoto 2014	4399	0.37 [0.24, 0.58]	P<0.0001
Pellino 2014b	4443	0.39 [0.25, 0.60]	P<0.0001
Pellino 2014 (breast subgroup)	4423	0.39 [0.25, 0.61]	P<0.0001
Pellino 2014 (colorectal subgroup)	4423	0.40 [0.26, 0.62]	P<0.0001
Selvaggi 2014	4423	0.41 [0.27, 0.62]	P<0.0001
Tan et al 2017	4431	0.39 [0.25, 0.60]	P<0.0001
Van der Valk 2017	4453	0.35 [0.24, 0.53]	P<0.00001
RCTs ony			
All RCTs	1804	0.51 [0.31, 0.82]	P=0.006
Hyldig 2018a	928	0.51 [0.25, 1.04]	P=0.07

Table 16: Further sensitivity analyses

Outcome or Subgroup	Studies	Participants	Statistical Method	OR, 95%CIs	Statistical significance
Surgical Site Infection (powered studies only)	3	955	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.14, 0.76]	P=0.009
Surgical Site Infection (all studies)	19	4473	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.24, 0.57]	P<0.0001
RCT SSI (powered studies only)	2	925	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.25, 0.75]	P=0.002
RCT SSI (all studies)	8	1804	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.31, 0.82]	P=0.006
Observational SSI (powered studies only)	1	30	Odds Ratio (M-H, Random, 95% CI)	0.09 [0.01, 0.89]	P=0.04
Observational SSI (all studies)	11	2669	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.14, 0.53]	P=0.0001

3.9 Ongoing studies

The EAC accepted the search terms that the sponsor used and re-ran the searches in the same databases but limited to records posted from August 2018-present, as well as a non-date limited search of the WHO ICTRP and PROSPERO databases. In total there were 1819 records retrieved, 1811 following de-duplication. Full details of the search strategies are included in Appendix A (Ongoing Studies).

From these the EAC identified 21 records of ongoing registered trials in which the intervention was PICO (including the 12 identified by the sponsor). With the exception of "*Stannard et al unpublished - NCT02064270"* none of the trials have made any preliminary results available. In addition, 1 of the included records for ongoing studies (NCT02578745) is now actually published and corresponds to Tuuli 2017, a pilot open label single-centre RCT compared PICO with standard dressing in 120 women undergoing C-section that has been included in the sponsor's submission. The EAC also identified a systematic review which will focus on PICO and Prevena (KCI Medical, San Antonio, Texas, USA) as the intervention. All ongoing trials are tabulated in Appendix D.

One of the clinical experts reported that the SUNRRISE RCT will be recruiting patients undergoing emergency laparotomy from 9 UK centers and it is due to be completed in 2021. The trial will focus on single-use negative pressure dressings.

4 Economic evidence

4.1 Published economic evidence

Critique of the company's search strategy

The sponsor conducted an economic evidence search to identify studies of relevant interventions for the prevention of surgical site complications following closed surgical incisions on PubMed and Embase. Additional electronic searches were supplemented by hand searching the following sources, contacting clinical authors, and NICE guidelines. Unpublished grey literature in the Health Economic Evaluation database, NHS Economic Evaluation Database, DARE, Tufts Cost-effectiveness Analysis registry. A total of 504 papers were reviewed, and finally 5 full economic evaluations were included.

The EAC reviewed the search strategy and conducted its own search (see Appendix A) to confirm no relevant papers have been missed out. Following application of cost and economic filters, the searches retrieved 110 abstracts related to economic evidence. After reviewing these abstracts, the EAC confirmed that no economic evidence additional to that included by the sponsor was available for the technology.

Critique of the company's study selection

The sponsor selected studies based on the scope: population included patients with closed surgical incisions; intervention included PICO single-use negative pressure wound therapy system compared to standard post-operative wound dressings; outcomes included any health economics outcomes (Cost, QALYs, complications avoided). Study designs included cost utility analysis, cost effectiveness analysis, cost consequence analysis, Burden of illness, cost of illness or cost evaluation studies. The following exclusion criteria were applied: populations with chronic wounds, interventions such as traditional negative pressure wound therapy (non-single use) and other non-PICO negative pressure devices. Studies prior to PICO obtaining CE mark approval (prior to 2010) were also excluded. The EAC reviewed the inclusion and exclusion criteria and determined that they were appropriate. The EAC also used the same inclusion and exclusion criteria.

Included and excluded studies

The sponsor included five studies (Nherera 2017, Nherera 2018, Galiano 2018b, Heard 2017, Hyldig 2018b). Three studies used a decision analytic approach and included probabilistic sensitivity analysis (Nherera 2017, Nherera 2018, Galiano 2018b), and two were economic evaluations conducted alongside clinical trials (Heard 2017, Hyldig 2018b). Hyldig 2018 is

in press at the time of the EAC's review and Galiano 2018b is in preparation. The studies were conducted in the UK, US, Denmark, Germany and Australia. The EAC concluded that there were no additional studies with relevant economic evidence on PICO.

Overview of methodologies of all included economic studies

Nherera (2017) constructed a decision analytic model from UK National Health Service perspective using data from patients undergoing primary hip and knee replacements. Data were drawn from a single centre trial in the UK (Karlakki 2016). Outcomes included dressing changes, length of stay, surgical site complications, costs and quality adjusted life years. The trial reported a reduction in dressing changes and length of stay in favour of single-use negative pressure wound therapy (sNPWT); the mean length of stay for sNPWT was 3.8 days vs 4.7 days for standard care. The decision model generated a reduction in complications of 0.06 for sNPWT and a QALY gain of 0.001. The model assumed a single sNPWT device is required (despite evidence of additional device use in Karlakki 2016). The model showed that there was a cost saving of £1,132 in favour of sNPWT compared to standard care.

The EAC has some concerns with this paper. The reporting of the model inputs is unclear; the cost associated with an SSI is not reported. It appears that the analysis applied costs per additional bed day and associated resource use rather than a single cost per SSI, but it is not clear how this integrates into the simple decision model reported. The authors report sensitivity analysis on both complication rates and LOS which raises the concern that the impact of SSI has been counted both directly and again through the impact on LOS. The authors report a minimal impact on overall costs of varying the effectiveness of sNPWT over the range for the OR of 0.02 and 0.95, with the latter effectiveness still generating cost savings of over £1,000 for sNPWT. Other sensitivity analysis such as varying the impact of sNPWT on LOS over the range -0.2 to 2.5 days generates a suspiciously small range of values (from -£1,413 to -£1,132).

Nherera (2018) recently developed a decision analytic model in Germany over a 12 week time horizon, comparing sNPWT with standard of care in patients following coronary artery bypass grafting surgery. Baseline data on SSC, revision operations, length of stay and readmissions were obtained from a prospective observation study of 2,621 patients in Germany. Effectiveness data for sNPWT was taken from a randomised trial of 80 patients in Poland. Effectiveness data reported an increase in wounds that healed without

complications in the sNPWT group (92.5% vs 75%). The model estimated that sNPWT avoided an additional 0.037 complications compared to standard care. Cost data were taken from the relevant diagnostic related groups and published literature. The estimated mean cost per patient was €19,986 for sNPWT compared to € 20,572 for standard care. The resulting mean cost-savings for sNPWT compared to standard care was €586.

The EAC notes that this second analysis from Nherera also appears to assign a benefit from sNPWT arising from both reduced LOS and reduction in the incidence of complications raising a potential concern of double counting. However, the baseline rate of complications of 5.2% derived from German observational data is conservative and the one-way sensitivity analysis reported plausible ranges of values.

Heard (2017) undertook an economic evaluation conducted alongside a randomised trial of sNPWT amongst obese women undergoing elective C-section in Australia. The rate of SSI was 25% in the sNPWT group compared to 35% in the standard dressing group. Resources were recorded alongside the trial data and unit prices were derived from appropriate administrative sources. Patients assigned to sNPWT received health care costing AU$5887 and reported 0.069 QALYS compared to AU$5,754 and 0.066 QALYs for patients receiving standard care. Hence sNPWT was slightly more costly (AU$ 133) and more effective than standard care, resulting in an incremental cost-effectiveness ratio of AU$1,347 per SSI prevented and AU$42,340 per QALY gained. The EAC notes the high rates of SSI in this study but considered the paper methodologically sound.

The sponsor shared an unpublished paper which used a cost-effective decision analytic model in patients undergoing reduction mammoplasty (Galiano 2018b). The outcome of interest was the incidence of dehiscence. A probability of dehiscence per incision of 0.264 for standard care and 0.162 per incision for sNPWT was taken from the literature. A single sNPWT device per wound (two per patient) was assumed. The consequential cost of dehiscence was estimated from a retrospective analysis of a large anonymised US hospital claims database using a matched analysis of cases and controls. [redacted]
The EAC regarded the analysis as simple but sound. However, it notes that [redacted]. This raises a concern that these rates included marginal cases of dehiscence. The separate matching analysis to estimate the costs of dehiscence, which used administrative data,

may not have included marginal cases. The overall impact of this would be to overestimate the cost impact of dehiscence.

A further article, in press at the time of review, reported a trial based cost-effectiveness analysis of the use of sNWPT in obese women undergoing C-section in Denmark (Hyldig 2018b). Costs were estimated using data from four Danish national databases, with a time horizon of 35 days after C-section. Surgical site infection requiring antibiotic treatment within 30 days was 4.6% in the sNWPT arm, compared to 9.2% in the standard dressing arm. The average total health care costs in the intervention and control group were €5,667 and €5,625, respectively. The authors report that NWPT was cost-effective with an additional cost of €920 per surgical infection avoided and €112 per QALY gained. The authors note that 1.02 PICOs were used compared to 1.12 standard dressings, and an SSI was associated with additional costs of €2,205.

The EAC considered this publication weak. Quality of life observed at 30 days after surgery has been extrapolated over the patients' remaining average life expectancy to generate QALYs. This is likely to massively overestimate the QALY gain attributable to sNWPT rendering the cost per QALY data invalid. There are further concerns regarding the analysis of costs. The base case analysis was a complete case analysis which excluded two women in the intervention arm with missing hospital data who had a deep SSI requiring surgery. These women were included in a sensitivity analysis which showed a modestly larger cost increase for sNWPT compared with standard dressings. However, median costs were used to impute the missing data; given the nature of the women's infections this seems highly likely to underestimate their costs.

The EAC found the existing economic evidence to be of mixed quality. Given the short time horizon that would be sufficient to capture the incremental benefits and costs of sNPWT it is quite feasible to undertake evaluation alongside a trial and collect resource use data prospectively. For this reason the EAC would place more weight on evidence from trial based analysis. Both the trial based analyses estimated moderate additional costs associated with the use of sNPWT and one of the two trials may have underestimated those costs. The EAC considers this evidence to indicate that costs are increased, alongside an improvement in patient outcomes, with sNPWT in obese women undergoing C-section. The remaining analyses indicate the potential for sNWPT to reduce costs in other types of surgery, but here the evidence is weaker.

Overview and critique of the company's critical appraisal for each study

The sponsor used the suggested tables to summarise each study's location, model and comparators, patient population, costs, patient outcomes, and results for 5 studies. Further, the sponsor also completed quality assessment for each health economic study included. In the opinion of the EAC, the critical appraisal for each of the included studies has been appropriately performed.

Does the company's review of economic evidence draw conclusions from the data available?

The sponsor concludes that PICO was a cost-effective intervention in preventing SSC. Three studies (Nherera 2017, Galiano 2018b (unpublished), Nherera 2018 (in press) concluded that PICO was cost saving. Heard 2017 and Hyldig 2018b concluded that PICO was cost-effective in obstetric surgery. The overall conclusions from these studies is that PICO provides value for money to the healthcare payers and patients.

4.2 Company de novo cost analysis

Given the limitations of the existing economic analysis, the company has undertaken a de novo cost analysis exploiting data from a UK observational study amongst others on the cost and frequency of SSIs alongside the sponsor's own meta-analysis of the effectiveness of PICO in reducing SSI and dehiscence.

Patients

The model considers a generic surgery patient and patients undergoing surgery in six broad sub specialties: orthopaedic, colorectal, C-section, breast, vascular and cardiothoracic surgery. In addition, the sponsor has undertaken subgroup analysis for patients in each of the above sub specialties perceived to be at higher risk of complication due to the following risk factors: BMI>30; ASA grade≥3; smoking; or diabetes.

Technology

The technology, PICO, is a device for applying negative pressure to the wound bed. The device consists of an adhesive dressing to which a pump is attached. The device is designed for seven days use and it is then discarded. Each device is sold with an additional dressing that allows a single dressing change during the period.

Comparator(s)

The comparator is a standard film dressing. The sponsor's analysis assumes the dressing is changed four times (five dressings) during the course of post-operative recovery in hospital. Evidence to support this assumption was obtained from clinical experts consulted by the sponsor.

Model structure

The analysis uses a simple decision tree to estimate the total cost impact of using PICO compared with a standard dressing. The decision tree includes two potential complications, SSI, and dehiscence. The tree enables the calculation of the incremental cost of PICO compared to a standard dressing after including the dressing cost and the cost implications of a SSI or dehiscence. The model structure is shown in Figure 1 below.

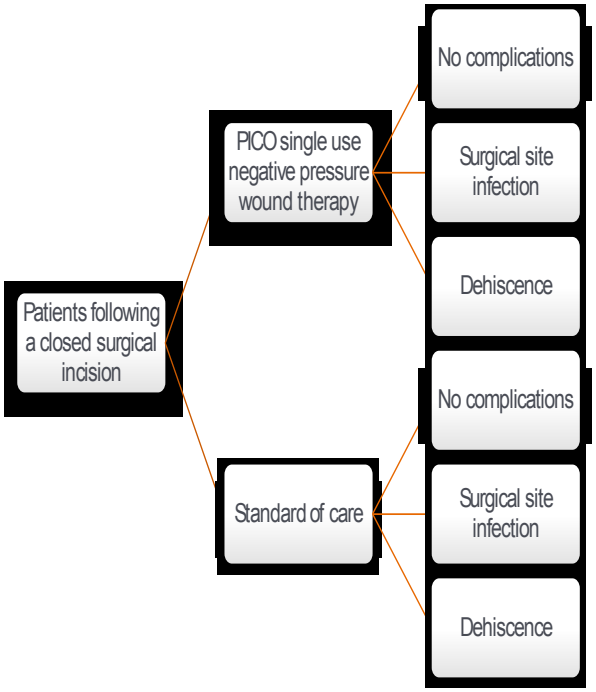


Figure 1: Structure of the decision tree in the sponsor's cost model.

The model makes some simple assumptions with regard to the cost of dressing the wound. A single PICO kit or 5 standard dressings are assumed sufficient for the duration of the patient's post-operative recovery. Further, any staff costs to apply or change the dressings during healing are implicitly assumed to be the same across the 2 comparators. The sponsor indicates the model applies a time horizon of 90 days in as far as it assumes that any adverse events influenced by dressing choice will manifest in this period. The EAC notes that the main source of data on the incidence of SSI covers a period of 28 days following surgery.

The sponsor was unable to find detailed data on the cost of dehiscence and has assumed that the cost of managing dehiscence is the same as the cost of managing SSI either overall, or according to the particular type of surgery.

The EAC considers the model structure to be appropriate.

Summary of the base case

The sponsor's analysis indicates a cost saving with PICO, both overall and for colorectal, vascular and cardiothoracic surgery. Costs with PICO are modestly higher for othopeadic, C-section and breast surgery. The results are summarised below.

Table 17: Company's base case results

	Cost of dressings and adverse events		
Surgical area	PICO	Standard dressing	Cost saving for PICO
All surgery	£454	£555	£101
colorectal surgery	£1,389	£2,033	£644
vascular surgery	£283	£308	£25
cardiothoracic surgery	£251	£552	£302
orthopeadic surgery	£243	£215	-£27
C-section	£212	£153	-£59
breast surgery	£120	£189	-£69

The company undertook sensitivity analysis varying the following parameters: effectiveness of PICO on SSI, effectiveness of PICO on dehiscence, baseline SSI rate, baseline dehiscence rate, SSI cost, dehiscence cost (assumed zero), and PICO cost. Ranges were informed by 95%CIs or +/-25% for costs. Sensitivity analysis was presented for all surgery rather than by category and indicated that the finding that PICO is cost saving was robust to parameter uncertainty.

Clinical parameters and variables

The sponsor has taken data on the incidence of SSI and dehiscence from a number of sources including a trial of PICO and observational studies. One large, recent UK observational study provides data on SSI for all surgery and in the categories of vascular, breast and cardiothoracic surgery (Jenks 2014). The EAC considers this an appropriate source and notes that the study is large, relevant to UK practice and appears to have been thoroughly executed. The study documents SSIs occurring during admission, during readmission

and during the 28-day period post discharge. The latter data was collected by mailed questionnaire with telephone follow-up (if necessary) to confirm infection. The EAC notes that the sponsor references the source of the data on SSI following breast cancer to a different study (Tanner 2011). However, the data is consistent with Jenks (2014) and not Tanner (2011). The EAC regards Jenks 2014 as a more appropriate source, primarily due to the much larger sample size.

Data on the rate of SSI after C-section is drawn from a large observational study of 14 hospitals in the UK undertaken in 2009. The study collected evidence of infections up to 28 days postpartum in 4,107 women. The EAC considers this a robust source. However, the EAC believes that Jenks 2014, whilst reporting a smaller sample size of 1,837 women, to be a superior choice. The EAC considers it advantageous to use the same source for the rate of SSI and the cost of SSI where possible, since differences in definition and identification of SSI may affect both rates and costs.

Data on the rate of SSI following colorectal surgery is taken from an observational study of 105 patients in a single hospital in the UK. The rate is particularly high at 27%. The authors note that their findings are much higher than nationally reported rates at the time (Health Protection Agency 2008) and assign the difference to better surveillance in their study. The EAC notes that the sample is much smaller and the SSI rate is much higher in this study compared to Jenks 2014 (data on large bowel operations). The EAC regards Jenks 2014 as a better source of data on the rate of SSI after colorectal surgery.

Data on the rate of SSI in orthopaedic surgery is taken from the control arm of a trial of PICO in patients undergoing hip and knee replacement surgery. There were 6 reported infections in 107 patients. The EAC notes that this rate is high for hip and knee surgery and much higher than the rate reported in Jenks 2014, which included 980 patients undergoing hip surgery and 970 patients undergoing knee surgery. The EAC believes the data from Jenks 2014 is more representative of UK practice. The EAC notes that data on infection after orthopaedic surgery is also available from a recent meta-analysis (Krishnan 2016). That meta-analysis of 13 studies and 1,255 patients reported 38 infections generating a rate of SSI very similar to the rate reported by Jenks 2014.

Data on dehiscence after colorectal surgery is taken from a meta-analysis of 39 studies including 24,432 patients (Cong 2014). The authors reported a total rate of dehiscence of 8.6% and a rate of dehiscence requiring surgery of 5.4%. The EAC notes that there appears to be no statistical assessment of

the heterogeneity of studies prior to pooling data. However, given the sparsity of evidence, the EAC considers this the most appropriate source of data.

Data on dehiscence after orthopaedic surgery is taken from a recent meta-analysis of 7 studies including 749 patients and intended to compare rates of complications using staples and sutures to close wounds (Krishnan 2016). The EAC consider this an appropriate source of data.

Data on dehiscence after C-section is taken from Subramanian (2014). The study reports secondary analysis of risk factors for wound disruption based on data collected as part of an RCT comparing sutures with staples (Figueroa 2013). The analysis excluded 58 patients from the original trial due to infection or loss to follow-up, leaving 340. The sponsor has estimated the dehiscence rate on the original trial recruitment (n = 398) rather than the 340 reported in Subramanian (2014) generating a rate of 6.5%. The EAC notes the original trial (Figueroa 2013) reports dehiscence, SSI and a composite outcome consisting of both dehiscence and SSI. This allows the extraction of data on rates of dehiscence without SSI, which is important to avoid double counting the costs of SSI in the model. Figueroa (2013) reports 30 patients from 398 with dehiscence of which 4 had a co-infection. The resulting rate of dehiscence without SSI of 6.5% is consistent with the values applied by the sponsor.

Data on dehiscence after breast surgery is taken from a recent systematic review of complications following breast surgery (Piper 2016). The EAC notes that data has been pooled across 986 patients in 12 studies without assessment of heterogeneity. However, the EAC considers this study to be the most authoritative source. The EAC notes that the numerator and denominator for the dehiscence rate is incorrectly reported by the sponsor. However, the overall rate of 4.6% is correct.

Data on dehiscence after vascular surgery is taken from a Cochrane review of staples versus sutures for wound closure after vein graft harvesting that included 3 trials (Biancari 2010). The EAC considers the source appropriate.

Data on dehiscence after cardiothoracic surgery is taken from a large recent observational study at a single centre in Italy, which included 7,148 patients (Tarzia 2014). The EAC considers the source appropriate. However, the EAC notes that of the 152 patients with dehiscence, 66 had a co-occurring infection. The rate of dehiscence without infection is 1.2%. To avoid the risk of overcounting the costs of dehiscence and SSI the EAC believes that the rate of dehiscence without concomitant infection should be used.

In order to estimate the baseline risk of dehiscence across all surgeries the sponsor has pooled data across the six studies informing the risk of dehiscence across the sub specialties examined. The calculation is incorrect due to errors in the transcribing of data from Piper 2016. The impact of this is likely to be minor. Of more concern is that the data on colorectal surgery (Cong 2014) is from a large study and provides nearly three quarters of the overall total pooled patients. Assuming that dehiscence is more likely in colorectal surgery than in some other types of surgery, this is likely to overestimate the overall rate of dehiscence. The EAC accepts the need to derive an average rate from studies reporting rates of dehiscence for different types of surgery. The EAC believes a superior estimate could be derived by weighting dehiscence rates across the subspecialties by the number of procedures reported in that category by Jenks 2014.

Data on risk factors for SSI after different types of surgery is taken from analysis reported in a number of small studies. Data for orthopaedic surgery is reported to be taken from a trial of PICO including 220 patients in which 7 infections were reported (Karlakki 2016). However, the EAC was unable to reconcile the parameters used in the model with the data reported in Karlakki or Nherera 2017.

Data on risk factors for SSI after C-section is taken from Wloch 2012 which includes 4,107 women. The EAC regards this as an appropriate source. The study considered ASA grade, diabetes, and BMI amongst other risk factors, but not smoking. In a multivariable model, only BMI was significantly associated with risk of SSI. The sponsor reports extracting RR from Wloch. The EAC notes that RRs have been calculated from raw data on SSI across risk groups rather than by applying reported unadjusted or adjusted ORs from the study. Such an approach regenerates the raw SSI risk for the relevant subgroup when the RR is applied to the overall SSI risk in the cost model. The EAC considers this approach acceptable. The EAC regards Wloch 2012 as an appropriate source of data on risk factors for SSI after C-section.

Data on risk factors for SSI after breast surgery is taken from Tanner 2011. The EAC notes that this is a small study of 159 women. The sponsor has derived ratios from the raw data for risk groups compared with the overall rate of SSI rather than applying odds ratios derived from multivariable modelling. The EAC notes that the application of these ratios to the overall rate of SSI returns the raw risk for the relevant patient subgroup. The EAC considers this approach acceptable.

Data on the risk factors for SSI after cardiothoracic surgery is taken from Olsen 2002. The EAC considers this an appropriate source of data but was

unable to reconcile the ORs reported by the sponsor with the data reported in Olsen.

Data on the risk factors for SSI after vascular surgery is taken from NICE guidance on prevention of SSI (NICE CG74). The EAC considers this an appropriate source but notes that the document reviews the literature and provides estimates of ORs for different risk groups from a range of studies. Meta-analysis is not undertaken. It is not altogether clear which studies have provided the RR data used in the sponsor's model.

The EAC notes that the sponsor has taken a mean of the risk factors for SSI for each of the clinical areas (C-section, cardiothoracic, breast, colorectal, orthopaedic, and vascular) to derive the RR for SSI across elevated risk factors for all surgery. The EAC does not consider this approach sufficiently robust. The EAC considers the recent review published as part of the NICE guidance on prevention of SSI (NICE CG74) to be a better source of data on the impact of elevated risk factors across multiple types of surgery.

The sponsor reports contacting 10 clinicians with experience in surgery to assess the sponsor's clinical inputs and analysis. Five responded including a gynaecologist, a colorectal surgeon and two orthopaedic surgeons. The company also engaged two health economists to comment on the cost model. The advisors commented on the model and the source of parameters. It is unclear whether the model was revised following this consultation.

The sponsor has estimated the overall effectiveness of PICO on SSI and dehiscence by undertaking a meta-analysis to pool odds ratios reported across trials and observational studies. The resulting pooled odds ratio has been directly applied to the baseline risk for SSI or dehiscence both for all surgery and across surgical sub specialties. Such an approach is likely to overestimate the impact of PICO (Liberman 2005). A more robust approach is to convert the baseline risk of the event to odds, apply the relevant odds ratio, and then convert back to an adjusted risk. This method ensures that any adjusted risk falls within the range of 0-100%.

Resource identification, measurement and valuation

Data on the cost of SSI has been taken almost exclusively from Jenks 2014. This study used patient level information and costing system (PLICS) data to extract hospital costs for patients diagnosed with an SSI during the index stay or after readmission. The EAC considers this an appropriate source of data, as the study is relatively, large, recent, robustly executed, and exploits detailed costing data available from PLICS. Costs for patients with an SSI are

compared against costs for a cohort of patients matched on NNIS score (Culver 1991) using 8 matches for each patient with an SSI. The matching procedure is not reported in detail. The study reports the median cost attributable to an SSI for all surgeries and across 19 surgical sub specialties. The sponsor has estimated the mean cost using data on the median cost and range by applying a published method (Hozo 2005). Costs were then uprated to 2016 values.

The EAC notes that Jenks (2014) reports the total cost attributable to SSI along with the number of SSIs both overall and by surgical specialty allowing the calculation of the mean cost attributable to SSI. Hence, the EAC regards the mean cost calculated from the data in Jenks to be more appropriate than an estimate based on the median cost.

Data on the costs of colorectal surgery has been taken from Tanner 2009. The study followed 105 patients for 30 days post-operation by telephone for discharged patients. Costs were estimated based on resource use reported by the patients using standard UK sources for unit costs such as Unit Costs of Health and Social Care. This approach has the advantage that the data includes primary care costs (not captured by Jenks 2014). However, inpatient costs are likely to be less accurate than Jenks. Tanner (2009) reports that 15% of all costs were incurred in primary care. The sponsor has used this figure as the basis for an estimate of the costs of SSI treated in primary care. The EAC accepts this approach but notes that post discharge costs reported in Tanner (2009) may have accrued to patients readmitted as well as those treated in the community. Consequently, it may represent an overestimate of the relative costs of SSI treated in the community compared with SSIs occurring during the index admission or leading to readmission.

The sponsor has estimated the proportion of SSIs treated in hospital and applied the costs reported in Jenks 2014 to that proportion (with the exception of colorectal surgery where costs are taken from Tanner 2009). Costs for SSIs treated in the community are assumed to be 15% of the relevant costs reported in Jenks 2014. A weighted mean cost for SSIs treated in hospital and in the community is then calculated. The EAC considers this approach acceptable. However, the EAC could not reproduce the sponsor's estimates of the proportion of SSIs treated in hospital based on the data reported in Jenks 2014.

The sponsor has estimated the cost for an SSI across all surgeries by taking the weighted mean of the cost calculated across the 6 sub specialties (orthopaedic, colorectal, obstetric, breast, vascular and cardiothoracic surgery) considered. The EAC views the data in Jenks (2014) reported across all 19 specialties to be a better source of the estimate of the cost of an SSI

across all surgeries. The resulting cost is slightly lower than the value the sponsor has calculated and applied in the cost model.

The sponsor reports that very little data is available on the cost of dehiscence. The sponsor has assumed that the cost of treating dehiscence is the same as the cost of treating SSI. In support of this, the sponsor cites a study by Zoucas (2014) which reported the impact on costs of surgical complications including dehiscence and infection for 530 patients undergoing colorectal surgery in a single hospital in Sweden. The authors report total mean costs for patients with dehiscence of €47,000 (2010 Euro) compared to €27,000 €21,000 and €12,000 for patients with a deep wound infection, a superficial infection or no complication, respectively.

The EAC accepts the paucity of data on the cost of dehiscence. The EAC notes that an Australian study of the treatment of wound dehiscence in a primary care setting reported costs of $800 (2010AUD) equivalent to £400 (Sandy-Hodgetts 2016). The costs are likely to be an underestimate as they did not include staff overheads or travel costs. These costs are lower than the costs estimated by the sponsor for treating SSI in the community. The EAC also found a US study comparing the additional cost attributable to complications after cystectomy (Mossanen 2017). That study reported additional costs for wound and soft tissue complications (of which most were dehiscence) which were slightly lower than additional costs due to infection. The EAC considers the sponsor's assumption on the cost of treating dehiscence to be acceptable in the absence of stronger evidence.

Technology and comparators' costs

The sponsor has based the technology cost on a weighted average of the list price for PICO kits of different sizes. The sponsor reports that the weights are based on sales volume The EAC regards this as acceptable although it is unable to verify the weights. The sponsor has assumed that a single PICO kit is used for each patient. A justification for this assumption is not provided. The EAC notes that the limited data available on PICO indicates that more than one device is typical used. Data are reported predominantly in the form of dressing changes or LOS. Neither allow definitive calculation of the number of PICOs used. Karlakki (2016) report a mean number of dressing changes of 2.5 in the PICO arm (PICO comes with two dressings). This indicates a minimum of 1.25 PICOs per patient but is likely to be more. Galiano 2018b reports a mean duration of PICO application of 10.9 days (median 7 days) after excluding a centre that routinely applied PICO until discharge. A median of 7 days would infer that roughly half of patients required only one PICO (PICO is designed to be used for 7 days). On this basis, the data in Galiano (2018b) imply a minimum use of 1.5 PICOs per patient.

The sponsor has based the cost of the comparator on the cost of five standard foam dressings. The dressing cost is estimated at £2.50. The EAC considers the estimate of the dressing cost to be reasonable. However, the EAC believes that four dressing changes over the course of a week is an over estimate. The EAC consulted with expert advisers on this issue and most were of the view that a dressing should not be changed daily. The EAC believes that an estimate of one dressing change per week would be more appropriate. However, the relevant period of application of dressings is likely to be longer than one week. Data on PICO indicates it is used for a mean of 11 days (Galiano 2018b). Over the same period, the EAC believes that 2-3 dressing changes are likely, generating total dressing costs of £7.50 to £10 for standard care.

Sensitivity analysis

The sponsor has undertaken both one-way and probabilistic sensitivity analysis on the impact of parameter uncertainty for estimate of the cost impact across all type of surgery. Sensitivity of the results to all parameters in the model has been analysed. Where possible ranges for sensitivity analysis have been informed by 95% confidence intervals for the available data. This was not possible for costs and hence the sponsor has varied the cost of treating an SSI by +/-25%. The cost of PICO has been varied across the range of values forming the list prices for the different sized dressings. Appropriate distributions have been selected for each of the parameters in the probabilistic analysis. The sponsor has also undertaken analysis in which the impact of PICO on dehiscence is excluded. The EAC considers this approach acceptable.

The results of the one-way sensitivity analysis undertaken by the sponsor are tabulated in Table 18 below. The sponsor reports the results are robust to variation in each parameter and the graphical evidence supports this. The EAC notes that the lower estimate of the SSI incidence rate generates a cost saving for PICO that is very close to zero. The sensitivity analysis in which dehiscence is ignored generates the next largest impact on the cost saving for PICO. Unsurprisingly, uncertainty in the baseline rate of dehiscence and the effectiveness of PICO on dehiscence generates less variation in the overall cost saving attributable to PICO. The cost saving attributable to PICO is relatively stable to variation in the cost of SSI. Variation in the effectiveness of PICO on SSI and the cost of PICO have relatively little impact on the cost saving attributable to PICO.

Table 18: One-way sensitivity on key model parameters reported by the sponsor.

Parameter	Lower Figure	Upper figure	Lower Figure	Upper figure
PICO costs	£128	£147	-£103.73	-£83.87
SSI costs	£3,379	£5,632	-£46.17	-£155.29
Baseline SSI rates	0.015	0.18	-£1.79	-£455.27
Baseline dehiscence rates	0.013	0.093	-£37.31	-£127.42
Effectiveness PICO SSI	0.29	0.52	-£123.71	-£70.86
Effectiveness PICO dehiscence	0.57	0.99	-£156.94	-£25.79
Exclude dehiscence			-£22.67	

Inference from the one-way sensitivity analysis was supported by the probabilistic analysis in which only one of the 2000 simulations generated higher cost for PICO than the comparator.

The EAC regards the sponsor's approach to sensitivity analysis as appropriate. The EAC believes that the sensitivity of the results to the assumptions on the cost of SSI treated in primary care and the number of PICO devices required should be examined.

The sponsor has undertaken analysis of the impact of PICO on costs for patients at elevated risk in six different surgical sub specialties (C-section, breast, colorectal, vascular, cardiothoracic and orthopaedic surgery). The sponsor reports results for patients with ASA grade ≥3, BMI>30 and patients who smoke. The results are tabulated below. In the base case, PICO was cost saving in cardiothoracic, vascular, and colorectal surgery. Unsurprisingly, in each of these three surgical areas PICO remained cost saving for patients with elevated risk factors. In the base case, PICO was modestly cost incurring in orthopaedic surgery, C-section and breast surgery. For patients with elevated risk factors undergoing breast surgery and C-section, PICO remains cost incurring with the exception of obese patients undergoing C-section. For patients with any of the three elevated risk factors undergoing orthopaedic surgery, PICO is cost saving.

The EAC accepts the sponsor's approach to the evaluation of PICO in patients with elevated risk factors but notes the underlying concerns regarding the application of ORs for PICO in the model, the cost of PICO and the particular concerns regarding the estimation of the baseline risk of SSI in orthopaedic surgery.

Table 19: Subgroup analysis in patients with elevated risk factors for SSI undertaken by the sponsor.

	Cost saving for PICO					
Risk Factor	Colorectal	Cardio-thoracic	Vascular	Ortho-paedic	C-section	Breast
Base case	£644	£302	£25	-£27	-£59	-£69
ASA≥3	£685	£1,238	£123	£173	-£32	-£49
Diabetes	£715	£1,036	£126	£137	-£31	-£31
BMI≥30	£1,166	£968	£48	£98	£59	-£35

4.3 Interpretation of economic evidence

The EAC accepted much of the data that underpins the sponsor's submission and considered the sponsor's model to be appropriate. However, The EAC favoured the use of a single source of data on the incidence of SSI and the cost of treating those incidents. The EAC thinks it likely that a broader definition of SSI will generate a higher incidence but a lower mean treatment cost as more minor infections are included. For this reason the EAC used Jenks 2014 as the source of data on the incidence of SSI and the inpatient cost implications. Lacking data on the cost of SSI treated in the community the EAC retained the assumption in the sponsor's model that these costs would be 15% of the inpatient cost (based on the data in Tanner 2009).

The EAC notes that while Jenks 2014 appears to have been a well-executed study in general, the authors do not mention the price year in which costs are reported. This raises the concern that costs falling in different years were not reflated to a single price year before pooling. Costs were collected over two financial years, 2010/11 and 2011/12. Hence the impact of not inflating costs is likely to be small. The sponsor has inflated costs from the year 2011/12 effectively assuming that costs in 2010/11 were inflated to 2011/12. The EAC thinks this is a reasonable assumption but notes that if half the data were collected in the previous year and not inflated, costs will have been underestimated by about 1%.

The EAC considered the assumption that a single PICO device would be used per patient to be inappropriate. Whilst the available evidence on the number of PICOs used is limited that evidence suggests that more than one device will be used on average. The EAC made the following assumptions: the PICO device would be used for the entirety of the inpatient stay; the same device would be used to treat SSI and dehiscence when either occurred. The EAC selected data on length of stay (LOS) with and without infection from Jenks 2014. That data is reported as the median. The EAC assumed LOS is normally distributed (and hence mean = median) and that the standard deviation was one quarter of the mean value. The EAC was then able to estimate the number of PICOs required according to the distribution of LOS and assuming that each additional week commenced in hospital required the use of a new device. The EAC notes that the true distribution of the LOS data is likely to be right skewed and that an assumption that the standard deviation is one quarter of the mean is likely to be an underestimate. For both of these reasons the EAC is likely to have underestimated the number of weeks patients commence in hospital. If a new PICO is used at the start of each new week, the number of PICOs used per patient will also have been

underestimated. The EAC made the same assumptions regarding the use of a standard dressing with the exception that it was assumed that a standard dressing is changed every three days. The EAC retained the sponsor's assumptions regarding the costs of PICO and standard dressings of £130 and £2.50, respectively.

The EAC calculated mean costs for SSI from the data on total costs of SSI and the number of SSIs in Jenks 2014 rather than generating an estimate from the median costs reported in Jenks 2014, as the sponsor chose to do. The EAC applied data from Jenks 2014 on costs combined across all surgical sub specialties; this is a change from the sponsor's submission in which mean costs for SSI for all surgeries was calculated as a weighted mean costs for SSI across the six sub specialties (cardiothoracic, vascular, colorectal, orthopaedic, breast and C-section) reported in Jenks 2014. The EAC notes a slight irregularity in Jenks 2014 in that the total costs for all 282 SSIs does not equal the sum of the total costs across each of the 19 sub specialties reported. The difference is around 0.1% and seems likely to have arisen from an error of reporting for one of the figures.

The EAC retained the sponsor's assumption that the cost of dehiscence is the same as the cost of SSI. More specifically, the EAC assumed the cost of dehiscence was the weighted mean of inpatient and outpatient SSI costs taken from data in Jenks 2014 and assuming outpatient costs are 15% of inpatient costs. The EAC accepted the sources of data on the incidence of dehiscence in the sponsor's submission but revised estimates for cardiothoracic surgery to exclude cases of dehiscence and SSI. This was done to avoid double-counting the cost of SSI. The EAC also revised the sponsor's estimate of the overall rate of dehiscence for all surgery. The EAC took a weighted mean of values for each of the sub specialties (cardiothoracic, vascular, colorectal, orthopaedic, breast and C-section) with weights derived from the number of procedures in each category in the total sample of patients in Jenks 2014.

The EAC used a simple mean of costs for hip and knee surgery, by category and overall, to report the impact of PICO on orthopaedic costs after noting that the number of hip and knee procedures reported by Jenks (2014) is very similar (970 and 980).

The EAC updated the sponsor's estimates of the effectiveness of PICO on SSI and dehiscence based on the meta-analysis conducted by the EAC and applying odds ratios derived from meta-analyses of RCTs only. There were two exceptions where the EAC did not apply an OR derived from meta-analyses of RCTs only. Only one observational study was available for cardiothoracic surgery so the OR derived from this study was used. Only a

single very small RCT was available for colorectal surgery so the OR derived from meta-analyses of observational studies and RCTs in colorectal surgery was applied.

Finally, the EAC converted risks of SSI or dehiscence to odds prior to application of the relevant odds ratio to estimate the impact of PICO. The resulting amended odds were converted back to a risk prior to application in the model. The impact of this change in the application of the odds ratio will have been to slightly increase the likelihood of complications with PICO (where the odds ratio is less than one).

4.4 Results of EAC analysis

Base-case analysis results

Table 20 reports the cost impact of PICO compared with standard dressings, both overall and for each of the sub specialties: C-section, cardiothoracic, vascular, colorectal, orthopaedic, and breast surgery. The EAC found PICO to be cost incurring in the sub specialties of orthopaedic surgery, C-section and breast surgery. Overall, and in the sub specialties of colorectal surgery, vascular surgery and cardiothoracic surgery PICO was cost saving. It is notable that the number of PICOs used is higher in these sub specialties, driven by higher LOS. PICO is cost saving despite this due to the costs of SSIs avoided. These cost savings, in turn, are driven by the higher incidence of SSI in these sub specialties, and in the case of cardiothoracic surgery the high effectiveness of PICO. It should also be noted that the effectiveness of PICO in vascular and colorectal surgery is derived from meta-analyses of studies that were primarily or entirely observational studies. The EAC observed a tendency for observational studies to find higher effectiveness of PICO that that derived from RCTs.

Table 20: Base case cost estimates

Specialty	Costs with PICO					Costs with standard dressing					Cost saving for PICO
	Inpat SSI	Outpat SSI	Dehisc	Dress	Total	Inpat SSI	Outpat SSI	Dehisc	Dress	Total	
All surgery	£98	£24	£176	£143	£440	£186	£45	£210	£6	£446	£6
colorectal surgery	£229	£20	£348	£236	£833	£523	£49	£383	£9	£963	£131
vascular surgery	£67	£13	£362	£169	£612	£256	£51	£396	£7	£710	£98
cardiothoracic surgery	£57	£29	£60	£206	£352	£462	£221	£76	£8	£767	£415
othopeadic surgery	£23	£5	£115	£165	£308	£63	£14	£140	£6	£223	-£85
C-section	£29	£21	£46	£131	£227	£57	£39	£82	£3	£180	-£47
Breast surgery	£20	£8	£61	£130	£219	£55	£21	£73	£3	£152	-£68

Inpat SSI – inpatient managed surgical site infection, Outpat SSI – SSI managed in primary care; Dehisc – dehiscence; Dress – dressing

Sensitivity analysis results

The EAC undertook sensitivity analysis on the impact on overall surgical costs of varying the following parameters: cost of PICO; cost of standard dressing; cost of SSI managed in primary care as a proportion of the inpatient cost; PICO effectiveness; baseline risk of SSI; cost of SSI; and cost of dehiscence. Where data on the variance of the statistic for the original estimate was available this informed the range over which the parameter was varied. Otherwise, the parameter was varied over the range +\-50%. We assumed the magnitude of the confidence interval for the mean cost of SSI for all surgeries was the same as the magnitude of the confidence interval for the median cost attributable to SSI for all surgeries as reported in Jenks 2014, and that the point estimate was similarly located within the range of values. In addition, the EAC undertook a sensitivity analysis in which the effectiveness for PICO was derived from the meta-analysis undertaken by the EAC of RCTs and observational studies combined. The results are tabulated in Table 21 along with the base case values for comparison.

Table 21: One-way sensitivity analysis undertaken by the EAC.

		PICO		Standard dressing		Cost saving for PICO
Parameter varied	Value	Comp costs	Dress costs	Comp costs	Dress costs	
Base case		£298	£143	£441	£6	£6
PICO cost	£65	£298	£71	£441	£6	£77
	£195	£298	£214	£441	£6	-£65
Standard dress cost	£1.25	£298	£143	£441	£3	£3
	£3.75	£298	£143	£441	£8	£9
PICO effectiveness	0.31	£250	£143	£441	£6	£54
	0.82	£373	£143	£441	£6	-£70
Risk of inpatient SSI	1.74%	£286	£142	£419	£6	-£4
	2.20%	£309	£143	£462	£6	£15
Risk SSI primary care	2.87%	£296	£143	£437	£6	£4
	3.44%	£300	£143	£445	£6	£8
Cost of inpatient SSI	£8,836	£278	£143	£412	£6	-£3
	£10,933	£344	£143	£510	£6	£28
SSI cost primary care	£709	£269	£143	£398	£6	-£8
	£2,127	£327	£143	£483	£6	£20
Dehiscence cost	£2,255	£210	£143	£336	£6	-£11
	£6,764	£386	£143	£545	£6	£23
PICO eff. from RCTs and obs. studies	0.37	£264	£143	£441	£6	£40
Comp – complication; Dress – dressing; eff. – effectiveness; obs. studies – observational studies						

The inference that PICO is cost saving is sensitive to the majority of parameters varied. This is unsurprising as the base case suggests a small cost saving with PICO. The parameter that had the largest impact on overall cost was the cost of PICO. When this was varied across the range +\-50% the overall cost saving with PICO varied from -£65 to £77. However, the EAC notes that the cost of PICO is determined by the manufacturer and uncertainty in this parameter relates to future pricing strategy rather than sampling uncertainty. The parameter with the second largest impact on overall cost was the effectiveness of PICO. Across the range spanned by the 95% confidence interval for this parameter, the cost saving for PICO varied from -£70 to £54. Other parameters had a smaller impact on the cost saving attributable to PICO; the largest negative cost saving of -£11 was associated with a 50% reduction in the cost of managing dehiscence.

The EAC undertook further sensitivity analysis to examine in detail the impact on overall costs of the variation in price for PICO dressings of different sizes. Sensitivity analysis was undertaken for the category of all surgeries. The results are tabulated in Table 22 below. The breakeven price of PICO is £135.

Table 22: Sensitivity analysis using list prices for different sized PICO dressings

PICO Dressing sizes	Unit cost	Cost saving for PICO
10cm x 20cm	£128.09	£8
10cm x 30cm; 15cm x 15cm; 15cm x 20cm; 15cm x 20cm	£127.45	£9
10cm x 40cm; 15cm x 30cm; 20cm x 20cm; 25cm x 25cm; 20cm x 25cm	£146.86	-£13

Subgroup analysis

The EAC undertook subgroup analysis for patients with elevated risk factors for all surgery and for C-section. The EAC considered patients with diabetes, patients who smoked, patients with ASA grade≥3, and patients with BMI>30. For C-section the EAC retained the data on the impact of elevated risk factors extracted from Wloch by the sponsor. This study was considered large enough to support such an analysis as it reported on over 4,000 women. The EAC sought evidence from studies which reported the raw data rather than increased risk in the form of ORs or RRs. Application of a RR or an OR to the rate for all patients observed in Jenks 2014 would have over-estimated the incidence of SSI in that group. This is because the data in Jenks 2014 includes patients with elevated risk. Consequently, the EAC used the raw data

to derive an OR for patients from the study with an elevated risk factor compared to all patients in the study. The OR was applied to the odds of acquiring a SSI derived from Jenks 2014 and the resulting adjusted odds converted back to a risk before application in the model.

Data on the impact of ASA grade on risk of SSI in all surgeries was taken from Kaye 2005 that reported data on 144,485 patients at 11 hospitals undergoing a range of procedures of which 41% were orthopaedic surgery. Kaye reported an odds ratio of 3.0 for an ASA grade≥3 compared to patients with ASA grade<3. The raw data shows a rate of SSI of 1.2% overall, 0.73% in patients with ASA grade<3 and 2.1% in patients with ASA grade ≥3. Data on the impact of smoking, diabetes and BMI>30 on risk of SSI in all surgeries was taken from Ridderstolpe 2001 which reported data on 3008 patients at Linkoping university hospital, Sweden undergoing cardiac surgery. The overall rate of SSI was 9.67%.

Table 23 and Table 24below report the impact of elevated risk on costs for all surgeries and for C-section. Not surprisingly, for all surgeries combined there is a cost saving associated with PICO use and this is higher than the base case. For patients in the groups ASA grade≥3, diabetes and BMI>30, the ORs for elevated risk of complications are of a similar magnitude, and the cost savings with PICO fall in the range £82-95. In the case of C-section PICO is not cost saving in any of the three risk groups: ASA grade≥3, diabetes and BMI>30.

Table 23: Impact of elevated risk on costs across all surgeries

		PICO		Standard dressing		Cost saving for PICO
Risk factor	OR	Comp costs	Dress costs	Comp costs	Dress costs	
ASA grade≥3	1.78	£538	£147	£761	£6	£82
Diabetes	1.87	£566	£147	£796	£6	£89
BMI>30	1.95	£594	£148	£832	£6	£95
Smoker	1.20	£357	£144	£523	£6	£28
Comp – complication; Dress – dressing; eff. – effectiveness; obs. studies – observational studies						

Table 24: Impact of elevated risk on costs for C-section

		PICO		Standard dressing		Cost saving for PICO
Risk factor	OR	Comp costs	Dress costs	Comp costs	Dress costs	
ASA grade≥3	1.51	£146	£131	£261	£3	-£14
Diabetes	1.57	£152	£131	£270	£3	-£10
BMI>30	1.62	£157	£131	£278	£3	-£8

Comp – complication; Dress – dressing; eff. – effectiveness; obs. studies – observational studies

The EAC applied the OR for patients with BMI>30 (1.95) to the risk of complications for patients undergoing orthopaedic and breast surgery, as neither group demonstrated cost savings with PICO in the base case. For both orthopaedic and breast surgery PICO was not cost saving after increasing the risk of complications.

The EAC undertook further subgroup analysis in which the cost impact of PICO was assessed for each of the following additional surgical specialties reported in Jenks 2014 in which over 100 operations were reported: limb amputation; reduction long bone fracture; repair neck of femur; cranial; spinal; abdominal hysterectomy; Bile duct, liver, pancreatic; gastric; small bowel; and multiple intra-abdominal. Data on incidence of SSI and the additional cost attributable to SSI was taken from Jenks 2014. Incidence of dehiscence was assumed the same as that for all surgeries. The effectiveness of PICO across all surgeries in reducing SSI (OR 0.51) and in reducing dehiscence (OR 0.77) was applied in each sub specialty. PICO was cost saving in only two sub specialties: gastric and small bowel surgery.

Model validation

The EAC model was checked for errors internally but the EAC did not attempt to validate model outputs against external data.

4.5 EAC Interpretation of economic evidence

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The EAC retained the cost model submitted by the sponsor and the primary source of evidence on the incidence of SSI and the additional cost arising from SSI (Jenks 2014). The EAC also retained the sponsor's data sources on the rate of dehiscence and the assumptions regarding the additional cost attributable to dehiscence. However, The EAC made a number of changes to the way in which data was used in the model. The additional cost of an inpatient SSI estimated by the EAC from Jenks 2014 (£9,453) was very modestly lower than the estimate derived by the sponsor (£9,655). The EAC applied ORs derived from meta-analysis of the effectiveness of PICO to the odds of an SSI rather than the risk. The effect of this change is a small increase in the risk of SSI with PICO. The EAC assumed that a standard dressing would be changed every three days whereas the manufacturer

assumed five standard dressings for all procedures. The impact of this was to reduce the cost of standard dressings. The EAC assumed that PICO is used throughout the inpatient stay (including readmissions for SSI), and this led to higher costs with PICO. The impact of this assumption varies across sub specialties but for all surgery, the EAC estimated that 1.09 devices would be required per patient. The EAC notes that some patients may have extended stay in hospital for reasons unrelated to wound closure, and that for these patients, PICO may not be used for the entirety of their stay. To the extent that factors unrelated to wound closure extend LOS, the EAC's calculation will have overestimated the number of PICOs used. The number of devices estimated was considerably higher in some sub specialties: 1.81 for colorectal surgery and 1.58 for vascular surgery. The EAC's decision to derive the effectiveness of PICO from meta-analysis of RCTs (with observational studies excluded) had the largest impact on costs. The OR for SSI with PICO was revised from 0.39 to 0.51. Each of the changes listed above reduced the cost saving estimated for PICO.

5 Conclusions

5.1 Conclusions on the clinical evidence

The sponsor included in their submission 29 clinical studies (23 published in full text, 5 as conference abstracts and 1 unpublished). The EAC identified 2 more relevant conference abstracts Caswell 2015 and Luciani 2016. From the included studies, 13 were RCTs (Chaboyer 2014, Galiano 2018a, Gillespie 2015, Hyldig 2018a, Nordmeyer 2016, Karlakki 2016, O'Leary 2016, Svensson 2018, Tanaydin 2018, Tuuli 2017, Uchino 2016, Witt 2015, Zotes 2015). Five of the RCTs were adequately powered to detect a difference in the primary outcome (Galiano 2018a, Hyldig 2018a, Karlakki 2016, O'Leary 2016, Uchino 2016). The rest of the studies were non-randomised controlled studies.

The sponsor submitted a meta-analysis of all the included studies. The SSI rate analysis included 4473 participants reported in 19 full text publications (21 with conference abstracts included). Combining data from 8 RCTs including all medical specialties, provided evidence that use of PICO reduces the rate of SSIs (OR 0.49, 95%CI 0.33-0.72, p=0.0003). The pooled analysis of the 11 observational studies confirmed this result (OR 0.28, 95%CI 0.17-0.46, p <0.0001). The EAC ran additional meta-analyses based on the critical appraisal of the sponsor's analyses using a random effects model and conducting further sensitivity analyses on the results. The additional analyses confirmed the findings of the sponsor with small changes in the estimated ORs and 95%CIs for the pooled SSI rate. From the subgroup analyses, there is evidence to support the reduction of SSIs in obstetric and orthopaedic surgery, the latter mainly driven from the effect of non-randomised comparative studies. The reduction in seroma and dehiscence rates is also mainly driven by the effect of non-randomised controlled studies. The clinical experts' views and similar literature for the field of NPWT systems supports the transferability of the results in terms of the overall superiority of PICO vs. standard dressing among different surgical procedures. However, it should be noted that given the wide 95%CIs and the variability of risk factors in clinical practice, it is difficult to estimate the size of the effect for each surgical procedure separately.

5.2 Conclusions on the economic evidence

The EAC estimated a very modest saving from the use of PICO across all surgeries. This estimate was sensitive to uncertainty in the estimate of effectiveness of PICO. The estimate was less sensitive to other parameters, but the inference that PICO is cost saving was sensitive to changes in the majority of parameters examined, reflecting the small magnitude of the cost

saving in the base case. Analysis across surgical sub specialties was illuminating. Based on the data reported in Jenks 2014 PICO was not cost saving in the majority of surgical sub specialties. It was cost saving for colorectal, small bowel, gastric, cardiothoracic, and vascular surgery. These areas are notable for a higher incidence of SSI a higher additional cost attributable to SSI or both. This probably reflects the invasive nature of the surgery and comorbidities in the typical patient. The analysis undertaken by the EAC suggests that PICO is cost saving for highly invasive surgery; for surgery commonly undertaken on healthier patients such as C-section and orthopaedic surgery PICO is unlikely to be cost saving.

The EAC investigated the impact of elevated risk factors in patients undergoing more routine surgery such as breast surgery, orthopaedic surgery, and C-section. The impact of elevated risks on the baseline rate of SSI and dehiscence was insufficient to offset the additional cost of PICO. Hence the EAC concludes that is unlikely that PICO will be cost saving in routine surgery in patients at elevated risk of complications.

6 Summary of the combined clinical and economic sections

There is evidence to support the superiority of PICO in reducing the rates of SSI in comparison with standard dressing in patients with high-risk factors for SSCs. From the subgroup analyses, there is evidence to support the reduction of SSIs in obstetric and orthopaedic surgery, the latter mainly driven from the effect of non-randomised comparative studies. However, it should be noted that given the wide 95%CIs and the variability of risk factors in clinical practice, it is difficult to estimate the size of the effect for each surgical procedure separately. From the rest of the SSC some evidence exist to support the reduction in seroma and dehiscence rates, however, this is mainly driven by the effect of non-randomised controlled studies.

The EAC finds considerable uncertainty in the likelihood that PICO is cost saving. This arises because the additional cost of using PICO is similar in magnitude to the savings generated from reductions in surgical complications. The EAC notes that the evidence of effectiveness of PICO indicates the likelihood of a health benefit which would suggest that the likelihood that PICO is cost-effective is higher than the likelihood that it is cost saving.

7 Implications for research

There is a lack of adequately powered RCTs to investigate the effectiveness of PICO in SSC beyond the SSI rate. There is also a lack of adequately powered RCTs to investigate the effectiveness of PICO in quality of life. Future studies should prioritise the inclusion of a population with explicit high-risk profile for SSCs using national and international criteria. The population

selection should be based on the calculation of pre-test calculation of risk based on a validated scoring system.

Whilst there is considerable trial evidence on the effectiveness of PICO, evidence on cost-effectiveness is relatively weak. Well-designed trials including prospective data collection on resource use in both secondary and primary care, and appropriately analysed, might provide greater clarity on the cost-effectiveness of PICO.

References

Adogwa, O., P. Fatemi, E. Perez, et al. (2014) "Negative pressure wound therapy reduces incidence of postoperative wound infection and dehiscence after long-segment thoracolumbar spinal fusion: a single institutional experience." The Spine Journal 14(12): 2911-2917

Caswell, J. F., S. Graham and P. A. Whitehouse (2015) "Prophylactic Use of PICO TM Negative Pressure Wound Therapy to Reduce Surgical Site Infections Following Large Bowel Surgery." British Journal of Surgery 102(98-98

Chaboyer, W., V. Anderson, J. Webster, et al. (2014) "Negative Pressure Wound Therapy on Surgical Site Infections in Women Undergoing Elective Caesarean Sections: A Pilot RCT." Healthcare 2(4): 417-428

Culver DH, Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG, Banerjee SN, Edwards JR, Tolson JS, Henderson TS, Hughes JM. Surgical wound infection rates by wound class, operative procedure, and patient risk index. The American journal of medicine. 1991 Sep 16;91(3):S152-7.

De Vries FE, Wallert ED, Solomkin JS, Allegranzi B, Egger M, Dellinger EP, Boermeester MA. A systematic review and meta-analysis including GRADE qualification of the risk of surgical site infections after prophylactic negative pressure wound therapy compared with conventional dressings in clean and contaminated surgery. Medicine (Baltimore). 2016 Sep;95(36):e4673.

Dingemans, S. A., M. F. N. Birnie, M. Backes, et al. (2018) "Prophylactic negative pressure wound therapy after lower extremity fracture surgery: a pilot study." International Orthopaedics 42(4): 747-753

Figueroa D, Jauk VC, Szychowski JM, Garner R, Biggio JR, Andrews WW, Hauth J, Tita AT. Surgical staples compared with subcuticular suture for skin closure after cesarean delivery: a randomized controlled trial. Obstetrics and gynecology. 2013 Jan;121(1).

Fleming, C. A., M. Kuteva, K. O'Hanlon, et al. (2018) "Routine use of PICO dressings may reduce overall groin wound complication rates following peripheral vascular surgery." Journal of Hospital Infection 99(1): 75-80

Galiano, R. D., D. Hudson, J. Shin, et al. (2018) "Incisional Negative Pressure Wound Therapy for Prevention of Wound Healing Complications Following Reduction Mammaplasty." Plastic and Reconstructive Surgery Global Open 6(1): e1560 (Galiano 2018a)

Galiano RD et al; (2018b) The cost-effectiveness of single-use negative pressure wound therapy (PICOTM) vs standard care for the prevention of wound dehiscence in patients undergoing bilateral reduction mammaplasty in the USA (Manuscript under preparation) (Galiano 2018b)

Gillespie, B. M., C. M. Rickard, L. Thalib, et al. (2015) "Use of Negative-Pressure Wound Dressings to Prevent Surgical Site Complications After Primary Hip Arthroplasty: A Pilot RCT." Surgical Innovation 22(5): 488-495

Hackney, L. and A. McCoubrey (2017) "The effect of negative pressure dressings (PICO) on wound complications, readmission rates and length of stay." Colorectal Disease 19(S2): 60

Hester, T., S. Mahmood and F. Moftah (2015) "Is Single Use Portable Incisional Negative Pressure Wound Therapy System Suitable for Revision Arthroplasty?" Advances in Orthopedic Surgery 2015(4

Hickson, E., J. Harris and D. Brett (2015) "A Journey to Zero: Reduction of Post-Operative Cesarean Surgical Site Infections over a Five-Year Period." Surgical Infections 16(2): 174-177

Holt, R. and J. Murphy (2015) "PICO™ incision closure in oncoplastic breast surgery: a case series." British Journal of Hospital Medicine 76(4): 217-223

Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005 Apr 20;5:13

Hyldig, N., C. A. Vinter, M. Kruse, et al. (2018) "Prophylactic incisional negative pressure wound therapy reduces the risk of surgical site infection after caesarean section in obese women: A pragmatic randomised clinical trial."BJOG2018; https://doi.org/10.1111/1471-0528.15413 (Hyldig 2018a)

Hyldig, N. , Joergensen, J. S., Wu, C. , Bille, C. , Vinter, C. A., Sorensen, J. A., Mogensen, O. , Lamont, R. F., Möller, S. and Kruse, M. (2018), Cost-effectiveness of incisional negative pressure wound therapy compared to standard care after caesarean section in obese women: A trial-based economic evaluation. BJOG: Int J Obstet Gy. Accepted Author Manuscript. (Hyldig 2018b)

Irwin, G., L. Highton and J. Murphy (2018) "Negative pressure dressings significantly decrease rates of wound breakdown and may reduce implant loss rates in prepectoral breast reconstruction." European Journal of Surgical Oncology 44(6):

Karlakki, S. L., A. K. Hamad, C. Whittall, et al. (2016) "Incisional negative pressure wound therapy dressings (iNPWTd) in routine primary hip and knee arthroplasties." Bone & Joint Research 5(8): 328-337

Kawakita, T., S. N. Iqbal, S. Desale, et al. (2018) "540: Negative pressure wound therapy (PICO) in morbidly obese women after cesarean delivery compared with standard dressing." American Journal of Obstetrics and Gynecology 218(1, Supplement): S323

Kaye KS, Schmit K, Pieper C, Sloane R, Caughlan KF, Sexton DJ, Schmader KE. The effect of increasing age on the risk of surgical site infection. The Journal of infectious diseases. 2005 Apr 1;191(7):1056-62.

Liberman AM. How much more likely? The implications of odds ratios for probabilities. American Journal of Evaluation. 2005 Jun;26(2):253-66.

Luciani, D., A. Mazzotti, P. Capra, et al. (2016) "Efficacy of "PICO" negative pressure wound therapy (NPWT) versus traditional dressing for the treatment of postoperative wound care management in hip." Journal of Wound Care 26(Sup6b): 156

Matsumoto, T. and S. G. Parekh (2015) "Use of Negative Pressure Wound Therapy on Closed Surgical Incision After Total Ankle Arthroplasty." Foot & Ankle International 36(7): 787-794

Mossanen M, Krasnow RE, Lipsitz SR, Preston MA, Kibel AS, Ha A, Gore JL, Smith AB, Leow JJ, Trinh QD, Chang SL. Associations of specific postoperative complications with costs after radical cystectomy. BJU international. 2018 Mar;121(3):428-36.

Nordmeyer, M., J. Pauser, R. Biber, et al. (2015) "Negative pressure wound therapy for seroma prevention and surgical incision treatment in spinal fracture care." International Wound Journal 13(6): 1176-1179

O'Leary, D. P., C. Peirce, B. Anglim, et al. (2017) "Prophylactic Negative Pressure Dressing Use in Closed Laparotomy Wounds Following Abdominal Operations: A Randomized, Controlled, Open-label Trial The P.I.C.O. Trial." Annals of Surgery 265(6): 1082-1086

Pappala, S., B. Mitchell, J. Riley, et al. (2015) "Reducing caesarean section (CS) surgical site infection (SSI) rate with PICO (R) negative pressure wound therapy (NPWT) in high-risk pregnancies." Bjog-an International Journal of Obstetrics and Gynaecology 122(82-82

Pellino, G., G. Sciaudone, G. Candilio, et al. (2013) "Effects of a New Pocket Device for Negative Pressure Wound Therapy on Surgical Wounds of Patients Affected With Crohn's Disease: A Pilot Trial." Surgical Innovation 21(2): 204-212

Pellino, G., G. Sciaudone, G. Candilio, et al. (2014) "Preventive NPWT over closed incisions in general surgery: Does age matter?" International Journal of Surgery 12(S64-S68

Ridderstolpe L, Gill H, Granfeldt H, Åhlfeldt H, Rutberg H. Superficial and deep sternal wound complications: incidence, risk factors and mortality. European journal of cardio-thoracic surgery. 2001 Dec 1;20(6):1168-75.

Sandy-Hodgetts K, Leslie GD, Lewin G, Hendrie D, Carville K. Surgical wound dehiscence in an Australian community nursing service: time and cost to healing. Journal of wound care. 2016 Jul 2;25(7):377-83.

Searle, R. J. and D. Myers (2017) "A survey of caesarean section surgical site infections with PICOTM Single Use Negative Pressure Wound Therapy System in high-risk patients in England and Ireland." Journal of Hospital Infection 97(2): 122-124

Selvaggi, F., G. Pellino, G. Sciaudone, et al. (2014) "New advances in negative pressure wound therapy (NPWT) for surgical wounds of patients affected with Crohn's disease." Surg Technol Int 24(83-89

Stannard JP, Atkins BZ, O'Malley D, Singh H, Bernstein B, Fahey M, Masden D, Attinger CE. Use of negative pressure therapy on closed surgical incisions: a case series. Ostomy Wound Manage. 2009 Aug 1;55(8):58-66. Review. Erratum in: Ostomy Wound Manage. 2009 Sep 15;55(9):6. PubMed PMID: 19717857.

Svensson-Björk, R., J. Hasselmann and S. Acosta (2018) "Evaluation of inguinal vascular surgical scars treated with closed incisional negative pressure wound therapy using three-dimensional digital imaging—A randomized controlled trial on bilateral incisions." Wound Repair and Regeneration 26(1): 77-86

Strugala V, Martin R. Meta-Analysis of Comparative Trials Evaluating a Prophylactic Single-Use Negative Pressure Wound Therapy System for the Prevention of Surgical Site Complications. Surg Infect (Larchmt). 2017 Oct;18 (7):810-819

Tan, K. W., Z. J. Lo, Q. Hong, et al. (2017) "Use of Negative Pressure Wound Therapy for Lower Limb Bypass Incisions." Annals of Vascular Diseases 10(4): 386-390

Tanaydin, V., J. Beugels, A. Andriessen, et al. (2018) "Randomized Controlled Study Comparing Disposable Negative-Pressure Wound Therapy with Standard Care in Bilateral Breast Reduction Mammoplasty Evaluating Surgical Site Complications and Scar Quality." Aesthetic Plastic Surgery 42(4): 927-935

Timmons, J. (2013) "Single use negative pressure wound therapy: A risk-based approach to the management of caesarean section procedures to reduce and prevent surgical site infections." BJOG: An International Journal of Obstetrics and Gynaecology 1)(417-418

Tuuli, M. G., S. Martin, M. J. Stout, et al. (2017) "412: Pilot randomized trial of prophylactic negative pressure wound therapy in obese women after cesarean delivery." American Journal of Obstetrics and Gynecology 216(1, Supplement): S245

Uchino, M., K. Hirose, T. Bando, et al. (2016) "Randomized Controlled Trial of Prophylactic Negative-Pressure Wound Therapy at Ostomy Closure for the Prevention of Delayed Wound Healing and Surgical Site Infection in Patients with Ulcerative Colitis." Digestive Surgery 33(6): 449-454

Van der Valk, M. J. M., E. J. R. de Graaf, P. G. Doornebosch, et al. (2017) "Incisional Negative-Pressure Wound Therapy for Perineal Wounds After Abdominoperineal Resection for Rectal Cancer, a Pilot Study." Advances in Wound Care 6(12): 425-429

Witt-Majchrzak, A., P. Zelazny and J. Snarska (2015) "Preliminary outcome of treatment of postoperative primarily closed sternotomy wounds treated using negative pressure wound therapy." Pol Przegl Chir 86(10): 456-465

Zotes, V., J. M. Mier and G. Cortes (2015) "P-187NEGATIVE PRESSURE WOUND THERAPY IN A POTENTIALLY INFECTED WOUND AFTER EMPYEMA SURGERY." Interactive CardioVascular and Thoracic Surgery 21(suppl_1): S51-S51

Appendices

Appendix A: Search strategies

Clinical evidence

The EAC's search located 11,346 records and following de-duplication 4847. Re-running the sponsor's search yielded 4133 records.

Following an initial review of the titles and abstracts of all the records by 3 independent reviewers, the EAC excluded 4797 records. The EAC reviewed the full-texts of 60 studies plus the 28 studies included by the sponsor. By re-running the sponsor's search the EAC also identified a further 23 studies which were not included by the sponsor.

- Embase 1974 to 2018 Week 37
- Search date: 11th September 2018

1	Negative pressure wound therapy.tw.	1819
2	NPWT.tw.	1050
3	PICO.tw.	2350
4	Topical negative pressure.tw.	317
5	or/1-4	4479
	limit to 2011-present	3237

1	Negative pressure wound therapy.tw.	1819
2	NPWT.tw.	1050
3	PICO.tw.	2350
4	Topical negative pressure.tw.	317
5	or/1-4	4479
6	limit 5 to yr="2011 -Current"	3237
7	PICO.ti,ot.	284
8	PICO.dv.	109
9	((smith adj2 nephew) and pico).af.	36

10	npwt*.tw.	1066
11	negative pressure wound therap*.tw.	1823
12	Negative-Pressure Wound Therapy/	3788
13	inpwt*.tw.	13
14	exp vacuum assisted closure/	5458
15	negative pressure therap*.tw.	513
16	vacuum assisted closure*.tw.	1496
17	topical vacuum*.tw.	1
18	topical negative pressure*.tw.	321
19	or/7-18	6509
20	limit 19 to yr="2011 -Current"	4488
21	20 not 6	2678

- PubMed
- Search date: 11th September 2018

Search	Query	Items found
#6	Search (#1 OR #2 OR #3 OR #4) Filters: Publication date from 2011/01/01 Sort by: [pubsolr12]	2612
#5	Search (#1 OR #2 OR #3 OR #4)	3653
#4	Search Topical negative pressure[tiab]	269
#3	Search PICO[tiab]	1760
#2	Search NPWT[tiab]	894
#1	Search Negative pressure wound therapy[tiab]	1658

Search	Query	Items found
#31	Search (#30 not #6) Filters: Publication date from 2011/01/01	1067
#30	Search (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29) Filters: Publication date from 2011/01/01	2680
#29	Search topical negative pressure*[tiab] Filters: Publication date from 2011/01/01	120

#28	Search topical vacuum*[tiab] Filters: Publication date from 2011/01/01	74
#27	Search vacuum assisted closure*[tiab] Filters: Publication date from 2011/01/01	612
#26	Search inpwt*[tiab] Filters: Publication date from 2011/01/01	12
#25	Search Negative-Pressure Wound Therapy[MH] Filters: Publication date from 2011/01/01	1756
#24	Search negative pressure wound therap*[tiab] Filters: Publication date from 2011/01/01	1381
#23	Search npwt*[tiab] Filters: Publication date from 2011/01/01	785
#22	Search ((smith & nephew) AND (pico)) Filters: Publication date from 2011/01/01	16
#21	Search PICO[ti] Filters: Publication date from 2011/01/01	118
#6	Search (#1 OR #2 OR #3 OR #4) Filters: Publication date from 2011/01/01 Sort by: [pubsolr12]	2612
#5	Search (#1 OR #2 OR #3 OR #4)	3653
#4	Search Topical negative pressure[tiab]	269
#3	Search PICO[tiab]	1760
#2	Search NPWT[tiab]	894
#1	Search Negative pressure wound therapy[tiab]	1658

- Cochrane (CDSR and CENTRAL)
- Search date: 11th September 2018

ID	Search	Hits
#1	Negative pressure wound therapy:ti,ab	413
#2	NPWT:ti,ab	199
#3	PICO:ti,ab	148
#4	Topical negative pressure:ti,ab	127
#5	#1 OR #2 OR #3 OR #4 with Cochrane Library publication date from Jan 2011 to present, in Cochrane Reviews, Trials	507

#1	Negative pressure wound therapy:ti,ab	413
#2	NPWT:ti,ab	199
#3	PICO:ti,ab	148
#4	Topical negative pressure:ti,ab	127
#5	#1 OR #2 OR #3 OR #4 with Cochrane Library publication date from Jan 2011 to present, in Cochrane Reviews, Trials	507
#6	PICO:ti	39
#7	((smith NEAR/2 nephew) and pico)	7
#8	npwt*:ti,ab,kw	199
#9	negative pressure wound therap*:ti,ab,kw	520

#10	MeSH descriptor: ["Negative-Pressure Wound Therapy"] explode all trees	142
#11	inpwt*:ti,ab,kw	12
#12	MeSH descriptor: ["vacuum assisted closure"] explode all trees	142
#13	vacuum assisted closure*:ti,ab,kw	272
#14	topical vacuum*:ti,ab,kw	37
#15	topical negative pressure*:ti,ab,kw	135
#16	{OR #6-#15} with Cochrane Library publication date from Jan 2011 to present	638
#17	#16 not #5	172

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 10, 2018
- Search date: 11th September 2018

1	PICO.ti,ot.	253
2	((smith adj2 nephew) and pico).af.	16
3	npwt*.tw.	904
4	negative pressure wound therap*.tw.	1611
5	Negative-Pressure Wound Therapy/	2355
6	inpwt*.tw.	12
7	negative pressure therap*.tw.	396
8	vacuum assisted closure*.tw.	1221
9	topical vacuum*.tw.	0
10	topical negative pressure*.tw.	263
11	or/1-10	4080
12	limit 11 to yr="2011 -Current"	2700

- Web of Science
- Search date: 11th September 2018

#9	3,422	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2011-2018
#8	282	TS=(topical negative pressure*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2011-2018
#7	175	TS=(topical vacuum*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2011-2018
#6	1,600	TS=(vacuum assisted closure*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2011-2018
#5	11	TS=(inpwt*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2011-2018
#4	1,815	TS=(negative pressure wound therap*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2011-2018
#3	730	TS=(npwt*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2011-2018
#2	7	TS=((smith NEAR/2 nephew) and pico) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2011-2018
#1	684	TI=PICO Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2011-2018

- CINAHL
- Search date: 11th September 2018

Search ID#	Search Terms	Search Options	Actions

S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	Limiters - Published Date: 20110101-20181231 Search modes - Boolean/Phrase	View Results (1,177) View Details Edit
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	Search modes - Boolean/Phrase	View Results (1,984) View Details Edit
S9	TX topical negative pressure*	Search modes - Boolean/Phrase	View Results (175) View Details Edit
S8	TX topical vacuum*	Search modes - Boolean/Phrase	View Results (12) View Details Edit
S7	TX vacuum assisted closure*	Search modes - Boolean/Phrase	View Results (314) View Details Edit
S6	TX inpwt*	Search modes - Boolean/Phrase	View Results (5) View Details Edit
S5	MW Negative-Pressure Wound Therapy	Search modes - Boolean/Phrase	View Results (1,588) View Details Edit
S4	TX negative pressure wound therap*	Search modes - Boolean/Phrase	View Results (1,789) View Details

			Edit
S3	TX npwt*	Search modes - Boolean/Phrase	View Results (449) View Details Edit
S2	TX smith & nephew AND TX pico	Search modes - Boolean/Phrase	View Results (7) View Details Edit
S1	TI PICO	Limiters - Published Date: 20110101- Search modes - Boolean/Phrase	View Results (25) View Details Ed

- Global Health 1973 to 2018 Week 35
- HMIC Health Management Information Consortium 1979 to July 2018
- Search date: 11th September 2018

1	PICO.ti,ot.	24
2	((smith adj2 nephew) and pico).af.	2
3	npwt*.tw.	45
4	negative pressure wound therap*.tw.	83
5	inpwt*.tw.	0
6	negative pressure therap*.tw.	17
7	vacuum assisted closure*.tw.	70
8	topical vacuum*.tw.	0
9	topical negative pressure*.tw.	14
10	or/1-9	194
11	limit 10 to yr="2011 -Current"	127

	Re-run in HMIC	0

Grey literature

- www.greylit.org/
- ntrl.ntis.gov/NTRL/
- Search date: 11th September 2018

Search term “pico” – 6 records found

Ongoing studies

The EAC accepted the search terms that the sponsor used but re-ran the searches in the same databases limited to records posted from August 2018-present, as well as a non-date limited search of the WHO ICTRP and PROSPERO databases.

Total records retrieved: 1819

Total following de-duplication: 1811

- ClinicalTrials.gov
- Search date 17th September 2018

"Negative pressure wound therapy" OR NPWT OR PICO OR "Topical negative pressure" ***(expert search; limited to August 2018-current)***	with results	0
	without results	0

- ISRCTN
- Search date 17th September 2018

"Negative pressure wound therapy" OR NPWT OR PICO OR "Topical negative pressure" ***(text search; limited to August 2018-current)***	0 results

- WHO ICTRP
- Search date 17th September 2018

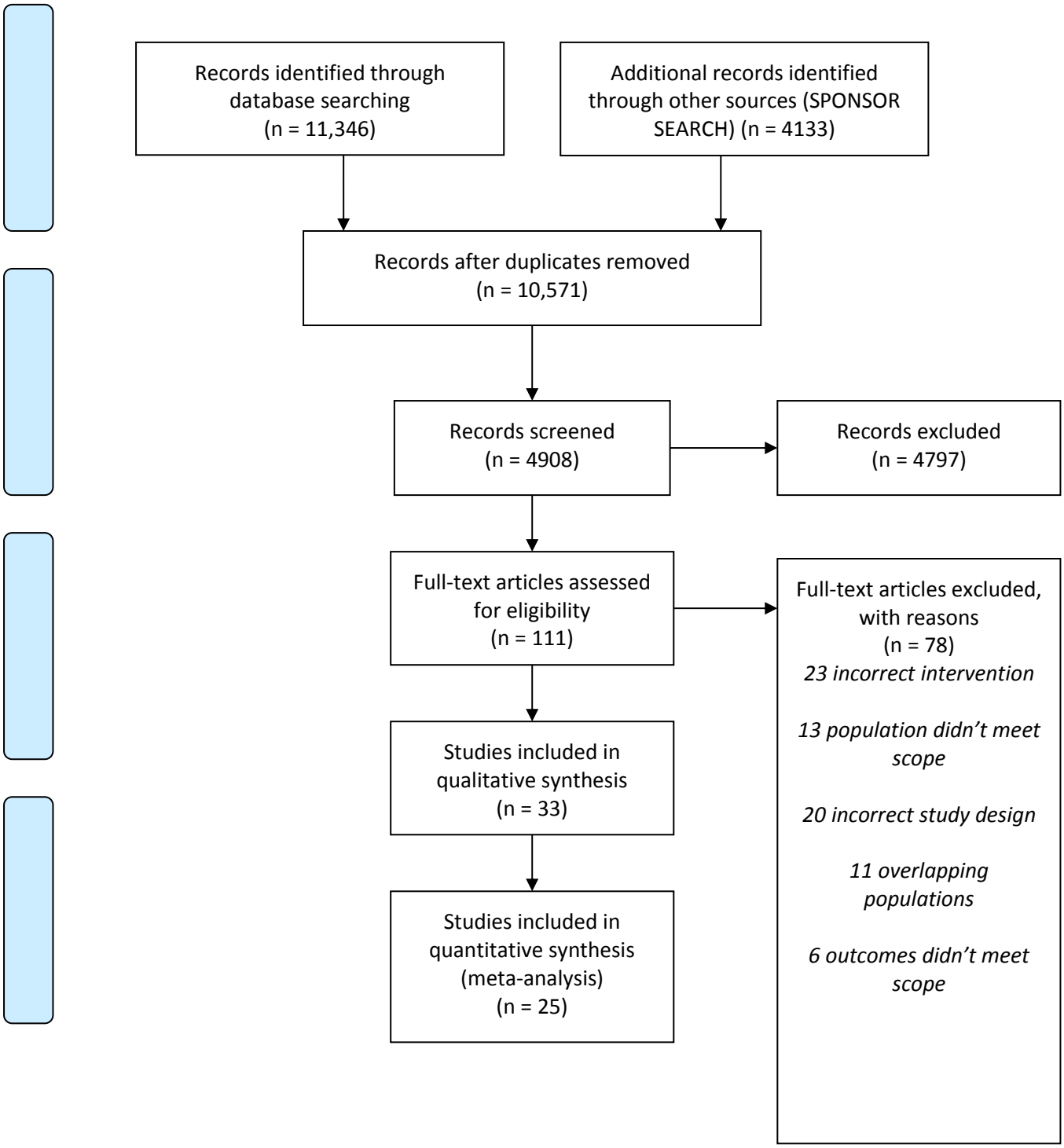
Negative pressure wound therapy OR NPWT OR PICO OR Topical negative pressure	869

- PROSPERO
- Search date 17th September 2018

Line	**Search for**	**Hits**
#1	"negative pressure wound therapy"	24

#2	npwt	13
#3	pico	926
#4	"topical negative pressure"	2
#5	#1 or #2 or #3 or #4	950

PRISMA 2009 Flow Diagram



Appendix B: Methodological quality template

Study identification Smith 2016					
Guideline topic:	**Review question no:**				
Checklist completed by: PWD					
		Circle or highlight one option for each question:			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors	~~Yes~~	~~No~~	Unclear	Retrospective study. It is not known why patients received any particular device.
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	~~Yes~~	No	~~Unclear~~	The paper reports differences in potential confounders across comparison groups
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	~~No~~	~~Unclear~~	Baseline characteristics were comparable between patients with different devices from manufacturers
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	~~Yes~~	~~No~~	Unclear	N/A

B2	Participants receiving care were kept 'blind' to treatment allocation	~~Yes~~	~~No~~	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect? Paper does not report this detail.					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	Of the 746 patients, 94 were excluded from the analysis because they were lost to follow-up within a month after device because they chose to follow-up in a clinic closer to their place of residence. In 2016 further losses to follow-up (n = 25) appear to be entirely in one comparator group.
C2	**a. How many participants did not complete treatment in each group?**				
	b. The groups were comparable for treatment completion	~~Yes~~	~~No~~	Unclear	Paper does not show how many patients were censored due to competing risks.
C3	a. For how many participants in each group were no outcome data available?				
	b. The groups were comparable with respect to the availability of outcome data	Yes	~~No~~	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					

~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	~~Yes~~	No	~~Unclear~~	N/A
D2	The study used a precise definition of outcome	Yes	~~No~~	~~Unclear~~	Data suggest that all devices were used for same reason
D3	A valid and reliable method was used to determine the outcome	Yes	~~No~~	~~Unclear~~	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	~~Yes~~	No	~~Unclear~~	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	~~Yes~~	~~No~~	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					

Appendix C: Adverse events

Categorisation of MAUDE reported injuries from 1st May 2011 to 22nd August 2018.	
System Organ Class/Preferred Term	*Number of Adverse Events Reported*
Vascular disorders	
Haematoma	*2*
Haemorrhage	*3*
Total	*5*
Injury poisoning or procedural complications	
Skin graft failure	*2*
Wound complication	*16*
Total	*18*
General disorders and administration site conditions	
Device failure	*7*
Necrosis	*3*
Device allergy	*4*
Pain	*4*
Death	*1*
Application site inflammation	*16*
Application site erosion	*2*
Application site injury	*7*
Total	*44*
Skin and subcutaneous tissue disorders	
Decubitus ulcer	*1*
Skin stripping	*4*
Burn	*1*
Blister	*19*
Cellulitis	*2*
Dermatitis	*7*
Skin Reaction	*7*
Skin Maceration	*25*
Total	*66*
Infections and infestations	
Infection	*12*
Purulent discharge	*1*
Fungal infection	*1*
Total	*14*
TOTAL ADVERSE EVENTS	*147*

Appendix D: Ongoing studies

Data source	*Study name (acronym)*	*Population*	*Inter-vention*	*Comparator*	*Identified by sponsor*
Unpublished relevant studies with early results available					
Stannard et al unpublished - Https://clinicaltrials.gov/show/NCT02064270	*Study to Compare Negative Pressure Wound Therapy or Standard Dressings After Orthopaedic Surgery*	*Patients who had undergone THA or TKA*	*PICO*	*Standard of care*	*YES*
Unpublished relevant studies with no results available					
Https://clinicaltrials.gov/show/NCT03082664	*Negative Pressure Wound Therapy to Prevent Wound Complications Following Cesarean Section in High Risk Patients*	*Patients at high risk of wound complications following caesarean section (e.g. BMI >30, diabetes, HIV/AIDS, etc)*	*PICO*	*Standard dressing*	*YES*
Https://clinicaltrials.gov/show/NCT03010137	*Incisional Negative Pressure Wound Therapy in High Risk Patients Undergoing Panniculectomy: A Prospective Randomized Controlled Trial*	*All patients undergoing panniculectomy in preparation for renal transplantation*	*PICO*	*Standard of care*	*YES*
Https://clinicaltrials.gov/show/NCT02408835	*Negative Pressure Wound Therapy in Groin Dissection*	*Patients undergoing inguinal lymphadenectomy for metastatic carcinoma of cutaneous origin*	*PICO*	*Conventional wound care*	*YES*

Https://clinicaltrials.gov/show/NCT02664168	*A Comparative Study to Assess the Prevention of Surgical Site Infection (SSI's) in Revision Total Joint Arthroplasty Patients Treated With Single-Use Negative Pressure Wound Therapy (PICO™) or Standard Care Dressings (AQUACEL® Ag SURGICAL Dressing)*	*Patients undergoing revision TKA and THA*	*PICO*	*Standard of care dressings*	*YES*
Https://clinicaltrials.gov/show/NCT02558764	*Effects of Preventive Negative Pressure Wound Therapy With PICO on Surgical Wounds of Kidney Transplant Patients*	*Patients undergoing kidney trans-planation surgery*	*PICO*	*Basic wound contact absorbent dressings (standard of care)*	*YES*
Https://clinicaltrials.gov/show/NCT03180346	*A Prospective, Randomized, Comparative Study to Assess the Prevention of Surgical Site Infection (SSI's) in Revision Total Joint Arthroplasty Patients Treated With Single-Use Negative Pressure Wound Therapy (PICO) or Standard Care Dressings (AQUACEL Ag SURGICAL Dressing).*	*Patients undergoing hip and knee arthroplasty*	*PICO*	*Standard care dressings*	*YES*

Https://clinicaltrials.gov/show/NCT02578745	*Prophylactic Incisional Care in Obese Women at Caesarean*	*Obese (BMI ≥30) women undergoing caesarean section*	*PICO*	*Standard dressing*	*YES*
Https://clinicaltrials.gov/show/NCT02883010	*Comparison of Surgical Incision Complications in Patients Receiving PICO or Standard Care Following Colorectal Surgery*	*Colorectal patients at high risk of SSCs*	*PICO*	*Standard care*	*YES*
Https://clinicaltrials.gov/show/NCT02492854	*Standard Versus PICO Dressings in Lower-Extremity Bypass Patients*	*Patients undergoing lower-extremity bypass surgery*	*PICO*	*Standard of care dressings*	*YES*
Https://clinicaltrials.gov/show/NCT03460262	*Negative Pressure Wound Therapy for prevention of groin infection following vascular surgery*	*Vascular surgery patients*	*PICO*	*Standard dressing*	*YES*
https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12615000286549	Adding negative pRESSure to improve healING (the DRESSING trial)	*Obese (BMI ≥30) women undergoing caesarean section*	*PICO*	*Standard dressing*	*NO*
http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=7412	Closed Incision Wound Therapy (PICO) On Wound Healing and Scar Quality.	*Mastectomies in Transgender Men*	*PICO*	*Standard care*	*NO*
*Https://clinicaltrials.gov/show/*NCT03414762	PICO Negative Pressure Wound Therapy in Obese Women Undergoing Elective Cesarean Delivery.	*Obese (BMI ≥35) women undergoing caesarean section*	*PICO*	*Standard dressing*	*NO*

Https://clinicaltrials.gov/show/NCT01913132	PICO Above Incisions After Vascular Surgery	*Elective vascular surgery (groin incision, transverse or longitudinal)*	*PICO*	*Standard dressing*	*NO*
Https://clinicaltrials.gov/show/NCT03576222	Preventive PICO on Surgical Wounds After Large Incisional Hernia Repair (PICO)	*Large Incisional Hernia Repair (type W2 or W3)*	*PICO*	*MEPORE (standard dressing)*	*NO*
https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12615000598583	The effectiveness of negative pressure wound therapy - PICO™ in the reduction of seroma formation following unilateral mastectomy, a case control study	elective unilateral mastectomy	*PICO*	*Standard dressing*	*NO*
https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12615000175572	Do suction assisted negative pressure dressings reduce the incidence of surgical site infections after abdominal surgery: a randomized controlled trial.	laparotomy (where abdominal incision breaches peritoneum, and wound is large enough at least to fit the surgeons' hand); High risk for SSI	*PICO*	*Standard dressing*	*NO*
https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12612000550808	The use of negative wound therapy to treat surgical incisions after hip arthroplasty: a pilot study	*Patients undergoing hip arthroplasty*	*PICO*	*Primapore (standard dressing)*	*NO*

Https://clinicaltrials.gov/show/NCT02331485	Randomised Control Study to Asses the Role of Negative Pressure Wound Therapy (NPWT) in the Management of Wound in Surgical Patient	*Laparotomy, high risk patients*	*PICO + Acticoat*	*MEPORE (standard dressing)*	*NO*
http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018090298	Negative pressure wound therapy on closed incisions for the prevention of surgical site infections after vascular surgery - a systematic review and meta analysis	*Elective vascular surgery*	*PICO, Prevena*	no wound dressing, all types of non-NPWT dressings and placebos	*NO*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

PICO negative pressure wound therapy for closed surgical incision wounds

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains no confidential information. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Claimed benefits and decision problem

1 The technology

PICO (Smith & Nephew) is a canister-free, single-use negative pressure wound therapy (NPWT) system consisting of a sterile pump and multi-layered adhesive dressings. PICO is available in 7 bundles which vary in the number and sizes of dressings per pack, and in the version of the device included. All have the same mode of action and operation; newer versions have additional power which is designed to manage leakage, and a belt click to allow easy transport of the device by the patient (PICO7) while PICO7Y allows for the use of a single pump with 2 dressings for bilateral surgical incisions.

The pump is operated by 2 AA batteries and delivers a continuous negative pressure of 80 mmHg to a sealed wound. Once activated, using a push button, the battery drives the pump for up to 7 days and light-emitting diodes (LEDs) provide alerts for low-battery status and pressure leaks.

Each dressing has 4 layers: a silicone adhesive wound contact layer, which is designed to minimise pain and damage during peel back and to reduce lateral tension; an airlock layer for even distribution of pressure; an absorbent layer to remove exudate and bacteria from the wound; and a top film layer, which acts as a physical barrier and allows moisture to evaporate. The dressing comes in 10 sizes (up to 25 cm × 25 cm). This includes a multisite dressing of up to 20 cm × 25 cm, which is used for awkward anatomical areas. PICO dressings can remain on during MRI scans, if detached from the pump.

PICO is promoted for a range of wound types. The scope of this evaluation focuses on its use in closed surgical incisions with low to moderate levels of exudate.

2 Proposed use of the technology

2.1 Disease or condition

Surgical incisions often heal following wound closure. However, in some cases surgical site complications (SSCs) may develop. These complications include surgical site infection, dehiscence, seroma, haematoma, delayed

healing and abnormal scarring. The World Union of Wound Healing Societies (WUWHS) Closed Surgical Incision Management Consensus Document notes that people can be considered to be at high risk of developing an SSC due to intrinsic patient factors such as a high BMI, uncontrolled insulin-dependent diabetes, renal dialysis and poor physical status (based on the American Society of Anaesthesiologists physical status classification). High risk can also be procedurally defined; for example, emergency procedures such as bladder and bowel operations are considered to be a risk factor for surgical complications.

According to NICE guideline on preventing and treating surgical site infections (currently being updated), 20% of all health-care associated infections are surgical site infections and 5% of patients undergoing a surgical procedure develop a surgical site infection. Infection in a surgical wound may prevent healing taking place and result in the separation of wound edges or it may cause an abscess to form in the deeper tissues. Surgical site infections are one of the most common SSCs following surgeries. They are associated with longer hospital stays, additional surgical procedures, readmissions, and increased mortality, having a negative impact on patient's physical and mental health (Badia et al. 20117). This has an impact on the health system with additional costs arising from further investigation and treatment (Tanner et al. 2009). SSI is implicated in one-third of postoperative deaths and accounts for 8% of all deaths caused by a health-care associated infection (Coello et al. 2005).

2.2 Patient group

PICO dressings are indicated for the treatment and prevention of SSCs such as infection and dehiscence which can occur in closed incisions. Before undergoing a surgical procedure, patients are assessed for their risk of developing a SSC based on intrinsic patient and procedural factors. The scope of this evaluation is the use of PICO to prevent SSCs in people with closed surgical incisions with low to moderate level of exudate who are

considered to be at high risk of SSCs such as surgical site infections and dehiscence.

A Public Health England report on the surveillance of surgical site infections in NHS hospitals in England notes that from April 2012 to March 2017 data for a total of 662,743 procedures across 17 surgical categories were submitted by 221 participating NHS hospitals and 9 NHS treatment centres. The cumulative SSI incidence ranged from 9.2% in large bowel surgery to less than 1% in hip and knee prosthesis.

2.3 Current management

The NICE guideline on preventing and treating surgical site infections, highlights that patients should have post-surgical care that involves:

- applying wound dressings using aseptic techniques
- wound cleaning with sterile saline for up to 48 hours and cleaning with tap water afterwards
- antibiotics, if an SSI is suspected. If dead or infected tissues seem to be slowing down the healing process, debridement (which may involve surgery) can be used to remove the dead tissue.

Sometimes presence of superficial or deep infections may result in wound dehiscence. If a deep infection is ruled out, a NPWT may be used to manage the dehisced surgical wound to promote healing by secondary intention.

2.4 Proposed management with new technology

PICO is intended to be applied to patients with a closed incision wound and low levels of exudate who have been risk stratified as being at high risk of developing SSCs immediately after an operation.

3 Company claimed benefits and the decision problem

The company's claimed benefits and decision problem from the scope are attached as Appendix D. The company did not propose any variation from the scope. The EAC noted that, while the company's description of the population and intervention partially match the scope, as there is a lack of consensus on the definition of a high-risk population for developing SSCs after surgical procedures and no evidence is available on the newest versions of PICO (PICO 7 and PICO 7Y).

4 The evidence

4.1 Summary of evidence of clinical benefit

The company presented 29 studies, including 28 published clinical studies (23 in full text, 5 as conference abstracts) and 1 unpublished study, for various surgical specialities in its submission. The EAC stated that the company did not search all the expected databases and conducted an additional search which identified 2 new abstracts (Luciani 2016; Caswell 2015) in addition to the studies identified by the company. The EAC did not exclude any of the studies identified by the company.

Methodological details of studies identified are summarised in Table 1, which provides details of patient characteristics for the included studies and further details can be found in section 3.3 of the assessment report.

Table 1 Summary of studies assessed by the EAC, reproduced from table 3.3 of the assessment report

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
Adogwa 2014	Retrospective, before-after, single-centre, observational study. PICO or standard dressing (control). All patients received antibiotics following surgery. ●	USA. 160 patients undergoing thoracolumbar fusion for spinal deformity (46 PICO and 114 standard dressing) Included: patients aged over 18, multilevel (more than four vertebral levels) posterior spinal fusion using pedicle screws and rod instrumentation. Excluded: history of infections at surgical site, severe coexistent pathology, history of immunosuppression or chronic systemic infection, and pregnancy. ●	30- and 90-day follow-up for wound dehiscence, SSI, length of stay, 30-day readmission, return to operating theatre rates ●	Wound dehiscence: PICO 6.38% vs. control 12.28% (p=0.02) SSI: PICO 10.63% vs. control 14.91% (p=0.04) Other outcomes (length of stay, 30-day admissions, return to operating theatre rates) not significantly different between the groups.

[1] Green, amber or red colour coding indicates whether the study matches the scope fully, partially, or not at all: ●●●.

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
Caswell 2015	Retrospective, before-after, single-centre, observational study. PICO or standard dressing (control). ●	UK. 221 patients undergoing emergency laparotomy for large bowel surgery (119 in control cohort vs.102 in study cohort, of whom 27 had PICO). Included: All patients were at high risk of wound complications: patients aged over 70, BMI>35, emergency operation, diabetes, immunosuppression or immunocompromised, or consultant-based decision. ●	SSI (incisional and deep), the length of follow-up was not reported in the abstract ●	SSI: PICO 3.7% vs. control 7.69%.
Chaboyer 2014	Pilot RCT, single centre. PICO or standard dressing (control). ●	Australia. 92 elective C-section patients (randomised 1:1). Included: pre-pregnancy BMI≥30, Excluded: emergency procedures. ●	SSI at 4 weeks following caesarean section (incisional, deep and organ-space), dehiscence, haematoma, bleeding, seroma, blisters, length of stay, 28-day readmissions. ●	Outcomes (SSI rates) were not significantly different between the groups.

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
Dingemans 2018	Pilot before-after study, single centre. PICO (prospective) or standard dressing (retrospective control). ●	Netherlands. (60 patients) 47 matched pairs of foot or ankle fracture patients (primary or secondary surgery). Included: procedures with incision of ≥3cm. Excluded: percutaneous surgery, open fractures or active infections, concomitant antibiotics, immunodeficiency. ●	SSI at the 30-days post-operation (superficial with an incision 3cm or less and deep), dehiscence/delayed closure without infection, patient satisfaction with PICO. ●	Outcomes (SSI rates) were not significantly different between the groups.
Fleming 2018	Retrospective observational study, single centre. PICO or standard dressing (control). ●	Ireland. 151 peripheral vascular surgery patients with groin wounds (73 PICO, 78 control). Included: patients aged over 18. Main risk factors were age, smoking status and diabetes. ●	Wound complications at 6-weeks post-operations (seroma, infection, haematoma, or dehiscence). Requirement for antibiotic therapy, readmissions, length of stay, time to resolution of wound complications. ●	Wound complications: PICO 8.2% vs. control 19.2% (p=0.042); infection and dehiscence were not significantly different between the groups. Resolution of wound complications: PICO 52 days vs. control 96 days (p=0.015).

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
Galiano 2018	Multi-centre open label RCT. PICO or standard dressing (control). ●	USA (3), France, South Africa and the Netherlands. 200 reduction mammoplasty patients recruited (randomised 1:1, within-patient) Included: patients age over 18, bilateral reductions with similar incision lengths on each breast. Excluded: pregnancy or lactation, steroids or immunomodulators, history of radiation therapy, tattoos, skin conditions, history of scar problems. Post-surgical active bleeding, incisions >30cm. ●	SSC complications at 21 days and 90 days after the procedure (infection (superficial or deep), dehiscence, delayed healing). Postsurgical complications: skin necrosis, nipple and areola necrosis, cellulitis, abscess, suture abscess, or hematoma occurring within 21, 42, and 90 days postoperatively. ●	Healing complications: PICO 56.8%, control 61.8%ve (p=0.004); dehiscence: PICO 16.2% control 26.4% (p<0.001). Skin necrosis: PICO 2, control 7 (p=0.008). Other outcomes were not significantly different between the groups.
Gillespie 2015	Pilot open label RCT, single centre. PICO or standard dressing (control). ●	Australia. 70 elective primary hip arthroplasty patient (randomised 1:1). Majority (94.3%) were ASA grade II-III.	SSI at the 6-weeks follow-up (superficial, deep, organ space). Individual SSI indicators (erythema, swelling, leakage, purulence), wound	Bleeding: PICO 8 patients, control 1 (p=0.04). Complications: PICO 24 patients, control 15 (p=0.04).

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
		Included: patients aged 18 or over. Excluded: existing infection. ●	complications (dehiscence, haematoma, seroma, bleeding), dressing replaced before day 5, length of stay, and readmissions. ●	Dressing replaced before day 5: PICO 35, control 15 (p=0.0001). Other outcomes were not significantly different between the groups.
Hackney 2017	Retrospective observational study, single centre. PICO or unspecified control. ●	UK. 71 open abdominal surgery patients (39 PICO, 32 control). Included: emergency and elective. ●	Wound complications (unspecified), readmissions, length of stay (the length of study follow-up not reported in the abstract) ●	Wound complications: PICO 7.6%, control 15.6%. Length of stay: PICO 14.49, control 13.9.
Hester 2015	Retrospective observational study, single centre. PICO or standard dressing (control). ●	UK. 36 revision arthroplasty patients (18 PICO, 18 control). 9 hip, 27 knee. Inclusion: Main risk factors were the nature of the procedure (revision surgery), age, BMI, and ASA score ●	Wound infection requiring further surgery or antibiotics at 6-weeks follow-up. Dressing related complications. ●	Outcomes (wound complications) were not significantly different between the groups.

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
Hickson 2015	Before-after retrospective observational study, single centre. PICO or standard dressing (control). ●	USA. 1948 C-section patients (964 PICO, 984 control). High risk patients (BMI >35, or 2 of diabetes, steroid use, autoimmune disease, haematological disorders, immunosuppressant medication, hypertension, multiple C-sections, history of wound infections, pre-existing skin problems, or emergent birth) ●	SSI at 6-weeks follow-up ●	SSI: PICO 0.1%, control 0.61%.
Holt 2015	Retrospective observational study, single centre. PICO or standard dressing (control). ●	UK. 24 oncoplastic breast surgery patients (within-patient comparison) or skin-sparing mastectomy followed by immediate reconstruction with implant) Therapeutic mammoplasty or skin-sparing mastectomy and immediate reconstruction with inferior	Delayed healing, wound breakdown (dehiscence), fat necrosis, days to adjuvant healing. ●	Dehiscence: PICO 4.2%, control 16.7%. Mean time to healing: PICO 10.7 days, control 16.1 days.

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
		dermal flap and implant. Contralateral side had symmetrising reduction. ●		
Hyldig 2018	Multicentre open label RCT PICO or standard dressing (control). ●	Denmark. 827 women undergoing caesarean section (1:1 allocation to PICO or standard dressing) Included: pregnant women undergoing elective or emergency caesarean section, aged ≥18 years, who had a pre-pregnancy BMI ≥30, and could read and understand Danish Excluded: subsequent vaginal delivery ●	SSI within 30 days of surgery Wound exudate, dehiscence, and health-related quality of life ●	SSI:PICO 4.6% vs. control 9.2% (p=0.007) Wound exudate: PICO 22.4% vs. control 32.9% (p=0.001) Minor dehiscence: PICO 15.1% vs. control 16.6% (p=0.66) The health-related quality of life did not differ between the PICO and the control arm.
Irwin 2018	Prospective database audit, single centre PICO or standard dressing (control). ●	UK. 155 people (254 breasts) undergoing prepectoral implant-based reconstruction procedures (102 PICO and 152 standard dressing)	Wound dehiscence, reconstructive failure.(the length of study follow-up not reported in the abstract) ●	Wound dehiscence: PICO 0 cases vs. 9 cases standard dressing (p=0.01)

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
		Included: Not reported. Excluded: Not reported. ●		Reconstructive failure: PICO 0 cases vs. 6 cases (p=0.08)
Karlakki 2016	Non-blinded single centre RCT. PICO or standard dressing (control). All patients received antibiotics following surgery. ●	UK. 220 people undergoing hip and knee arthroplasty (102 PICO and 107 standard dressing) Included: people undergoing elective hip or knee arthroplasty (for any indication) Excluded: people who had known allergies to dressings, were undergoing revision joint surgery, were unwilling to attend additional clinics, and those on warfarin. ●	Wound complications, length of stay, level of exudate, dressing changes at the 6-weeks follow-up ●	LOS (mean days): PICO 3.8 days vs. 4.7 standard dressing p=0.07 Wound complications: PICO 2.0% vs. standard dressing 8.4% p = 0.06 Post-surgical exudate: PICO 4% had grade 4 exudate as compared with 16% in the control group p = 0.007 Dressing changes (mean): PICO 2.5 vs. 4.2 p = 0.002
Kawakita 2018	Single centre, retrospective cohort study. PICO or standard dressing (control). ●	US. 759 women undergoing caesarean section (PICO 176 and 583 standard dressing)	Wound complication, endometritis before discharge, endometritis after discharge, deep wound infection, other severe	Wound complication: (standard dressing 7.9% vs. PICO 9.6%; OR 1.02, not significant)

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
		Included: women with BMI ≥ 40 undergoing a caesarean section Excluded: Unclear ●	infection, cellulitis, hematoma/seroma, and wound dehiscence (the length of study follow-up not reported in the abstract) ●	Endometritis before discharge (standard dressing 1.7% vs. PICO 1.2%; OR 0.22, not significant) Endometritis after discharge (standard dressing 1.2% vs. PICO 0.6%; OR 1.21, not significant) Deep wound infection (standard dressing 0.7% vs. PICO 2.4%); OR 7.34, not significant) Other severe infection (standard dressing 1.0% vs. PICO 1.2%; OR not available) Cellulitis (standard dressing 3.7% vs. PICO 3.0%; OR 0.86, not significant) Haematoma/seroma (standard dressing 2.0% vs.

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
				PICO 3.6%; OR 3.07, not significant) Wound dehiscence (standard dressing 2.4% vs. 7.8%; OR 2.35, not significant)
Luciani 2016	Blinded RCT PICO or standard dressing (control). ●	Italy. 100 people undergoing hip or knee replacement revision surgery (PICO 50 and 50 standard dressing) Included: people with diagnosis of hip prosthesis aseptic loosening or knee prosthesis aseptic loosening Excluded: Unclear ●	Asepsis Score (AS) to assess wound healing, number of wound dressing changes, patient comfort and satisfaction (the length of study follow-up not reported in the abstract) ●	All people in the PICO group versus 90% of people in the standard care group (n=45) had satisfactory healing according to the AS scale. People in the PICO group reported lower levels of pain that in the standard care group (VAS score 2.6 in the PICO group vs. 4.8 in standard care). The PICO group had significantly fewer blisters (p= 0.048) and dressing changes (p < 0.001). The

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
				PICO group reported lower mean pain level during dressing changes than the standard care group (mean reported numeric rating scale (NRS) pain level of 2.84 vs. 5.14).
Matsumoto 2015	Before-after retrospective observational study, single centre. PICO or standard dressing (control). ●	USA. 74 total ankle arthroplasty patients (37 PICO, 37 control). Excluded: revision surgeries. ●	Wound healing problems (dehiscence, eschar, drainage), SSIs. Patients were followed-up at 1 week (when the dressing was removed), at 3 weeks, and every 4 weeks thereafter if they presented with complications (total follow-up time unknown). ●	Wound healing problems: PICO 3%, control 24% (p=0.014). SSIs not significantly different between the groups.
Nordmeyer 2015	Unblinded single centre RCT. PICO or standard dressing (control).●	Germany. 20 internal fixation of spinal fracture patients (randomised 1:1).	Volume of wound exudate at 5- and 10-days.	Volume of exudate at 5-days: PICO 0ml, control 1.9ml (p=0.0007). At 10-days: PICO 0.5ml, control 1.6ml (p<0.024).

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
		Included: open reduction surgery.●	Nursing time, number of dressings (compresses) used.●	Mean nursing time: PICO 13.8 minutes, control 31 minutes (p=0.0005). Compresses: PICO 11, control 35 (p=0.0376).
O'Leary 2017	Unblinded single centre RCT. PICO or standard dressing (control), antibiotic prophylaxis in all patients. ●	Ireland. 50 laparotomy for open abdominal surgery patients (randomised 1:1). Included: patients aged between 18 and 80, emergency and elective, class I, II and III wounds. Excluded: class IV wounds, BMI≥40, ASA>3. ●	SSI at 30 days after the procedure, length of stay, VAS, POSAS wound score. ●	SSI (ITT analysis 2-sided test): PICO 12%, control 32% (p=0.095). Length of stay: PICO 6.1 days, control 14.7 days (p=0.019). Other outcomes were not significantly different between the groups.
Selvaggi 2014	Unblinded single centre observational. PICO or standard dressing (control), antibiotic prophylaxis in all patients.	Italy. 50 adults with Crohn's disease undergoing abdominal surgery. Included: ≥18-year-old, established Crohn's disease, symptomatic Crohn's	SSI, re-admission rates, length of stay, usability at the 12-months follow-up	SSI (PP analysis 2-sided test): PICO 8%, control 48% (p=0.004). Seroma data needs to be added: PICO 2 (8%) vs SC 11 (44%), p = 0.008.

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
	•	disease not amenable for medical treatment, laparotomy, converted-laparoscopy, or hand-assisted laparoscopy (HAL) with bowel resection/s or strictureplasty/ies, primary wound closure, adherence to periodical follow-up Excluded: Unconverted laparoscopy, explorative laparotomy/laparoscopy without bowel opening, massive bowel resections (less than 30% of anatomical length preserved) •		Re-admission rates: PICO 0%, control 24% days (p=0.02). Length of stay: PICO 7 days, control 12 days (p=0.0001). 2 patients reported issues with using PICO. Both were adequately resolved.
Svensson 2018	Open label, multi-centre, within-patient, RCT. PICO or standard dressing (control), antibiotic prophylaxis in all patients. •	Sweden. 34 people who underwent bilateral inguinal vascular surgery (randomised 1:1). Included: Elective vascular surgery with inguinal incisions	Assessment of scar quality using 3 tools: SBSES objective measure, NRS10 overall scar quality, PSAS subjective measure, post-operatively (no fixed time	Both the objective and subjective scar evaluations showed no statistically significant difference

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
		Excluded: Non-SSI wound complication, presence of SSI, advanced terminal disease, non-completed NPWT device usage, advanced dementia ●	point was defined). (a median follow-up of 808 days)	between PICO and standard dressing
Tan 2017	Retrospective, single-centre observational study. PICO or standard dressing (OpSite, control), antibiotic prophylaxis in all patients. ●	Singapore. 42 people undergoing lower limb bypass. (PICO: n=14, control: n=28) Included: Patients who underwent lower limb arterial bypass with reversed great saphenous vein Excluded: Not reported ●	SSI, surgical debridement, length of stay, re-admission rates up to 30 days	SSIs PICO = 0% vs. 32% at the control group (p=0.019).
Tanaydin 2018	Open label, single-centre, within-patient, RCT PICO or fixation strips (control), antibiotic prophylaxis not reported.	Netherlands. 32 women who underwent bilateral breast reduction mammoplasty (randomised 1:1) Included: Women aged >18 years, bilateral superomedial	SSCs at the 1-year follow-up , Scar quality	SSCs lower in PICO group (p=0.004).

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
	•	pedicle Wise-pattern breast reduction mammoplasty, postsurgical incisions of similar length on each breast Excluded: pregnancy, lactation, using steroids or other immune modulators, history of radiation of the breast, tattoos in the area of incision, skin conditions resulting in poor healing or widened scars, patients with a known history of scar problems, known allergies to product components, incision still actively bleeding, exposure of blood vessels, organs, bone or tendon at the base of the reference wound, incisions > 30cm maximum dimension •		

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
Tuuli 2017	A pilot open label, single-centre RCT. PICO or standard dressing (control), antibiotic prophylaxis not reported. ●	USA. 120 women undergoing C-section (randomised 1:1). Included: Obese women (BMI≥30), C-section Excluded: - Non-availability for postoperative follow-up, contraindication to NPWT, pre-existing infection around incision site, bleeding disorder, therapeutic anticoagulation, allergy to any component of the dressing ●	SSC, pain score, adverse skin reactions 30 days postoperatively	SSCs: PICO: 8.3% vs. control 5.0%, RR 1.67, 95%CI 0.42-6.67; p=0.72. Pain score: PICO 0 (0-1) vs. control 1 (0-3), p=0.02. Adverse skin reactions: PICO 2 (3.3) vs control 0 (0), p=0.50
Uchino 2016	Open label, multi-centre RCT. PICO+PSS vs. PSS alone (control). All patients received 100% prophylactic antibiotics. ●	Japan. 59 adults with ulcerative colitis scheduled to elective undergo ileostomy closure (randomised 1:1). Included: ≥18 years old, established ulcerative colitis, scheduled to undergo	Complete wound healing at the 8-weeks follow-up	There was no statistically significant difference for the mean duration of wound healing between the 2 groups (37.6 days in the

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
		elective closure of ileostomy - including a restorative proctocolectomy with ileal pouch anal anastomosis Excluded: Death, dirty/infected wound, urgent/emergency surgery, separated double-barrel ileostomy, patients whose incision was extended due to adhesions during surgery, patients displaying complicated dermatitis due to adhesives, patients with SSIs during follow-up periods were excluded from prophylactic NPWT and from comparison of wound-healing duration as NPWT was terminated after SSI diagnosis		PSS-alone and 33.5 in the PPS+PICO group).
Van der Valk 2017	Single-centre, before-after, observational study.	Netherlands. 20 people undergoing	SSC up to 34 weeks in the PICO and 24 weeks in the	SSC (PP analysis): No statistically significant difference in the SSCs

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
	PICO vs. a historical cohort that used conventional wound care (control). Prophylactic antibiotic use not reported. ●	abdominoperineal resection for rectal cancer. Included: Patients undergoing laparoscopic abdominoperineal resection for rectal cancer. Excluded: Patients undergoing extralevator APR or treated with a perineal subcutaneous drain. ●	control group, time to wound healing	between the two groups was noted (PICO 70% vs. control 40%, 95%CI not reported, p value not reported). Time to wound healing: PICO = 8.5 (mean 10.4, range 0-34) vs. control = 13 (mean 11.4, range 0-24), p=0.87
Witt 2015	Open label, single-centre RCT. PICO vs. conventional wound dressing (control). All patients received prophylactic antibiotics. ●	Poland. 80 people undergoing coronary artery bypass grafting surgery (randomised 1:1) Included: Main risk factors were BMI> 30, ASA score 2, and prolonged surgery >2 h. Excluded: Not reported ●	Wound healing defined as absence of SSCs post-operatively (6-weeks follow-up).	The PICO group achieved higher statistically significant wound healing rates at the 6-weeks follow-up (PICO 92.5% vs. control group 75%, p=0.0.339).

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
Zotes 2015	Pilot open label, single-centre RCT. PICO vs. standard dressing (control). No information on prophylactic use of antibiotics reported. ●	Mexico. 20 people undergoing thoracotomy for empyema (randomised 1:1). Included: Main risk factors were diabetes, nutritional status, steroids therapy, prolonged surgery >2 h Excluded: Not reported ●	SSC within 10 days of surgery	Although the SSC rate was higher in the PICO group than the standard dressing group (50% vs 10%), the difference was not statistically significant.
Stannard unpublished - NCT02064270	Multi-centre, RCT PICO vs. standard dressing (control). Use of prophylactic antibiotics not reported. ●	USA. [redacted] Included: adults, primary or revision total hip or knee arthroplasty, patients able to have an advanced technology device capable of digital photography Excluded: Pregnancy, history of poor compliance with medical treatment,	Incision appearance, SSC	[redacted]

Included reference	Design and intervention(s)[1]	Participants and setting	Outcomes	Results
		allergy to silicone adhesives or polyurethane films, unwillingness to participate in a RCT ●		

EAC critical appraisal of the clinical evidence

The company conducted and reported a number of fixed-effect model meta-analyses and subgroup analyses for combined post- surgical wound complications by surgical specialty. The EAC noted that clinical heterogeneity and statistical heterogeneity were expected to be high across the included studies due to a wide variation in the characteristics of the study populations. The EAC ran additional meta-analyses using a random-effect model in which the pooled estimates of SSI rates were similar to those in the company's fixed-effect model analyses. Overall, there was a significant reduction in SSIs in the PICO group in all individual surgical specialities (see table 2).

Table 2: Estimated effect of PICO in the meta analyses

	Fixed-effect model	**Random effect model**
Odd ratio (95% CI), all studies (n=19)	0.39 (0.29 to 0.52)	0.37 (0.24 to 0.57)
RCTs (n=8)	0.49 (0.33 to 0.72)	0.51 (0.31 to 0.82)
Observational studies (n=11)	0.28 (0.17 to 0.46)	0.27 (0.14 to 0.53)

The EAC sought expert opinion on the validity and reliability of a pooled estimate across different surgical procedures in view of the significant variations in included studies, definitions of SSI and risk profiling. In populations undergoing different surgical procedures , results were considered transferable, as the experts noted that the risk of SSCs vary between surgical procedures, and NPWT on closed incisions is effective due to a number of different modes of actions; therefore the effectiveness of PICO in different specialities may contribute to different modes of action.

In the subgroup analyses, there were statistically significant reductions in SSI rates with PICO for orthopaedic and obstetric surgery (see table 3). The pooled estimates showed a statistical reduction in SSI rates for plastic and

breast surgery and vascular in the fixed-effect model analyses; however the EAC found the differences were not non-significant when a random effect model was applied. Both cardiothoracic and colorectal surgeries showed no statistically significant difference.

Table 3: estimated effect by surgical speciality in the meta analyses

	Fixed-effect model	**Random effect model**
Orthopaedic surgery SSI, Odd ratio (95% CI) (n=5 studies, 607 patients)	0.43 [0.21, 0.86]	0.45 [0.22, 0.91]
Colorectal SSI (n=5, 209 patients)	0.46 [0.21, 0.99]	0.39 [0.07, 2.11]
Obstetric surgery SSI (n=3, 2911 patients)	0.47 [0.29, 0.74]	0.48 [0.30, 0.76]
Plastics/Breast surgery SSI (n=2, 420 patients)	0.36 [0.14, 0.97]	0.35 [0.09, 1.45]
Vascular surgery SSI (n=2, 193 patients)	0.22 [0.05, 0.87]	0.25 [0.05, 1.25]
Cardiothoracic surgery SSI (n=1, 80 patients)	0.12 [0.01, 1.03]	0.12 [0.01, 1.03]
Mixed surgery SSI (n=1, 49 patients)	0.19 [0.04, 1.03]	0.19 [0.04, 1.03]

The EAC noted that there was no statistically significant difference in other SSCs such as dehiscence, haematoma and time to healing between PICO and control group except that the use of PICO was associated with a reduction in seroma rates (7 studies, n=771, OR 0.23, 95%CI 0.11 to 0.45). See table 14 of the assessment report for further details.

There were variations in defining high risk population groups who may develop SSCs following surgical procedures in the included studies so the EAC sought expert advice on

- variations of SSI rates by populations and surgical specialities
- the applicability of WUWHS's risk factors in a UK setting

The EAC noted that based on responses received there is national and local variation in the SSI rates across different specialities in the UK. Such data may not be routinely collected and the true rate of SSI is likely to be underestimated. The experts confirmed that the classification of risk factors for SSI was similar to that of WUWHS in clinical practice, and patient-related risk factors include ASA greater than 3, increased BMI, older age, diabetes, being a current smoker, and procedure-related risk factors include emergency dirty procedures such as bladder and bowel operations and by surgical speciality. There was not sufficient evidence from the included studies on rates of SSI by patients' risk factors. The primary outcome reported was SSI. Regarding follow-up, experts reported that the time for an SSI to occur depends on the surgical procedure. They also noted that the frequency and setting of reviews during the follow up time may determine how easily an SSC is identified. Further details are in section 3.5 of the assessment report.

4.2 Summary of economic evidence

The company conducted a search for economic evidence and identified 5 relevant studies. The EAC considered the company's search to be appropriate and its de novo search did not identify any new economic studies. For a full description of the EAC's assessment of the economic evidence see section 4.1 of the assessment report.

- Nherera (2017) built a decision analytic model from the UK NHS perspective over a time horizon of 6 weeks, evaluating the use of single-use negative pressure wound therapy (sNPWT) in patients undergoing primary hip and knee replacements compared with

standard care. Parameter inputs were based on the UK study, Karlakki (2016). The model estimates a 0.06 reduction in complications, a QALY gain of 0.001 and cost savings of £1,132 in favour of sNPWT. Sub-group analysis suggested greater cost savings in patients with elevated risk of surgical complications.

- Nherera (2018) built a decision analytic model from the Germany Statutory Health Insurance payer's perspective over a 12-week time horizon, comparing sNPWT with standard of care in patients following coronary artery bypass grafting surgery. Baseline and effectiveness data was taken from a German and a Polish study respectively (Cristofolin 2012 and Witt-Majchrzak 2015). The model estimated that sNPWT avoided 0.037 complications and generated 0.03 additional QALYs. The mean cost-saving for sNPWT compared to standard care was €586.

- Heard (2017) conducted an economic evaluation alongside a randomised trial of sNPWT amongst obese women undergoing elective C-section in Australia. The SSI rate was 10% lower for the sNPWT group compared to the standard dressing group. The sNPWT was more costly (AUS$133) and more effective (0.003 QALYs) than standard care.

Two unpublished economic studies (Galiano 2018b and Hyldig 2018) conducted in the US and Denmark respectively, were reported by the company – see section 4.1 of the assessment report for further details. The EAC agreed with both the company's critical appraisal of the identified studies and the conclusion that the economic evidence suggests that PICO is cost-saving.

The EAC noted the quality of existing economic evidence was varied. Both trial based analyses indicated moderate additional costs associated with the use of sNPWT amongst obese women undergoing C-section, while the

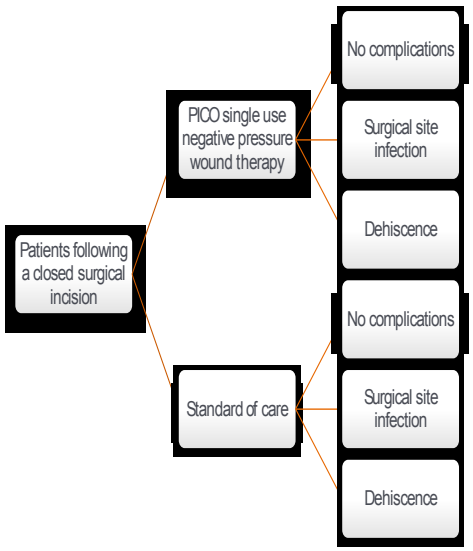
remaining analyses suggested the potential for sNPWT to reduce the cost in other types of surgery.

De novo analysis

The company submitted a decision tree model assessing 2 surgical outcomes – SSI and dehiscence, and the incremental cost of PICO compared to a standard dressing, including the dressing cost and the cost implications of a SSI or dehiscence.

The EAC noted that the model structure is appropriate for the scope. The model considers surgery patients at risk of developing an SSC and patients undergoing specific surgical procedures including orthopaedic, colorectal, C-section, breast, vascular and cardiothoracic surgery.

Figure 1: Company model schematic, reproduced from Figure 1 in the assessment report



Clinical parameters

The majority of the baseline data on complication rates were sourced from a UK based study (Jenks 2014). This study reported a baseline SSI rate for all surgery from an observational data set which is representative of standard care in the UK. The EAC considered this data source appropriate and noted that the study is large and well executed.

Data on SSI rates for some surgical sub-specialities were taken from a variety of sources which the EAC felt were inappropriate as noted in section 4.2 of the assessment report. The baseline rate of dehiscence used by the company was based on pooled data from 6 studies. The EAC considered the company's calculations inaccurate due to incorrect reporting of data in Piper 2016 by the company.

Data on the association between risk factors and SSI rates for different types of surgery was taken from a number of small studies. The EAC accepts the company's approach to evaluate PICO in patients with elevated risk factors but the EAC judged that the use of the mean risk factors for SSI rates for each of clinical specialities (C-section, cardiothoracic, breast, colorectal, orthopaedic and vascular) to derive the relative risk (RR) for SSIs across elevated risk factors for all surgical procedures was not robust. The EAC considered the recent review published as part of the NICE guidance on preventions of SSI (NICE CG 74) to be a better source of data on the impact of elevated risk factors across different types of surgical procedures.

Cost and resource use

The cost of an SSI in the UK used in the model was taken mainly from Jenks 2014. The EAC considered this source of data is appropriate as this study is relatively large and its analysis was robust. The company estimated the cost for an SSI across all surgeries by taking the weighted mean of the cost calculated across the 6 sub specialties (orthopaedic, colorectal, obstetric, breast, vascular and cardiothoracic surgery) considered. The EAC considered the mean cost attributable to SSI along with the number of SSIs across all 19 specialties in Jenks 2014 was more appropriate. The cost of an inpatient SSI estimated by the EAC from Jenks 2014 (£9,453) was slightly lower than the estimate derived by the sponsor (£9,655). The company made an assumption that the cost of treating dehiscence is the same as the cost of an SSI. The EAC accepted this assumption considering the paucity of data on the cost of dehiscence.

The company estimated the PICO cost based on a weighted average of the list price for PICO kits of different sizes, and assumed that a single PICO kit was used for each patient. A justification for this assumption was not provided. The EAC noted that no robust data was available to calculate the number of PICO used for each patient, and based on data from included studies, calculated a minimum use of PICO ranged from 1.25 to 1.5 kits per patient .

Results

The company's base case analysis showed that PICO is cost saving for colorectal, vascular and cardiothoracic surgery, with colorectal surgery having the highest per-patient savings of £644 (see table 17 of the assessment report). The EAC's revised base case analysis also showed colorectal, vascular and cardiothoracic surgery to be cost saving, with a lower saving for colorectal surgery of £415. Orthopaedic surgery, C-section and breast surgery were noted to be cost incurring in both the base case for the company and following EAC's revisions.

The company undertook a one-way scenario-based deterministic sensitivity analysis for all surgery varying the following parameters: effectiveness of PICO on SSI, effectiveness of PICO on dehiscence, the baseline SSI rate, baseline dehiscence rate, SSI cost, dehiscence cost, and the cost of PICO. Ranges were informed by 95%CIs or +/-25% for costs. The company's analysis is most sensitive to the effect of PICO on dehiscence and that at extreme values of parameters varied PICO remains cost saving. In the EAC's one way sensitivity analysis the cost of PICO had the greatest impact on the results, with overall costs with PICO varying from a £65 saving to £77 more, for the different surgeries (see table 21 in the assessment report).

5 Ongoing research

The EAC identified 21 ongoing studies from trials registries (section 3.9 Assessment report). Most studies have no preliminary results available, and 1 trial (NCT02578745) is now published as an abstract (Tuuli et al. 2017). This is an open label RCT compared PICO with standard dressing in 120 women

undergoing C-section, and has been included in the sponsor's submission. The EAC also identified a systematic review which will focus on PICO and another single-use NPWT (Prevena [KCI Medical]) as the intervention.

One of the clinical experts reported that 1 of the 21 studies identified is the SUNRRISE RCT which aims to recruit patients undergoing emergency laparotomy from 9 UK centres and it is due to be completed in 2021. The trial will focus on single-use negative pressure dressings.

6 Issues for consideration by the Committee

What is the clinical importance of the PICO in treating and preventing SSCs after invasive surgical procedures? The evidence shows a statistically significant reduction in SSI rates in the PICO group when all surgical procedures were combined, and also individual significant reductions in orthopaedic and obstetric surgery but the clinical significance of this is unclear. Would, for example, a statistically significant difference in SSIs always be considered to be clinically significant?

Will the effectiveness of PICO be generalisable to the NHS? The evidence of pooled estimates of the treatment effects of the PICO are based on non-UK studies as well as UK studies. Three of 4 published UK studies (Hackney et al. 2017; Karlakki 2016; Holt et al. 2015) showed that the PICO was associated with lower rates of wound complications and dehiscence compared to control interventions but 1 observational study showed no difference in rates of wound complications between treatment groups (Hester et al. 2015). Whether a significant reduction in SSI rates in all surgical specialities in all included studies is applicable to a UK setting?

What key indicators should be considered when deciding whether to use PICO in a clinical setting? The additional cost analysis undertaken by the EAC suggests that PICO is cost saving for highly invasive surgery. For surgery commonly undertaken on healthier patients such as C-section and orthopaedic surgery PICO is unlikely to be cost saving. What surgical

specialities (procedures) are most likely to see a cost saving from using PICO?

7 Authors

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Lizzy Latimer Technical Advisor

NICE Medical Technologies Evaluation Programme

November 2018

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- King's Technology Evaluation Centre. PICO negative pressure would therapy for closed surgical incision wounds. Anastasia Chalkidou, Mark Pennington.

B Submissions from the following sponsors:

- Smith & Nephew

C Related NICE guidance:

- Surgical site infections: prevention and treatment. NICE clinical guideline (2008, being updated). Available from https://www.nice.org.uk/guidance/cg74

D References

Adogwa, O., P. Fatemi, E. Perez, et al. (2014) "Negative pressure wound therapy reduces incidence of postoperative wound infection and dehiscence after long-segment thoracolumbar spinal fusion: a single institutional experience." The Spine Journal 14(12): 2911-2917

Caswell, J. F., S. Graham and P. A. Whitehouse (2015) "Prophylactic Use of PICO TM Negative Pressure Wound Therapy to Reduce Surgical Site Infections Following Large Bowel Surgery." British Journal of Surgery 102(98-98

Chaboyer, W., V. Anderson, J. Webster, et al. (2014) "Negative Pressure Wound Therapy on Surgical Site Infections in Women Undergoing Elective Caesarean Sections: A Pilot RCT." Healthcare 2(4): 417-428

Culver DH, Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG, Banerjee SN, Edwards JR, Tolson JS, Henderson TS, Hughes JM. Surgical

wound infection rates by wound class, operative procedure, and patient risk index. The American journal of medicine. 1991 Sep 16;91(3):S152-7.

Dingemans, S. A., M. F. N. Birnie, M. Backes, et al. (2018) "Prophylactic negative pressure wound therapy after lower extremity fracture surgery: a pilot study." International Orthopaedics 42(4): 747-753

Figueroa D, Jauk VC, Szychowski JM, Garner R, Biggio JR, Andrews WW, Hauth J, Tita AT. Surgical staples compared with subcuticular suture for skin closure after cesarean delivery: a randomized controlled trial. Obstetrics and gynecology. 2013 Jan;121(1).

Fleming, C. A., M. Kuteva, K. O'Hanlon, et al. (2018) "Routine use of PICO dressings may reduce overall groin wound complication rates following peripheral vascular surgery." Journal of Hospital Infection 99(1): 75-80

Galiano, R. D., D. Hudson, J. Shin, et al. (2018) "Incisional Negative Pressure Wound Therapy for Prevention of Wound Healing Complications Following Reduction Mammaplasty." Plastic and Reconstructive Surgery Global Open 6(1): e1560

Galiano RD et al; The cost-effectiveness of single-use negative pressure wound therapy (PICOTM) vs standard care for the prevention of wound dehiscence in patients undergoing bilateral reduction mammaplasty in the USA (Manuscript under preparation 2018b)

Gillespie, B. M., C. M. Rickard, L. Thalib, et al. (2015) "Use of Negative-Pressure Wound Dressings to Prevent Surgical Site Complications After Primary Hip Arthroplasty: A Pilot RCT." Surgical Innovation 22(5): 488-495

Hackney, L. and A. McCoubrey (2017) "The effect of negative pressure dressings (PICO) on wound complications, readmission rates and length of stay." Colorectal Disease 19(S2): 60

Hester, T., S. Mahmood and F. Moftah (2015) "Is Single Use Portable Incisional Negative Pressure Wound Therapy System Suitable for Revision Arthroplasty?" Advances in Orthopedic Surgery 2015(4

Hickson, E., J. Harris and D. Brett (2015) "A Journey to Zero: Reduction of Post-Operative Cesarean Surgical Site Infections over a Five-Year Period." Surgical Infections 16(2): 174-177

Holt, R. and J. Murphy (2015) "PICO™ incision closure in oncoplastic breast surgery: a case series." British Journal of Hospital Medicine 76(4): 217-223

Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005 Apr 20;5:13

Hyldig, N., C. A. Vinter, M. Kruse, et al. (2018) "Prophylactic incisional negative pressure wound therapy reduces the risk of surgical site infection after caesarean section in obese women: A pragmatic randomised clinical trial." BJOG: An International Journal of Obstetrics & Gynaecology 0(ja):

Irwin, G., L. Highton and J. Murphy (2018) "Negative pressure dressings significantly decrease rates of wound breakdown and may reduce implant loss rates in prepectoral breast reconstruction." European Journal of Surgical Oncology 44(6):

Karlakki, S. L., A. K. Hamad, C. Whittall, et al. (2016) "Incisional negative pressure wound therapy dressings (iNPWTd) in routine primary hip and knee arthroplasties." Bone & Joint Research 5(8): 328-337

Kawakita, T., S. N. Iqbal, S. Desale, et al. (2018) "540: Negative pressure wound therapy (PICO) in morbidly obese women after cesarean delivery compared with standard dressing." American Journal of Obstetrics and Gynecology 218(1, Supplement): S323

Kaye KS, Schmit K, Pieper C, Sloane R, Caughlan KF, Sexton DJ, Schmader KE. The effect of increasing age on the risk of surgical site infection. The Journal of infectious diseases. 2005 Apr 1;191(7):1056-62.

Liberman AM. How much more likely? The implications of odds ratios for probabilities. American Journal of Evaluation. 2005 Jun;26(2):253-66.

Luciani, D., A. Mazzotti, P. Capra, et al. (2016) "Efficacy of "PICO" negative pressure wound therapy (NPWT) versus traditional dressing for the treatment of postoperative wound care management in hip." Journal of Wound Care 26(Sup6b): 156

Matsumoto, T. and S. G. Parekh (2015) "Use of Negative Pressure Wound Therapy on Closed Surgical Incision After Total Ankle Arthroplasty." Foot & Ankle International 36(7): 787-794

Mossanen M, Krasnow RE, Lipsitz SR, Preston MA, Kibel AS, Ha A, Gore JL, Smith AB, Leow JJ, Trinh QD, Chang SL. Associations of specific postoperative complications with costs after radical cystectomy. BJU international. 2018 Mar;121(3):428-36.

Nordmeyer, M., J. Pauser, R. Biber, et al. (2015) "Negative pressure wound therapy for seroma prevention and surgical incision treatment in spinal fracture care." International Wound Journal 13(6): 1176-1179

O'Leary, D. P., C. Peirce, B. Anglim, et al. (2017) "Prophylactic Negative Pressure Dressing Use in Closed Laparotomy Wounds Following Abdominal Operations: A Randomized, Controlled, Open-label Trial The P.I.C.O. Trial." Annals of Surgery 265(6): 1082-1086

Pappala, S., B. Mitchell, J. Riley, et al. (2015) "Reducing caesarean section (CS) surgical site infection (SSI) rate with PICO (R) negative pressure wound therapy (NPWT) in high-risk pregnancies." Bjog-an International Journal of Obstetrics and Gynaecology 122(82-82

Pellino, G., G. Sciaudone, G. Candilio, et al. (2013) "Effects of a New Pocket Device for Negative Pressure Wound Therapy on Surgical Wounds of Patients Affected With Crohn's Disease: A Pilot Trial." Surgical Innovation 21(2): 204-212

Pellino, G., G. Sciaudone, G. Candilio, et al. (2014) "Preventive NPWT over closed incisions in general surgery: Does age matter?" International Journal of Surgery 12(S64-S68

Ridderstolpe L, Gill H, Granfeldt H, Åhlfeldt H, Rutberg H. Superficial and deep sternal wound complications: incidence, risk factors and mortality. European journal of cardio-thoracic surgery. 2001 Dec 1;20(6):1168-75.

Sandy-Hodgetts K, Leslie GD, Lewin G, Hendrie D, Carville K. Surgical wound dehiscence in an Australian community nursing service: time and cost to healing. Journal of wound care. 2016 Jul 2;25(7):377-83.

Searle, R. J. and D. Myers (2017) "A survey of caesarean section surgical site infections with PICOTM Single Use Negative Pressure Wound Therapy System in high-risk patients in England and Ireland." Journal of Hospital Infection 97(2): 122-124

Selvaggi, F., G. Pellino, G. Sciaudone, et al. (2014) "New advances in negative pressure wound therapy (NPWT) for surgical wounds of patients affected with Crohn's disease." Surg Technol Int 24(83-89

Stannard JP, Atkins BZ, O'Malley D, Singh H, Bernstein B, Fahey M, Masden D, Attinger CE. Use of negative pressure therapy on closed surgical incisions: a case series. Ostomy Wound Manage. 2009 Aug 1;55(8):58-66. Review. Erratum in: Ostomy Wound Manage. 2009 Sep 15;55(9):6. PubMed PMID: 19717857.

Svensson-Björk, R., J. Hasselmann and S. Acosta (2018) "Evaluation of inguinal vascular surgical scars treated with closed incisional negative pressure wound therapy using three-dimensional digital imaging—A

randomized controlled trial on bilateral incisions." Wound Repair and Regeneration 26(1): 77-86

Tan, K. W., Z. J. Lo, Q. Hong, et al. (2017) "Use of Negative Pressure Wound Therapy for Lower Limb Bypass Incisions." Annals of Vascular Diseases 10(4): 386-390

Tanaydin, V., J. Beugels, A. Andriessen, et al. (2018) "Randomized Controlled Study Comparing Disposable Negative-Pressure Wound Therapy with Standard Care in Bilateral Breast Reduction Mammoplasty Evaluating Surgical Site Complications and Scar Quality." Aesthetic Plastic Surgery 42(4): 927-935

Timmons, J. (2013) "Single use negative pressure wound therapy: A risk-based approach to the management of caesarean section procedures to reduce and prevent surgical site infections." BJOG: An International Journal of Obstetrics and Gynaecology 1)(417-418

Tuuli, M. G., S. Martin, M. J. Stout, et al. (2017) "412: Pilot randomized trial of prophylactic negative pressure wound therapy in obese women after cesarean delivery." American Journal of Obstetrics and Gynecology 216(1, Supplement): S245

Uchino, M., K. Hirose, T. Bando, et al. (2016) "Randomized Controlled Trial of Prophylactic Negative-Pressure Wound Therapy at Ostomy Closure for the Prevention of Delayed Wound Healing and Surgical Site Infection in Patients with Ulcerative Colitis." Digestive Surgery 33(6): 449-454

Van der Valk, M. J. M., E. J. R. de Graaf, P. G. Doornebosch, et al. (2017) "Incisional Negative-Pressure Wound Therapy for Perineal Wounds After Abdominoperineal Resection for Rectal Cancer, a Pilot Study." Advances in Wound Care 6(12): 425-429

Witt-Majchrzak, A., P. Zelazny and J. Snarska (2015) "Preliminary outcome of treatment of postoperative primarily closed sternotomy wounds treated using negative pressure wound therapy." Pol Przegl Chir 86(10): 456-465

Zotes, V., J. M. Mier and G. Cortes (2015) "P-187negative pressure wound therapy in a potentially infected wound after empyema surgery." Interactive CardioVascular and Thoracic Surgery 21(suppl_1): S51-S51

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Mr John Murphy, Consultant Oncoplastic Breast Surgeon, Nightingale Breast Unit, UHSM NHS Foundation Trust

Mr Sudhir Karlakki, Consultant Orthopaedic Surgeon, Robert Jones and Agnes Hunt Orthopaedic Hospital

Ms Pauline Whitehouse, Consultant General and Colorectal Surgeon, Worthing Hospital (Western Sussex Hospitals NHS Foundation Trust)

Mr Thomas Pinkney, Senior Lecturer and Consultant Colorectal Surgeon, Academic Department of Surgery, University of Birmingham

Ms Joanne Beresford, Tissue Viability Nurse Specialist, Leeds Community Healthcare NHS Trust

Dr Fania Pagnamenta, Nurse Consultant (Tissue Viability), Newcastle upon Tyne Hospitals NHS Foundation Trust

Ms Caryn Carr, Lead tissue viability nurse, Southern Health Foundation Trust

- The experts considered that the technology is innovative in comparison to standard dressing.
- All the experts were familiar with the technology.
- Two experts considered that patients would benefit from a reduced postoperative dehiscence, reduced implant loss and fewer delays to adjunctive treatments. One expert also noted improved patients' quality of life because PICO allows for more patient mobility.

- One expert considered the use of the technology may be associated with fewer SSI, shorter hospital stays, and reduced bed and community nursing care costs.
- One expert noted that the importance of training on dressing application, as wrong application would result in wasted resources.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient organisations were contacted and no response was received.

- Age Related Diseases and Health Trust
- Arthritis Action
- Arthritis and Musculoskeletal Alliance (ARMA)
- Arthritis Research UK
- British Obesity Surgery Patients Association (BOSPA)
- British Skin Foundation (BSF)
- Cardiovascular Care Partnership (UK)
- Children's Burn Trust (CBT)
- Colostomy Association
- Core (Digestive Disorders Foundation)
- Crohn’s and Colitis UK (NACC)
- Dan's Fund for Burns
- Diabetes UK
- Foot in Diabetes UK
- IA (Ileostomy and Internal Pouch Support Group)
- Independent Age
- InDependent Diabetes Trust
- Leg Ulcer Charity
- Lindsay Leg Club Foundation
- National Childbirth Trust (NCT)
- National Rheumatoid Arthritis Society
- Pressure Ulcers UK
- Pumping Marvellous Foundation
- Scleroderma and Raynaud's UK
- Short Bowel Survivors and Friends
- The Circulation Foundation
- The Relatives and Residents Association

- Trauma Care
- Ulcerative Colitis UK
- Your Turn

Appendix D: Claimed benefits and decision problem

The benefits to patients in acute care settings from the addition of the PICO negative pressure wound therapy to standard care claimed by the company are:

- Reduced incidence of surgical site complications
- Ease of use

The benefits to the healthcare system claimed by the company are:

- Reduced healthcare utilisation
- Lower rates of readmission and reoperation
- Reduced length of hospital stay
- Less resource use
- Reduced overall treatment cost

	Scope issued by NICE
Population	Patients having closed surgical incisions with low to moderate levels of exudate who are considered to be at high risk of developing a surgical site complication particularly SSI and dehiscence
Intervention	PICO single-use negative pressure wound therapy system
Comparator(s)	Conventional post-surgical wound dressings
Outcomes	The outcome measures to consider include: 8 rate of post-surgical wound complications (SSI, dehiscence, seroma, hematoma, delayed healing and abnormal scarring) 9 length of hospital stay as a result of surgical complications 10 time to heal 11 number of dressing changes 12 staff time to apply device 13 amount of wound exudate 14 rates of re-operation for wound complications 15 ease of use of the device by the patient

	16 device-related adverse events	
Cost analysis	Comparator(s): Costs will be considered from an NHS and personal social services perspective. Hospital and community settings should be considered. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Sub-groups to be considered	17 individual surgical specialities* 18 wounds with low to moderate exudate 19 hard to heal wounds * including but not limited to obstetric, colorectal, abdominal, orthopaedic, cardiothoracic, gynaecology etc.	
Special considerations, including those related to equality	The device may be beneficial to women who have had obstetric and gynaecology and breast surgery. Certain ethnic groups are more prone to poor wound healing due to increased risk of diabetes or keloid formation. Older people are also more at risk of poor wound healing. Sex, race and age are protected characteristic under the equality act 2010.	
Special considerations, specifically related to equality issues	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

SCOPE

PICO single-use negative pressure wound therapy system for closed surgical incisions

1 Technology

1.1 Description of the technology

PICO (Smith & Nephew) is a canister-free, single-use negative pressure wound therapy (NPWT) system consisting of a single-use sterile pump and 1 or 2 multi-layered adhesive dressings. The proprietary dressing layer is designed to consistently deliver negative pressure across the incision and zone of injury while protecting the wound, with the aim of promoting healing by increasing blood supply. This evaluation focuses on the use of PICO for closed surgical incision wounds with low to moderate levels of exudate.

The pump included in PICO is battery powered and delivers a continuous negative pressure of 80 mmHg to a sealed wound. The pump is activated using a push button and the battery drives the pump for up to 7 days. If necessary the pump can be activated intermittently. Light-emitting diodes (LEDs) on the pump provide alerts for low-battery status and pressure leaks.

Each dressing in the PICO system is made up of 4 layers; a top film layer which acts as a physical barrier and allows evaporation of moisture; an absorbent layer to remove exudate and prevent bacteria from entering the wound; a proprietary airlock layer for even distribution of pressure and to prevent leak back of exudate to the incision site; a silicone adhesive layer closest to the skin, designed to minimise pain and damage during peel back and to contribute to the aesthetics of scar formation. The layers are designed to reduce lateral tension. The dressings are rectangular or square in shape

and come in 10 sizes (up to 25 cm × 25 cm). This includes a multisite dressing of up to 20 cm × 25 cm, which is used for awkward anatomical areas. A pair of larger dressings can absorb up to 300 ml of exudate over a 7 day period. Each dressing holds an average of 150ml of exudate. PICO is available for both inpatients and outpatients.

Training on the use of PICO is provided by the manufacturer at no additional cost.

1.2 Regulatory status

The PICO negative pressure wound therapy received a CE mark in July 2011 as a class IIb medical device.

1.3 Claimed benefits

The benefits to patients in acute care settings from the addition of the PICO negative pressure wound therapy to standard care claimed by the company are:

- Reduced incidence of surgical site complications
- Ease of use

The benefits to the healthcare system claimed by the company are:

- Reduced healthcare utilisation
- Lower rates of readmission and reoperation
- Reduced length of hospital stay
- Less resource use
- Reduced overall treatment cost

1.4 Relevant diseases and conditions

The PICO single-use negative pressure wound therapy system is intended to prevent and treat surgical site complications (SSC) such as surgical site infections (SSI) and dehiscence which can occur in closed surgical incisions

wounds. These complications can delay healing and result in considerable mortality and morbidity.

All patients undergoing surgery are at a theoretical risk of developing a surgical incision complication. The World Union of Wound Healing Societies (WUWHS) Closed Surgical Incision Management Consensus Document cites that patient and surgery related factors may put a patient at a high risk of developing surgical site complications. Intrinsic patient factors include uncontrolled insulin-dependent diabetes, renal dialysis, increased age, poor physical status (based on the American Society of Anaesthesiologists [ASA] physical status classification) and a high BMI. Emergency procedures including caesarean section or certain elective procedures such as cardiac or colorectal surgery and extended surgical procedures may increase the risk of SSC. In addition, hypothermia during surgery may put a patient at increased risk of SSC.

According to NICE guideline on preventing and treating surgical site infections (currently being updated), 20% of all health-care associated infections are surgical site infections and 5% of patients undergoing a surgical procedure develop a surgical site infection.

1.5 Current management

The NICE guideline on preventing and treating surgical site infections notes that patients should have post-surgical wound care which involves:

- using aseptic non-touch techniques for removing and changing surgical wound dressings
- wound cleaning with sterile saline for up to 48 hours and cleaning with tap water afterwards
- antibiotics treatment, if a surgical site infection is suspected. If dead or infected tissues seem to be slowing down the healing process,

debridement (which may involve surgery) can be undertaken to remove the dead tissue.

Although closed incisions are intended to heal by primary intention, the WUWHS Closed Surgical Incision Management Consensus Document notes that NPWT shows promise for use on closed surgical incisions to aid healing in patients who are at increased risk of surgical site complications such as SSI, seroma, haematoma and dehiscence. When dehiscence occurs and if a deep infection is ruled out, a NPWT may sometimes be helpful to promote healing by secondary intention.

2 Statement of the decision problem

	Scope issued by NICE
Population	Patients having closed surgical incisions with low to moderate levels of exudate who are considered to be at high risk of developing a surgical site complication particularly SSI and dehiscence
Intervention	PICO single-use negative pressure wound therapy system
Comparator(s)	Conventional post-surgical wound dressings
Outcomes	The outcome measures to consider include: • rate of post-surgical wound complications (SSI, dehiscence, seroma, hematoma, delayed healing and abnormal scarring) • length of hospital stay as a result of surgical complications • time to heal • number of dressing changes • staff time to apply device • amount of wound exudate • rates of re-operation for wound complications • ease of use of the device by the patient • device-related adverse events
Cost analysis	Comparator(s): Costs will be considered from an NHS and personal social services perspective. Hospital and community settings should be considered. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.

Sub-groups to be considered	• individual surgical specialities* • wounds with low to moderate exudate • hard to heal wounds * including but not limited to obstetric, colorectal, abdominal, orthopaedic, cardiothoracic, gynaecology etc.	
Special considerations, including those related to equality	The device may be beneficial to women who have had obstetric and gynaecology and breast surgery. Certain ethnic groups are more prone to poor wound healing due to increased risk of diabetes or keloid formation. Older people are also more at risk of poor wound healing. Sex, race and age are protected characteristic under the equality act 2010.	
Special considerations, specifically related to equality issues	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No

3 Related NICE guidance

Published

- NICE clinical guideline 74(2008, last updated 2017) Surgical site infections: prevention and treatment
- NICE clinical guideline 65 (2008, last updated 2016) Hypothermia: prevention and management in adults having surgery

Under development

None

4 External organisations

4.1 Professional organisations

4.1.1 Professional organisations invited to participate in the evaluation

The following societies have been have been invited to register as stakeholders:

- Arthritis and Musculoskeletal Alliance (ARMA)
- Association of Breast Surgery
- Association of Surgeons of Great Britain and Ireland
- British Association for Nursing Cardiovascular Care
- British Association for Surgery of the Knee
- British Association of Paediatric Surgeons
- British Association of Plastic Reconstructive and Aesthetic Surgeons
- British Obesity and Metabolic Surgery Society
- British Obesity Surgery Patients Association (BOSPA)
- British Obesity Surgery Society
- Colostomy Association
- National Rheumatoid Arthritis Society
- Royal College of Emergency Medicine
- Royal College of General Practitioners
- Royal College of Midwives
- Royal College of Nursing
- Royal College of Obstetricians and Gynaecologists
- Royal College of Surgeons
- Royal College of Surgeons of Edinburgh
- Royal College of Surgeons of England
- Society for Cardiothoracic Surgery of GB and Ireland
- Society of Vascular Nurses
- Surgical Dressing Manufacturers Association

4.2 Patient organisations

At the selection stage, NICE's Public Involvement Programme contacted the following organisations for patient commentary and alerted them to the availability of the draft scope for comment:

- Age Related Diseases and Health Trust
- Arthritis Action
- Arthritis and Musculoskeletal Alliance (ARMA)
- Arthritis Research UK
- British Obesity Surgery Patients Association (BOSPA)
- British Skin Foundation (BSF)
- Cardiovascular Care Partnership (UK)
- Children's Burn Trust (CBT)
- Colostomy Association
- Core (Digestive Disorders Foundation)
- Crohn's and Colitis UK (NACC)
- Dan's Fund for Burns
- Diabetes UK
- Foot in Diabetes UK
- IA (Ileostomy and Internal Pouch Support Group)
- Independent Age
- InDependent Diabetes Trust
- National Childbirth Trust (NCT)
- National Rheumatoid Arthritis Society
- Pressure Ulcers UK
- Pumping Marvellous Foundation
- Scleroderma and Raynaud's UK
- Short Bowel Survivors and Friends
- The Relatives and Residents Association
- Trauma Care
- Ulcerative Colitis UK

- Your Turn

Adoption scoping report: MTG PICO negative pressure wound therapy

Summary – for first meeting

Adoption levers

- Small and portable
- Less pressure than other negative pressure systems
- Easy and quick to apply.
- Manufacturer refund option if benefits not observed.
- *Prevention*: reduced Surgical Site Infection (SSI), reduced Surgical Site Complications (SSC), reduced length of stay.
- *Treatment*: reduces number of dressing changes required for oozing wounds, potentially helps wound healing – good clinician acceptance.

Adoption barriers

- Cost
- *Prevention*: lack of clinical confidence about effectiveness, clinical opinion of low incidence of SSC and SSI, poor communication with onward referrals
- *Treatment*: appropriate selection of patients.

1 Introduction and contributors

The adoption team has collated information from 7 NHS healthcare professionals with experience of using PICO negative pressure wound therapy for either *preventing* SSC in at risk patients (closed surgical incision wounds), and/or for *treating* closed surgical incision wound site complications.

These were 3 tissue viability nurse specialists, 1 cardiac wound care clinical nurse specialist, 1 orthopaedic surgeon, 1 consultant spinal surgeon and 1 consultant oncoplastic surgeon (breast). Adoption was also discussed with the manufacturer.

This adoption scoping report includes some of the benefits and difficulties that may be faced by organisations when planning to adopt the technology into routine NHS use.

Three sites (as summarised below) used PICO for ***prevention*** of surgical site complications of closed incisions in people at risk (data and figures are estimates).

Setting	Caseload	Frequency of Use	Duration of Use
Oncoplastic surgery	60-70 breast reconstructions per year.	No estimates for PICO use for prevention. Use could be guided by pre trial return to theatre rates of 2-3% and infection rates of 4.5%.	3 month trial using free dressings Also used for ***treatmen***t since 2014
Cardiac surgery	Average yearly caseload of 300 patients undergoing CABG or valve repairs.	30 PICO dressings in 3 months (= ~10%) (this equates to ~120pa).	6 months Also used for ***treatment*** for past 3 years
Orthopaedic surgery	350 patients with emergency surgery for fractured neck of femur per year. (90% high risk of SSC). 350 elective arthroplasties per year (60% high risk of SSC)	At least 100 patients for this purpose in 3 months (this equates to annual usage of 315 and 210 pts respectively)	3 months trial using educational grant from manufacturer

Six sites use PICO for treatment of the early signs of site complications in closed surgical incisions.

2 General experiences of using the device

- All contributors remove the PICO pump and dressing after 7 days in line with manufacturer instructions. If further treatment is required a new pump and dressing is applied.
- The 2 dressings are sufficient for the 7 day period, if more are required to absorb exudate, PICO is not suitable. Once a dressing has been peeled back or removed it cannot be re-applied.
- Batteries are reliable however, one contributor said having only 7 day functionality led to wastage and that other manufacturers had achieved 2 week functionality.

- Three contributors said the pump and dressing pack should only include 1 dressing with the option to buy more if required, to prevent wastage.
- All said that the sizes available are suitable for the wounds they deal with.
- It is only the largest dressing that can absorb up to 300 ml (150ml per dressing).
- The dressing is easy to apply and takes only a few minutes longer to apply than standard absorbent dressing.
- Failure of the seal is uncommon (estimated 10%).
- Certain wound locations had a higher incidence of seal failure (sternal in female patients and knees).

3 Use of PICO for prevention of surgical site complications in cases at high risk

Benefits as reported by the contributors

- Reduced SSIs
  - ◊ the cardiac team reported a 50% reduction in SSI in 3 months when using PICO as part of an overall strategy.
- Reduction in SSCs
  - ◊ the cardiac team reported spending £2,500 less in equipment to treat SSC over a 3 month period when using PICO as part of an overall strategy.
- Reduced length of stay

Patient selection

Determination of "high risk of SSC" is routinely established pre-operatively using the following clinical factors; BMI 35+, diabetes, ASA 3+, emergency procedure, smoker. Two contributors use the Brompton and Harefield Infection Score. There are also additional procedure specific factors such as a bilateral procedure (breast surgery), HbA1c and ventricular function (cardiac surgery) and surgery revision (orthopaedic surgery) used in the risk assessment.

Care Pathway

PICO is applied in theatre by the surgeon. Effective systems are required to ensure PICO is available in theatre and relevant staff know when it is needed. PICO is

commonly used for 5-7 days and removed prior to discharge or at a nurse led outpatient clinic. One contributor said it can be used for up to 2 weeks (1 new pump/dressing per week).

If a patient is discharged from hospital with PICO, clear guidance is needed by the receiving community team on instructions for use.

Overall, contributors agreed that the wound management with PICO is very similar to that of an absorbent dressing.

Training

Training is not onerous however there are a large volume of staff who span a surgical patient's care pathway that require training (surgeon, theatre teams, wards, critical care, community nursing teams).

Clinical confidence

The oncoplastic breast surgeon is currently trialling the use of PICO for prevention and commented that there is not much evidence to support its use in this area.

Surgical teams who do not believe they have a problem with SSC and SSI are unlikely to adopt this technology. Contributors indicated this is common.

Where improvements with PICO have been observed, contributors attributed this to a good post-operative care pathway of which PICO was one element.

Cost

The cost of the technology was identified as a barrier to adoption in particular where a large proportion of the caseload would be classed as 'high risk'.

Additional costs of using PICO are met by the trust and not commissioners. The cases for adoption were based on the savings from reduced SSI, SSC and length of stay.

Where a patient is discharged to the community and requires a second PICO dressing, commonly GPs will not prescribe it because of cost.

The manufacturer has developed risk share agreements where they offer a refund if pre agreed benefits are not observed in practice.

Owing to the high cost of the technology, sites have adopted systems to prevent theft including using named surgeon prescribing, close monitoring of prescriptions and locking cupboards. One contributor reported an incidence of fraud involving these dressings.

4 Use of PICO for treatment for early signs of SSC

Benefits as reported by the healthcare professionals

- Small, easy to carry, and allows the patient to be mobile during treatment
- Offers a lesser pressure than other negative pressure devices, which for some wounds is more suitable
- Easy and quick to apply
- Most contributors thought it helped wound healing indicating good clinician confidence
- Requires less dressing changes than conventional absorbent dressings thereby reducing nursing time

Patient selection

PICO is only initiated following a thorough assessment to ensure no other underlying causes or deeper wound problems, and tissue viability nurse or surgeon agreement.

All contributors said PICO is not suitable for high volumes of exudate. Assessing the amount of exudate is difficult and down to clinical experience. Sometimes PICO and other absorbent dressings have to be tried to evaluate level of saturation.

The skin around the wound can be viewed. If frequent inspections of the wound are needed, PICO is not suitable because of the wastage.

PICO may not be suitable for people in whom the tubing could cause injury, for example those at risk of falls.

Care pathway

Availability of the technology in the right place at the right time is important for adoption. Commonly, tissue viability nurses stock PICO within their supplies.

One contributor said PICO would be used as an adjunct to other treatments for surgical site complications such as debridement, irrigation and antibiotics. Length of use varies from 1 week to 6 weeks. Trusts have protocols about when to stop if no improvements have been noted. These range from 2-6 weeks.

No significant change to the care pathway is required.

Training

Training is needed for tissue viability nurses, community nurses and nurse specialists about when to apply PICO and how. Experience in using the dressing helps with trouble shooting and achieving the best seals for the vacuum.

Clinical confidence

One clinician who had used PICO on spinal wounds did not think it was very effective and said that 80% of the patients he used it on returned to theatre for the wounds to be treated. He felt it important to try to rectify any problems surgically as soon as possible. This observation may be specific to these type of wounds.

Cost

The cost of PICO is a barrier to use. Those agreeing to fund PICO sought reassurance that it is only being used on selected patients, for a certain length of time and by certain healthcare professionals such as tissue viability nurses.

5 Comparators

Contributors identified alternatives to PICO were absorbent dressings, higher pressure negative pressure systems and return to theatre for the wound to be inspected and re done. Two contributors identified comparators to PICO; Uno portable (Gendayne), Avelle (Convatec) and Prevena, (KCL).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence

Evaluation title:	MT390 PICO negative pressure wound therapy
Sponsor:	Smith & Nephew
Date sections A and B submitted:	2nd September, 2018
Date section C submitted:	

August 2011 (Version 1.1)

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Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]').Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of full journal articles or reports – in electronic or hard copy form – included in the submission, if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. This clearance must be wide enough to allow NICE to make further copies, store the article electronically for a limited period of time on a shared drive to be accessed by a limited number of staff. Additionally, any full article obtained and submitted in electronic format must be done so in a manner compliant with the relevant contractual terms of use permitting the sponsor electronic access to the article. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished research. NICE will then itself obtain full copies of all relevant papers or reports, paying a copyright fee where necessary. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

Glossary of terms

Term	Definition
ASA	American Society of Anesthesiology
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CD	Crohn's disease
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
C-section	Caesarean section
DFU	Diabetic foot ulcer
DM	Diabetes mellitus
ECDC	European Centre for Disease Control and Prevention
EWMA	European Wound Management Association
HPA	Health Protection Agency
HSCIC	Health and Social Care Information Centre
IBD	Inflammatory bowel disease
LOS	Length of stay
NHS	National Health Service
NNIS	National Nosocomial Infections Surveillance
NPWT	Negative pressure wound therapy
OR	Odds ratio
PAD	Peripheral arterial disease
PCS	Physical component summary score
PVD	Peripheral vascular disease
QOL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SF-12	12-item SF-36
SF-36	Short-form 36
SOC	Standard of care
SSC	Surgical site complication

SSI	Surgical site infection
VLU	Venous leg ulcer

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem

Table 1 Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	Patients having closed surgical incisions with low to moderate levels of exudate who are considered to be at high risk of developing a surgical site complication particularly SSI and dehiscence.	None	N/A
Intervention	PICO single-use negative pressure wound therapy system	None	N/A
Comparator(s)	Conventional post-surgical wound dressings	None	N/A
Outcomes	The outcomes measures to be considered: • Rate of post-surgical wound complications (SSI, dehiscence, seroma, haematoma, delayed healing and abnormal scarring. • Length of hospital stay, as a result of surgical complications • Time to heal • Number of dressing changes • Staff to apply device • Amount of wound exudate • Rates of re-operation for wound complications • Ease of use of the device by the patient • Device related adverse events	None	N/A
Cost analysis	Comparator(s): Costs will be considered from an NHS and personal social services perspective. Hospital and community settings should be considered. The time horizon for the cost analysis will be sufficiently long and reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combination of devices are needed.	None	N/A
Subgroups to be considered	Individual surgical specialities* Wounds with low to moderate exudate Hard to heal wounds	None	N/A

	*including but not limited to obstetric, colorectal, abdominal, orthopaedic, cardiothoracic, gynaecology etc.		
Special considerations, including issues related to equality	The device may be beneficial to women who have had obstetric and gynaecology and breast surgery. Certain ethnic groups are more prone to poor wound healing due to increased risk of diabetes or keloid formation. Older people are also more at risk of poor wound healing. Sex, race and age are protected characteristic under the equality act 2010.	None	None

If the sponsor considers that additional parameters should be included in the submission, which are not stated in the decision problem, this variation from the scope and the rationale for it must be clearly described in the relevant columns in table A1.

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

PICO single-use negative pressure wound therapy device

Table 2 PICO Variant Launches

Product Name	Year of launch	Content of kit	Dressing sizes (cms)
PICO	2011	1 pump + 2 dressings	10 sizes - 10x20, 10x30, 10x40, 15x20, 15x30, 15x15, 20x20, 25x25, small multisite, large multisite
PICO	2011	1 pump + 1 dressing	5 sizes - 10x20, 10x30, 10x40, 15x15, 20x20
PICO 7	2018	1 pump + 2 dressings	10 sizes - 10x20, 10x30, 10x40, 15x20, 15x30, 15x15, 20x20, 25x25, small multisite, large multisite
PICO 7	2018	1 pump + 1 dressing	10 sizes - 10x20, 10x30, 10x40, 15x20, 15x30, 15x15, 20x20, 25x25, small multisite, large multisite
PICO Multipacks	2018	Box of 5 dressings	10 sizes - 10x20, 10x30, 10x40, 15x20, 15x30, 15x15, 20x20, 25x25, small multisite, large multisite
PICO 7Y	2018	1 pump with Y connector + 2 dressings	1 size - Large multisite

Summary of technology:

PICO is a canister-free single-use negative pressure wound therapy (NPWT) system consisting of a single-use sterile pump and a multi-layered adhesive dressing.

The pump is operated by 2 AA batteries and delivers a continuous negative pressure of 80 mmHg to a sealed wound. Once activated, using a push button, the battery drives the pump for up to 7 days and light-emitting diodes (LEDs) provide alerts for low-battery status and pressure leaks.

The dressing comes in 10 sizes (as detailed above). This includes a multisite dressing of up to 20 cm × 25 cm, which is used for awkward anatomical areas. PICO dressings can absorb up to 800 ml of exudate during 1 week of therapy.

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

PICO has a multimodal mechanism of action that minimises the risk of non-healing or wound complications, such as infection and dehiscence in closed wounds.

Evidence suggests that optimal healing of a closed surgical incision can be promoted by managing both the incision site and the surrounding skin. Although traditional NPWT systems have been shown to contribute to improve healing of closed surgical incisions, they were designed primarily to manage chronic wounds through the application of negative pressure to the wound bed. In contrast, the PICO system delivers negative pressure through a perforated silicone wound contact layer across the entire width of the dressing, which is positioned to include the wound and a substantial area of adjacent peri-wound skin. When applied to closed surgical wounds, PICO can contribute to the healing process through multiple mechanisms:

- Protecting the incision from external contamination;
- Providing physical closure of the wound by holding the closed incision together, reducing lateral tensile forces across the incision which can cause the wound to re-open (dehiscence);
- Increasing the activity of the lymphatic system in deep tissue;
- Maintaining an efficient blood supply to the wound (perfusion), which helps support the immune response;
- Increasing the efficiency of functional lymph vessels helping to reduce oedema.

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technologyis being considered in the scope issued by NICE.

Surgical site complications defined

In the majority of cases, surgical wounds heal in a predictable way following closure. However, in a significant minority of cases, complications can occur which result in the wound re-opening and requiring further intervention to achieve closure (Scalise et al, 2015[30]).

Surgical site complications (SSC) include:

- surgical site infections (SSI);
- wound dehiscence;
- haematomas/seromas;
- necrosis, skin/fascial dehiscence or blistering.

Incidence/prevalence of surgical site infections (SSI)

SSI can be classified as:

- Superficial incisional;
- Deep incisional;
- Organ/space infections.

Guidelines on the prevention and management of SSI from NICE in England suggest that around 5% of all patients undergoing a surgical procedure experience a SSI[23]. However, SSI rates vary considerably depending on the definition applied, type of surgery and the methods used for surveillance.

A prospective surveillance study of patients undergoing major surgical procedures at a single hospital in England between April 2010 and March 2012, including rigorous post-discharge surveillance, illustrates the scale of under-reporting inherent in routine monitoring (Jenks et al, 2014[18]). The findings report an overall rate of SSI of 5.1%

across all procedures. Infection rates for specific surgical procedures were more than twice the rate reported in standard surveillance studies (e.g. European centre for disease control) in some instances – for example 3.2% compared to 0.7% for knee replacement. Whilst some of the observed difference may be attributable to practice in this single facility, more rigorous post-operative monitoring is believed to account for the majority of the observed difference (**Table A3)**.

Table 3 Rates of Surgical Site Infection reported in NHS Study

Rates of SSI as reported in a prospective surveillance study in a NHS hospital in England 2010–2012 (Jenks et al, 2014)[18]

Surgical procedure	No. of procedures	Total SSIs, n (%)[a]
Cardiac	1672	180 (10.8)
Limb amputation	291	13 (4.5)
Hip replacement	980	16 (1.6)
Knee replacement	970	31 (3.2)
Spinal	1827	18 (1.0)
C-section	1837	139 (7.6)
Breast	1016	49 (4.8)
Large bowel	673	86 (12.8)
Small bowel	259	24 (9.3)

C-section, Caesarean section; SSI, surgical site infection. [a]Includes number of SSIs during admission, on readmission, and postdischarge.

Incidence/prevalence of wound dehiscence

Fewer data are available on wound dehiscence, compared to SSI. Wound dehiscence, which involves separation of the wound edges along the incision, is considered as a surrogate safety/quality indicator in the United States due to its considerable impact on morbidity, hospital length of stay (LOS) and readmission rates (Webster et al, 2014[39]; Shanmugam et al, 2015[32]). In a retrospective analysis of electronic health data from 25,636 eligible patients who had undergone abdominopelvic surgery in a large hospital system in the USA, 786 (3%) had wound dehiscence (Shanmugam et al, 2015[32]). The highest prevalence of dehiscence was observed in patients undergoing vascular or hernia surgery where more than 1 in 20 (5.7%) and 1 in 25 (4%) of patients respectively experienced dehiscence (**Table A4**).

Table 4 Rates of dehiscence following surgery

Rates of wound dehiscence following abdominopelvic surgery (Shanmugam et al, 2015)[32]

Surgery	Dehiscence Y/N	Dehiscence, %
Vascular	13/216	5.7
Hernia	70/1661	4.0
Laparotomy	95/2671	3.4
Abdominopelvic surgery, unspecified	529/16,549	3.1
Laparoscopy	19/606	3.0
Gynaecological	42/1675	2.4
Urological	16/1135	1.4
Prostate/seminal vesicles	2/1123	0.1

[a]Patients were >18 years of age and had undergone inpatients abdominopelvic surgery with a LOS >2 days.

Risk factors for SSC

Development of SSC involves a complex interaction between patient- and surgery-related factors, each of which presents significant challenges for the maintenance of wound closure and prevention of complications (Pellino et al, 2014b[28]). The majority of the evidence on risk factors for SSI is derived from regression analysis of large observational datasets. These studies were considered by the National Institute for Health & Clinical Excellence (NICE) as part of the development of guidelines on SSI prevention and treatment[23]. The guideline identified a number of commonly reported risk factors associated with increased likelihood of infection:

- Age;
- Presence of co-morbidities, including diabetes mellitus, renal failure and malnutrition;
- American Society of Anaesthesiologists' (ASA) score of 3 or more;
- Immuno-suppressant treatment (radiotherapy, steroid use);
- Obesity;
- Smoking;
- Wound classification (clean or contaminated);
- Duration of surgery >75% percentile for the procedure.

However, the guideline also recognises that there are some procedure specific risk factors which also need to be taken into account. For example, analysis of patients undergoing total joint replacement surgery identifies that revision surgery significantly increases the risk of infection.

In their analysis of dehiscence following abdominopelvic surgery, Shanmugam et al, 2015[32], identified a number of risk factors that were common with SSI, although the number of risk factors considered was limited by reliance on routinely collected patient data. Age, sex (male) and obesity were all associated with increased risk of dehiscence. Co-morbidities correlated with increased risk of dehiscence include COPD, anaemia, pneumonia and diabetes.

A large-scale surveillance study from the UK illustrates the degree to which individual risk factors can impact on rates of infection. Wloch et al conducted a multi-centre observational study at 14 National Health Service (NHS) hospitals in England to identify rates of SSI and associated risk factors. The study identified a clear correlation between the development of SSI and body mass index (BMI) as illustrated below (Wloch et al, 2012)[42] (**Table A5.**) The rate of infection in women with a BMI>35 was twice the population average, with almost 1 in 5 women in this group developing an infection. Similarly, rates of infection in women with diabetes were almost 1.5 times higher than the mean rate[42].

Table 5 Risk of SSI following C-Section

Risk of SSI following C-section in England according to BMI (Wloch et al, 2012[42]

Risk factor	Infection rate, %	Operations, n	Adjusted OR (95% CI)	p-value
BMI category, n=3910				
25–29.9	9.65	1140	1.64 (1.22–2.20)	<0.01
30–34.9	13.45	565	2.41 (1.73–3.37)	<0.01
≥35	19.28	415	3.67 (2.62–5.16)	<0.01

BMI, body mass index; CI, confidence interval; OR, odds ratio; SSI, surgical site infection.

SSC can have a severe impact on patient's quality of life and well-being (Gray, 2011[11]; Andersson et al, 2010[2]) and also significantly increase the risk of post-operative mortality (Kirkland K et al, 1999[21]).

Kirkland K et al (1999)[21] conducted a matched cohort study, to identify the impact of SSI on post-operative clinical and economic outcomes. Their findings suggest that patients who develop a SSI are twice as likely to die as a result of their surgery compared to patients that do not develop an infection. As a further indicator of the excess morbidity associated with infections, patients who developed a SSI were five times more likely to be readmitted to hospital and 1.6 times more likely to be admitted to ICU. These findings, illustrate the importance of early and proactive management of closed surgical incisions.

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

The PICO single-use negative pressure wound therapy system is intended to prevent and treat surgical site complications (SSC) such as surgical site infections (SSI) and dehiscence, which can occur in closed surgical incisions wounds. These complications can delay healing and result in considerable mortality and morbidity.

According to NICE guideline on preventing and treating surgical site infections (currently being updated), 20% of all health-care associated infections are surgical site infections and 5% of patients undergoing a surgical procedure develop a surgical site infection[23].

NICE Specific guidance – PICO MIB 149[24]

The MIB reports the prophylactic use of PICO as a potentially more effective alternative to standard surgical dressings in the prevention of surgical site complications (SSCs)[21].

WHO Guidelines – Global guidelines for the prevention of surgical site

Infection[40]

The panel suggests the use of prophylactic negative pressure wound therapy (pNPWT) in adult patients on primarily closed surgical incisions in high-risk wounds, for the purpose of the prevention of SSI, while taking resources into account. Recommendation – conditional[40]

WUWHS Consensus document - Closed surgical incision management:

Understanding the role of NPWT[43]

All patients undergoing surgery are at a theoretical risk of developing a surgical incision complication. The World Union of Wound Healing Societies (WUWHS) Closed Surgical Incision Management Consensus Document cites that patient and surgery related factors may put a patient at a high risk of developing surgical site complications. Intrinsic patient factors include uncontrolled insulin-dependent diabetes, renal dialysis, increased age, poor physical status (based on the American Society of Anaesthesiologists [ASA] physical status classification) and a high BMI.

Emergency procedures including caesarean section or certain elective procedures such as cardiac or colorectal surgery and extended surgical procedures may increase the risk of SSC. In addition, hypothermia during surgery may put a patient at increased risk of SSC[43].

WUWHS Consensus document – Surgical wound dehiscence (SWD): Improving prevention and outcomes

Impact of SWD is considerable with huge burden to the healthcare system in both acute and community care. There is a recognised increase in mortality (9.6%), increase in hospitalisation (9.4 days) and $40k of hospital costs with SWD. PICO plays an important role in the prevention of SWD and is recommended for prophylactic use on patients where patient or surgical risk factors are present.[43]

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

In the hospital, PICO single-use NPWT system should be utilised in place of conventional post-surgical wound dressings to prevent or treat SSIs in closed surgical incision wounds with low to moderate exudate level. Other elements of the care pathway would remain the same and aligned to the current recommendations in the NICE guideline on current NICE guideline on preventing and treating surgical site infections.

Patients undergoing surgery should be risk stratified based on intrinsic patient factors such as high BMI, poor physical status (ASA score), Diabetes Mellitus. In addition to this a patient might also be considered to be at risk if they have emergency procedures, particularly relating to cardiac or colorectal surgery. In the majority of the studies reported herein, PICO was applied prophylactically immediately post-operatively, in the theatre. Whilst PICO can be applied on the ward following surgery, any delay in application may increase the risk of infection or complication.

In the community setting (outside the hospital), the PICO single-use NPWT system can be utilised in the treatment of postoperative surgical site complications.

The PICO system can be applied by all healthcare professionals, surgeons, doctors and nurses. At the end of therapy PICO can also be removed by a lay user e.g. the patient or caregiver, and disposed of appropriately.

No additional procedures or consultations are required to manage PICO and it may even reduce the number of nurse consultations required to manage the wound post-operatively.

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

The current NICE guideline on preventing and treating surgical site infections, which is currently being updated, identifies key steps that should be taken to minimise complications post-surgery.

Despite the widespread application of best practice guidelines, there remains a small but significant rate of surgical site infections (estimated to be ~5% by NICE[23]). The actual rate of infection varies widely in published literature due to different approaches to data capture, follow-up and definitions. Prospective, observational studies, including post-operative follow-up, provide the most accurate estimates.

Hypotheses for these persistent infections include:

- Inconsistent application of best practice across providers;
- Inconsistent application of best practice across multiple sites of care, particularly in the transfer of patients from acute to community care settings;
- Failing to risk stratify patients and put in place mitigating steps for those patients contributes to the greatest risk of developing complications.

PICO is intended to be applied in acute care settings but can be left in place for up to 7 days, thereby promoting continuity of care across care settings. The evidence on PICO is mainly derived from patients at elevated risk of surgical site complications and has been shown to effectively mitigate risk factors in these patient groups.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

Patients should be treated in line with the existing guidance on surgical site complications. However, patients with one major risk factor or multiple moderate risk factors (as per WUWHS guidelines in closed incision management[43]) should be considered as candidates for PICO. This risk assessment should be undertaken prior to surgery so the PICO device is available at the time of the operation. PICO should be used in place of a standard post-operative wound dressing. PICO should be left in

place for up to 7 days and post-acute care providers should be informed of the use of the dressing.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

- Risk assessment prior to surgery to identify PICO eligible patients.
- Replacement of a standard post-operative dressing with PICO at the time of the surgery.
- Advice to the patient and post-acute care provider at the time of discharge on how to manage the PICO device.

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

The addition of an eligibility criteria, specific to PICO, as part of standard pre-operative planning and assessment.

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

None – the PICO device would simply be used in place of a standard post-operative dressing in eligible patients.

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology

Studies in multiple surgical specialties have illustrated the potential for PICO to reduce healthcare resource use, including:

- Excess and unpredictable hospital stays as a result of surgical site complications (Rodden & Taylor, 2015[29]; Pellino et al, 2014a[27], 2014b[28]; Selvaggi et al, 2014[31]);
- Hospital readmission/return to theatre rates (Bullough et al, 2014[4], 2015a[5], 2015b[6]; Selvaggi et al, 2014[31]; Pellino et al, 2014b[28]);
- Dressing changes and associated resources, including nurse time (Gillespie et al, 2015[10]; Karlakki *et al* 2016[19]; Nordmeyer et al, 2015[25]).

The avoidance of these adverse outcomes can increase the predictability of recovery, allowing scare hospital resources, such as beds and operating theatre time, to be optimally deployed. These can also result in monetary savings for healthcare providers.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

As detailed above, the appropriate use of PICO should reduce the rates of surgical site complications and thereby reduce:

- excess and unpredictable hospital stays as a result of surgical site complications (Rodden & Taylor, 2015[29]; Pellino et al, 2014a[27], 2014b[28]; Selvaggi et al, 2014[31]);
- hospital readmission/return to theatre rates (Bullough et al, 2014[3], 2015a[4], 2015b[5]; 2015; Selvaggi et al, 2014[31]; Pellino et al, 2014b[28]);
- dressing changes and associated resources, including nurse time (Gillespie et al, 2015[10]; Karlakki *et al* 2016[19]; Nordmeyer et al, 2015[25]).

Following discharge, PICO may also reduce the need for multiple community nurse visits to manage post-operative dressings.

Whilst these benefits may not result in disinvestment opportunities, as many of the resources are sunk, they do allow for resource re-allocation which will increase efficiency.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- instructions for use
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- quality systems (ISO 13485) certificate (if required).

PDF copies have been attached in the submission

4.1 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Answer: Yes

PICO 7Y – 21/Aug/2018
PICO 7 – 24/Jan/2018
PICO – 12/Jun/2014

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

- PICO 7Y – Cleared for sale in Europe
- PICO 7 – Cleared for sale in Europe, Canada, USA, Australia & New Zealand
- PICO - Europe, Canada, USA, Japan, UAE, Indonesia, Korea, Taiwan, Peru, Argentina, Australia, New Zealand and most major markets.

4.3 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

Answer: Not applicable

4.4 If the technology has been launched in the UK provide information on the use in England.

PICO is utilised in over 112 hospitals across the UK although usage in most cases is limited to one or two surgeons in any given department in the majority of hospitals.

The current penetration rate is based on the number of procedures in our focus hospitals based on the high risk percentage of patients. The breakdown is as follows:

- Orthopaedic usage: 9% of high risk patients
- Obstetric: 4% of high risk patients
- Colorectal: 5% of high risk patients
- Breast: 20% of high risk patients

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Table 6 Ongoing scientific studies

Indication	Number of studies	Estimated number of patients
Orthopaedics	4	2,460
Obs / Gynae	2	250
Abdominal	2	140
Cardiothoracic	1	210
Breast & Plastics	1	30
Vascular	2	200
Total	12	3,290

This should include unpublished and ongoing studies, and studies awaiting publication. Also include post-marketing surveillance and register data.

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

In the UK we run real world audit studies in order to establish a baseline of the scale of the issue with post-surgical complications and then track the impact of utilising PICO on the high risk patients. These audit studies tend to be tailored to the hospital in question with the surgeon inputting on the key risk factor(s) related the demographics of their local patient population.

The studies that are ongoing or about to begin are listed below:

Table 7 Ongoing real world evidence studies

Speciality	Type of study	Number of hospitals
Colorectal/abdominal surgery	RWE audit study	2 hospitals
Breast surgery	RWE audit study on PICO 7Y	10 hospitals
Cardiac surgery	RWE audit study on PICO 7Y	1 hospital

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

PICO should be considered for patients at elevated risk of surgical site complications. This may restrict access to PICO for patients considered to be at lower risk of surgical site complications.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

None.

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

No equality issues were identified

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

This review was performed by the manufacturer by individuals from the Clinical, Scientific and Medical Affairs (CSMA) department who were experienced at performing systematic literature reviews and interpreting clinical data.

A broad search strategy was defined, intended to capture all relevant publications on the PICO device. No limits or MESH terms were used to identify specific endpoints, given the long list of endpoints considered in the scope.

A search of multiple electronic bibliographic databases was performed and included Medline, Embase, the Cochrane Library and Medline® In-process. Searches were limited by publication date from 1st January 2011 to August 2018. Inclusion criteria limited searches to English language studies.

A 'snowballing technique' was used to search reference lists for all included studies to identify further relevant studies. References were managed using EndNote (version 8.0.1; Thomson Reuters, USA).

Full details of the search strategy executed to identify relevant published studies are given in Appendix 1.

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Searches of the ClinicalTrials.gov and ISRCTN registry databases were performed to identify unpublished sources of potentially relevant data. These searches were performed on 14th August 2018 and used the same search terms as the published studies searches.

Full details of the search strategy executed to identify relevant unpublished studies are detailed in Appendix 1.

7.2 Study selection

Published studies

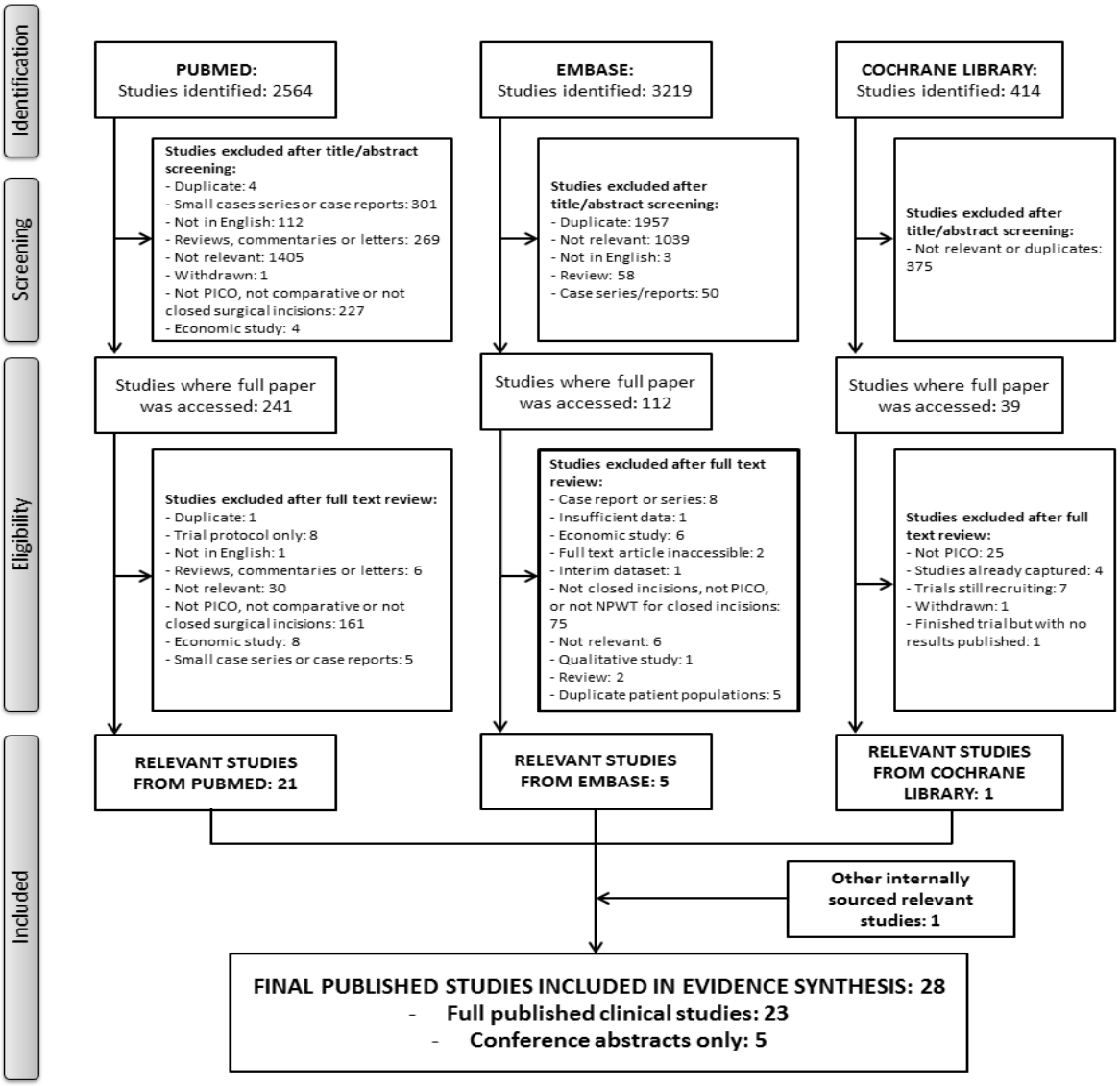
7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table 8 Selection criteria used for published studies

Inclusion criteria	
Population	*Patients having closed surgical incisions who were considered to be at high risk of developing a surgical site complication*
Interventions	*PICO single-use negative pressure wound therapy system*
Outcomes	*All clinical outcomes were considered but outcomes of particular interest were:* • *Surgical site infection* • *Dehiscence* • *Seroma* • *Haematoma* • *Delayed healing* • *Abnormal scarring* • *Skin/fat necrosis* • *Ease of use* • *Readmission rates* • *Reoperation rates* • *Length of hospital stay* • *Time to heal* • *Number of dressing changes* • *Staff time to apply* • *Amount of wound exudate* • *Adverse events*
Study design	*Comparative studies: randomised controlled trials or retrospective/prospective observational studies with at least 10 patients in each treatment arm*

Language restrictions	*English*
Search dates	*Studies published from 01/01/2011 to 01/08/2018*
Exclusion criteria	
Population	*Patients with open surgical incisions or any non-surgical wound*
Interventions	*Other forms of NPWT, such as traditional NPWT or non-disposable devices, were excluded*
Outcomes	*N/A*
Study design	*Non-comparative studies: case reports, case-series, studies with less than 10 patients in each treatment arm. Non-clinical studies: letters, commentaries, notes, reviews and editorials*
Language restrictions	*Not in English*
Search dates	*Studies published before 2011*

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.



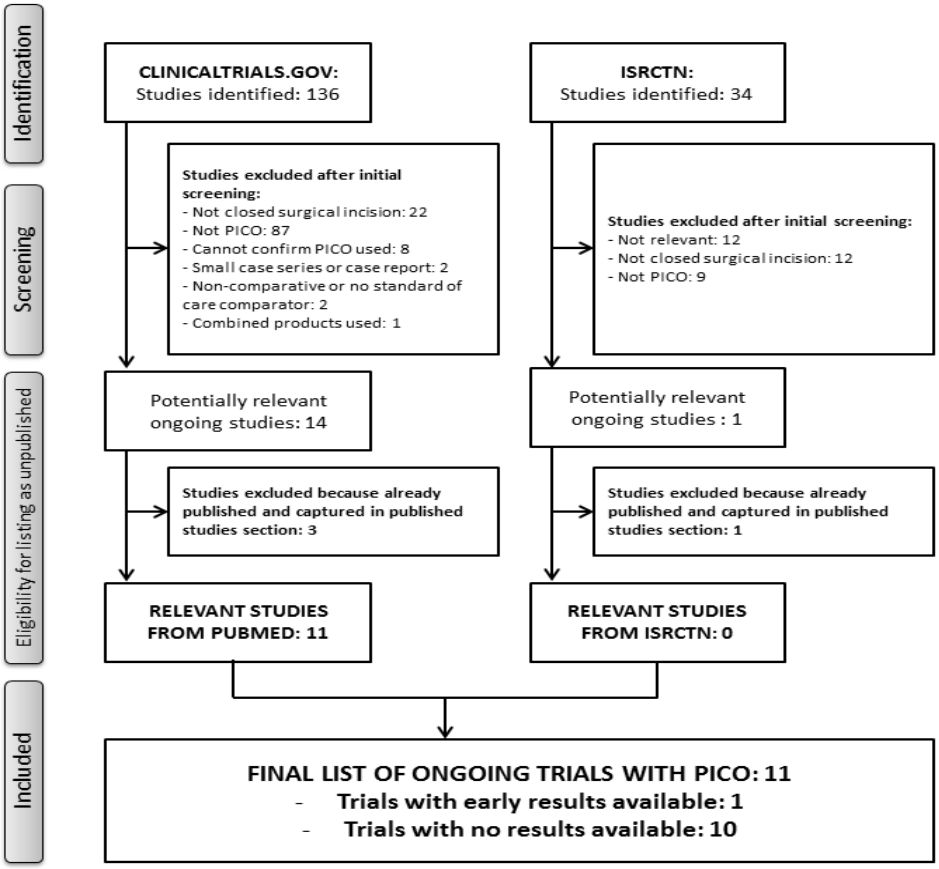
Unpublished studies

7.2.3 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B2 Selection criteria used for unpublished studies*Inclusion criteria*	
Population	*Patients having closed surgical incisions who were considered to be at high risk of developing a surgical site complication*
Interventions	*PICO single-use negative pressure wound therapy system*
Outcomes	*All clinical outcomes were considered but outcomes of particular interest were:* • *Surgical site infection* • *Dehiscence* • *Seroma* • *Haematoma* • *Delayed healing* • *Abnormal scarring* • *Skin/fat necrosis* • *Ease of use* • *Readmission rates* • *Reoperation rates* • *Length of hospital stay* • *Time to heal* • *Number of dressing changes* • *Staff time to apply*

	• *Amount of wound exudate* • *Adverse events*
Study design	*Comparative studies: randomised controlled trials or retrospective/prospective observational studies with at least 10 patients in each treatment arm*
Language restrictions	*English*
Search dates	*Clinical trials registered on or after 01/01/2011*
Exclusion criteria	
Population	*Patients with open surgical incisions or any non-surgical wound*
Interventions	*Other forms of NPWT, such as traditional NPWT or non-disposable devices, were excluded*
Outcomes	*N/A*
Study design	*Non-comparative studies: case reports, case-series, studies with less than 10 patients in each treatment arm. Non-clinical studies: letters, commentaries, notes, reviews and editorials*
Language restrictions	*Not in English*
Search dates	*Clinical trials registered before 2011*

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.



7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished studies. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Full published journal articles:				
Adogwa et al 2014	Not reported	Orthopaedic (thoracolumbar spine fusions)	PICO	Standard care
Chaboyer et al 2014	Not reported	Obstetric (C section)	PICO	Standard care (Comfeel Plus®)
Dingemans et al 2018	Negative Pressure Wound Therapy for Surgical Wounds of the Foot and Ankle (NEWTON)	Orthopaedic	PICO	Regular dressings
Fleming et al 2018	Not reported	Arterial bypass surgery of the lower limbs	PICO	Mepore® dressing (Molnlycke, Oldham, UK)
Galiano et al 2018	Not reported	Breast patients	PICO	Standard care
Gillespie et al 2015	Not reported	Orthopaedic: primary total hip arthro-plasty (THA)	PICO	Standard care (Comfeel Plus®)
Hester et al 2015	Not reported	Orthopaedic (revision hip and knee arthroplasty)	PICO	Regular dressings

Hickson et al 2015	*Not reported*	*Obstetric (C section)*	*PICO*	*Standard care*
Holt and Murphy 2015	*Not reported*	*Breast patients*	*PICO*	*Conventional dressings – brand not recorded*
Hyldig et al 2018	*Not reported*	*Obstetric (C section)*	*PICO*	*Standard postoperative dressing*
Karlakki et al 2016	*Not reported*	*Orthopaedic THA and total knee arthro-plasty (TKA)*	*PICO*	*Standard postoperative dressing*
Matsumoto and Parekh 2015	*Not reported*	*Orthopaedic*	*PICO*	*Conventional dressing*
Nordmeyer et al 2016	*Not reported*	*Orthopaedic (spinal fracture)*	*PICO*	*Standard wound dressing*
O'Leary et al 2016	*Not reported*	*Laparotomy patients*	*PICO*	*Transparent waterproof dressing*
Pellino et al 2014a	*Not reported*	*Breast and colorectal patients*	*PICO*	*Wound contact absorbent dressing*
Pellino et al 2014b	*Not reported*	*Colorectal patients*	*PICO*	*Conventional dressing – brand name not stated*
Selvaggi et al 2014	*Not reported*	*Colorectal patients with Crohn's disease*	*PICO*	*Wound contact absorbent dressing*
Svensson-Bjork et al 2018	*Incisional Negative pressure wound therapy on Vascular surgical Incisions in the*	*Inguinal vascular surgery*	*PICO*	*ViTri Pad (ViTri Medical, Stockholm, Sweden)*

	Prevention of surgical Site infection (INVIPS)			
Tan et al 2017	*Not reported*	*Lower limb arterial bypass patients*	*PICO*	*Standard postoperative dressing*
Tanaydin et al 2018	*Not reported*	*Breast patients*	*PICO*	*Standard care*
Uchino et al 2016	*Not reported*	*Ileostomy patients*	*PICO*	*Standard wound dressing*
van der Valk 2017	*Not reported*	*Colorectal patients*	*PICO*	*Conventional wound care*
Witt-Majchrzak 2015	*Not reported*	*Cardiothoracic (CABG) patients*	*PICO*	*Standard care*
Conference abstracts:				
Hackney and McCoubrey 2017	*Not reported*	*Colorectal patients*	*PICO*	*Control – product not stated*
Irwin et al 2018	*Not reported*	*Breast patients*	*PICO*	*Standard dressings – brand not recorded*
Kawakita et al 2018	*Not reported*	*C-Section*	*PICO*	*Standard dressing – brand name not recorded*
Tuuli et al 2017	*Prophylactic incisional care in obese women at caesarean (PICO-C)*	*C-Section*	*PICO*	*Standard dressing – brand name not recorded*
Zotes et al 2015	*Not reported*	*Cardiothoracic patients*	*PICO*	*Traditional wound care – brand not recorded*

Table 9 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
Unpublished relevant studies with early results available				
Stannard et al unpublished - NCT02064270	Study to Compare Negative Pressure Wound Therapy or Standard Dressings After Orthopaedic Surgery	Patients who had undergone THA or TKA	PICO	Standard of care
Unpublished relevant studies with no results available				
NCT03082664	Negative Pressure Wound Therapy to Prevent Wound Complications Following Cesarean Section in High Risk Patients	Patients at high risk of wound complications following caesarean section (e.g. BMI >30, diabetes, HIV/AIDS, etc)	PICO	Standard dressing
NCT03010137	Incisional Negative Pressure Wound Therapy in High Risk Patients Undergoing Panniculectomy: A Prospective Randomized Controlled Trial	All patients undergoing pannicul-ectomy in preparation for renal transplant-atation	PICO	Standard of care
NCT02408835	Negative Pressure Wound Therapy in Groin Dissection	Patients undergoing inguinal lymphaden-ectomy for metastatic carcinoma of cutaneous origin	PICO	Conventional wound care
NCT02664168	A Comparative Study to Assess the Prevention of Surgical Site Infection (SSI's) in Revision Total Joint Arthroplasty Patients Treated With Single-Use Negative Pressure	Patients undergoing revision TKA and THA	PICO	Standard of care dressings

	Wound Therapy (PICO™) or Standard Care Dressings (AQUACEL® Ag SURGICAL Dressing)			
NCT02558764	*Effects of Preventive Negative Pressure Wound Therapy With PICO on Surgical Wounds of Kidney Transplant Patients*	*Patients undergoing kidney trans-planation surgery*	*PICO*	*Basic wound contact absorbent dressings (standard of care)*
NCT03180346	*A Prospective, Randomized, Comparative Study to Assess the Prevention of Surgical Site Infection (SSI's) in Revision Total Joint Arthroplasty Patients Treated With Single-Use Negative Pressure Wound Therapy (PICO) or Standard Care Dressings (AQUACEL Ag SURGICAL Dressing).*	*Patients undergoing hip and knee arthroplasty*	*PICO*	*Standard care dressings*
NCT02578745	*Prophylactic Incisional Care in Obese Women at Caesarean*	*Obese (BMI ≥30) women undergoing caesarean section*	*PICO*	*Standard dressing*
NCT02883010	*Comparison of Surgical Incision Complications in Patients Receiving PICO or Standard Care Following Colorectal Surgery*	*Colorectal patients at high risk of SSCs*	*PICO*	*Standard care*

NCT02492854	*Standard Versus PICO Dressings in Lower-Extremity Bypass Patients*	*Patients undergoing lower-extremity bypass surgery*	*PICO*	*Standard of care dressings*
NCT03460262	*Negative Pressure Wound Therapy for prevention of groin infection following vascular surgery*	*Vascular surgery patients*	*PICO*	*Standard dressing*

7.3.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

The five conference abstracts that were identified were excluded from the main meta-analysis results (Tuuli et al 2017, Kawakita et al 2018, Hackney and McCoubrey 2017, Zotes et al 2015, and Irwin et al 2018). The reason for this is that these abstracts contained limited information making it difficult to assess the methodology, determine potential biases, and appropriately interpret the results.

In addition to this, of the 11 unpublished studies identified, only one had early results made available to the manufacturer. This study by Stannard et al was excluded from the main analysis because it did not contain all necessary data. The data were not finalised and key figures were missing from the data that we were able to access.

7.4 Summary of methodology of relevant studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Table 10 Summary of methodology for randomised controlled trials

Full published journal articles:

Study name	***Hyldig et al 2018 - Prophylactic incisional negative pressure wound therapy reduces the risk of surgical site infection after caesarean section in obese women: A pragmatic randomised clinical trial***
Objectives	*To investigate the number of wound healing complications, scar appearance and scar quality in 32 women who underwent bilateral breast reduction mammoplasty and who were treated with PICO on one breast and standard postoperative dressings on the other.*
Location	*5 centres (2 tertiary referral centres and 3 teaching hospitals) in Denmark*
Design	*Prospective, pragmatic, comparative, open, multicentre, randomised controlled trial.*
Duration of study	*September 2013 – October 2016, follow-up concluded in November 2016 (38-39 months)*
Sample size	*876*
Inclusion criteria	*- Women aged ≥18 years* *- Elective/emergency caesarean section* *- Pre-pregnancy BMI ≥30kg/m^2* *- Can read and understand Danish*
Exclusion criteria	*- Women aged <18 years* *- Women who had consented, but went on to deliver vaginally* *- For secondary outcome analysis, women with missing outcome data were excluded*
Method of randomisation	*Web-based randomisation programme with 1:1 ratio and block size of 4-6, stratified by centre and type of C-section (emergency/elective)*
Method of blinding	*Physicians and patients not blinded due to obvious differences in appearance of dressings.*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 432* *Standard of care = 444*
Baseline differences	*Baseline demographics and perioperative patient characteristics were similar between groups (p-values not reported)*

Duration of follow-up, lost to follow-up information	*- Follow-up appointment at day 5-6, postal questionnaire follow-up at 30 days.* *- Women lost to follow-up at 30 days were n=22 for PICO and n=27 for SC*
Statistical tests	*Power calculations showed a sample size of 870 was need to determine a 50% reduction in SSI in PICO compared to baseline of 10% in control group, with two-sided significance level of 5% and power of 80%.* *Outcomes estimated by crude and weighted relative risks (RR) with 95% CI. Number needed to treat (NNT) calculated as 1/absolute risk reduction.* *Potential confounders were determined by logistic regression to estimate odds ratio (OR) with 95% CI using risk factors identified in the literature.*
Primary outcomes (including scoring methods and timings of assessments)	*Number of surgical site complications requiring treatment with antibiotics within 30 days of surgery for both incisional NPWT and standard care.*
Secondary outcomes (including scoring methods and timings of assessments)	*Presence of wound exudate, minor wound dehiscence and health related quality of life (determined by EQ-5D-5L)*

Study name	***Chaboyer et al 2014 - Negative Pressure Wound Therapy on Surgical Site Infections in Women Undergoing Elective Caesarean Sections: A Pilot RCT***
Objectives	*To investigate the potential of conducting a large scale RCT of single-use NPWT in obese women BMI≥30 in order to determine the sample size needed and the outcomes to be collected.*
Location	*Australia*
Design	*Parallel group pilot randomised control trial*
Duration of study	*July 2012 to April 2014*
Sample size	*92*
Inclusion criteria	*- Women booked for elective caesarean section surgery* *- Recorded pre-pregnancy BMI of ≥30*

	- Able to provide written informed consent
Exclusion criteria	*- Women whose condition changes to warrant an urgent or emergency caesarean section* *- Previous participation in this trial* *- Existing infection after admission to hospital and prior to caesarean section* *- Unable to speak or understand English with no interpreter present*
Method of randomisation	*Centralised web-based randomisation*
Method of blinding	*Not blinded.*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 46* *Standard of care - Comfeel Plus® (Coloplast, City, Denmark)= 46*
Baseline differences	*There were more smokers in standard of care group than PICO group (23.3% vs 6.8%, p=0.032) and difference in surgery time (p=0.002)*
Duration of follow-up, lost to follow-up information	*Outcomes were assessed daily until discharge then at 4 weeks post discharge*
Statistical tests	*- For normal continuous variables, the authors used independent t-tests otherwise the Mann Whitney U test.* *- Categorical variables tested using Chi-squared test or Fisher's exact test, as appropriate.*
Primary outcomes (including scoring methods and timings of assessments)	*Surgical site infection (SSI)*
Secondary outcomes (including scoring methods and timings of assessments)	*- Type of SSI–superficial infection, deep infection or organ/body space using the CDC criteria* *- Wound complications (i.e., dehiscence, haematoma, bleeding, seroma, blisters);* *- Hospital length of stay* *- Hospital readmissions (within 28 days)*

Study name	***Gillespie et al 2015 - Use of Negative-Pressure Wound Dressings to Prevent Surgical Site Complications After Primary Hip Arthroplasty: A Pilot RCT***
Objectives	*To assess the use of NPWT on surgical sites to prevent infections and other wound complications after elective primary hip arthroplasty and to consider feasibility of a larger trial.*
Location	*Australia*
Design	*Non-blinded, single-centre randomised, controlled, parallel group pilot study*
Duration of study	*March 2013 – May 2014 (15 months)*
Sample size	*76 recruited, 70 randomised*
Inclusion criteria	*- Undergoing elective primary THA* *- Aged ≥18 years* *- Able to provide informed consent* *- Attended the hospital's preadmission clinic*
Exclusion criteria	*- Existing infection* *- Had previously participated in the trial* *- Unable to speak and understand English*
Method of randomisation	*In-house computer-generated randomisation schedule (1:1 ratio, randomly varied blocks)*
Method of blinding	*Physicians and patients not blinded due to obvious differences in appearance of dressings, but independent outcome assessors for SSI as well as the data analyst were blinded*
Intervention(s) (n =) and comparator(s) (n =)	*PICO: 35* *Standard of care: 35*
Baseline differences	*No significant differences in population relative to age, gender and most pre-existing risk factors apart from number of medications (higher in PICO group, $p<0.05$) and use of wound glue (higher in standard of care group, $p<0.001$).*
Duration of follow-up, lost to follow-up information	*Six weeks post-op (median discharge time 5-6 days; patients were followed up every day until discharge and then at 30 days and 6 weeks post-surgery). 4 patients were lost to follow-up from each group at 30 days, and 1 additional patient per group was lost at 6 weeks post-op (10 total, 5 per group).*

Statistical tests	*Risk ratios (RR) with 95% CI calculated for clinical outcome data. Interrater reliability analysis using κ was performed for SSI to determine consistency among raters.*
Primary outcomes (including scoring methods and timings of assessments)	*SSI (including superficial, deep and organ/space)*
Secondary outcomes (including scoring methods and timings of assessments)	*- Individual SSI indicators (erythema, swelling, leakage, purulence) and any SSI indicator* *- Individual wound complications (dehiscence, seroma, haematoma) and any wound complication* *- Proportion of patients who had dressing replaced before/on day 5* *- Hospital length of stay* *- Readmission*

Study name	***Karlakki et al 2016 - Incisional negative pressure wound therapy dressings (iNPWTd) in routine primary hip and knee arthroplasties: a randomised controlled trial***
Objectives	*To assess the potential benefits of a portable, single use, incisional negative pressure wound therapy dressing (iNPWTd) on wound exudate, length of stay (LOS), wound complications, dressing changes and cost-effectiveness following total hip and knee arthroplasties.*
Location	*United Kingdom*
Design	*Non-blinded, single-centre randomised, controlled, parallel group study*
Duration of study	*October 2012 – October 2013 (13 months)*
Sample size	*Intention to treat analysis: 220, Per protocol analysis: 209*
Inclusion criteria	*All willing and eligible patients undergoing elective THA or TKA (for any indication) at the study institution during the study period*
Exclusion criteria	*- Known allergies to dressings* *- Revision joint surgery* *- Unwilling to attend additional clinics* *- Taking warfarin (length of stay likely to be affected)*

Method of randomisation	*Sealed envelope, block size of 20 with 1:1 ratio.*
Method of blinding	*Physicians and patients not blinded due to obvious differences in appearance of dressings.*
Intervention(s) (n =) and comparator(s) (n =)	*PICO: ITT = 110, PP = 102* *Standard of Care: ITT = 110, PP = 107*
Baseline differences	*Based on the per protocol population, there were no significant differences between groups apart from patients with BMI >35: 17% in PICO group, 8% in control group.*
Duration of follow-up, lost to follow-up information	*Six weeks post-op (mean discharge time 3 days, PICO group seen at 1 week, control group follow-up per telephone at 2 weeks, all followed up in clinic at 6 weeks).*
Statistical tests	*The exudate level measurements were summarised as a single variable by their peak level. Distributions of all variables were investigated for normality using Quantile-Quantile (Q-Q) plots, which plot the quantiles of a variable against the quantiles of a normal distribution with the same mean and standard deviation. Analysis of LOS was based on the intention to treat (ITT) population, whereas analyses of wound properties were based on the per protocol (PP) population because those outcomes were only collected for this population. Subanalysis based on stratification by hip or knee surgery was performed. Mean length of stay of the two groups was analysed using a non-parametric method specifically developed for highly skewed data (method T3). Differences in peak wound exudate level and complication rates were analysed using Fisher's exact test. The influence of confounding factors was analysed using a logistic regression model or a proportional odds logistic model. Conditional inference trees and model-based recursive partitioning were used to find meaningful treatment-subgroup interactions. The sample size was chosen to permit detection of a difference in LOS of 0.6 days, assuming a two-tailed significance level of p = 0.05 and 80% power, and based on a standard deviation of 1.5 days as found in an earlier study at our institution*
Primary outcomes (including scoring methods and timings of assessments)	*- Wound healing* *- Length of stay* *- Level of exudate*
Secondary outcomes (including scoring methods and timings of assessments)	*- Wound complications (prolonged wound exudate, superficial wound infections)* *- Number of dressing changes* *- Cost-effectiveness of dressing*

Study name	***Nordmeyer et al 2016 - Negative pressure wound therapy for seroma prevention and surgical incision treatment in spinal fracture care***
Objectives	*To evaluate the clinical use and economic aspects of NPWT after dorsal stabilisation of spinal fractures*
Location	*Germany*
Design	*Prospective, randomised controlled trial*
Duration of study	*Not stated*
Sample size	*20*
Inclusion criteria	*- Patients with spinal fractures scheduled for internal fixation* *- Informed consent*
Exclusion criteria	*Not stated*
Method of randomisation	*Not stated*
Method of blinding	*Blinding not possible due to obvious difference in appearance between treatments.*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 10* *Standard dressing = 10*
Baseline differences	*Not stated, except patients in PICO group had a mean age of 52.30±16.32 years compared to the standard care group which was 57.80±15.24 years.*
Duration of follow-up, lost to follow-up information	*10 day follow-up. Daily clinical examination with ultrasonography analysis on day 5 and 10 post-surgery. No patients lost to follow-up reported.*
Statistical tests	*Student's t-test was used for Gaussian distributed data. Mann-Whitney test was used for non-Gaussian distributed data.*
Primary outcomes (including scoring methods and timings of assessments)	*- Economic aspects of wound management scored by number of dressing changes, wound care time, time and number of used gloves and compresses used for dressing changes.* *- Wound healing scored by wound drainage volume (2 days post operatively) wound draining days and seroma volume*

Secondary outcomes (including scoring methods and timings of assessments)	*Not reported*

Study name	***Uchino et al 2016 - Randomized Controlled Trial of Prophylactic Negative-Pressure Wound Therapy at Ostomy Closure for the Prevention of Delayed Wound Healing and Surgical Site Infection in Patients with Ulcerative Colitis***
Objectives	*To evaluate the efficacy and safety of prophylactic use of negative-pressure wound therapy after ileostomy closure*
Location	*Hyogo College of Medicine, Hyogo, Japan*
Design	*Prospective, randomised, controlled study*
Duration of study	*November 2014 - September 2015 (11 months)*
Sample size	*59*
Inclusion criteria	*- ≥18 years old* *- Established ulcerative colitis* *- Scheduled to undergo elective closure of ileostomy - including a restorative proctocolectomy with ileal pouch anal anastomosis*
Exclusion criteria	*- Death* *- Dirty/infected wound* *- Urgent/emergency surgery* *- Separated double-barrel ileostomy* *- Patients whose incision was extended due to adhesions during surgery* *- Patients displaying complicated dermatitis due to adhesives* *- Patients with Surgical Site Infection (SSI) during follow-up periods were excluded from prophylactic NPWT and from comparison of wound-healing duration as NPWT was terminated after SSI diagnosis*

Method of randomisation	*Opaque envelopes containing the treatment option for each patient were opened in the operating room by a surgical nurse*
Method of blinding	*Study was not blinded*
Intervention(s) (n =) and comparator(s) (n =)	*Purse-string suture (PSS) + PICO = 28* *PSS alone = 31*
Baseline differences	*No significant differences were observed in patient characteristics, preoperative treatments, or blood examinations*
Duration of follow-up, lost to follow-up information	*- All patients visited the outpatient clinic 4 weeks after discharge. Patients visited every 4 weeks thereafter if presenting any complications. Patients self-checked wound healing, to assess the precise duration of wound healing* *- Patients lost to follow-up were n=1 for PSS+PICO and n=1 for PSS alone* *- Patients excluded from wound healing duration analysis, due to Surgical Site Infection's (SSI's) were n=3 for PSS+PICO and n=1 for PSS alone*
Statistical tests	*- Comparative analysis of continuous variables was performed using the Mann-Whitney U test.* *- Chi squared test with Yates' correction or Fisher's exact test were used to compare categorical variables.*
Primary outcomes (including scoring methods and timings of assessments)	*- Duration of complete wound healing* *- Number of postoperative complications i.e. SSI's, wound bleeding, enterocutaneous fistula, bowel obstruction*
Secondary outcomes (including scoring methods and timings of assessments)	*- Duration of surgery* *- Amount of blood loss during surgery* *- Postoperative blood sugar level*

Study name	***Svensson-Bjork et al 2018 - Evaluation of inguinal vascular surgical scars treated with closed incisional negative pressure wound therapy using three-dimensional digital imaging—A randomised controlled trial on bilateral incisions***

Objectives	*To evaluate the effects of iNPWT on scar formation with 3D digital imaging after bilateral inguinal vascular surgery in a RCT. The secondary aim of the study was to evaluate correlations between overall subjective and objective scores.*
Location	*Sweden*
Design	*Multi-centre randomised controlled trial*
Duration of study	*November 2013 – February 2016 (27 months)*
Sample size	*75*
Inclusion criteria	*Elective vascular surgery with inguinal incisions*
Exclusion criteria	*- Non-SSI wound complication* *- SSI* *- Advanced terminal disease* *- Non-completed NPWT device usage* *- Advanced dementia*
Method of randomisation	*Randomisation via opaque envelopes containing equal numbers of notes representing the two dressing types.*
Method of blinding	*Not blinded*
Intervention(s) (n =) and comparator(s) (n =)	*Intervention n = 34, Comparator n = 34*
Baseline differences	*None*
Duration of follow-up, lost to follow-up information	*Follow-up was reported as median (IQR) time between surgery and photography (days): 808 (726-999)*
Statistical tests	*- Pearson correlation coefficient for continuous variables.* *- Objective scorings were evaluated for intra- and inter-rater reliabilities and expressed by an intra-class correlation coefficient with a 95% confidence interval.* *- McNemar's test was used for paired nominal data* *- Wilcoxon signed-rank test was used for paired continuous data*

Primary outcomes (including scoring methods and timings of assessments)	*Scar assessment (SBSES, NRS10, and PSAS) at a median of 808 days post-operatively*
Secondary outcomes (including scoring methods and timings of assessments)	*Correlations between overall subjective and objective scores (PSAS vs. SBSES total scores and PSAS vs. NRS10 total scores)*

Study name	***Witt-Majchrzak et al 2015 - Preliminary outcome of treatment of postoperative primarily closed sternotomy wounds treated using negative pressure wound therapy***
Objectives	*To evaluate wound healing in patients after an off-pump coronary artery bypass grafting procedure, using the internal mammary artery, treated with the PICO negative pressure wound therapy system.*
Location	*Poland*
Design	*Prospective, open label trial*
Duration of study	*Not reported*
Sample size	*80*
Inclusion criteria	*Patients after an off-pump coronary artery bypass grafting procedure, using the internal mammary artery*
Exclusion criteria	*Not reported*
Method of randomisation	*Not reported*
Method of blinding	*Not blinded*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 40* *Standard of Care =40*
Baseline differences	*No statistically significant differences between groups, except for age (PICO mean 66.2 years vs standard care mean 62.1 years; p = 0.0438).*
Duration of follow-up, lost to follow-up information	*- PICO was changed on day 2 or 3 then removed on day 5 or 6*

	- Standard care dressings were changed daily *- Patients were followed up for 6 weeks post discharge*
Statistical tests	*- For normal continuous variables, the authors used independent t-tests otherwise the Mann Whitney U test* *- For categorical variables, the authors performed Chi-square tests*
Primary outcomes (including scoring methods and timings of assessments)	*Wound healing defined as absence of surgical site complications (SSC), as defined by the European Centres for Disease Control and Prevention, i.e. dehiscence of wound margins or infection of sternotomy wound with clinical signs or documented by bacteriological tests.*
Secondary outcomes (including scoring methods and timings of assessments)	*- Reoperation* *- Duration of surgery* *- Post-operative drainage* *- Blood transfusion products* *- Anastomoses* *- Catecholamine usage* *- Intraoperative blood loss* *- Infections other than SSI* *- Perioperative bacteriological characteristics* *- Wound healing characteristics*

Study name	***Tanaydin et al 2018 - Randomised Controlled Study Comparing Disposable Negative Pressure Wound Therapy with Standard Care in Bilateral Breast Reduction Mammoplasty Evaluating Surgical Site Complications and Scar Quality***
Objectives	*To investigate the number of wound healing complications, scar appearance and scar quality in 32 women who underwent bilateral breast reduction mammoplasty and who were treated with PICO on one breast and standard care on the other.*
Location	*VieCuri Medical Centre, The Netherlands*

Design	*Prospective, intra-patient, comparative, open, randomised controlled trial. Part of a larger multicentre RCT.*
Duration of study	*1-June-2012 to 9-Apr-2014 (22 months)*
Sample size	*32 patients (64 breasts)*
Inclusion criteria	*- Women aged >18 years* *- Bilateral superomedial pedicle Wise-pattern breast reduction mammoplasty* *- Postsurgical incisions of similar length on each breast*
Exclusion criteria	*- Pregnancy* *- Lactation* *- Using steroids or other immune modulators known to affect healing* *- History of radiation of the breast* *- Tattoos in the area of incision* *- Skin conditions such as cutis laxa which would result in poor healing or widened scars* *- Patients with a known significant history of scar problems (i.e. hypertrophic scarring or keloids)* *- Known allergies to product components* *- Incision still actively bleeding, exposure of blood vessels, organs, bone or tendon at the base of the reference wound* *- Incisions > 12 inches (30 cm) maximum linear dimension*
Method of randomisation	*Digital (www.sealedenvelope.com)*
Method of blinding	*Physicians and patients not blinded due to obvious differences in appearance of dressings; data analysis was performed blinded*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 32 patients, 32 breasts* *Standard of Care = 32 patients, 32 breasts*
Baseline differences	*None – same patient received both treatments, one on each breast*
Duration of follow-up, lost to follow-up information	*- Day 0 (baseline), 7, 21, 42, 90, 180 and 365 (post-surgery).* *- Lost to follow up not defined. Results section reports no patients were lost to follow-up.*

Statistical tests	*- Post-hoc sample size calculated using nQuery 4.0* *- Primary outcome: no information* *- Secondary outcomes: Sensitivity analyses. POSAS and VAS scores: paired t-test (parametric) or Wilcoxon signed-rank test (non-parametric)*
Primary outcomes (including scoring methods and timings of assessments)	*- Number of surgical site complications within 21 days of surgery for both incisional NPWT and standard care using fixation strips.* *- Wound healing complications were defined as: delayed healing (incision not 100% closed within 7 days post-surgery) or infection or dehiscence within 21 days post-surgery*
Secondary outcomes (including scoring methods and timings of assessments)	*- Aesthetic appearance and quality of scarring were assessed at days 42, 90, 180 and 365.*

Study name	***Galiano et al 2018 – Incisional Negative Pressure Wound Therapy for Prevention of Wound Healing Complications Following Reduction Mammaplasty***
Objectives	*To investigate the potential of a single-use NPWT device in preventing composite wound morbidity (infection, dehiscence and delayed wound healing) compared with standard care in patients undergoing bilateral reduction mammaplasty.*
Location	*- United States (3 sites)* *- France (1 site)* *- South Africa (1 site)* *- The Netherlands (1 site)*
Design	*Prospective, intra-patient, comparative, open, multi-centre, randomised control trial.*
Duration of study	*1-June-2012 to 9-Apr-2014 (22 months)*
Sample size	*200 patients (400 breasts)*
Inclusion criteria	*- Women aged >18 years* *- Undergone elective surgery for bilateral reduction mammoplasty*

	- Postsurgical incisions of similar length on each breast
Exclusion criteria	*- Pregnancy* *- Lactation* *- Using steroids or other immune modulators known to affect healing* *- History of radiation of the breast* *- Tattoos in the area of incision* *- Skin conditions such as cutis laxa that would results in poor healing or widened scars* *- Patients with a known significant history of scar problems (i.e. hypertrophic scarring or keloids)* *- Known allergies to product components* *- Incision still actively bleeding* *- Incisions > 12 inches (30 cm) maximum linear dimension*
Method of randomisation	*Central web site (www.sealedenvelope.com)*
Method of blinding	*Not blinded*
Intervention (s) (n =) and comparator(s) (n =)	*PICO = 200 breasts* *Standard of Care = 200 breasts*
Baseline differences	*None – same patient received both treatments, one on each breast*
Duration of follow-up, lost to follow-up information	*- Day 0* *- First dressing change (3-7 days post-op)* *- Day 21* *- Day 42* *- Day 90*

	- Lost to follow up not defined. Results section reports 14 patients were lost to follow-up.
Statistical tests	*- For sample size: 2-sided McNemar's test* *- Primary and secondary outcome analysis: sensitivity analysis*
Primary outcomes (including scoring methods and timings of assessments)	*- Assessed whether an incision developed healing complications within 21 days of surgery for both incisional NPWT and the comparator dressing.* *- A healing complication was defined as presence of at least one of the following conditions:* *- Infection (superficial or deep) or,* *- Dehiscence (partial, superficial or deep) or,* *- Delayed healing (incision not 100% closed within 10 days of the first surgical procedure)*
Secondary outcomes (including scoring methods and timings of assessments)	*- The number and type of these complications individually including other postsurgical complications:* *- Skin necrosis or,* *- Nipple and areola necrosis or,* *- Cellulitis or,* *- Abscess or,* *- Suture abscess or,* *- Haematoma or,* *Occurring within 21, 42 and 90 days post-operatively.* *- Aesthetic appearance and scar quality were assessed at day 42 and day 90* *- Subset of patients from single centre were followed up to 1 year in relation to scar quality outcome.* *- Aesthetic appearance and scar quality outcomes are to be reported as a separate publication, from healing and post-surgical complications.*

Study name	***O'Leary et al 2016 - Prophylactic Negative Pressure Dressing Use in Closed Laparotomy Wounds Following Abdominal Operations***
Objectives	*To assess SSI rates following the use of an NPWT dressing.*

Location	*Ireland*
Design	*Randomised, controlled, open-label trial*
Duration of study	*February 2013 – April 2016 (38 months)*
Sample size	*49 patients (50 patients eligible for intervention, 1 patient discontinued intervention and was excluded from the analysis)*
Inclusion criteria	*- Patients between the ages of 18 and 80 years* *- Undergoing open elective and emergency abdominal surgery for clean (class I), clean contaminated (class II) or contaminated wounds (class III)*
Exclusion criteria	*- Class IV dirty wounds* *- Body mass index (BMI) ≥40* *- American Society of Anesthesiologists (ASA) grade >3.*
Method of randomisation	*Randomisation was performed on a 1:1 basis to either the negative pressure dressing group or the control group using a closed envelope method. Randomisation codes were generated on www.randomisation.com.*
Method of blinding	*The operating surgeon was not blinded to the dressing being applied to the wound.*
Intervention(s) (n =) and comparator(s) (n =)	*Intervention – PICO (n = 24); comparator – a transparent waterproof Smith and Nephew dressing (n = 25)*
Baseline differences	*There were no statistically significant baseline differences between the two groups.*
Duration of follow-up, lost to follow-up information	*Last follow-up was 30 days post-operatively. No patients were reported as lost to follow-up, however 1 patient in the PICO group had their dressing removed on post-operative day 2, and was excluded from the analysis.*
Statistical tests	*Univariate categorical variable analysis was performed using a Chi-squared test if the number of observations were >5 and Fisher exact test if the number of observations were ≤5. Continuous variables were analysed using a Student t test for parametric data and Mann-Whitney U test for nonparametric data. Multivariate analysis was performed using a linear regression model.*
Primary outcomes (including scoring	*SSI rate at 30 days postoperatively.*

methods and timings of assessments)	
Secondary outcomes (including scoring methods and timings of assessments)	*- SSI rate at day 4 postoperatively* *- Length of stay* *- Cosmetic wound appearance* *- Patient satisfaction.*

Published conference abstracts:

Study name	***Tuuli et al 2017 - Pilot randomised trial of prophylactic negative pressure wound therapy in obese women after caesarean delivery***
Objectives	*To assess the feasibility of a definitive randomised trial (RCT) to test the effectiveness and safety of prophylactic NPWT in obese women after caesarean.*
Location	*Barnes-Jewish Hospital, Saint Louis, Missouri, USA*
Design	*Pilot randomised controlled trial*
Duration of study	*6 months*
Sample size	*120*
Inclusion criteria	*- Obese women (BMI≥30)* *- Caesarean section*
Exclusion criteria	*- Non-availability for postoperative follow-up (follow-up is needed to ascertain study outcomes)* *- Contraindication to NPWT applicable to women undergoing caesarean (device will not be used in patients with contraindications):* *- Pre-existing infection around incision site,* *- Bleeding disorder* *- Therapeutic anticoagulation,* *- Allergy to any component of the dressing (e.g. silicone, adhesive tape)*
Method of randomisation	*Not stated*
Method of blinding	*This was not a blinded study*

Intervention(s) (n =) and comparator(s) (n =)	*PICO = 60* *Standard dressing = 60*
Baseline differences	*Comparable between the two groups*
Duration of follow-up, lost to follow-up information	*- 30 days post operatively* *- Lost to follow up not stated*
Statistical tests	*- Fisher's Exact Test or Mann Whitney U Test*
Primary outcomes (including scoring methods and timings of assessments)	*- Composite of superficial or deep SSI within 30 days or other wound complications including separation ≥2cm, hematoma or seroma*
Secondary outcomes (including scoring methods and timings of assessments)	*- Pain score on postoperative day 2* *- Adverse skin reactions*

Study name	***Zotes et al 2015 - Negative pressure wound therapy in a potentially infected wound after empyema surgery***
Objectives	*To assess the use of negative pressure wound therapy in thoracotomy wounds after empyema surgery and compare to traditional wound care*
Location	*Instituto Nacional de Enfemedades Respiratorias, Mexico City, Mexico*
Design	*Prospective, randomised, comparative study*
Duration of study	*October 2014 to December 2014 (2 months)*
Sample size	*20*
Inclusion criteria	*Thoracotomy wounds after empyema surgery*
Exclusion criteria	*Not reported*
Method of randomisation	*Not reported*
Method of blinding	*Not a blinded study*

Intervention(s) (n =) and comparator(s) (n =)	*PICO = 10* *Traditional wound care = 10*
Baseline differences	*Not reported*
Duration of follow-up, lost to follow-up information	*- 10 days post operatively* *- No lost to follow up information stated*
Statistical tests	*Not reported*
Primary outcomes (including scoring methods and timings of assessments)	*- Wound complications at 10 days post operatively* *- The scoring used for the above outcome was not stated*
Secondary outcomes (including scoring methods and timings of assessments)	*- Seroma at 10 days post operatively* *- Wound abscess at 10 days post operatively* *- Wound dehiscence at 10 days post operatively* *- Length of stay*

Unpublished studies:

Study name	***Stannard et al 2018.*** *Unpublished* *Working title:* [redacted]
Objectives	*To assess the impact of iNPWT on wound appearance, early complications and late infection rates following hip and knee Total Joint Arthroplasty (TJA) compared with a standard surgical dressing.*
Location	*Hospitals within the University of Missouri Health System, located in Columbia (Missouri, USA).*

Design	*Prospective randomised controlled trial*
Duration of study	[redacted]
Sample size	[redacted]
Inclusion criteria	*- Consenting age* *- Surgical treatment with primary or revision total hip arthroplasty* *- Surgical treatment with primary or revision total knee arthroplasty* *- Patients were required to have an advanced technology device capable of digital photography*
Exclusion criteria	*- Pregnancy* *- History of poor compliance with medical treatment* *- Allergy to silicone adhesives or polyurethane films* *- Unwillingness to participate in a randomised clinical trial*
Method of randomisation	*Not reported*
Method of blinding	*Wound appearance was assessed from a patient provided photograph by a single trained research team member, blinded to time point and treatment allocation*
Intervention(s) (n =) and comparator(s) (n =)	[redacted]
Baseline differences	*Demographic comparisons of the iNPWT and SOC treatment groups indicated similar mean patient age, male gender and non-significant proportional differences in diabetes, and tobacco use. Mean body mass index was lower among patients who were treated with an iNPWT device. The patient population evaluated in this study was potentially at a higher risk for wound-related complications with 46 hips (43%) and 161 knees (55.5%) having a body mass index > 35 kg/m^2.*

Duration of follow-up, lost to follow-up information	*- Wound healing and early complications were assessed at 7, 14 and 35 days post-surgery* *- Late infection rates were determined at a mean 2 year follow-up*
Statistical tests	*- Paired student's t-test for continuous variables* *- Two side Fisher's exact test for proportional comparisons between cohorts*
Primary outcomes (including scoring methods and timings of assessments)	*- Primary wound appearance at 7, 14 and 35 days after surgery - blinded assessment*
Secondary outcomes (including scoring methods and timings of assessments)	*- Patient reported wound drainage* *- Dressing related complications* *- Oral antibiotic use* *- Reoperation* *- Superficial and/or late wound infection incidence at 2 years follow-up*

Table 11 Summary of methodology for observational studies

Full published journal articles:

Study name	***Hickson et al 2015 - A Journey to Zero: Reduction of Post-Operative Caesarean Surgical Site Infections over a Five-Year Period***
Objective	*To investigate the effect of single-use NPWT and standard of care on women undergoing caesarean section over a 5 year period.*
Location	*US*
Design	*Clinical chart review*
Duration of study	*5 years (2007 to 2012)*

Patient population	*- Women indicated for caesarean section either emergency or non-emergency. Women were then categorised into either low or high risk based on a standard algorithm.* *- High risk factors included BMI≥35 or any two of the identified risk factors such as diabetes, smoking, immunosuppression, emergency caesarean section, history of wound infection, hypertensive disorders*
Sample size	*1948 for 2011 (before PICO) and 2012 (with PICO) period*
Inclusion criteria	*Women indicated for caesarean section*
Exclusion criteria	*Not stated*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 964* *Standard care (non-PICO) dressing in 2011 = 984*
Baseline differences	*No differences*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*In hospital assessment at day 5-7 and post discharge at 2-3 weeks and 6 weeks*
Statistical tests	*Fisher's exact test.*
Primary outcomes (including scoring methods and timings of assessments)	*Surgical site infection*
Secondary outcomes (including scoring methods and timings of assessments)	*Costs*
Study name	***Matsumoto and Parekh 2015 - Use of Negative Pressure Wound Therapy on Closed Surgical Incision After Total Ankle Arthroplasty***

Objective	*To investigate the utility of iNPWT in decreasing the rate of wound problems in total ankle arthroplasty (TAA) patients.*
Location	*USA*
Design	*Retrospective cohort study*
Duration of study	*PICO cohort: June 2012 to August 2013 (14 months)* *Control cohort: February 2009 to May 2012 (39 months)*
Patient population	*All patients undergoing TAA by a single surgeon*
Sample size	*74*
Inclusion criteria	*All patients undergoing TAA*
Exclusion criteria	*Revision TAA patients*
Intervention(s) (n =) and comparator(s) (n =)	*Intervention – PICO (n = 37)* *Comparator – standard dressing with Tefla gauze and ABD pads (n =37)*
Baseline differences	*None reported*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*Patients visited the clinic 4 weeks after the discharge, and every 4 weeks thereafter if they presented with complications. There were no participants lost to follow-up reported.*
Statistical tests	*The Chi-squared test or Fisher exact test was conducted for univariate comparisons of the proportions between groups. When these tests showed significant differences, adjusted residual analysis was performed to identify the categories responsible for it. In multivariate logistic regression analysis, all variables having a p value of less than 0.05 in univariate analysis were entered into the model.*
Primary outcomes (including scoring methods and timings of assessments)	*Wound healing problem – number of patients (%)*

Secondary outcomes (including scoring methods and timings of assessments)	*Superficial site infection – number of patients (%)*

Study name	***Dingemans et al 2018 - Prophylactic negative pressure wound therapy after lower extremity fracture surgery: a pilot study***
Objective	*To investigate the feasibility of a new portable single-use negative pressure wound therapy device in patients undergoing major foot ankle surgery. Secondary aim was to compare the incidence of SSI in patients treated with prophylactic NPWT to the incidence in a matched cohort of patients treated with regular dressings.*
Location	*Academic Medical Centre, Amsterdam, The Netherlands*
Design	*Prospective case matched cohort*
Duration of study	*10 months*
Patient population	*All adult patients scheduled for an orthopaedic (trauma) procedure of the foot and/or ankle (including secondary procedures for treating complications of fracture surgery (e.g. secondary arthrodesis)) with an incision length of at least 3 cm.*
Sample size	*60 patients*
Inclusion criteria	*- Adult patients* *- Orthopaedic (trauma) procedure of the foot and/or ankle (including secondary procedures for treating complications of fracture surgery (e.g. secondary arthrodesis))* *- Incision length of at least 3 cm*
Exclusion criteria	*- Open fractures or active infections* *- Antibiotic treatment at the time of the operation for a concomitant disease or infection* *- Patients with immune deficiencies*

	- Incision location not suitable for negative pressure wound therapy device *- Inability to adhere to therapy* *- Incomprehensive understanding of the Dutch language.*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 53* *Matched cohort of patients who received conventional surgical dressings = 47*
Baseline differences	*Patients who had received NPWT were matched in a 1:1 ratio to patients who had not received NPWT. Matching criteria were type of incision (identical), gender (identical), age (± 10 years), smoking (identical), diabetes (identical), and (in case of secondary procedure) whether they had experienced a SSI following earlier surgery (identical). Matching was performed using R-studio v 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*- Patients were routinely assessed at the outpatient clinic at 2 to 4 weeks following discharge.* *- All outcomes were assessed during the above period.* *- All patients completed the follow up period.*
Statistical tests	*- Normality was assessed using histograms and plots.* *- McNemars test for related samples was used to compare categorical data* *- T test for related samples or Wilcoxon signed rank test for continuous data where appropriate as matched data requires paired testing.*
Primary outcomes (including scoring methods and timings of assessments)	*- SSI within 30 days as classified by the CDC classification*

Secondary outcomes (including scoring methods and timings of assessments)	*- Incidence of superficial SSI* *- Incidence of deep SSI* *- Excessive leakage demanding 3 or more dressing changes for NPWT group* *- Failure of NPWT device* *- Withdrawal of informed consent for reasons related to NPWT device*

Study name	***Hester et al 2015 - Is Single Use Portable Incisional Negative Pressure Wound Therapy System Suitable for Revision Arthroplasty?***
Objective	*To determine the complication rate associated with a single use iNPWT system and the rate of wound infection in revision hip and knee arthroplasty.*
Location	*United Kingdom*
Design	*Retrospective, comparative clinical study.*
Duration of study	*January 2013 – January 2014 (12 months)*
Patient population	*All patients who underwent revision arthroplasty surgery*
Sample size	*36*
Inclusion criteria	*All revision knee and hip arthroplasty surgeries carried out by the senior author in the specified time frame*
Exclusion criteria	*Exclusion criteria consisted of known allergy to the NPWT dressing or any adhesive dressing that was similar.*
Intervention(s) (n =) and comparator(s) (n =)	*Intervention – PICO (n = 18; 4 hips, 14 knees), Comparator – bandaging for knees or pressure dressing for hips (n = 18; 5 hips, 13 knees)*
Baseline differences	*None reported*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration	*- Patients were followed-up 6 weeks post-operatively. No patients were reported lost to follow-up.* *- Authors reported that antibiotics were continued for 6 weeks via a peripherally inserted central catheter, therefore it is likely that the patients were followed-up at the institution where operations were performed.*

of follow-up, participants lost to follow-up	
Statistical tests	*Not stated*
Primary outcomes (including scoring methods and timings of assessments)	*Wound infection requiring further surgery or antibiotics in addition to cefuroxime or clarithromycin, which were used intraoperatively.*
Secondary outcomes (including scoring methods and timings of assessments)	*Any dressing related complications such as blistering.*

Study name	***Adogwa et al 2014 - Negative pressure wound therapy reduces incidence of postoperative wound infection and dehiscence after long-segment thoracolumbar spinal fusion: a single institutional experience***
Objective	*To assess the incidence of wound infection and dehiscence in patients undergoing elective long-segment thoracolumbar fusion before and after the routine use of NPWT*
Location	*US*
Design	*Retrospective (before and after) study*
Duration of study	*6 year period (January 2007 to January 2013)*
Patient population	*Patients undergoing elective long-segment thora-columbar spine fusions*
Sample size	*160*
Inclusion criteria	*- Age >18 years* *- Had undergone multilevel (more than four vertebral* *levels) posterior spinal fusion in the thoracolumbar spine using screws and rod instrumentation*

Exclusion criteria	*- History of infections at the surgical site* *- Severe coexistent pathology that could confound the assessment of operative outcome such as rheumatoid arthritis, osteoarthritis, metabolic bone disease* *- History of immunosuppression* *- Chronic systemic infection* *- Pregnancy* *- Minimally invasive cases*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 46* *Standard care = 14*
Baseline differences	*No baseline differences were observed*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*To assess long-term complications including SSI and wound dehiscence, the review period was 90 days.*
Statistical tests	*Parametric data = Student t test* *Nonparametric data = Mann Whitney U test.* *Nominal data = Chi-squared test* *Time to event data = Kaplan-Meier plots*
Primary outcomes (including scoring methods and timings of assessments)	*- SSI* *- Wound dehiscence*
Secondary outcomes (including scoring methods and timings of assessments)	*- Post-operative complications* *- Return to operating room* *- 30 day readmission rate*

Study name	***Selvaggi et al 2014 - New Advances in Negative Pressure Wound Therapy (NPWT) for Surgical Wounds of Patients Affected with Crohn's Disease***
Objective	*To evaluate the potential for a new NPWT device in reducing SSC in patients undergoing abdominal surgery for Crohn's disease and its effect on length of stay and patients' compliance with the device.*
Location	*Italy*
Design	*Prospective, open-label, controlled study*
Duration of study	*January 2010 – December 2012 (36 months)*
Patient population	*Crohn's disease patients*
Sample size	*50*
Inclusion criteria	*- ≥18-year-old* *- Established Crohn's disease* *- Symptomatic Crohn's disease not amenable for medical treatment* *- Laparotomy, converted-laparoscopy, or hand-assisted laparoscopy (HAL) with bowel resection/s or strictureplasty/ies* *- Primary wound closure* *- Adherence to periodical follow-up* *- Signed informed consent*
Exclusion criteria	*- Unconverted laparoscopy* *- Explorative laparotomy/laparoscopy without bowel opening* *- Massive bowel resections (less than 30% of anatomical length preserved)*
Intervention(s) (n =) and comparator(s) (n =)	*PICO: 25* *Standard of care: 25*
Baseline differences	*No significant baseline differences in populations*
How were participants followed-up (for example, through pro-active follow-	*12 month follow-up. After discharge patients were seen at 7, 15 and 30 days, then subsequently every two weeks for 3 months. No lost to follow-up reported or indicated in Results.*

up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	*Categorical data were compared using 2-tailed Fisher's exact test or Chi-squared test; continuous variables were compared using Mann-Whitney test.*
Primary outcomes (including scoring methods and timings of assessments)	*- Surgical site complications* *- Readmission rates (within 6 months)*
Secondary outcomes (including scoring methods and timings of assessments)	*- Patients' compliance with the device and difficulty in managing it (timeline not specified)*

Study name	***Pellino et al 2014a - Preventive NPWT over closed incisions in general surgery: Does age matter?***
Objective	*To assess the use of NPWT on breast and colorectal surgical patients from a single centre with respect to prevention of surgical site events (SSEs), as well as any age effects (> or <65 years of age).*
Location	*Italy*
Design	*Open label, prospective, controlled trial*
Duration of study	*September 2012 – May 2014 (21 months)*
Patient population	*Breast and colorectal closed incisions*
Sample size	*100*
Inclusion criteria	*Not reported*
Exclusion criteria	*Not reported*
Intervention(s) (n =) and comparator(s) (n =)	*PICO: Breast: 25 (patients aged >65: 10); Colorectal: 25 (patients aged >65: 10)* *Standard of Care: Breast: 25 (patients aged >65: 10); Colorectal: 25 (patients aged >65: 10)*

Baseline differences	*No significant differences between PICO and control groups within breast or colorectal cohorts. (There were significant differences between the breast and colorectal cohorts for the following baseline characteristics: male gender (more in colorectal cohort, p<0.0001), duration of surgery (longer in colorectal, p<0.0001) and wound length (longer in colorectal, p=0.003)).*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*After discharge, standard follow-up intervals for this study were at 7, 15 and 30 days, subsequently every two weeks for 3 months, no patients reported as lost to follow-up*
Statistical tests	*Categorical data were compared using 2-tailed Fisher's exact test or Chi-squared test, continuous variables were compared using Mann-Whitney test.*
Primary outcomes (including scoring methods and timings of assessments)	*Incidence of surgical site events*
Secondary outcomes (including scoring methods and timings of assessments)	*- Efficacy and safety of PICO in elderly patients* *- Outcome differences between breast and abdominal patients*

Study name	***Pellino et al 2014b - Effects of a new pocket device for negative pressure wound therapy on surgical wounds of patients affected with Crohn's disease: a pilot trial***
Objective	*To compare a portable device for negative pressure wound therapy (PICO, Smith & Nephew, London, UK) to conventional gauze dressings in patients undergoing surgery for stricturing Crohn's disease*
Location	*Department of Surgery, Second University of Naples, Italy*
Design	*Prospective non-randomised trial*

Duration of study	*1 year and 10 months*
Patient population	*Patients suffering from structuring Crohn's disease scheduled for small bowel resection or strictureplasty*
Sample size	*30 patients*
Inclusion criteria	*- Age ≥18 years* *- Established Crohn's disease* *- Stricturing Crohn's disease with symptomatic stenosis* *- Unsuitable for medical treatment* *- Laparotomy* *- Converted laparoscopy or hand-assisted laparoscopy (HAL) with bowel resection/s or strictureplasty/ies* *- Primary wound closure* *- Adhesion to periodical follow-up* *- Signed informed consent.*
Exclusion criteria	*- Unconverted laparoscopy* *- Explorative laparotomy/laparoscopy without bowel opening* *- Penetrating disease* *- Massive bowel resections (<30% of anatomical length preserved) with risk for intestinal failure/short bowel syndrome.*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 13* *Conventional gauze = 17*
Baseline differences	*No differences were observed between groups, with the exception of patients receiving steroids at the time of surgery (NPWT group n=7; Conventional gauze group n=5)*

How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*- For SSI and wound complications follow up was out to 30 days post-surgery* *- Cosmetic outcome was assessed at 3 month post-surgery* *- Zero patients were lost to follow-up*
Statistical tests	*- Categorical data = 2-tailed Fisher's exact test or X^2 test* *- Continuous variable = Mann-Whitney test*
Primary outcomes (including scoring methods and timings of assessments)	*Incidence of SSI and wound related complications in patients affected with structuring Crohn's disease undergoing bowel resection or strictureplasty*
Secondary outcomes (including scoring methods and timings of assessments)	*- Compliance with NPWT device* *- Length of Stay* *- Cosmetic results*

Study name	***van der Valk 2017 - Incisional Negative-Pressure Wound Therapy for Perineal Wounds After Abdominoperineal Resection for Rectal Cancer, a Pilot Study***
Objective	*To evaluate the potential of a new portable negative-pressure wound therapy device in reducing wound complications and accelerating wound healing for patients undergoing APR for rectal cancer.*
Location	*IJsselland Hospital, The Netherlands.*
Design	*Single centre prospective feasibility study (Historical control)*
Duration of study	*January 1st 2015 to December 31st 2015 (12 months)*
Patient population	*Patients undergoing laparoscopic APR for rectal cancer*
Sample size	*20*
Inclusion criteria	*Patients undergoing laparoscopic abdominoperineal resection for rectal cancer*
Exclusion criteria	*Patients undergoing extralevator APR or treated with a perineal subcutaneous drain.*

Intervention(s) (n =) and comparator(s) (n =)	*PICO = 10* *Conventional Wound Care = 10*
Baseline differences	*No significant differences for age, ASA score, Charlson index and BMI*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*- All patients were assessed daily by staff surgeon and specialised nurses following the operation.* *- The dressing was changed in the event of vacuum failure, leakage, or dressing saturation.* *- In case of repeated device failure, iNPWT was aborted.*
Statistical tests	*A two-sided unpaired T-test was used for the comparison of two means. A Kruskal–Wallis test was used for the comparison of two medians.*
Primary outcomes (including scoring methods and timings of assessments)	*Incidence of wound complications.*
Secondary outcomes (including scoring methods and timings of assessments)	*Wound complication severity score assessed with the Clavien–Dindo classification (CD), time taken for wound to heal and number of days taken to diagnose wound infections.*

Study name	***Holt and Murphy 2015 - PICO™ incisions closure in oncoplastic breast surgery: a case series***
Objective	*To assess whether negative pressure wound therapy (NPWT) on closed incisions in complex breast wounds promotes wound healing*
Location	*Nightingale and Genesis Breast Centre, University Hospital South Manchester*
Design	*Clinical audit with intra-patient control arm*
Duration of study	*20 months*
Patient population	*Patients undergoing the following procedures:* - *Therapeutic mammoplasty*

	- *Skin-sparing mastectomy and immediate reconstruction with inferior dermal flap and implant*
Sample size	*24 patients (48 breasts)*
Inclusion criteria	*Inclusion was based on procedure type:* - *Therapeutic mammoplasty* - *Skin-sparing mastectomy and immediate reconstruction with inferior dermal flap and implant*
Exclusion criteria	*No exclusion criteria stated*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 24 patients, 24 breasts* *Conventional dressings = 24 patients, 24 breasts*
Baseline differences	*None reported*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*- Clinic visits at 6 and 12 days post op.* *- Lost to follow up not recorded*
Statistical tests	*Descriptive statistics were used*
Primary outcomes (including scoring methods and timings of assessments)	*- Wound breakdown – as per surgeon clinical judgement*
Secondary outcomes (including scoring methods and timings of assessments)	*- Fat necrosis – as per surgeon clinical judgement* *- Delays to adjuvant therapy – as per surgeon clinical judgement* *- Delayed healing – as per surgeon clinical judgement*

Study name	***Tan et al 2017 - Use of Negative Pressure Wound Therapy for Lower Limb Bypass Incisions***
Objective	*Investigating the outcomes of NPWT in preventing SSIs in patients with lower limb arterial bypass incisions.*

Location	*Singapore*
Design	*Retrospective, comparative, controlled trial.*
Duration of study	*March 2014 – June 2016 (28 months)*
Patient population	*Patients with lower limb arterial bypass incisions*
Sample size	*42*
Inclusion criteria	*Patients who underwent lower limb arterial bypass with reversed great saphenous vein*
Exclusion criteria	*Not specified*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 14* *Standard of care = 28*
Baseline differences	*No significant differences for gender distribution, ethnicity, age, comorbidities, Rutherford classification and SSI risk*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*- Follow-up time not specified, longest outcome reported at 30 days.* *- No mention of patients lost to follow-up, judging by Results section there were no drop outs.*
Statistical tests	*Continuous variables were analysed using Student's t-test, and categorical variables were analysed using Fisher's and Chi-squared tests.*
Primary outcomes (including scoring methods and timings of assessments)	*- SSI incidence* *- Subsequent need for surgical debridement*
Secondary outcomes (including scoring methods and timings of assessments)	*- Length of stay* *- Need for 30-day readmission* *- Need for secondary vascular procedures*

Study name	***Fleming et al 2018 - Routine use of PICO dressings may reduce overall groin wound complication rates following peripheral vascular surgery***
Objective	*To determine whether groin wound complications were reduced following the routine introduction of PICO negative pressure wound therapy dressings in patients who underwent peripheral vascular surgery.*
Location	*Ireland*
Design	*Retrospective comparative study*
Duration of study	*January 2011 to December 2016 (71 months)*
Patient population	*All consecutive patients undergoing peripheral vascular (arterial) surgery of the lower limbs from January 2011 to December 2016 at a single vascular surgery centre*
Sample size	*151 patients*
Inclusion criteria	*Patients >18 years of age who underwent peripheral arterial surgery of the lower limb in whom a PICO dressing or standard dressing was used postoperatively*
Exclusion criteria	*None stated*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 73* *Standard of care = 78*
Baseline differences	*Smoking (higher in PICO group, p = 0.034), femoral endarterectomy cases (higher in PICO group, p = 0.001)*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*Not stated; follow-up was a minimum of 6 weeks, no participant reported as lost to follow-up.*
Statistical tests	*Categorical variables were analysed using Chi-squared test if there were less than five observations, and Fisher's exact test if there were five observations or more. Continuous variables were analysed using Student's t-test for parametric data, and Mann-Whitney U-test was used for analysis of nonparametric data. In all instances, $p < 0.05$ was considered to indicate statistical significance.*

Primary outcomes (including scoring methods and timings of assessments)	*Post-operative wound complications rates*
Secondary outcomes (including scoring methods and timings of assessments)	*Wound management and re-admission rates following wound complications: microbiology (n =), antibiotics required (n =), antibiotic duration (days: mean, SD), VAC required (n =), hospital re-admission (n =), re-admission length of stay (days: mean, SD), time to full resolution (days: mean, SD).* *Cost-effectiveness of prophylactic use of PICO dressings in peripheral vascular surgery: number of PICO dressings (n=: mean, SD, range, total number, total cost), re-admission length of stay (days: mean, SD, range, total bed-days, total cost of LOS), total cost (Euros)*

Published conference abstracts:

Study name	***Kawakita et al 2018 - Negative pressure wound therapy (PICO) in morbidly obese women after caesarean delivery compared with standard dressing***
Objective	*To examine the rate of surgical site infection (SSI) in morbidly obese women (BMI ≥ 40Kg/m^2) who received NPWT compared with those who received standard dressing.*
Location	*MedStar Washington Hospital Center, Washington DC, USA*
Design	*Retrospective cohort study*
Duration of study	*3 years and 3 months*
Patient population	*Morbidly obese women having caesarean delivery*
Sample size	*759*
Inclusion criteria	*- BMI≥ 40Kg/m^2* *- Caesarean section*
Exclusion criteria	*Not reported*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 167* *Standard dressing = 759*
Baseline differences	*Baseline characteristics were controlled for the following:*

	- *Age* - *Race* - *Gestational age* - *Rupture of membranes* - *Labor* - *Chorioamnionitis* - *Diabetes* - *BMI*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*Not stated*
Statistical tests	*- Multivariable logistic regression models* *- Adjusted pdds ratios*
Primary outcomes (including scoring methods and timings of assessments)	*- Composite wound complications (scoring methods and timing of assessments were not recorded)*
Secondary outcomes (including scoring methods and timings of assessments)	*- Endometritis diagnosed before discharge* *- Endometritis diagnosed after discharge* *- Deep wound infection* *- Other severe infections* *- Cellulitis* *- Hematoma or seroma* *- Dehiscence* *Scoring methods and timing of assessments was not recorded*

Study name	***Hackney and McCoubrey 2017 - The effect of negative pressure dressings (PICO) on wound complications, readmissions rates and length of stay***
Objective	*To assess the effect of negative pressure dressings (PICO) on wound complications.*
Location	*South West Acute Hospital, Enniskillen, Northern Ireland*
Design	*Retrospective cohort study*
Duration of study	*Six months*
Patient population	*Open abdominal surgery – elective and emergency*
Sample size	*71*
Inclusion criteria	*- Open abdominal procedures* *- Emergency or elective surgery*
Exclusion criteria	*Not reported*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 39* *Control = 32*
Baseline differences	*Not stated*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*Not stated.*
Statistical tests	*Not stated*
Primary outcomes (including scoring methods and timings of assessments)	*Wound complications*

Secondary outcomes (including scoring methods and timings of assessments)	*- Readmission* *- Length of stay*

Study name	***Irwin et al 2018 - Negative pressure dressings significantly decrease rates of wound breakdown and may reduce implant loss rates in prepectoral breast reconstruction***
Objective	*To report findings from a cohort study of PICO use in prepectoral breast reconstruction*
Location	*Nightingale Breast Unit, Manchester University NHS Foundation Trust*
Design	*Prospective database audit*
Duration of study	*Not reported*
Patient population	*Prepectoral implant-based reconstruction procedures*
Sample size	*155*
Inclusion criteria	*- Patients undergoing prepectoral implant-based reconstruction procedures* *- Patients receiving PICO* *- Patients receiving standard dressings*
Exclusion criteria	*Not stated*
Intervention(s) (n =) and comparator(s) (n =)	*PICO = 102* *Standard dressings = 152*
Baseline differences	*ASA classification, weight or comorbidities were not significantly different between the groups.*
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	*Not stated*
Statistical tests	*Fisher's exact*

Primary outcomes (including scoring methods and timings of assessments)	*Wound breakdown*
Secondary outcomes (including scoring methods and timings of assessments)	*Reconstructive failures*

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

During the screening of abstracts, multiple outputs (often a conference abstract and full-text journal article) were found for several studies. These were screened out at the abstract screening stage to ensure that the same patient populations were not double-counted in the evidence synthesis and meta-analyses presented in this report. However, for completeness, the following outputs were identified as being related to the same clinical study:

- *A conference abstract identified in Embase by Holt, Shotton and Murphy 2015 ("Negative pressure wound therapy (NPWT) on complex closed breast incisions promotes wound healing") was found to be the same clinical study as the Holt and Murphy 2015 study included in this analysis.*

- *A conference abstract identified in Embase by Kuteva, Fleming, Hanlon, McGreal and O'Brien 2017 ("Pico dressings significantly reduce overall wound complications following peripheral vascular surgery") was found to be the same clinical study as the Fleming et al 2017 study included in this analysis.*

- *A conference abstract identified in Embase by Pellino, Sciaudone, Candilio, Campitiello, Selvaggi and Canonico 2014 ("Effects of a new pocket device for NPWT on surgical wounds in Crohn's disease") was found to be the same clinical study as the Pellino et al 2014b study included in this analysis.*

- *A conference abstract identified in Embase by van der Valk, Doornebosch, De Graaf and Vermaas 2016 ("Incisional negative pressure therapy for perineal wounds after abdominoperineal resection") was found to be the same clinical study as the van der Valk et al 2017 study included in this analysis.*

- *A conference abstract identified in Embase by Carter, Burton, Anglim, Concannon, Pierce, Coffey, Wijewardene, Burton, Waldron, Hickey and Coffey 2016 ("A randomised controlled trial of negative pressure wound therapy at primary closure of midline laparotomy wounds") was found to be the same clinical study as the*

O'Leary et al 2017 study included in this analysis. This was confirmed via communication with one of the study authors.

Further to these excluded abstracts, the study by Tanaydin et al 2018 was identified as having a subset of the patients that were included in the study by Galiano et al 2018. For this reason, duplicate results from Tanaydin et al 2018 were excluded from the meta-analysis but still captured in this report as they reported some outcomes which were not captured in the larger study.

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

Although PICO was applied prophylactically after a surgical site incision in all studies, there was considerable diversity in the surgery performed prior to PICO application. Within the orthopaedic speciality, relevant studies relating to hip and knee arthroplasty (Gillespie et al 2015, Hester et al 2015), long-segment thoracolumbar spine fusions (Adogwa et al 2014), major foot ankle fracture surgery (Dingemans et al 2018), surgery for spinal fracture (Nordmeyer et al 2016) and total ankle arthroplasty (Matsumoto and Parekh 2015) were identified. Studies related to the field of C-Section were also well represented, particularly for caesarean sections (Hyldig et al 2018, Hickson et al 2015, Chaboyer et al 2014, Kawakita et al 2018). Breast surgery studies were also identified (Galiano et al 2018, Tanaydin et al 2018, Pellino et al 2014a, Irwin et al 2018, Holt and Murphy 2015). Studies related to abdominal surgery contained patients who had undergone operations for specific indications such as Crohn's disease (Selvaggi et al 2014, Pellino et al 2014b) and ulcerative colitis (Uchino et al 2016) as well as more generalised colorectal indications (Hackney and McCoubrey 2017, van der Valk et al 2017, O'Leary et al 2016). Finally, vascular operations were represented principally by studies of the lower limbs (Fleming et al 2018, Svensson-Bjork et al 2018, Tan et al 2017) but also included a study by Witt-Majchrzak et al 2015 which followed patients with closed sternotomy incisions after off-pump coronary artery bypass grafting procedures.

The identified studies represented the major geographical regions of Europe, North America, Australia and Asia with outcomes reported for multiple different countries.

Studies from the United Kingdom included Karlakki et al 2016, Hackney and McCoubrey 2017, Irwin et al 2018, Hester et al 2015, and Holt and Murphy 2015.

The identified studies also differed in their inclusion criteria. Several studies included patient populations which were broadly representative of the underlying general surgical population (e.g. Galiano et al 2018, Gillespie et al 2015, Selvaggi et al 2014, Pellino et al 2014a, Pellino et al 2014b, Dingemans et al 2018, Hester et al 2015, Matsumoto and Parekh 2015, Uchino et al 2016, and Nordmeyer et al 2016). It is noteworthy that in some surgical specialities, for example vascular surgery, the underlying patient population had high incidence of risk factors for wound complications (e.g. high BMI, smokers, diabetics); thus, even in these unselected patient populations, the majority of patients would have been at high risk of wound complications (e.g. Fleming et al 2018, Svensson-Bjork et al 2018, Tan et al 2017, Karlakki et al 2016, Witt-Macjchrzak et al 2015). Other studies had inclusion criteria to ensure that only patients at higher risk of wound complications were included. This was particularly true of the obstetric studies (e.g. Hyldig et al 2018, Chaboyer et al 2014, Kawakita et al 2018, Tuuli et al 2017) which applied obesity/high BMI as an eligibility criterion. This reflects the evidence on surgical site complications following caesarean section which indicates that obesity significantly increases risk.

There were also some methodological differences between studies. In some of the breast studies (Galiano et al 2018, Tanaydin et al 2018) and one of the vascular studies (Svensson-Bjork et al 2018), the bilateral nature of the operation allowed the patient to have both PICO and the standard of care, effectively allowing them to be their own control. In other studies, the introduction of PICO allowed a historic control to be used as the comparator – a 'before & after' analysis based on patient notes (e.g. Hickson et al 2015, Adogwa et al 2014, Dingemans et al 2018, van der Valk et al 2017, Hester et al 2015, Matsumoto and Parekh 2015). The other studies included in this report were more traditional comparative studies, either observational non-randomised (e.g. Hackney and McCoubrey 2017, Pellino et al 2014a, Pellino et al 2014b, Selvaggi et al 2014, Irwin et al 2018) or randomised controlled trials (e.g. Chaboyer et al 2014, Tuuli et al 2017, Zotes et al 2015, O'Leary et al 2016, Uchino et al 2016, Nordmeyer et al 2016).

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

The majority of studies did not include subgroup analyses. Of those that did, Selvaggi et al 2014 performed a subgroup analysis of patients receiving steroids at surgery. Their results demonstrated a significant reduction of infectious surgical site complications with PICO compared with conventional medications (p = 0.001) in this subgroup, however, they did not state whether this analysis was pre-planned or post-hoc.

Pellino et al 2014a performed sub-analyses of patients aged over 65. In these sub-analyses, PICO demonstrated an advantage over conventional care, whereas in the whole cohort (all ages) this difference was not statistically significant. Again, the authors did not specify whether this analysis was pre-planned or post-hoc.

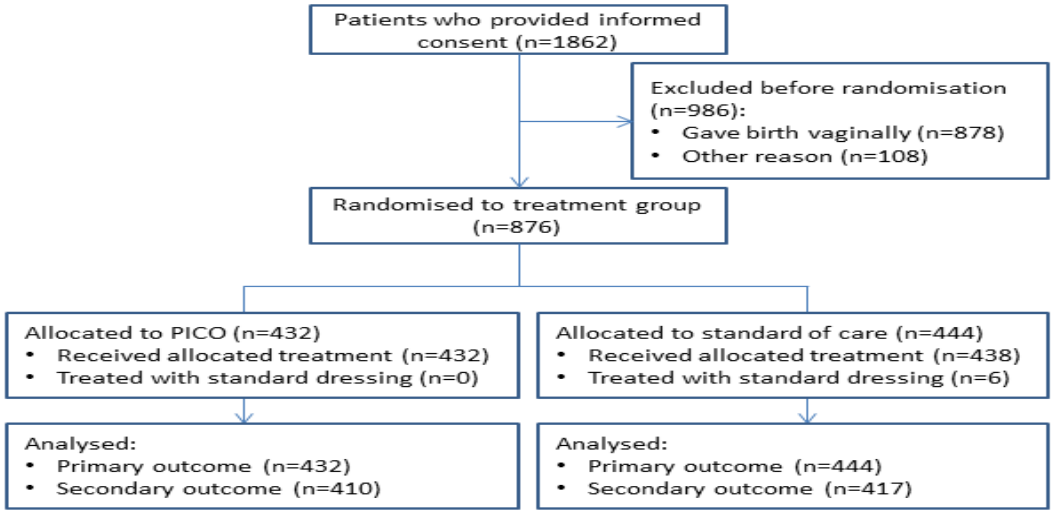
Galiano et al 2018 stratified their patient population by BMI and found that the benefits seen with PICO over the standard of care increased with increasing BMI. The authors did not specify whether this analysis was pre-planned or post-hoc.

The study by Karlakki et al 2016 included patients that had undergone either a total knee arthroplasty or a total hip arthroplasty. The authors included pre-planned subanalyses looking at the outcomes for each of these groups.

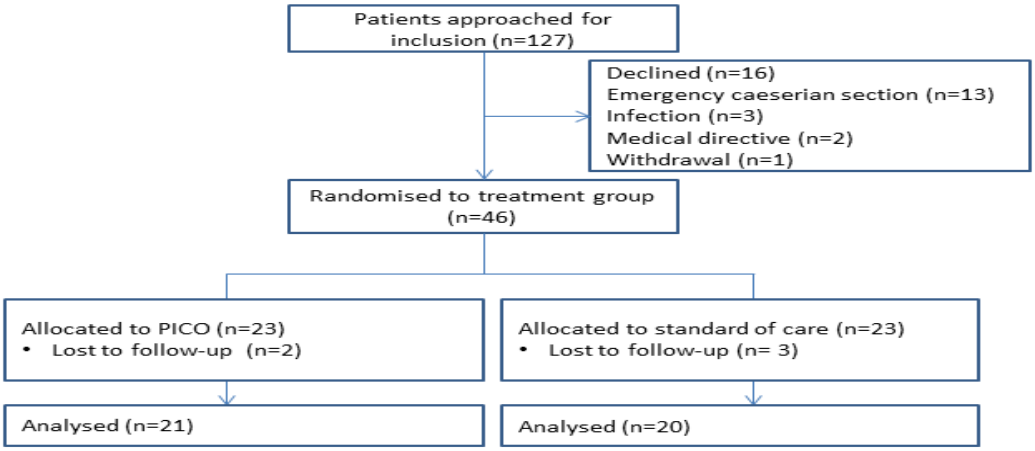
7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

CONSORT diagrams were made for all randomised controlled trials published within a peer-reviewed journal included within this report:

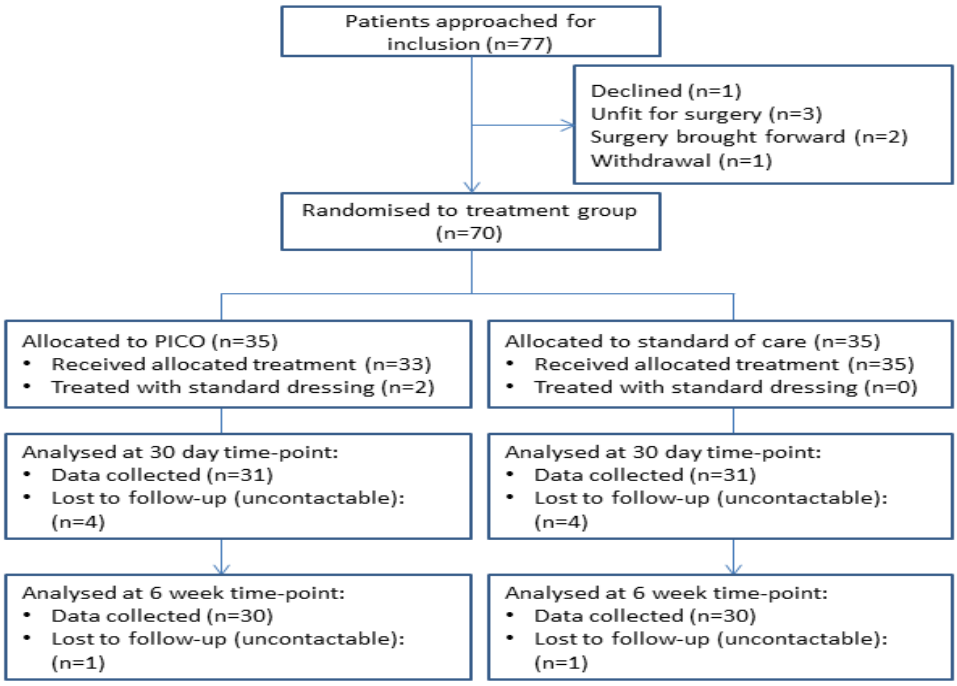
Hyldig et al 2018:



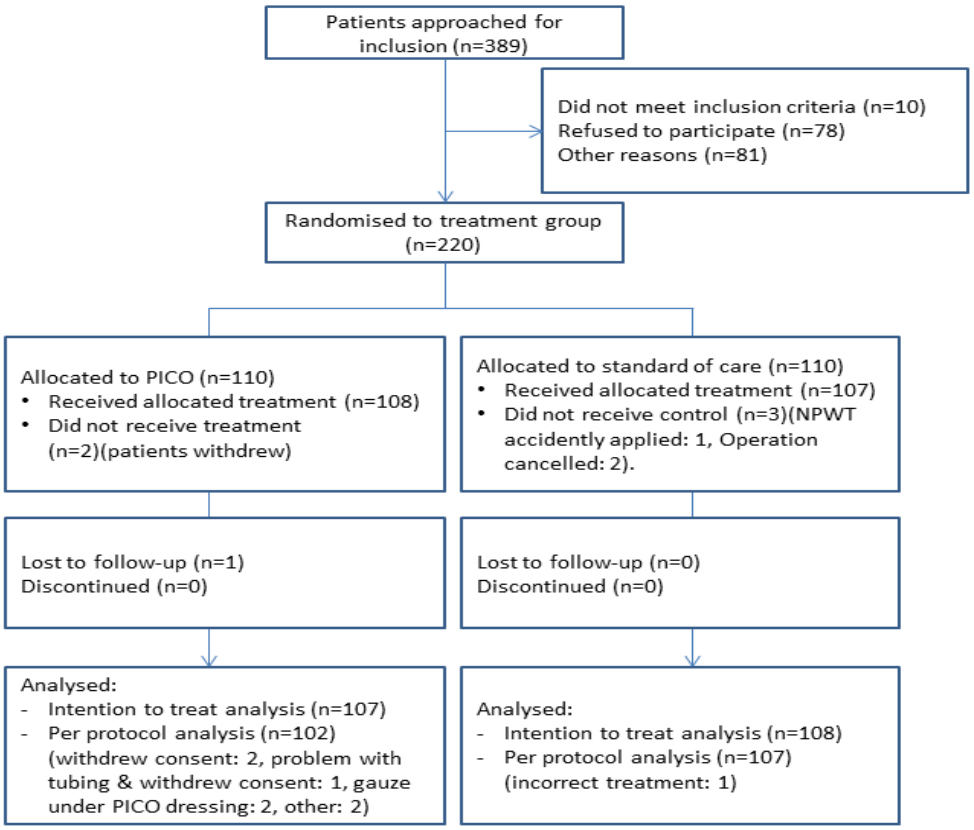
Chaboyer et al 2014:



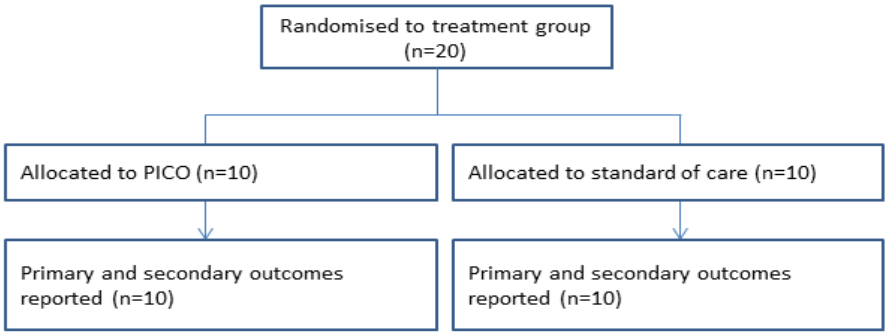
Gillespie et al 2015:



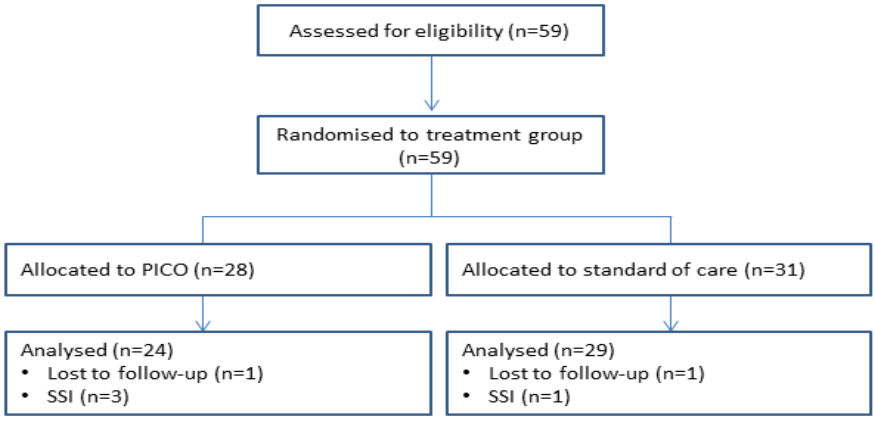
Karlakki et al 2016:



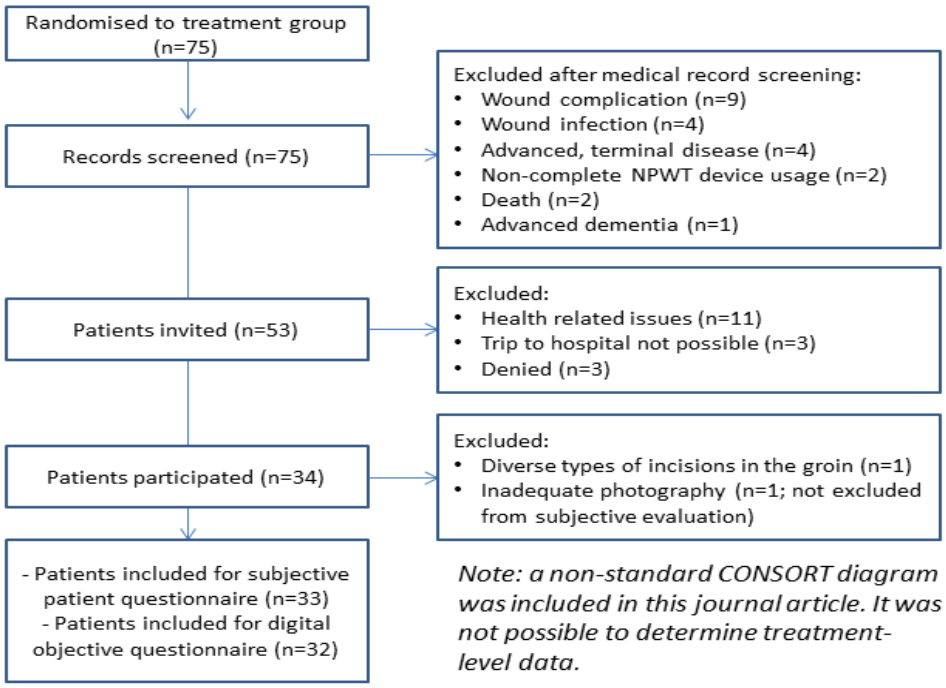
Nordmeyer et al 2016:



Uchino et al 2016:

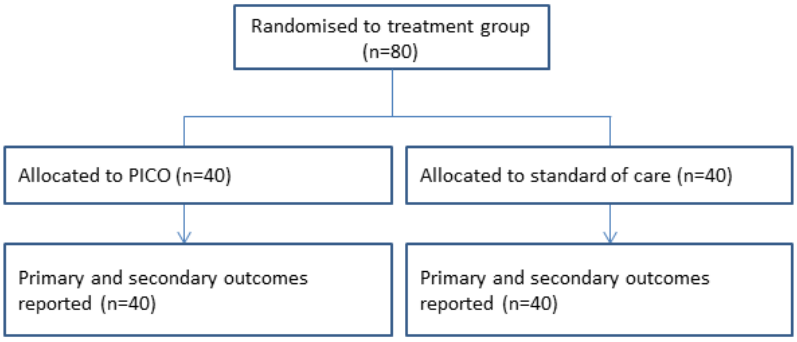


Svensson-Bjork et al 2018:

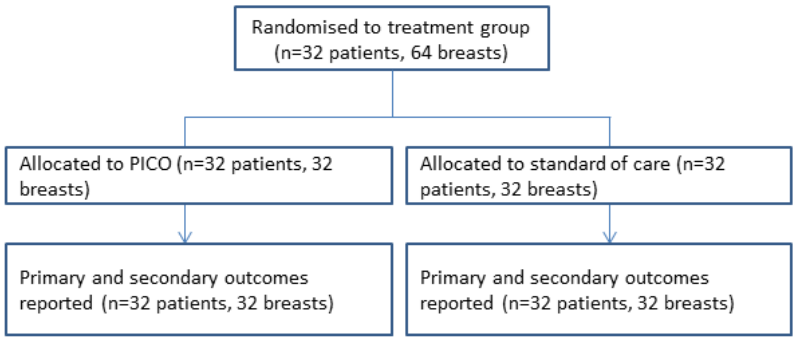


Note: a non-standard CONSORT diagram was included in this journal article. It was not possible to determine treatment-level data.

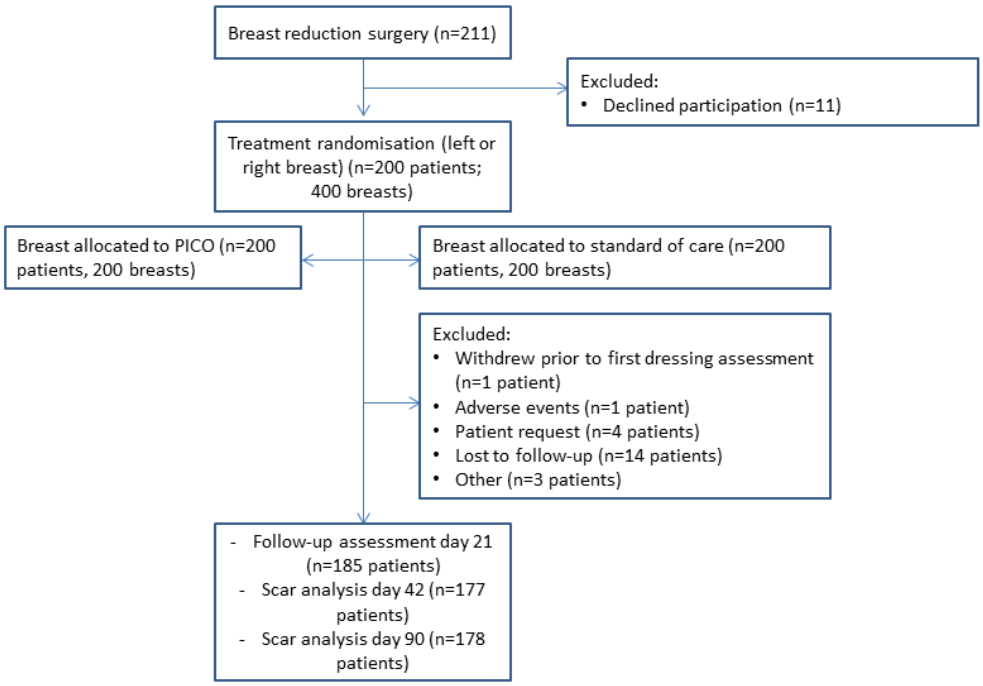
Witt-Majchrzak et al 2015:



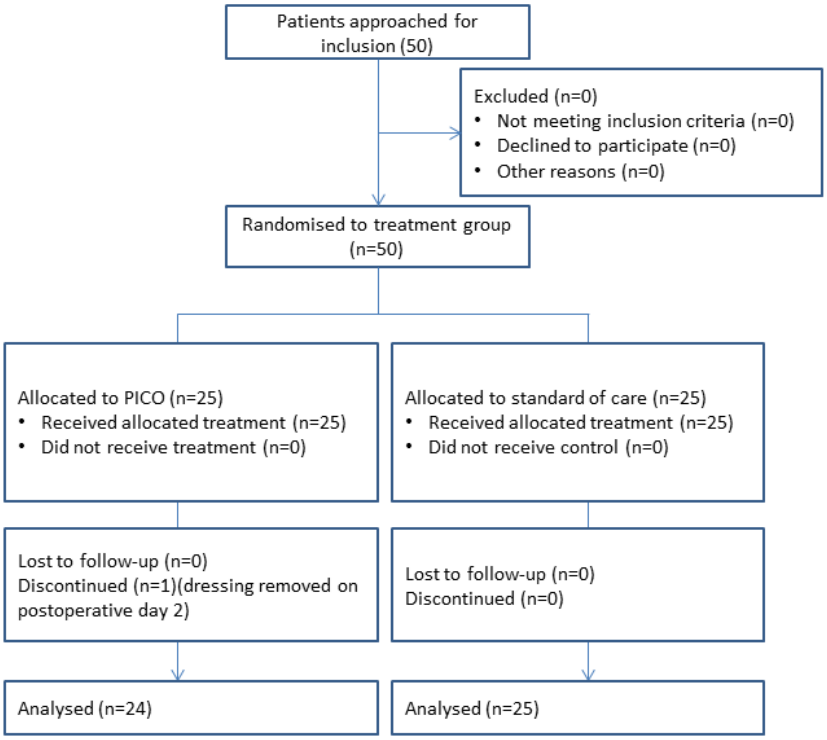
Tanaydin et al 2018:



Galiano et al 2018:



O'Leary et al 2016:



7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

Where information was available, this has been captured in the CONSORT diagrams in Section 7.4.5.

7.5 Critical appraisal of relevant studies

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

Table 12 Critical appraisal of randomised control trials

Published journal articles:

Study name	***Hyldig et al 2018 - Prophylactic incisional negative pressure wound therapy reduces the risk of surgical site infection after caesarean section in obese women: A pragmatic randomised clinical trial***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Yes*	*Utilised a centralised randomisation portal.*
Was the concealment of treatment allocation adequate?	*N/A*	*Blinding not possible due to obvious difference in appearance between treatments.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*Yes*	*Baseline demographics were similar for both groups. Crude and weighted relative risks and 95% CIs were the same.*
Were the care providers, participants and outcome assessors blind to treatment	*No*	*Assessors were not blinded. Trial was open label.*

allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*No*	*Drop-out rates were similar in both groups and there were no differences in prognostic characteristics at baseline between those who responded and those who dropped out.*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No.*	*All outcomes detailed in the methods were reported in the results section.*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Yes*	*Intention-to-treat analysis was used and inclusion of results outside the per-protocol population were justified.*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	***Chaboyer et al 2014 - Negative Pressure Wound Therapy on Surgical Site Infections in Women Undergoing Elective Caesarean Sections: A Pilot RCT***	
Study question	***Response***	***How is the question addressed in the study?***

	(yes/no/ not clear/N/A)	
Was randomisation carried out appropriately?	*Yes*	*Utilised a centralised web-based randomisation system*
Was the concealment of treatment allocation adequate?	*N/A*	*Blinding not possible due to obvious difference in appearance between treatments.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*No*	*There were more smokers in the control group and patients in the control group took longer to operate on*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	*N/A*	*Assessors were not blinded due to the type of intervention*
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*No*	*Similar numbers dropped out: 2 vs 3 for intervention and control, respectively*
Is there any evidence to suggest that the authors	*No*	

measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*No*	*The publication does not mention the use of an intention-to-treat analysis*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	***Gillespie et al 2015 - Use of Negative-Pressure Wound Dressings to Prevent Surgical Site Complications After Primary Hip Arthroplasty: A Pilot RCT***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Yes*	*Computer-generated randomisation schedule with randomly varied blocks and 1:1 ratio (developed by statistician not involved in recruitment)*
Was the concealment of treatment allocation adequate?	*N/A*	*Blinding not possible due to obvious difference in appearance between treatments, but independent assessors and analysts were blinded.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*Yes*	*Baseline demographics were not significantly different for the two groups (p-values not reported), apart from pre-existing medication use (higher in PICO, $p<0.05$) and use of wound glue (higher in standard care, $p<0.001$)*
Were the care providers, participants and outcome assessors blind to treatment	*No*	*Physicians and patients could not be blinded due to appearance of dressings, but independent assessors for SSI and data analysts were blinded.*

allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*No*	*Dropouts occurred equally on both sides and all were explained.*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No*	*All outcomes detailed in the methods were reported in the results section.*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Yes*	*Intention-to-treat population was used for all analyses, even though two patients in the NPWT group were treated with standard care due to elongated incisions during surgery. 14% drop out by 6 weeks post-op in both groups - this was not accounted for and no analyses of per protocol population were performed, but this is unlikely to affect results.*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	***Karlakki et al 2016 - Incisional negative pressure wound therapy dressings (iNPWTd) in routine primary hip and knee arthroplasties: a randomised controlled trial***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Yes*	*Patients randomised to treatment by sealed envelope with block size of 20 and 1:1 ratio*

Was the concealment of treatment allocation adequate?	*N/A*	*Blinding not possible due to obvious difference in appearance between treatments.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*Yes*	*Baseline demographics were not significantly different between the two groups, apart from patients with BMI >35 where number was twice as high in PICO group: 17% vs 8% in control group*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	*No*	*Assessors were not blinded. Trial was open label.*
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*No*	*Dropouts occurred on both sides and all were explained.*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No.*	*All outcomes detailed in the methods were reported in the results section, though cost effectiveness of dressing was not investigated in depth (authors suggested separate financial modelling should be performed)*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Yes*	*ITT population was used to analyse length of stay, but PP population was used to analyse wound complications as these outcomes could not be collected for drop-outs. Where possible both ITT and PP results were presented.*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	***Nordmeyer et al 2016 – Negative pressure wound therapy for seroma prevention and surgical incision treatment in spinal fracture care***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Not clear*	*Details on randomisation were not provided in the manuscript.*
Was the concealment of treatment allocation adequate?	*N/A*	*Blinding not possible due to obvious difference in appearance between treatments.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*Not Clear*	*Baseline demographics for both groups not stated in study.*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	*N/A*	*Not a blinded trial.*
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*No*	*No drop-outs reported.*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No*	*All outcomes detailed in the methods were reported in the results section.*

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*No*	*Per protocol analysis used. No missing data.*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	***Uchino et al 2016 - Randomised Controlled Trial of Prophylactic Negative-Pressure Wound Therapy at Ostomy Closure for the Prevention of Delayed Wound Healing and Surgical Site Infection in Patients with Ulcerative Colitis***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Yes*	*Opaque envelopes containing the treatment option for each patient were opened in the operating room by a surgical nurse*
Was the concealment of treatment allocation adequate?	*N/A*	*Blinding not possible due to obvious difference in appearance between treatments.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*Yes*	*Baseline demographics were not significantly different for the two groups*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on	*No*	*Assessors were not blinded. Trial was open label.*

the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*Yes*	- *One patient was lost to follow up in each group* - *Patients excluded from wound healing duration analysis due to SSI were n=3 for PSS+PICO and n=1 for PSS alone*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No*	*All outcomes detailed in the methods were reported in the results section*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Yes*	*Intention-to-treat analysis was carried out on all outcomes except for the primary outcome mean duration of wound healing, due to the exclusion of patients diagnosed with SSI, as NPWT was terminated following SSI diagnosis.*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	***Svensson-Bjork et al 2018 - Evaluation of inguinal vascular surgical scars treated with closed incisional negative pressure wound therapy using three-dimensional digital imaging—A randomised controlled trial on bilateral incisions***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Yes*	*Randomisation was achieved via opaque envelopes containing equal numbers of notes representing the two dressing types. The drawn note reflected the dressing for the right inguinal incision, whereas the left incision was automatically assigned the alternate dressing type.*

Was the concealment of treatment allocation adequate?	*N/A*	*Due to the visible differences between dressing type, concealment was not possible.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*N/A*	*Patients have undergone bilateral operations with alternate dressing on each side.*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	*No*	*Due to the visible differences between dressing type, blinding was not possible. There likely was no impact on the risk of bias, as each patient was treated with the intervention and comparative dressing simultaneously.*
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*No*	*Patients have undergone bilateral operations with alternate dressing on each side; therefore any drop-outs would have affected both groups simultaneously.*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No*	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*No*	*Per protocol analysis only*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	***Witt-Majchrzak et al 2015 - Preliminary outcome of treatment of postoperative primarily closed sternotomy wounds treated using negative pressure wound therapy***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Not clear*	
Was the concealment of treatment allocation adequate?	*N/A*	*Due to the visible differences between dressing type, concealment was not possible.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*Yes*	*Groups were similar, except for age p=0.0438. PICO patients were slightly older 66 years vs 62 years*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	*N/A*	*Assessors were not blinded due to the type of intervention*
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*No*	*No drop outs*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No*	

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*No*	*The publication does not mention the use of an intention-to-treat analysis.*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	***Tanaydin et al 2018 - Randomized Controlled Study Comparing Disposable Negative Pressure Wound Therapy with Standard Care in Bilateral Breast Reduction Mammoplasty Evaluating Surgical Site Complications and Scar Quality***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Yes*	*Utilised a randomisation portal.*
Was the concealment of treatment allocation adequate?	*N/A*	*Blinding not possible due to obvious difference in appearance between treatments.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*N/A*	*The study used intra-patient trial design, therefore patient acted as their own control.*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on	*No*	*Assessors were not blinded. Trial was open label. Attempts were made to blind investigators assessing the Patient Scale and Observer Scale (POSAS) and Visual Analogue Scale (VAS) by concealing randomisation schedule and asking patients not to reveal this. There was potential bias as POSAS and VAS scores, which were given by non-blinded patients and investigators, showed significant superiority of PICO over standard*

the risk of bias (for each outcome)?		*care, whereas objective scar viscoelasticity measurements showed no statistically significant differences between the two treatment groups.*
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*No*	*The study used intra-patient trial design therefore if a patient did withdraw it was equal across both groups.*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No.*	*All outcomes detailed in the methods were reported in the results section.*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*No*	*The publication does not mention the use of an intention-to-treat analysis.*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	***Galiano et al 2018 - A prospective, randomised, intra-patient, comparative, open, multi-centre study to evaluate the efficacy of a single-use negative pressure wound therapy (NPWT) system on the prevention of postsurgical incision healing complications in patients undergoing reduction mammaplasty***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Yes*	*Utilised a central randomisation portal, which was standard across all six sites.*

Was the concealment of treatment allocation adequate?	*N/A*	*Blinding not possible due to obvious difference in appearance between treatments*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*N/A*	*The study used intra-patient trial design, therefore patient acted as their own control.*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	*N/A*	*Assessors were not blinded. Trial was open label.*
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*No*	*The study used intra-patient trial design therefore if a patient did withdraw it was equal across both groups.*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*Yes*	*The outcomes on scar quality and aesthetic appearance are to be reported as a separate publication from the healing and post-surgical wound complications.*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*No*	*The publication does not mention the use of an intention-to-treat analysis; however, from the description of the results the outcomes were based on the number of patients who completed the time-point and not all patients randomised (as per ITT).*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	***O'Leary et al 2016 - Prophylactic Negative Pressure Dressing Use in Closed Laparotomy Wounds Following Abdominal Operations***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Yes*	*Randomisation was performed on a 1:1 basis to either the negative pressure dressing group or the control group using a closed envelope method. Randomisation codes were generated on www.randomisation.com*
Was the concealment of treatment allocation adequate?	*No*	*Concealment not possible due to the visible differences between dressings in the treatment and control groups.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*Yes*	*There was no statistical difference in any of the patient, surgery, or wound characteristics between the control and treatment groups.*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	*No*	*Blinding not possible due to the visible differences between dressings in the treatment and control groups.*
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*Yes*	*No patients were reported as lost on follow-up, however one patient in the PICO group had their dressing removed on postoperative day 2 and was excluded from data analysis. The exclusion was carried out to ensure that all analyses were performed at postoperative days 4 and 30, for all patients involved.*
Is there any evidence to suggest that the authors	*No*	

measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Yes*	*Intention-to-treat and per protocol analyses performed for the primary outcome. No ITT analysis performed for secondary outcomes.*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Published conference abstracts:

Study name	***Tuuli et al 2017 - Pilot randomised trial of prophylactic negative pressure wound therapy in obese women after caesarean delivery***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Not Clear*	*Abstract did not give details on how the randomisation procedure was carried out.*
Was the concealment of treatment allocation adequate?	*N/A*	*This study was not blinded.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*Yes*	*Abstract stated that the baseline characteristics of the groups were similar.*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these	*No*	*This was not a blinded study and all participants and investigator staff would be aware of what intervention the patients received.*

people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*Not clear*	*The abstract did not give information in relation to patients being lost to follow-up.*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No*	*Abstract stated and reported the outcomes described.*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Yes*	*Intention to treat was an appropriate analysis for this type of study. The study did not state information relating to missing data.*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	***Zotes et al 2015 - Negative pressure wound therapy in a potentially infected wound after empyema surgery***	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Not clear*	*Conduct of randomisation was not provided in study abstract.*

Was the concealment of treatment allocation adequate?	*Not clear*	*This was not reported in the study abstract*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*Yes*	*Details were limited but the authors stated that in the PICO group 90% presented with at least 1 risk factor, compared to 80% in the conventional group.*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	*No*	*This was not a blinded trial.*
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*Not clear*	*This was not reported as part of the study abstract.*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No*	*The abstract clearly stated the outcomes reported.*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Not clear*	*The type of analysis was not reported in the study abstract. As a randomised trial, it would be expected to conduct an intention to treat analysis.*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Unpublished studies:

Study name	*Stannard et al 2018. Unpublished* *Working title:* [redacted]	
Study question	***Response (yes/no/ not clear/N/A)***	***How is the question addressed in the study?***
Was randomisation carried out appropriately?	*Not*	*The draft data does not state how randomised was conducted.*
Was the concealment of treatment allocation adequate?	*Yes*	*The draft data stated that patient and operating surgeons were not blinded to the treatments, however a single assessor was blinded to treatment and completed wound appearance using a 100 scale validated VAS.*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*Yes*	*The draft data reported the differences between baseline characteristics, including patient demographics and identified a sub group of patients with a known higher risk of wound complication within this surgical procedure type.*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	*No*	*The draft data reported that this study was not a blinded study. However the primary outcome was the assessment of wound appearance/healing by a blinded assessor. This would remove any bias in terms of the assessment by this clinician, who was unaware of treatment allocation.*

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	*Not clear*	*The number lost to follow up was not reported*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No*	*All outcomes reported in the draft data were stated.*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Not clear*	*The draft data did not state what type of analysis was conducted.*
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table 13 Critical appraisal of observational studies

Published journal articles:

Study name	***Hickson et al 2015 – A Journey to Zero: Reduction of Post-Operative Caesarean Surgical Site Infections over a Five-Year Period***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	*This was a before and after study for PICO, all eligible high risk caesarean section women were given PICO*
Was the exposure accurately measured to minimise bias?	*Yes*	

Was the outcome accurately measured to minimise bias?	*Yes*	
Have the authors identified all important confounding factors?	*Yes*	*An algorithm was used to classify women into risk bands (low and high risk)*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Yes*	
Was the follow-up of patients complete?	*Yes*	
How precise (for example, in terms of confidence interval and p values) are the results?	*N/A*	*Only percentages were provided*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*		

Study name	***Matsumoto and Parekh 2015 - Use of Negative Pressure Wound Therapy on Closed Surgical Incision After Total Ankle Arthroplasty***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	*All patients who had undergone total ankle arthroplasty by a single surgeon were managed with NPWT between June 2012 and August 2013. These patients were compared with a control group who had undergone TAA between February 2009 and May 2012, before the application of NPWT to TAA.*

Was the exposure accurately measured to minimise bias?	*Yes*	*The number of dressings used was accurately reported. Surgical time was reported as mean and SD with no decimal places. Time to heal has not been reported.*
Was the outcome accurately measured to minimise bias?	*Yes*	*All wound complications have been accurately captured and presented for both groups.*
Have the authors identified all important confounding factors?	*Yes*	*Authors have collected patient demographic information such as age, sex, and BMI. They also have recorded the type of implant used, as well as the diagnosis. Risk factors, such as smoking status, alcohol use, comorbidities, and lymphocyte count have been recorded.*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Yes*	*Confounding factors have been compared between the group of patients with successful wound healing and the patients with wound healing problems, as well as between the control and NPWT groups.* *There were no significant differences between the control and iNPWT groups in terms of confounding factors, however authors have shown that the group of patients with wound healing problems was significantly older that the group with successful wound healing; there were significantly more patients diagnosed with rheumatoid arthritis in the wound healing problem group; that group had a significantly higher corticosteroid use as well. Patients with successful wound healing had a significantly higher number of NPWT applications than the problem group.*
Was the follow-up of patients complete?	*Yes*	*There were no patients reported lost to follow-up.*
How precise (for example, in terms of confidence interval and p values) are the results?		*All 95% CIs and most p values were reported to 2 decimal places.* *Some p values were reported as p = 1.0.* *All percentages were reported with 1 decimal place.* *Overall, NPWT was found to reduce wound healing problems with an odds ratio of 0.10; the upper 95% CI was 0.50 which was still well clear of 1.*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence		

Study name	***Dingemans et al 2018 - Prophylactic negative pressure wound therapy after lower extremity fracture surgery: a pilot study***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	*Patients were consented to receive NPWT per set inclusion/exclusion criteria. A historical case-matched cohort was analysed to allow for a comparator to the intervention group.*
Was the exposure accurately measured to minimise bias?	*Yes*	*The study reported comprehensive inclusion and exclusion criteria.*
Was the outcome accurately measured to minimise bias?	*Yes*	*The primary outcome was assessed using a validated diagnostic tool. The intervention group had been case matched to a control group, using a strict methodology.*
Have the authors identified all important confounding factors?	*Yes*	
Have the authors taken account of the confounding factors in the design and/or analysis?	*Yes*	*Within the current methodology, all confounding factors for the outcomes measured have been factored into the design.*
Was the follow-up of patients complete?	*Yes*	*Study stated that all patients completed the follow-up period.*
How precise (for example, in terms of confidence interval and p values) are the results?	*Yes*	*Study reported, comprehensively, all of the statistical tests used for the analysis. For the primary outcome measure the most appropriate statistical test was used and the significance level of $p<0.05$ was acceptable.*

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*

Study name	***Hester et al 2015 - Is Single Use Portable Incisional Negative Pressure Wound Therapy System Suitable for Revision Arthroplasty?***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	*All patients who underwent revision arthroplasty surgery by the senior author were identified and case notes reviewed.*
Was the exposure accurately measured to minimise bias?	*Yes*	*Patients were allocated to the different dressing groups based on time of presentation; therefore the dressings were not picked according to the patient presentation, reducing the risk of bias.*
Was the outcome accurately measured to minimise bias?	*Yes*	*The outcome measurement performed by the authors was the number of wound complications, which has been reported.*
Have the authors identified all important confounding factors?	*Yes*	*Authors reported the reasons for revision for both patients groups.*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Not clear*	*It has not been made clear how, and if, the authors had taken account of the confounding factors. When reporting on wound complications the authors did report the reason for revision; however it was not taken into account for the statistical analysis, most likely due to the low number of complications (3 in the standard group and 1 in the NPWT group)*
Was the follow-up of patients complete?	*Yes*	*No patients were reported as lost to follow-up*
How precise (for example, in terms of confidence interval and p values) are the results?		*The authors did not specify which statistical tests were used to analyse the data. No confidence intervals were reported. The p value was reported to 2 decimal places.*

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*

Study name	***Adogwa et al 2014 – Negative pressure wound therapy reduces incidence of postoperative wound infection and dehiscence after long-segment thoracolumbar spinal fusion: a single institutional experience***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	
Was the exposure accurately measured to minimise bias?	*Yes*	
Was the outcome accurately measured to minimise bias?	*Yes*	*CDC definition was applied and infection was confirmed through laboratory diagnosis/ radiologic studies*
Have the authors identified all important confounding factors?	*Yes*	*The key ones identified were rheumatoid arthritis, osteoarthritis, metabolic bone disease*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Yes*	*Patients with rheumatoid arthritis, osteo-arthritis, metabolic bone disease were excluded from the study*
Was the follow-up of patients complete?	*Yes*	
How precise (for example, in terms of confidence interval and p values) are the results?	*N/A*	*These were not provided in the paper as only number of events and percentages were reported*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence		

Study name	***Selvaggi et al 2014 - New Advances in Negative Pressure Wound Therapy (NPWT) for Surgical Wounds of Patients Affected with Crohn's Disease***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	*Study enrolled 50 consecutive patients suffering from stricturing Crohn's disease scheduled for bowel resection or strictureplasty between Jan 2010 and Dec 2012 in the authors' institution.*
Was the exposure accurately measured to minimise bias?	*Yes*	*Follow-up and dressing changes were standardised and adhered to in both study arms. NPWT was applied for 7 days as standard, but in select patients could be re-applied for a further 4 days – average PICO wear time and standard deviation was captured in results.*
Was the outcome accurately measured to minimise bias?	*Yes*	*N number and % or mean +/- standard deviation presented for all outcomes, in addition to p-values.*
Have the authors identified all important confounding factors?	*Yes*	*Multivariate analysis done to identify independent risk factors for SSI.*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Yes*	*Significant variables were included in sub-group analyses.*
Was the follow-up of patients complete?	*Yes*	*No patients lost to follow-up.*
How precise (for example, in terms of confidence interval and p values) are the results?	*Yes*	*Very precise – n-number and % or mean +/- SD presented for all outcomes, and odds ratios with 95% CIs included when relevant. Exact p-values reported. The odds ratio presented for surgical site complications had a relatively tight confidence interval in favour of PICO.*

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*		
Study name	***Pellino et al 2014a - Preventive NPWT over closed incisions in general surgery: Does age matter?***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	*All patients scheduled for breast or colorectal surgery in the study institution during the study period were considered for inclusion.*
Was the exposure accurately measured to minimise bias?	*Yes*	
Was the outcome accurately measured to minimise bias?	*Yes*	*Mean +/- SD or n (%) reported for all outcomes.*
Have the authors identified all important confounding factors?	*Not clear*	*Patients aged >65 years were analysed as sub-population and baseline demographics were analysed and were well matched between treatment and control groups. No separate analysis performed to find other independent risk factors.*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Yes*	*Patients aged >65 years were analysed as sub-population and baseline demographics were analysed and were well matched between treatment and control groups.*
Was the follow-up of patients complete?	*Yes*	*No patients lost to follow-up*
How precise (for example, in terms of confidence interval and p values) are the results?	*Yes*	*Very precise – mean +/- SD or n (%) reported for all outcomes and exact p-values reported for all comparisons.*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*		

Study name	***Pellino et al 2014b - Effects of a new pocket device for negative pressure wound therapy on surgical wound so patients affected with Crohn's disease: a pilot trial***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	*Study reported that patients were given the option to receive intervention and if they did not wish to receive intervention (NPWT) they were placed in control group.*
Was the exposure accurately measured to minimise bias?	*Yes*	*The study reported that all patients were diagnosed with the same underlying disease (Crohn's disease). There were two different types of procedures included, but both were consistent in terms of wound classification (i.e. class IV dirty surgery).*
Was the outcome accurately measured to minimise bias?	*Yes*	*The study reported that all patients underwent the same type of procedure and the primary outcome measure was standardised using an accepted, SSI type definition.*
Have the authors identified all important confounding factors?	*Yes*	*The study reported that patients included were only eligible if they had an underlying disease and were undergoing the same wound classification type surgery. Furthermore the baseline characteristics were similar between the groups.*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Not clear*	*The study reported that this was not a randomised controlled trial. The patients were given the option to receive NPWT, and if there was underlying knowledge of NPWT by the patient, this could have led to bias. By utilising randomisation this level of bias would have been removed.*
Was the follow-up of patients complete?	*Yes*	*Study stated that all the patients included had completed follow up.*
How precise (for example, in terms of confidence interval and p values) are the results?	*Yes*	*From the data and type of outcomes reported, the type of statistical analysis and subsequent significance levels were appropriate for the sample reported.*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence		

12 questions to help you make sense of a cohort study

Study name	***van der Valk et al 2017 – Incisional Negative-Pressure Wound Therapy for Perineal Wounds After Abdominoperineal Resection for Rectal Cancer, a Pilot Study***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Not clear*	*Unclear how the PICO group were recruited.* *Retrospective analysis of control group.*
Was the exposure accurately measured to minimise bias?	*Not clear*	*It was not clear why some patients received PICO and other patients received conventional wound care within the study time-scale.*
Was the outcome accurately measured to minimise bias?	*No*	*The time difference between the assessments of the control group and PICO group outcomes may have resulted in bias.*
Have the authors identified all important confounding factors?	*Yes*	*Patient baseline characteristics have been controlled.*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Yes*	*Authors declared study was too small to draw major conclusions.*
Was the follow-up of patients complete?	*NA*	*The follow-up was not stated.*
How precise (for example, in terms of confidence interval and p values) are the results?	*NA*	*Confidence intervals not recorded.* *p-values recorded to 2 or 3 decimal places.* *Diagnosis (day) and time for wound healing (weeks) reported to 1 decimal place (mean & median).*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*		

Study name	***Holt and Murphy 2015 - PICO™ incisions closure in oncoplastic breast surgery: a case series***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	*Consecutive patients identified and use of intra-patient control reduced bias*
Was the exposure accurately measured to minimise bias?	*No*	*The outcomes were based on clinical judgment and not validated outcome measures.*
Was the outcome accurately measured to minimise bias?	*Yes*	*The outcomes measured do reflect the wound healing progress for each patient. However the definition of wound breakdown is not recorded.*
Have the authors identified all important confounding factors?	*Yes*	*By using an intra-patient control group a direct comparison could be made, eliminating many biases such as patient age, comorbidities and other influencing factors*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Yes*	*By using an intra-patient control group, this eliminates biases including patient age and comorbidities.*
Was the follow-up of patients complete?	*Yes*	*All patients completed the 12 day post-operative assessment*
How precise (for example, in terms of confidence interval and p values) are the results?	*N/A*	*P values and confidence intervals were not stated as the sample size was too small to allow meaningful testing for statistical significance.*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*		

Study name	***Tan et al 2017 - Use of Negative Pressure Wound Therapy for Lower Limb Bypass Incisions***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Not clear*	*Authors stated they retrospectively reviewed 42 patients who underwent lower limb arterial bypass during the study period, but did not make it clear whether this included all eligible patients operated on during this time period.*
Was the exposure accurately measured to minimise bias?	*Not clear*	*No information about length of use for either group.*
Was the outcome accurately measured to minimise bias?	*Yes*	*N (%), mean values and ranges reported where relevant and exact p-values reported for all comparisons.*
Have the authors identified all important confounding factors?	*Yes*	*Comorbidities identified and quantified, mean SSI risk calculated for each group.*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Yes*	*No significant differences between groups in relation to demographics, comorbidities and SSI risk.*
Was the follow-up of patients complete?	*Yes*	*No patients lost to follow-up reported*
How precise (for example, in terms of confidence interval and p values) are the results?	*Yes*	*Very precise – n (%), mean values and ranges reported for all outcomes, as well as exact p-values.*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*		

Study name	***Fleming et al 2018 - Routine use of PICO dressings may reduce overall groin wound complication rates following peripheral vascular surgery***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	*Retrospective study of all consecutive patients undergoing peripheral vascular (arterial) surgery of the lower limbs from January 2011 to December 2016 at a single vascular surgery centre*
Was the exposure accurately measured to minimise bias?	*Yes*	*The number of dressings used was reported. Time to suture removal was reported as mean and SD, with mean reported to at least 2 decimal places, and SD reported to at least 1 decimal place, where appropriate. Surgical time has not been reported.*
Was the outcome accurately measured to minimise bias?	*Yes*	*All wound complications have been accurately captured and presented for both groups. The authors showed all the data they used for the cost analysis.*
Have the authors identified all important confounding factors?	*Yes*	*Authors have collected patient demographics, including age, sex, and BMI. They also compiled other patient factors associated with wound complications, such as smoking status, diagnosis of diabetes mellitus, pre-operative serum albumin level, and a history of MRSA. Authors also have compared the type of procedure performed, location of incision, drain placement, and the type of material used for skin closure. The only significant differences between the two patient groups were smoking status and type of procedure: femoral endarterectomy.*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Yes*	*All procedures were performed by two specialised senior consultant surgeons, and the study included all consecutive patients undergoing peripheral vascular surgery.*
Was the follow-up of patients complete?	*Yes*	*No patients were reported lost to follow-up.*

How precise (for example, in terms of confidence interval and p values) are the results?		*All p values are reported up to 3 decimal places. All percentages reported to 1 decimal place. Means and SDs reported to 2 decimal places where appropriate.*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*		

Published conference abstracts:

Study name	***Kawakita et al 2018 - Negative pressure wound therapy (PICO) in morbidly obese women after caesarean delivery compared with standard dressing***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	*Retrospective analysis of patient medical records.*
Was the exposure accurately measured to minimise bias?	*Not Clear*	*The abstract did not record why some patients received PICO and other patients received standard of care dressing.*
Was the outcome accurately measured to minimise bias?	*Not clear*	*The outcomes measured did not state if a validated score was used.*
Have the authors identified all important confounding factors?	*Yes*	*Patient baseline characteristics have been controlled.*
Have the authors taken account of the confounding factors in the design and/or analysis?	*No*	*The PICO group was much smaller than the standard dressing group which could have allowed for bias. Abstract did not explain why matched pair analysis was not carried out.*
Was the follow-up of patients complete?	*No*	*The follow up was not stated*

How precise (for example, in terms of confidence interval and p values) are the results?	*Not clear*	*Due to the multiple variables the analysis conducted was appropriate and would yield adjusted odds ratios per wound complication between the two groups.*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*		

Study name	***Hackney and McCoubrey 2017 – The effect of negative pressure dressings (PICO) on wound complications, readmission rates and length of stay***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Not clear*	*Not stated in the methods section of the abstract.*
Was the exposure accurately measured to minimise bias?	*Not clear*	*Wound complication outcome not clearly expressed in terms of what the complication meant, e.g SSI, dehiscence, delayed healing.*
Was the outcome accurately measured to minimise bias?	*Not clear*	*Outcome measures not defined.*
Have the authors identified all important confounding factors?	*Not clear*	*Baseline characteristics not reported*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Not clear*	*Not reported e.g. procedure types, wound classifications*
Was the follow-up of patients complete?	*Not clear*	*This was not stated in the abstract*

How precise (for example, in terms of confidence interval and p values) are the results?	*Not clear*	*This was not stated in the abstract*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*		

Study name	***Irwin et al 2018 - Negative pressure dressings significantly decrease rates of wound breakdown and may reduce implant loss rates in prepectoral breast reconstruction***	
Study question	***Response yes/no/not clear/N/A)***	***How is the question addressed in the study?***
Was the cohort recruited in an acceptable way?	*Yes*	*Eligible patients recruited from hospital database, which stored details of their breast implant-based reconstruction.*
Was the exposure accurately measured to minimise bias?	*Yes*	*ASA classification, weight and comorbidities were not significantly different between the two groups*
Was the outcome accurately measured to minimise bias?	*Yes*	*Both sets of patients underwent the same procedure, therefore their risk of developing the primary outcome measure (wound breakdown) was similar.*
Have the authors identified all important confounding factors?	*Yes*	*Both patient groups were similar in terms of baseline characteristics.*
Have the authors taken account of the confounding factors in the design and/or analysis?	*Not clear*	*The study did not explain why some patients received the PICO dressing and other received standard dressings.*
Was the follow-up of patients complete?	*No*	*The follow-up period was not stated in the abstract.*

How precise (for example, in terms of confidence interval and p values) are the results?	*Not clear*	*Confidence intervals were not stated. P values were stated from Fisher's exact test, which was an appropriate test to use within this sample.*
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence *12 questions to help you make sense of a cohort study*		

7.6 Results of the relevant studies

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

Table 14 Outcomes from published and unpublished studies

Published journal articles:

Study name		***Hyldig et al 2018 - Prophylactic incisional negative pressure wound therapy reduces the risk of surgical site infection after caesarean section in obese women: A pragmatic randomised clinical trial***
Size of study groups	***Treatment***	*432*
	Control	*444*
Study duration	***Time unit***	*38-39 months*
Type of analysis	***Intention-to - treat/per protocol***	*Intention-to-treat analysis*
Outcome 1	***Name***	*Primary outcome measure: Incidence of surgical site infection requiring antibiotics within 30 days post-surgery*
	Unit	*Number and % of patients*
Effect size	***Value***	*20/432 patients (4.6%, PICO) vs 41/444 (9.2%, SC); RR 0.50*
	95% CI	*0.30-0.84*
Statistical test	***Type***	*Not stated*
	p value	*P=0.007*
	Name	*Secondary outcome measure: Incidence of deep surgical site infection requiring surgery*

Other outcome	***Unit***	*Number and % of patients*
Effect size	***Value***	*8/432 (1.9%, PICO) vs 9/444 (2.0%, SC)*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*Not reported*
Other outcome	***Name***	*Secondary outcome measure: Presence of wound exudate within 30 days post-surgery*
	Unit	*Number and % of patients*
Effect size	***Value***	*92/410 (22.4%, PICO) vs 137/417 (32.9%, SC); RR 0.69*
	95% CI	*0.55-0.86*
Statistical test	***Type***	*Not reported*
	p value	*P=0.001*
Other outcome	***Name***	*Secondary outcome: minor wound dehiscence within 30 days post-surgery*
	Unit	*Number and % of patients*
Effect Size	***Value***	*62/410 (15.1%, PICO) vs 69/417 (16.6%, SC); RR 0.91*
	95% CI	*0.67-1.25*
Statistical test	***Type***	*Not reported*
	p value	*P=0.66*
Other outcome	***Name***	*Secondary outcome: endometritis within 30 days post-surgery*
	Unit	*Number and % of patients*
Effect size	***Value***	*8/410 (2.0%, PICO) vs 8/417 (1.9%, SC); RR 1.02*
	95% CI	*0.39-2.68*

Statistical test	***Type***	*Not reported*
	p value	*P=0.97*
Other Outcome	***Name***	*Secondary outcome: urinary tract infection within 30 days post-op*
	Unit	*Number and % of patients*
Effect Size	***Value***	*24/410 (5.9%, PICO) vs 17/417 (4.1%, SC); RR 1.44*
	95% CI	*0.78-2.63*
Statistical test	***Type***	*Not reported*
	p value	*P=0.25*
Other outcome	***Name***	*Secondary outcome: mastitis within 30 days post-surgery*
	Unit	*Number and % of patients*
Effect size	***Value***	*20/410 (4.9%, PICO) vs 17/417 (4.1%, SC); RR 1.20*
	95% CI	*0.64-2.25*
Statistical test	***Type***	*Not reported*
	p value	*P=0.58*
Comments		- *39 women (15 PICO and 24 SC) had pre-pregnancy BMI <30kg/m^2 and in 12 cases the NPWT dressing was removed earlier than scheduled due to malfunction.* - *6 women in the SC group were erroneously treated with NPWT dressings.* - *All were analysed as per randomisation.*

Study name		***Gillespie et al 2015 - Use of Negative-Pressure Wound Dressings to Prevent Surgical Site Complications After Primary Hip Arthroplasty: A Pilot RCT***
Size of study groups	***Treatment***	*35*
	Control	*35*
Study duration	***Time unit***	*15 months*

Type of analysis	***Intention-to-treat/per protocol***	*Intention-to-treat analysis*
Outcome 1	***Name***	*Primary outcome measure: SSI incidence*
	Unit	*Number and % of patients*
Effect size	***Value***	*PICO: 2 of 35 (5.7%), SC: 3 of 35 (8.6%); RR: 0.67*
	95% CI	*RR 0.1-3.7*
Statistical test	***Type***	*Chi squared, Mann-Whitney U test or t-test*
	p value	*P=0.65*
Other outcome	***Name***	*Primary outcome measure: SSI incidence by type (superficial, deep or organ/space)*
	Unit	*Number and % of patients*
Effect size	***Value***	***Superficial:*** *PICO: 1 of 35 (2.8%), SC: 3 of 35 (8.6%); RR 0.33* ***Deep:*** *none for either group* ***Organ/space:*** *PICO: 1 of 25 (2.8%), SC: 0 of 35 (0%); RR 3.0*
	95% CI	***Superficial:*** *RR 0.0-3.0,* ***Organ/space:*** *RR 0.1-71.2*
Statistical test	***Type***	*Chi squared, Mann-Whitney U test or t-test*
	p value	***Superficial:*** *p=0.33,* ***Organ/space:*** *p=0.50*
Other outcome	***Name***	*Secondary outcome: Individual SSI indicators (erythema, swelling, leakage, purulence) and any SSI indicator*
	Unit	*Number and % of patients*
Effect size	***Value***	***Erythema****: PICO: 1 of 35 (2.8%), SC: 1 of 35 (2.8%); RR: 1.0* ***Swelling****: PICO: 2 of 35 (5.7%), SC: 2 of 35 (5.7%); RR 1.0* ***Leakage****: PICO: 0 of 35 (0%), SC: 2 of 35 (5.7%); RR 0.2* ***Purulence****: PICO: 0 of 35 (0%), SC: 2 of 35 (5.7%); RR 0.2*

		***Any of the above**: PICO: 3 of 35 (8.6%), SC: 7 of 35 (20%); RR 0.43*
	95% CI	***Erythema:** RR 0.0-15.4, **Swelling:** RR 0.1-6.7, **Leakage:** RR 0.0-4.0, **Purulence:** RR 0.0-4.0, **All of the above:** RR 0.1-1.5*
Statistical test	***Type***	*Chi squared, Mann-Whitney U test or t-test*
	p value	***Erythema:** p=1.0, **Swelling:** p=1.0, **Leakage:** p=0.29, **Purulence:** p=0.29, **All of the above:** p=0.19*
Other outcome	***Name***	*Secondary outcome: individual wound complications (dehiscence, seroma, haematoma) and any wound complication*
	Unit	*Number and % of patients*
Effect size	***Value***	***Bruising:** PICO: 9 of 35 (25.7%), SC: 12 of 35 (34.3%); RR 0.75* ***Bleeding:** PICO: 8 of 35 (22.9%), SC: 1 of 35 (2.9%); RR 8.0* ***Haematoma:** PICO: 3 of 35 (8.6%), SC: 1 of 35 (2.9%); RR 3.0* ***Seroma:** PICO: 3 of 35 (8.6%), SC: 0 of 35 (0%); RR 7.0* ***Dehiscence:** PICO: 1 of 35 (2.9%), SC: 1 of 35 (2.9%); RR 1.0* ***All of the above:** PICO: 24 of 35 (68.5%), SC: 15 of 35 (42.8%); RR 2.3*
	95% CI	***Bruising:** RR 0.4-1.5, **Bleeding:** RR 1.0-60.3, **Haematoma:** RR 0.3-27.4, **Seroma:** RR 0.4-130.6, **Dehiscence:** RR 0.07-15.4 **All of the above:** RR 1.0-2.5*
Statistical test	***Type***	*Chi squared, Mann-Whitney U test or t-test*
	p value	***Bruising:** p=0.44* ***Bleeding:** p=0.04* ***Haematoma:** p=0.33* ***Seroma:** p=0.19* ***Dehiscence:** p=0.75* ***All of the above:** p=0.04*
	Name	*Secondary outcome: proportion of patients who had dressing replaced before/on day 5*

Other outcome	***Unit***	*Number and % of patients*
Effect Size	***Value***	*PICO: 35 of 35 (100%), SC: 15 of 35 (42.8%); RR 2.3*
	95% CI	*RR 1.6-3.3*
Statistical test	***Type***	*Chi squared, Mann-Whitney U test or t-test*
	p value	*P=0.0001*
Other outcome	***Name***	*Secondary outcome: hospital length of stay*
	Unit	*Days*
Effect size	***Value***	*PICO: 5.0 (3.0), SC: 6.0 (3.0) (median (IQR))*
	95% CI	*-*
Statistical test	***Type***	*Chi squared, Mann-Whitney U test or t-test*
	p value	*P=0.67*
Other outcome	***Name***	*Secondary outcome: readmissions >= 24 hrs*
	Unit	*Number and % of patients*
Effect size	***Value***	*PICO: 4 of 35 (11.4%), SC: 0 of 35 (0%); RR 9.0*
	95% CI	*RR 0.50-161.1*
Statistical test	***Type***	*Chi squared, Mann-Whitney U test or t-test*
	p value	*P=0.14*
Comments		- *Resource use was also mapped and showed that the total number of dressing changes during inpatient stay was (mean (SD)): 1.4 (0.91, PICO) vs 0.57 (1.0, SC), p=0.001, and the per-day cost in AU$ was: $38.40 ($13.6, PICO) vs $3.01 ($1.20, SC), p=0.0001.* - *Number of dressing changes on/before day 5 was measured as an outcome, but this was unrelated to soiling/condition of dressing as protocol required NPWT dressings to be changed on day 5.*

Study name		***Karlakki et al 2016 - Incisional negative pressure wound therapy dressings (iNPWTd) in routine primary hip and knee arthroplasties: a randomised controlled trial***
Size of study groups	***Treatment***	*Intention-to-treat (ITT): 110, Per-protocol (PP):102*
	Control	*ITT: 110, PP: 107*
Study duration	***Time unit***	*13 months*
Type of analysis	***Intention-to -treat/per protocol***	*Both analyses were performed*
Outcome 1	***Name***	*Primary outcome measure: Length of stay*
	Unit	*Days*
Effect size	***Value***	***ITT and PP:*** *PICO – mean 3.8, standard of care (SC) – mean 4.7*
	95% CI	***ITT:*** *PICO – 3.5-4.2, SC – 3.8-6.4,* ***PP:*** *PICO 3.5-4.3, SC – 3.8-6.4*
Statistical test	***Type***	*Zhou and Dinh's method T3*
	p value	***ITT:*** *p=0.07,* ***PP:*** *p=0.09*
Other outcome	***Name***	*Primary outcome measure: Length of stay (extreme outliers)*
	Unit	*Days*
Effect size	***Value***	*PICO range: 1-10 days, SC range: 2-61 days*
	95% CI	*Not reported*
Statistical test	***Type***	*Moses test*
	p value	*P=0.003*
Other outcome	***Name***	*Primary outcome measure: delayed wound healing*
	Unit	*Number of patients*

Effect size	***Value***	*1/102 (PICO) vs 3/107 (SC)*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*Not reported*
Other outcome	***Name***	*Primary outcome measure: Level of exudate*
	Unit	*Peak level exudate: 0 (none) to 4 (overt)*
Effect size	***Value***	*PICO: 0: 50 of 102 patients (49%); 1: 39 of 102 patients (38%); 2: 8 of 102 patients (8%); 3: 1 of 102 patients (1%); 4: 4 of 102 patients (4%)* *SC: 0: 51 of 107 patients (48%); 1: 25 of 107 patients (23%); 2: 10 of 107 patients (9%); 3: 4 of 107 patients (4%); 4: 17 of 107 patients (16%)*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's exact test*
	p value	*P=0.007*
Other outcome	***Name***	*Secondary outcome: Number of dressing changes*
	Unit	*Number of dressings*
Effect size	***Value***	*PICO: 2.5, SC: 4.2 (mean)*
	95% CI	*PICO: 2.2-2.8, SC: 3.6-5.2*
Statistical test	***Type***	*Not reported*
	p value	*P=0.002*
Comments		- *Prolonged exudate: 2/102 (PICO) vs 3/107 (SC); SSI: 1/102 (PICO) vs 6/107 (SC) – no statistical analysis reported.* - *Cost effectiveness was not fully explored, but authors commented that with reduced LOS, wound complications, dressing changes (nursing time), and potential cost savings*

	in the community the additional cost of the pump compared to traditional dressings seems justifiable. - *Haematoma was reported in 1 patient of 107 in the control group.*

Study name		***Uchino et al 2016 - Randomised Controlled Trial of Prophylactic Negative-Pressure Wound Therapy at Ostomy Closure for the Prevention of Delayed Wound Healing and Surgical Site Infection in Patients with Ulcerative Colitis***
Size of study groups	***Treatment***	*28*
	Control	*31*
Study duration	***Time unit***	*November 2014 - September 2015 (10 months)*
Type of analysis	***Intention-to -treat/per protocol***	*Per protocol analysis was carried out on the primary outcome mean duration of complete wound healing. Intention-to-treat analysis was carried out on all other outcomes.*
Outcome 1	***Name***	*Primary outcome measure: Mean duration of complete wound healing*
	Unit	*Days*
Effect size	***Value***	*33.5±10.0 (purse-string suture (PSS)+PICO), 37.6± 11.7 (PSS alone)*
	95% CI	*Not reported*
Statistical test	***Type***	*Mann-Whitney U test*
	p value	*0.18*
Other Outcome	***Name***	*Primary outcome measure: Incisional SSI*
	Unit	*Number and % of patients*
Effect size	***Value***	*n=3 (10.7%) (PSS+PICO), n=1 (3.2%) (PSS alone)*
	95% CI	*Not reported*
Statistical test	***Type***	*Chi squared test with Yates' correction or Fisher's exact test were used*
	p value	*0.76*

Other Outcome	***Name***	*Primary outcome measure: Wound bleeding*
	Unit	*Number and % of patients*
Effect size	***Value***	*n=0 (0%) (PSS+PICO), n=0 (0%) (PSS alone)*
	95% CI	*Not reported*
Statistical test	***Type***	*Chi squared test with Yates' correction or Fisher's exact test were used*
	p value	*Not estimable*
Other Outcome	***Name***	*Secondary outcome measure: Duration of surgery*
	Unit	*Minutes*
Effect size	***Value***	*91.6±32.9 (PSS+PICO), 90.5±28.3 (PSS alone)*
	95% CI	*Not reported*
Statistical test	***Type***	*Mann Whitney U test*
	p value	*0.89*
Other Outcome	***Name***	*Secondary outcome measure: Amount of blood loss*
	Unit	*mL*
Effect size	***Value***	*42.0±69.9 (PSS+PICO), 28.0±36.5 (PSS alone)*
	95% CI	*Not reported*
Statistical test	***Type***	*Mann Whitney U test*
	p value	*0.33*
Comments		*Patients with Surgical Site Infection (SSI) during follow-up periods were excluded from prophylactic NPWT and from comparison of wound-healing duration as NPWT was terminated after SSI diagnosis*

Study name		***O'Leary et al 2016 - Prophylactic Negative Pressure Dressing Use in Closed Laparotomy Wounds Following Abdominal Operations***
Size of study groups	***Treatment***	*24*
	Control	*25*
Study duration	***Time unit***	*38 months*
Type of analysis	***Intention-to - treat/per protocol***	*Per protocol, SSI incidence was also reported as ITT*
Outcome 1	***Name***	*SSI incidence at 30 days post-operative*
	Unit	*Patient number (%)*
Effect size	***Value***	*PP: 2 (8.3%, PICO), 8 (32%, standard)* *ITT: 12% (PICO), 32% (standard)*
	95% CI	*Not reported*
Statistical test	***Type***	*Chi-squared test if the number of observations were >5 and Fisher exact test if the number of observations were ≤5.*
	p value	*PP: 0.043 (1-sided), 0.074 (2-sided)* *ITT: 0.073 (1-sided), 0.095 (2-sided)*
Other outcome	***Name***	*Length of stay*
	Unit	*Mean and median days*
Effect size	***Value***	*Mean: 6.1 (PICO), 14.7 (standard)* *Median: 6 (PICO), 7 (standard)*
	95% CI	*Not reported*
Statistical test	***Type***	*Chi-squared test if the number of observations were >5 and Fisher exact test if the number of observations were ≤5.*
	p value	*Mean: 0.019 (2-sided)* *Median: 0.178 (2-sided)*
Other outcome	***Name***	*Visual Analogue Scale*

	Unit	*Score*
Effect size	***Value***	*65 (PICO), 61 (standard)*
	95% CI	*Not reported*
Statistical test	***Type***	*Continuous variables were analysed using a Student t test for parametric data and Mann-Whitney U test for nonparametric data.*
	P value	*0.74 (2-sided)*
Other outcome	***Name***	*POSAS wound score*
	Unit	*Score*
Effect size	***Value***	*32.6 (PICO), 31.7 (standard)*
	95% CI	*Not reported*
Statistical analysis	***Type***	*Continuous variables were analysed using a Student t test for parametric data and Mann-Whitney U test for nonparametric data.*
	P value	*0.89 (2-sided)*
Comments		

Study name		***Chaboyer et al 2014 – Negative pressure wound therapy on surgical site infections in women undergoing elective caesarean sections: a pilot RCT***
Size of study groups	***Treatment***	*46*
	Control	*46*
Study duration	***Time unit***	*Daily in hospital and 4 weeks post discharge assessment*
Type of analysis	***Intention-to - treat/per protocol***	*Per protocol*
Outcome 1	***Name***	***Primary outcome measure: SSI***
	Unit	*Number and % of patients* *PICO 10/44 (22.7%)*

		SC 12/43 (27.9%)
Effect size	***RR***	*0.81*
	95% CI	*0.39-1.68*
	p value	*p=0.579*
Outcome 1(a)	***Name***	***Superficial infection*** *PICO 5/44 (11.4%)* *SC 7/43 (16.3%)*
Effect size	***RR***	*0.70*
	95% CI	*0.24-2.03*
	p value	*p=0.509*
Outcome 1(b)	***Name***	***Deep infection*** *PICO 4/44 (9.1%)* *SC 4/43 (9.3%)*
Effect size	***RR***	*0.98*
	95% CI	*0.26-3.66*
	p value	*p=0.972*
Outcome 1(c)	***Name***	***Organ/space infection*** *PICO 1/44 (2.3%)* *SC 1/43 (2.3%)*
Effect size	***RR***	*0.98*
	95% CI	*0.06-15.13*

	p value	*p=0.987*
Outcome 2	***Name***	***Readmission*** *PICO 1/44 (2.3%)* *SC 1/43 (2.3%)*
Effect size	***RR***	*-*
	95% CI	*-*
	p value	*p=0.987*
Outcome 3	***Name***	***Length of stay median (interquartile range)*** *PICO 3.0 (1.0)* *SC 3.0 (1.0)*
	p-value	*p= 0.724*
Other outcomes		***Type of wound complication (PICO vs SC)*** *Bleeding 2.3% vs 2.3% p=0.987* *Bruising 2.3% vs 9.3% p=0.199* *Other 9.1% vs 2.3% p=0.214* *Readmission 2.3% vs 2.3% p=0.987*
Comments		

Study name		***Hickson et al 2015 – A journey to zero: reduction of post-operative caesarean surgical site infections over a five-year period***
Size of study groups	***Treatment***	*964*
	Control	*984*

Study duration	***Time unit***	*6 weeks*
Type of analysis	***Intention-to - treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*SSI*
	Unit	*Surgical wounds*
Effect size	***Value***	*2011 (before PICO introduction): 6/984* *2012 (after PICO introduction): 1/964*
Secondary outcomes	***Costs***	*2007 low risk patients: $32.94. High risk patients with tNPWT $348.62 for 3 days.* *Post 2011: low risk: $42.69 and $245.30 for 7 days with sNPWT savings of $103.32 per patient.*
Comments		

Study name		***Nordmeyer et al 2016 - Negative pressure wound therapy for seroma prevention and surgical incision treatment in spinal fracture care***
Size of study groups	***Treatment***	*10*
	Control	*10*
Study duration	***Time unit***	*Not stated*
Type of analysis	***Intention-to - treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Wound secretion in Redon® drain canisters after 2 days*
	Unit	*mL*
Effect size	***Value***	*PICO: 454·0±229·6mL, SC: 621·5±286·5mL*

	95% CI	*Not reported*
Statistical test	***Type***	*Statistical t-test or Mann-Whitney test (statistical test not reported)*
	p value	*P=0.16*
Other outcome	***Name***	*Seroma volume underneath surgical wound (Day 5)*
	Unit	*mL*
Effect size	***Value***	*PICO: 0±0mL, SC: 1·9±2·7mL*
	95% CI	*Not reported*
Statistical test	***Type***	*Statistical t-test or Mann-Whitney test (statistical test not reported)*
	p value	*P=0.0007*
Other outcome	***Name***	*Seroma volume underneath surgical wound (Day 10)*
	Unit	*mL*
Effect size	***Value***	*PICO: 0.5±1.0mL, SC: 1·6±2·6mL*
	95% CI	*Not reported*
Statistical test	***Type***	*Statistical t-test or Mann-Whitney test (statistical test not reported)*
	p value	*P=0.024*
Other outcome	***Name***	*Dressing changes*
	Unit	*Number of dressing and Number per patient*
Effect size	***Value***	*PICO: 48 (4.8 per patient)* *SC: 79 (7.9 per patient)*
	95% CI	*Not reported*
Statistical test	***Type***	*Statistical t-test or Mann-Whitney test (statistical test not reported)*
	p value	*P=0.0007*
Other outcome	***Name***	*Wound secretion time*
	Unit	*Days*
Effect size	***Value***	*Shown in graph within paper (Figure 2); lower wound secretion time with PICO*
	95% CI	*Not reported*

Statistical test	***Type***	*Statistical t-test or Mann-Whitney test (statistical test not reported)*
	P value	*P=0.0055*
Other outcome	***Name***	*Wound care time*
	Units	*Minutes*
Effect size	***Value***	*Shown in graph within paper (Figure 3); lower wound care time with PICO*
	95% CI	*Not reported*
Statistical test	***Type***	*Statistical t-test or Mann-Whitney test (statistical test not reported)*
	P value	*P=0.0005*
Other outcome	***Name***	*Gloves used for dressing changes*
	Units	*Number of gloves*
Effect size	***Value***	*Shown in graph within paper (Figure 4); lower number of gloves used for dressing changes with PICO*
	95% CI	*Not reported*
Statistical test	***Type***	*Statistical t-test or Mann-Whitney test (statistical test not reported)*
	P value	*P=0.0006*
Other outcome	***Name***	*Compresses used for dressing changes*
	Units	*Number of compresses*
Effect size	***Value***	*Shown in graph within paper (Figure 5); lower compresses used for dressing changes with PICO*
	95% CI	*Not reported*
Statistical test	***Type***	*Statistical t-test or Mann-Whitney test (statistical test not reported)*
	P value	*P<0.0001*

Study name		***Matsumoto and Parekh 2015 - Use of Negative Pressure Wound Therapy on Closed Surgical Incision After Total Ankle Arthroplasty***
Size of study groups	***Treatment***	*37*
	Control	*37*
Study duration	***Time unit***	*Patients visited the clinic 4 weeks after the discharge, and every 4 weeks thereafter if they presented with complications*
Type of analysis	***Intention-to-treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Wound healing problem in the treatment group vs. the control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*1 (2.7%) vs. 9 (24.3%), respectively*
	95% CI	*Not reported*
Statistical test	***Type***	*Chi-squared test or Fisher exact test, not specified*
	p value	*0.014*
Other outcome	***Name***	*Total surgical site infections in the treatment group vs. the control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*1 (3%) vs. 3 (8%), respectively*
	95% CI	*Not reported*
Statistical test	***Type***	*Chi-squared test or Fisher exact test, not specified*
	p value	*0.615*
Other outcome	***Name***	*Superficial surgical site infections in the treatment group vs. the control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*0 (0%) vs. 2 (5%), respectively*
	95% CI	*Not reported*
Statistical test	***Type***	*Chi-squared test or Fisher exact test, not specified*

	p value	*0.493*
Other outcome	***Name***	*Deep surgical site infections in the treatment group vs. the control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*1 (3%) vs. 1 (3%), respectively*
	95% CI	*Not reported*
Statistical analysis	***Type***	*Chi-squared test or Fisher exact test, not specified*
	P value	*> 0.999*
Comments		

Study name:		***Dingemans et al 2018 - Prophylactic negative pressure wound therapy after lower extremity fracture surgery: a pilot study***
Size of study groups	***Treatment***	*PICO = 47*
	Control	*Convention surgical dressing = 47*
Study duration	***Time unit***	*10 months*
Type of analysis	***Intention-to - treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*SSI within 30 days as classified by the CDC classification*
	Unit	*Number of patients*
Effect size	***Value***	*PICO 2/47 (4.3%) vs comparator 7/47 (14.9%)*
	95% CI	*Not reported*
Statistical test	***Type***	*McNemars test*
	p value	*0.29*
Other outcome	***Name***	*Incidence of superficial SSI*
	Unit	*Number of patients*
Effect size	***Value***	*PICO 0/47 (0%) vs comparator 4/47 (8.5%)*

	95% CI	*Not reported*
Statistical test	***Type***	*McNemars test*
	p value	*0.08*
Other outcome	***Name***	*Incidence of deep SSI*
	Unit	*Number of patients*
Effect size	***Value***	*PICO 2/47 (4.3%) vs comparator 3/47 (6.4%)*
	95% CI	*Not reported*
Statistical test	***Type***	*McNemars test*
	p value	*0.99*
Comments		

Study name		***Hester et al 2015 - Is Single Use Portable Incisional Negative Pressure Wound Therapy System Suitable for Revision Arthroplasty?***
Size of study groups	***Treatment***	*18*
	Control	*18*
Study duration	***Time unit***	*12 months*
Type of analysis	***Intention-to - treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Number of wound complications in the treatment vs. control group*
	Unit	*Number of patients*
Effect size	***Value***	*1 hip patient (PICO) vs. 1 hip and 2 knees patients (control)*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*0.14*
Comments		*Authors reported that neither group experienced any dressing related complications, such as blistering, maceration, or skin tearing.*

Study name		***Adogwa et al 2014 – Negative pressure wound therapy reduces incidence of postoperative wound infection and dehiscence after long-segment thoracolumbar spinal fusion: a single institutional experience***
Size of study groups	***Treatment***	*46*
	Control	*114*
Study duration	***Time unit***	*6 year period - outcomes were measured during hospitalisation or 30 days post discharge*
Type of analysis	***Intention-to -treat/per protocol***	*Per protocol* *Outcomes were presented as numbers and percentages in brackets*
Outcome 1	***Name***	***SSI***
	Result	*PICO 5 (10.63)* *SC 17 (14.91)* *p-value 0.04*
Outcome 2	***Name***	***Dehiscence***
	Result	*PICO 3 (6.38)* *SC 14 (12.28)* *p-value 0.02*
Outcome 3	***Name***	***Return to operating room***
	Result	*PICO 6 (12.76)* *SC 12 (10.52)* *p-value 0.07*
Outcome 4	***Name***	***30-day readmission rate***
	Result	*PICO 9 (19.14)*

		SC 21 (18.42) *p-value 0.48*
Outcome 5	***Name***	***Pneumonia***
	Result	*PICO 0 (0.00)* *SC 3 (2.63)* *p-value 0.08*
Outcome 6	***Name***	***Urinary tract infection***
	Result	*PICO 10 (21.27)* *SC 20 (17.54)* *p-value 0.74*
Outcome 7	***Name***	***Cerebrospinal fluid leak***
	Result	*PICO 4 (8.51)* *SC 4 (3.51)* *p-value 0.27*
Outcome 8	***Name***	***Durotomy***
	Result	*PICO 6 (12.76)* *SC 22 (19.29)* *p-value 0.28*
Outcome 9	***Name***	***Spinal cord/nerve root injury***
	Result	*PICO 1 (2.12)* *SC 2 (1.75)* *p-value 0.88*
Comments		

Study name		***Selvaggi et al 2014 - New Advances in Negative Pressure Wound Therapy (NPWT) for Surgical Wounds of Patients Affected with Crohn's Disease***
Size of study groups	***Treatment***	*25*
	Control	*25*
Study duration	***Time unit***	*36 months*
Type of analysis	***Intention-to -treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Primary outcome measure: Effect of incisional NPWT on SSC rates*
	Unit	*Number of SSC*
Effect size	***Value***	*OR 0.21*
	95% CI	*0.15-0.5*
Statistical test	***Type***	*Multivariate analysis*
	p value	*P=0.001*
Outcome 1	***Name***	*Primary outcome measure: Infectious SSC incidence*
	Unit	*Number and % of patients*
Effect size	***Value***	*PICO: 2 of 25 (8%), SC: 12 of 25 (48%)*
	95% CI	*Not reported*
Statistical test	***Type***	*2-tailed Fisher's exact test or Chi-squared*
	p value	*P=0.004*
Other outcome	***Name***	*Primary outcome measure: Seroma*
	Unit	*Number and % of patients*
Effect size	***Value***	*PICO: 2 of 25 (8%), SC: 11 of 25 (44%)*
	95% CI	*Not reported*

Statistical test	***Type***	*2-tailed Fisher's exact test or Chi-squared*
	p value	*P=0.008*
Other outcome	***Name***	*Primary outcome measure: Readmission rates within 6 months for wound complications*
	Unit	*Number and % of patients*
Effect size	***Value***	*PICO: 0 of 25 (0%), SC: 6 of 25 (24%)*
	95% CI	*Not reported*
Statistical test	***Type***	*2-tailed Fisher's exact test or Chi-squared*
	p value	*P=0.02*
Other outcome	***Name***	*Secondary outcome: management of device*
	Unit	*Number and % of patients*
Effect size	***Value***	*Imperfect seal: 1 of 25 (4%)* *Disconnected tubing: 1 of 25 (4%)*
	95% CI	*NA*
Statistical test	***Type***	*NA*
	p value	*NA*
Comments		- *Both issues with device management were resolved at home by the patient* - *A link between corticosteroid use and increased risk of SSC was found by multivariate analysis (OR 1.95 (1.12-4.33), p=0.02). A subanalysis of this patient population revealed a decreased risk of SSC in the PICO group (1 in 13 vs 9 in 12 patients, p=0.001).* - *Length of stay was significantly longer in control group: 7 +/- 2 days vs 12 +/- 2 days, p=0.0001.*

Study name	***Pellino et al 2014a - Preventive NPWT over closed incisions in general surgery: Does age matter?***

Size of study groups	***Treatment***	*25 (10 patients >65 years)*
	Control	*25 (10 patients >65 years)*
Study duration	***Time unit***	*21 months*
Type of analysis	***Intention-to -treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Primary outcome measure: Infectious surgical site event incidence*
	Unit	*Number and % of patients*
Effect size	***Value***	*Breast: PICO: 2 of 25 (8%), SC: 9 of 25 (36%); Colorectal: PICO: 2 of 25 (8%), SC: 11 of 25 (44%)*
	95% CI	*Not reported*
Statistical test	***Type***	*2-tailed Fisher's exact or Chi-squared*
	p value	*Breast: P=0.04* *Colorectal: P=0.008*
Other outcome	***Name***	*Secondary outcome measure: Infectious SSE incidence in patients aged >65 years*
	Unit	*Number and % of patients*
Effect size	***Value***	*Breast: PICO: 0 of 10 (0%), SC: 5 of 10 (50%); Colorectal: PICO: 0 of 10 (0%), SC: 6 of 10 (60%)*
	95% CI	*Not reported*
Statistical test	***Type***	*2-tailed Fisher's exact or Chi-squared*
	p value	*Breast: P=0.003* *Colorectal: P=0.003*
Other outcome	***Name***	*Secondary outcome: Seroma incidence*
	Unit	*Number and % of patients*
Effect size	***Value***	*Breast: PICO: 1 of 25 (4%), SC: 5 of 25 (20%); Colorectal: PICO: 2 of 25 (8%), SC: 10 of 25 (40%)*

	95% CI	*Not reported*
Statistical test	***Type***	*2-tailed Fisher's exact or Chi-squared*
	p value	*Breast: P=0.1* *Colorectal: P=0.02*
Other outcome	***Name***	*Secondary outcome: Seroma incidence in patients aged >65 years*
	Unit	*Number and % of patients*
Effect size	***Value***	*Breast: PICO: 0 of 10 (0%), SC: 4 of 10 (40%); Colorectal: PICO: 1 of 10 (10%), SC: 4 of 10 (40%)*
	95% CI	*Not reported*
Statistical test	***Type***	*2-tailed Fisher's exact or Chi-squared*
	p value	*Breast: P=0.09* *Colorectal: P=0.3*
Other outcome	***Name***	*Secondary outcome: Outcome differences between breast and abdominal patients – Hospital length of stay (only significantly different outcome)*
	Unit	*Days (mean +/- SD)*
Effect Size	***Value***	*Breast: PICO: 2 +/- 1.2, SC: 2 +/- 0.5; Colorectal: PICO: 7.1 +/- 2.1, SC: 12 +/- 3.5*
	95% CI	*Not reported*
Statistical test	***Type***	*Mann-Whitney U test*
	p value	*P<0.0001*
Comments		- *Hospital stay in PICO vs SC in colorectal patients also differed significantly: p=0.001* - *There were no deaths in any group* - *Global ASEPSIS scores differed significantly between PICO and SC groups in both cohorts:* ***Breast:*** *PICO: 12 +/- 3.2 vs SC: 18.2 +/- 5.1, p=0.03.* ***Colorectal:*** *PICO: 14.6 +/- 4.7 vs SC: 25.3 +/- 3.3, p=0.01.*

Study name		***Pellino et al 2014b - Effects of a new pocket device for negative pressure wound therapy on surgical wound so patients affected with Crohn's disease: a pilot trial***
Size of study groups	***Treatment***	*PICO = 13*
	Control	*Conventional gauze = 17*
Study duration	***Time unit***	*1 year and 10 months*
Type of analysis	***Intention-to - treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Incidence of SSI and wound related complications in patients affected with stricturing Crohn's disease undergoing bowel resection or strictureplasty*
	Unit	*Number of patients*
Effect size	***Value***	*PICO: 1 out of 13* *Standard of care (SC): 8 out of 17*
	95% CI	*Not reported*
Statistical test	***Type***	*Chi-squared test*
	p value	*0.0417*
Other outcome	***Name***	*Operative time*
	Unit	*Minutes*
Effect size	***Value***	*PICO 133.5±49 versus SC 145.7±61.1*
	95% CI	*Not stated*
Statistical test	***Type***	*Mann-Whitney test*
	p value	*0.5*
	Name	*Length of stay*

Other outcome	***Unit***	*Days*
Effect size	***Value***	*PICO 7.5±1.8 versus SC 10.3±1.6*
	95% CI	*Not stated*
Statistical test	***Type***	*Mann-Whitney test*
	p value	*0.0007*
Other outcome	***Name***	*Major complications*
	Unit	*Number of complications in number of patients*
Effect size	***Value***	*PICO 3 complications in 3 patients versus SC 7 complications in 6 patients*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*>0.99*
Other outcome	***Name***	*Minor complications*
	Unit	*Number of complications in number of patients*
Effect size	***Value***	*PICO 3 complications in 2 patients versus SC 3 complications in 3 patients*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*>0.99*
Other outcome	***Name***	*Seroma*
	Unit	*Number of complications*
Effect size	***Value***	*PICO 1 versus SC 8*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*0.041*
	Name	*Superficial SSI*

Other outcome	***Unit***	*Number of complications*
Effect size	***Value***	*PICO 1 versus SC 4*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*>0.99*
Other outcome	***Name***	*Deep SSI*
	Unit	*Number of complications*
Effect size	***Value***	*PICO 0 versus SC 3*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*>0.99*
Other outcome	***Name***	*Organ/space SSI*
	Unit	*Number of complications*
Effect size	***Value***	*PICO 0 versus SC 1*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*>0.99*
Other outcome	***Name***	*Cosmetic results*
	Unit	*POSAS and VAS score*
Effect size	***Value***	*Not stated*
	95% CI	*Not stated*
Statistical test	***Type***	*2-tailed Fisher's exact test or X^2 test*
	p value	*>0.05*
Comments		

Study name		***van der Valk et al 2017 - Incisional Negative-Pressure Wound Therapy for Perineal Wounds After Abdominoperineal Resection for Rectal Cancer, a Pilot Study***
Size of study groups	***Treatment***	*10*
	Control	*10*
Study duration	***Time unit***	*January 1st to December 31st 2015*
Type of analysis	***Intention-to -treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Incidence of wound complications*
	Unit	*Number of patients*
Effect size	***Value***	*7/10 (70 %) PICO; 6/10 (60 %)* Control* **Table 2 of paper states 40 % of patients but calculations suggest this is a typo.*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*Not reported*
Other Outcome	***Name***	*Diagnosis of wound infections*
	Unit	*Number of days*
Effect size	***Value***	*PICO = median of 11.5 days after surgery* *(mean =12.6 days, range 5–21 days).* *Control = median 10.5 days after surgery* *(mean = 10 days, range 5–14 days).*
	95% CI	*Not reported*
Statistical test	***Type***	*Krustal-Wallis test*
	p value	*p=0.94*
	Name	*Wound Complication Severity Score*

Other Outcome	***Unit***	*Clavien–Dindo classification (CD)* *(% of patients)*
Effect size	***Value***	*PICO = 100 % CD-grade 1* *Control = 83.3 % CD-grade 1 & 16.7 % CD-grade 3B*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*Not reported*
Other outcome	***Name***	*Time to wound healing*
	Unit	*Weeks*
Effect size	***Value***	*PICO = 8.5 (mean 10.4, range 0-34)* *Control = 13 (mean 11.4, range 0-24)*
	95% CI	*Not reported*
Statistical test	***Type***	*Krustal-Wallis test*
	p value	*0.87*
Comments		

Study name		***Svensson-Bjork et al 2018 - Evaluation of inguinal vascular surgical scars treated with closed incisional negative pressure wound therapy using three-dimensional digital imaging—A randomised controlled trial on bilateral incisions***
Size of study groups	***Treatment***	*34*
	Control	*34*
Study duration	***Time unit***	*27 months*

Type of analysis	***Intention-to-treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Total Stony Brook Scar Evaluation Scale (SBSES)*
	Unit	*Median score (range)*
Effect size	***Value***	*4 (1-5, PICO), 4 (1-5, standard)*
	95% CI	*Not reported*
Statistical test	***Type***	*Wilcoxon signed-rank test*
	p value	*0.86*
Other outcome	***Name***	*Overall appearance on 10-point graded numeric ranking scale (NRS10)*
	Unit	*Median score (range)*
Effect size	***Value***	*9 (4-10, PICO), 9 (3-10, standard)*
	95% CI	*Not reported*
Statistical test	***Type***	*Wilcoxon signed-rank test*
	p value	*0.80*
Other outcome	***Name***	*Vascularity according to Vancouver Scar Scale (VSS) total score*
	Unit	*Median score (range)*
Effect size	***Value***	*0 (0-2, PICO), 0 (0-3, standard)*
	95% CI	*Not reported*
Statistical test	***Type***	*Wilcoxon signed-rank test*
	P value	*0.79*
Other outcome	***Name***	*Pigmentation according to Vancouver Scar Scale (VSS) total score*
	Unit	*Median score (range)*
Effect size	***Value***	*0 (0-2, PICO), 0 (0-2, standard)*
	95% CI	*Not reported*
	Type	*Wilcoxon signed-rank test*

Statistical analysis	***P value***	*1.0*
Other outcome	***Name***	*Patient Scar Assessment Score (PSAS) total*
	Unit	*Median score (range)*
Effect size	***Value***	*7 (7-29, PICO), 7 (7-51, standard)*
	95% CI	*Not reported*
Statistical analysis	***Type***	*Wilcoxon signed-rank test*
	P value	*0.13*
Comments		

Study name		***Witt-Majchrak et al 2014 - Preliminary outcome of treatment of post-operative primarily closed sternotomy wounds treated using negative pressure wound therapy***
Size of study groups	***Treatment***	*40*
	Control	*40*
Study duration	***Time unit***	*6 weeks*
Type of analysis	***Intention-to -treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Wound healing without complications*
	Unit	*Number of healed wounds*
Effect size	***Value***	*PICO 37/40 vs SC 30/40* *OR 0.24*
	95% CI	*0.06 to 0.96*
	Type	*Calculated in RevMan*

Statistical test	***p value***	*p=0.04*
Other outcome	***Name***	*SSIs*
	Unit	*Number of patients with SSIs*
Effect size	***Value***	*PICO 1/40 vs SC 7/40*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*Not reported*
Other outcome	***Name***	*Superficial wound infections treated only with antibiotics*
	Result	*PICO 0/40* *SC 4/40*
	p-value	*0.0254*
Other outcome	***Name***	*Superficial wound infections that required wound opening*
	Result	*PICO 1/40* *SC 3/40*
Effect size	***p-value***	*0.3049*
Other Outcome	***Name***	*Sternal instability*
	Result	*PICO 1/40* *SC 1/40*
Effect Size	***p-value***	*1*
Other outcome	***Name***	*Sterile dehiscence of wound margins following suture removal*
	Result	*PICO 1/40*

		SC 1/40
	p-value	*1*
Other outcome	***Value***	*Healing abnormalities resulting from wound ischemia*
	Result	*PICO 0/40* *SC 1/40*
	p-value	*0.3204*
Other outcome	***Name***	*Wounds with secondary suturing*
	Result	*PICO 2/40* *SC 5/40*
	p-value	*0.2490*
Statistical test	***Type***	*Sternal refixation*
	Result	*PICO 1/40* *SC 0/40*
	p value	*0.3081*
Other outcome	***Name***	***Secondary outcomes**: surgical time in minutes p=0.6339, anastomoses p=0.6476, catecholamines p=0.5388, intraoperative loss p=1, post-operative drainage p=0.8062, blood product transfusion p=0.4912, reoperation p=1, infection other than SSI p=0.6924* *No deep infections were recorded*
	Unit	
Comments		

Study name		***Tanaydin et al 2018 - Randomised Controlled Study Comparing Disposable Negative Pressure Wound Therapy with Standard Care in Bilateral Breast Reduction Mammoplasty Evaluating Surgical Site Complications and Scar Quality***
Size of study groups	***Treatment***	*32*
	Control	*32*

Study duration	***Time unit***	*22 months*
Type of analysis	***Intention-to-treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Primary outcome measure: Incidence of surgical site complications within 21 days post-surgery*
	Unit	*Number of patients*
Effect size	***Value***	*Not specified, but total number of wound complications was significantly lower for the NPWT-treated breasts*
	95% CI	*Not specified*
Statistical test	***Type***	*Not specified*
	p value	*P=0.004*
Other outcome	***Name***	*Primary outcome measure: Incidence of superficial dehiscence within 21 days post-surgery*
	Unit	*Number of patients*
Effect size	***Value***	*Not specified, but there was significantly less dehiscence for the breasts treated with NPWT*
	95% CI	*Not specified*
Statistical test	***Type***	*Not specified*
	p value	*P<0.001*
Other outcome	***Name***	*Secondary outcome: POSAS scores (both Patient score and Observer score)*
	Unit	*Within patient difference (NPWT – Standard Care)*
	Value	*Presented graphically in Figure 3 of the paper*

Effect Size	***95% CI***	*Presented graphically in Figure 3 of the paper*
Statistical test	***Type***	*Paired t-test (parametric) or Wilcoxon signed-rank test (non-parametric)*
	p value	*Day 42 and 90: p<0.05, Day 180 and 365: p>0.05*
Other outcome	***Name***	*Secondary outcome: VAS score*
	Unit	*Within patient difference (NPWT – Standard Care)*
Effect size	***Value***	*Presented graphically in Figure 4 of the paper*
	95% CI	*Presented graphically in Figure 4 of the paper*
Statistical test	***Type***	*Paired t-test (parametric) or Wilcoxon signed-rank test (non-parametric)*
	p value	*Total VAS score: Day 42, 90 and 180: p<0.05. Day 365: p>0.05. Global VAS score: Day 42 and 90: p<0.05. Day 180 and 365: p>0.05. ("Total VAS" and "Global VAS" not explained in text).*
Other Outcome	***Name***	*Secondary outcome: skin viscoelasticity*
	Unit	*Within patient difference (NPWT – Standard Care) in cutometer values*
Effect Size	***Value***	*Presented graphically in Figure 5 of the paper*
	95% CI	*Presented graphically in Figure 5 of the paper*
Statistical test	***Type***	*Not specified*
	p value	*Day 42: p<0.05. Day 90, 180 and 365: p>0.05.*
Other outcome	***Name***	*Secondary outcome: Transepidermal water loss (TEWL)*
	Unit	*Within patient difference (NPWT – Standard Care), g/h/m2*
Effect size	***Value***	*Presented graphically in Figure 6 of the paper*
	95% CI	*Presented graphically in Figure 6 of the paper*
Statistical test	***Type***	*Not specified*
	p value	*Day 42, 90 and 365: p>0.05. Day 180: p<0.05.*

Other outcome	***Name***	*Secondary outcome: Skin hydration*
	Unit	*Within patient difference (NPWT – Standard Care), arbitrary units*
Effect size	***Value***	*Presented graphically in paper*
	95% CI	*Presented graphically in paper*
Statistical test	***Type***	*Not specified*
	p value	*Day 42, 90, 180, 365: p>0.05*
Comments		*- Power calculations were performed post-hoc and showed that the study size was sufficiently powered (>80%) to accurately predict differences between NPWT and SC for POSAS and VAS scores at days 42 and 90. At days 180 and 365 a larger study population would be required.* *- Number of sites which experienced dehiscence within 7 days was detailed and difference between treatment groups was reported as p<0.001. Number of sites which experienced other surgical site complications within 21 days was not detailed, but significance of difference between treatment groups was given as p<0.004.* *- Of the five patients who had bilateral wound dehiscence, 2 (40%) experienced faster healing on the NPWT side (no further details given).* *- A correction has been issued for this study to change the significance level of the POSAS scores at 180 days from p<0.05 to not significant, reported in the abstract.*

Study name		***Galiano et al 2018 - A prospective, randomised, intra-patient, comparative, open, multi-centre study to evaluate the efficacy of a single-use negative pressure wound therapy (NPWT) system on the prevention of postsurgical incision healing complications in patients undergoing reduction mammaplasty***
Size of study groups	***Treatment***	*200*
	Control	*200*

Study duration	***Time unit***	*22 months*
Type of analysis	***Intention-to-treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Primary outcome measure: Incidence of healing complications within 21 days post-surgery*
	Unit	*Number of patients*
Effect size	***Value***	*113/200 for PICO versus 123/200 for standard care*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*p=0.004*
Other outcome	***Name***	*Secondary endpoint: incidence of wound dehiscence within 21 days of surgery*
	Unit	*Number of patients*
Effect size	***Value***	*32/200 for PICO versus 52/200 for standard care*
	95% CI	*5.1%-15.9% for the percentage difference*
Statistical test	***Type***	*Not reported*
	p value	*P<0.001*
Other outcome	***Name***	*Secondary outcome: incidence of infection*
	Unit	*Number of patients*
Effect Size	***Value***	*4/200 for PICO versus 6/200 for standard care*
	95% CI	*-1.9 to 4.3 for the percentage difference*

Statistical test	***Type***	*Not reported*
	p value	*p=0.532*
Other outcome	***Name***	*Secondary outcome: incidence of nipple and areola necrosis within 21 days post-surgery*
	Unit	*Number of patients*
Effect size	***Value***	*1/200 for PICO versus 2/200 for standard care*
	95% CI	*-2.8 to 1.5 for the percentage difference*
Statistical test	***Type***	*Not reported*
	p value	*P=0.530*
Other Outcome	***Name***	*Secondary outcome: incidence of haematoma within 21 days post-surgery*
	Unit	*Number of patients*
Effect Size	***Value***	*2/200 for PICO versus 3/200 for standard care*
	95% CI	*-2.0 to 3.2 for the percentage difference*
Statistical test	***Type***	*Not reported*
	p value	*p=0.681*
Other outcome	***Name***	*Secondary outcome: incidence of cellulitis 21 days post-surgery*
	Unit	*Number of patients*
Effect size	***Value***	*1/200 for PICO versus 2/200 for standard care*
	95% CI	*-1.5 to 2.8 for the percentage difference*
Statistical test	***Type***	*Not reported*
	p value	*p=0.530*
Other outcome	***Name***	*Secondary outcome: incidence of suture abscesses of extrusions 21 days post-surgery*
	Unit	
	Value	*3/200 for PICO versus 4/200 for standard care*

Effect size	***95% CI***	*-1.5 to 2.8 for the percentage difference*
Statistical test	***Type***	*Not reported*
	p value	*p=0.530*
Other outcome	***Name***	*Secondary outcome; incidence of other healing complications (e.g. epidermolysis and fat necrosis) within 21 days post-surgery*
	Unit	*Number of patients*
Effect size	***Value***	*9/200 for PICO versus 10/200 for standard care*
	95% CI	*-3.2 to 4.3 for the percentage difference*
Statistical test	***Type***	*Not reported*
	p value	*p=0.763*
Other outcome	***Name***	*Secondary outcome: incidence of wound dehiscence 21 days post-surgery per site (excluding site 5 – rationale in comments)*
	Unit	
Effect size	***Value***	*Effect size (LCI; UCI)* *All site = 10.2 (5.1; 15.9)* *All sites (excluding site 5) =9.3 (3.2; 16.4)* *Site 7 = -25.0 (-68.1; 17.8)* *Site 6 = 18.8 (4.9; 36.4)* *Site 5 = 11.8 (2.1; 22.7)* *Site 4 = -2.5 (-13.3; 7.1)* *Site 3 = 18.8 (-6.4; 45.6)* *Site 2 = NA no patients recruited from site 2* *Site 1 = 18.2 (4.8; 35.5)*
	95% CI	*3.2 to 16.4 for the percentage difference*
Statistical test	***Type***	*Not reported*
	p value	*P=0.005*

Comments	*- Outcomes on seroma and abscess reported as a descriptive statistic, where 1 patient developed seroma in SC group. No patients developed abscess.* *- Primary endpoint analysis was conducted with and without site 5 data as patient's randomised to site 5 had NPWT treatment longer than the other sites even if incision was healed/without complications. Both analyses showed no difference between results, primary outcome was still statistically significant (p=0.005; 95% CI 3.2:16.4).*

Study name		***Holt and Murphy 2015 - PICO™ incisions closure in oncoplastic breast surgery: a case series***
Size of study groups	***Treatment***	*PICO = 24*
	Control	*Conventional dressing = 24*
Study duration	***Time unit***	*12 days post-surgery*
Type of analysis	***Intention-to-treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Wound breakdown*
	Unit	*Percentage of patients*
Effect size	***Value***	*4.2% for PICO versus 16.7% for standard care*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*Not reported*
Other outcome	***Name***	*Mean time to healing*
	Unit	*Number of days*
Effect size	***Value***	*10.7 for PICO versus 16.1 for standard care*
	95% CI	*Not reported*

Statistical test	***Type***	*Not reported*
	P value	*Not reported*
Comments		*Statistical testing was not conducted as part of this study.*

Study name		***Tan et al 2017 - Use of Negative Pressure Wound Therapy for Lower Limb Bypass Incisions***
Size of study groups	***Treatment***	*14*
	Control	*28*
Study duration	***Time unit***	*28 months*
Type of analysis	***Intention-to - treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Primary outcome measure: Incidence of surgical site infection within 30 days post-surgery*
	Unit	*Number and % of patients*
Effect size	***Value***	*0/14 patients (0%, PICO) vs 9/28 (32%, SC)*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's Chi squared*
	p value	*P=0.019*
Other outcome	***Name***	*Primary outcome measure: Incidence of SSI requiring subsequent surgical debridement*
	Unit	*Number and % of patients*
Effect size	***Value***	*0/14 (0%, PICO) vs 3/28 (11%, SC)*
	95% CI	*Not reported*
Statistical test	***Type***	*Not reported*
	p value	*Not reported*

Other outcome	***Name***	*Secondary outcome measure: Mean length of hospital stay*
	Unit	*Days: mean (range)*
Effect size	***Value***	*PICO: 30 (6-217), SC: 52 (6-166)*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's Chi squared*
	p value	*P=0.186*
Other outcome	***Name***	*Secondary outcome: 30 day readmission rates*
	Unit	*Number and % of patients*
Effect Size	***Value***	*5/14 (36%, PICO) vs 10/28 (36%, SC)*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's Chi squared*
	p value	*P=1.000*
Other outcome	***Name***	*Secondary outcome: Need for secondary vascular procedure*
	Unit	*Number and % of patients*
Effect size	***Value***	*9/14 (64%, PICO) vs 17/28 (61%, SC)*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's Chi squared*
	p value	*P=0.314*
Comments		- *It was reported that of 26 patients (62%) who required secondary vascular procedures, 21 (50%) required wound debridement or amputation. Treatment group distribution was not specified.* - *Of 11 patients requiring 30 day readmission eight (19%) had graft thrombosis and three (7%) had wound dehiscence. Treatment group distribution was not specified.*

Study name		***Fleming et al 2018 - Routine use of PICO dressings may reduce overall groin wound complication rates following peripheral vascular surgery***
Size of study groups	***Treatment***	*73*
	Control	*78*
Study duration	***Time unit***	*71 months*
Type of analysis	***Intention-to -treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Wound complication in the intervention group vs. control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*6 (8.2%) for PICO vs. 15 (19.2%) for comparator*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's exact test*
	p value	*p = 0.042*
Other outcome	***Name***	*Wound infection in the intervention group vs. control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*2 (2.7%) for PICO vs. 5 (6.4%) for comparator*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's exact test or Chi-squared test (not specified)*
	p value	*0.249*
Other outcome	***Name***	*Wound seroma in the intervention group vs. control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*1 (1.4%) for PICO vs. 6 (7.7%) for comparator*
	95% CI	*Not reported*

Statistical test	***Type***	*Fisher's exact test or Chi-squared test (not specified)*
	p value	*0.069*
Other outcome	***Name***	*Wound haematoma in the intervention group vs. control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*2 (2.7%) for PICO vs. 3 (3.8%) for comparator*
	95% CI	*Not reported*
Statistical test	***Type***	*Chi-squared test*
	p value	*0.531*
Other outcome	***Name***	*Wound dehiscence in the intervention group vs. control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*1 (1.4%) for PICO vs. 1 (1.3%) for comparator*
	95% CI	*Not reported*
Statistical test	***Type***	*Chi-squared test*
	P value	*0.735*
Other outcome	***Name***	*Coagulase-negative Staphylococcus infection following wound complication in the intervention group vs. control group*
	Unit	*Number of patients*
Effect size	***Value***	*1 for PICO vs. 1 for comparator*
	95% CI	*Not reported*
Statistical analysis	***Type***	*Chi-squared test*
	P value	*0.01*
Other outcome	***Name***	*Coliform/anaerobe infection following wound complication in the intervention group vs. control group*
	Unit	*Number of patients*
Effect size	***Value***	*0 for PICO vs. 3 for comparator*
	95% CI	*Not reported*

Statistical analysis	***Type***	*Chi-squared test*
	P value	*Not reported*
Other outcome	***Name***	*MRSA infection following wound complication in the intervention group vs. control group*
	Unit	*Number of patients*
Effect size	***Value***	*1 for PICO vs. 1 for comparator*
	95% CI	*Not reported*
Statistical analysis	***Type***	*Chi-squared test*
	P value	*Not reported*
Other outcome	***Name***	*Antibiotics required following wound complication in the intervention group vs. control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*6 (100%) for PICO vs. 15 (100%) for comparator*
	95% CI	*Not reported*
Statistical analysis	***Type***	*Not reported*
	P value	*Not reported*
Other outcome	***Name***	*Antibiotic duration following wound complication in the intervention group vs. control group*
	Unit	*Days (mean ±SD)*
Effect size	***Value***	*7±1.41 for PICO vs. 7±3.84 for comparator*
	95% CI	*Not reported*
Statistical analysis	***Type***	*Student's t-test or Mann-Whitney U-test (not specified)*
	P value	*Not reported*
Other outcome	***Name***	*VAC required following wound complication in the intervention group vs. control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*3 (50%) for PICO vs. 6 (50%) for comparator*

	95% CI	*Not reported*
Statistical analysis	***Type***	*Fisher's exact test or Chi-squared test (not specified)*
	P value	*0.316*
Other outcome	***Name***	*Hospital re-admission following wound complication in the intervention group vs. control group*
	Unit	*Number of patients (%)*
Effect size	***Value***	*3 (50%) for PICO vs. 6 (40%) for comparator*
	95% CI	*Not reported*
Statistical analysis	***Type***	*Fisher's exact test or Chi-squared test (not specified)*
	P value	*0.523*
Other outcome	***Name***	*Hospital re-admission length of stay following wound complication in the intervention group vs. control group*
	Unit	*Days (mean ±SD)*
Effect size	***Value***	*2.83±3.71 for PICO vs. 5.67±8.89 for comparator*
	95% CI	*Not reported*
Statistical analysis	***Type***	*Student's t-test or Mann-Whitney U-test (not specified)*
	P value	*0.465*
Other outcome	***Name***	*Time to resolution following wound complication in the intervention group vs. control group*
	Unit	*Days (mean ±SD)*
Effect size	***Value***	*52.67±3.71 for PICO vs. 96±86.68 for comparator*
	95% CI	*Not reported*
Statistical analysis	***Type***	*Student's t-test or Mann-Whitney U-test (not specified)*
	P value	*0.015*
Comments		*Total cost of prophylactic use of the PICO dressing (EUR 34,718) vs. the control dressing (EUR 69,190) was measured; the total cost difference was EUR 34,472.*

Published conference abstracts:

Study name		***Tuuli et al 2017 - Pilot randomised trial of prophylactic negative pressure wound therapy in obese women after caesarean delivery***
Size of study groups	***Treatment***	*60*
	Control	*60*
Study duration	***Time unit***	*6 months*
Type of analysis	***Intention-to - treat/per protocol***	*Intention-to-treat analysis*
Outcome 1	***Name***	*Composite of superficial or deep SSI within 30 days or other wound complications including separation ≥2cm, hematoma or seroma*
	Unit	*Number of patients (%)*
Effect size	***Value***	*PICO 5/60 (8.3) versus SC 3/60 (5.0). RR: 1.67*
	95% CI	*RR: 0.42 - 6.67*
Statistical test	***Type***	*Fisher's exact test or Mann Whitney U Test*
	p value	*0.72*
Other outcome	***Name***	*Surgical site infection*
	Unit	*Number of patients (%)*
Effect size	***Value***	*PICO 3/60 (5.0) versus SC 2/60 (3.3)*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's exact test or Mann Whitney U Test*
	p value	*>0.99*
Other outcome	***Name***	*Skin separation*
	Unit	*Number of patients (%)*
Effect size	***Value***	*PICO 2/60 (3.3) versus SC 0 (0)*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's exact test or Mann Whitney U Test*

	p value	*0.50*
Other outcome	***Name***	*Seroma*
	Unit	*Number of patients (%)*
Effect size	***Value***	*PICO 0/60 (0) versus SC 1/60 (1.7)*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's exact test or Mann Whitney U Test*
	p value	*>0.99*
Other outcome	***Name***	*Hematoma*
	Unit	*Number of patients (%)*
Effect size	***Value***	*PICO 0 (0) versus SC 0 (0)*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's exact test or Mann Whitney U Test*
	p value	*Not reported*
Other outcome	***Name***	*Pain score on postoperative day 2*
	Unit	*Score, median (interquartile range)*
Effect size	***Value***	*PICO 0 (0-1) versus SC 1 (0-3)*
	95% CI	*Not reported*
Statistical test	***Type***	*Fisher's exact test or Mann Whitney U Test*
	p value	*0.02*
Other outcome	***Name***	*Adverse skin reactions*
	Unit	*Number of patients (%)*
Effect size	***Value***	*PICO 2 (3.3) versus SC 0 (0)*
	95% CI	*Not stated*
Statistical test	***Type***	*Fisher's exact test or Mann Whitney U Test*
	p value	*0.50*

Comments	*This study was a conference abstract so limited data were available.*

Study name		***Kawakita et al 2018 - Negative pressure wound therapy (PICO) in morbidly obese women after caesarean delivery compared with standard dressing***
Size of study groups	***Treatment***	*167*
	Control	*592*
Study duration	***Time unit***	*3 years and 3 months*
Type of analysis	***Intention-to -treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Composite wound complications*
	Unit	*Number of patients (%) and adjusted odds ratio (aOR)*
Effect size	***Value***	*PICO 16/167 (9.6) versus SC 47/592 (7.9), aOR = 1.02*
	95% CI	*0.42-2.35*
Statistical test	***Type***	*Not reported*
	p value	*Not reported*
Other outcome	***Name***	*Endometritis diagnosed before discharge*
	Unit	*Number of patients (%) and aOR*
Effect size	***Value***	*PICO 2/167 (1.2) versus SC 10/592 (1.7), aOR = 0.22*
	95% CI	*0.02-2.24*
Statistical test	***Type***	*Not reported*
	p value	*Not reported*
Other outcome	***Name***	*Endometritis diagnosed after discharge*
	Unit	*Number of patients (%) and aOR*
Effect size	***Value***	*PICO 1/167 (0.6) versus SC 7/592 (1.2), aOR = 1.21*
	95% CI	*0.08-18.52*

Statistical tests	***Type***	*Not reported*
	P value	*Not reported*
Other outcome	***Name***	*Deep wound infection*
	Unit	*Number of patients (%) and aOR*
Effect size	***Value***	*PICO 4/167 (2.4) versus SC 4/592 (0.7), aOR=7.34*
	95% CI	*0.85-6.12*
Statistical tests	***Type***	*Not reported*
	P value	*Not reported*
Other outcome	***Name***	*Other severe infections*
	Unit	*Number of patients (%)*
Effect size	***Value***	*PICO 2/167 (1.2) versus SC 6/592 (1.0)*
	95% CI	*Not recorded*
Statistical tests	***Type***	*Not recorded*
	P value	*Not recorded*
Other outcome	***Name***	*Hematoma or seroma*
	Unit	*Number of patients (%) and aOR*
Effect size	***Value***	*PICO 6/167 (3.6) versus SC 12/592 (2.0), aOR = 3.07*
	95% CI	*0.67-12.64*
Statistical tests	***Type***	*Not reported*
	P value	*Not reported*
Other outcome	***Name***	*Dehiscence*
	Unit	*Number of patients (%) and aOR*
Effect size	***Value***	*PICO 13/167 (7.8) versus SC 14/592 (2.4), aOR = 2.35*
	95% CI	*0.73-7.33*
	Type	*Not reported*

Statistical tests	***P value***	*Not reported*
Other outcome	***Name***	*Cellulitis*
	Unit	*Number of patients (%) and aOR*
Effect size	***Value***	*PICO 5/167 (3.0) versus SC 22/592 (3.7), aOR = 0.86*
	95% CI	*0.20-3.17*
Statistical tests	***Type***	*Not reported*
	P value	*Not reported*
Comments		

Study name		***Hackney and McCoubrey 2017 - The effect of negative pressure dressings (PICO) on wound complications, readmissions rates and length of stay***
Size of study groups	***Treatment***	*PICO = 39 Patients*
	Control	*Control = 32 Patients*
Study duration	***Time unit***	*6 months*
Type of analysis	***Intention-to -treat/per protocol***	*Not stated*
Outcome 1	***Name***	*Wound complications*
	Unit	*Number of patients*
Effect Size	***Value***	*3/39 for PICO vs 5/32 for comparator*
	95% CI	*Not stated*
Statistical text	***Type***	*Not stated*
	p value	*Not stated*
Other outcome	***Name***	*Length of stay*
	Unit	*Days*

Effect size	***Value***	*Mean 14.49 for PICO vs 13.9 for comparator. No SD values given.*
	95% CI	*Not stated*
Statistical test	***Type***	*Not stated*
	p value	*P=0.794*
Other outcome	***Name***	*Readmission*
	Unit	*Number of patients*
Effect size	***Value***	*1/39 for PICO vs 2/32 for comparator*
	95% CI	*Not stated*
Statistical test	***Type***	*Not stated*
	p value	*Not stated*
Comments		*Abstract had limited information in terms of the effect size, 95% CI and type of statistical texts used. All available information from the abstract has been recorded.*

Study name		***Zotes et al 2015 - Negative pressure wound therapy in a potentially infected wound after empyema surgery***
Size of study groups	***Treatment***	*10*
	Control	*10*
Study duration	***Time unit***	*3 months*
Type of analysis	***Intention-to - treat/per protocol***	*Not stated in the study abstract.*
Outcome 1	***Name***	*Wound complications at 10 days post-operatively*
	Unit	*Number of patients*
Effect size	***Value***	*5/10 for PICO vs 1/10 for the comparator*
	95% CI	*Not stated*

Statistical test	***Type***	*Not stated*
	p value	*The p value is not stated – however it was reported that the result was not significant.*
Other outcome	***Name***	*Wound dehiscence at 10 days post operatively*
	Unit	*Number of patients*
Effect size	***Value***	*1/10 for PICO vs 2/10 for the comparator*
	95% CI	*Not stated*
Statistical test	***Type***	*Not stated*
	p value	*Not stated*
Other outcome	***Name***	*Seroma at 10 days post operatively*
	Unit	*Number of patients*
Effect size	***Value***	*3/10 for PICO vs 0/10 for the comparator*
	95% CI	*Not stated*
Statistical test	***Type***	*Not stated*
	p value	*Not stated*
Other outcome	***Name***	*Wound abscess at 10 days post operatively*
	Unit	*Number of patients*
Effect size	***Value***	*2/10 for PICO vs 0/10 for the comparator*
	95% CI	*Not stated*
Statistical test	***Type***	*Not stated*
	p value	*Not stated*
Comments		*- Length of stay outcome stated in abstract, but results not reported.*

Study name		***Irwin et al 2018 - Negative pressure dressings significantly decrease rates of wound breakdown and may reduce implant loss rates in prepectoral breast reconstruction***
	Treatment	*PICO = 102*

Size of study groups	***Control***	*Standard dressings = 152*
Study duration	***Time unit***	*Not stated.*
Type of analysis	***Intention-to -treat/per protocol***	*Per protocol*
Outcome 1	***Name***	*Wound breakdown*
	Unit	*Number of cases*
Effect size	***Value***	*Favours PICO, exact value not stated*
	95% CI	*Not stated*
Statistical test	***Type***	*Fisher's exact test*
	p value	*P=0.01*
Other outcome	***Name***	*Reconstructive failure*
	Unit	*Number of cases*
Effect size	***Value***	*Favours PICO, exact value not stated*
	95% CI	*Not stated*
Statistical test	***Type***	*Fisher's exact test*
	p value	*P=0.08*
Comments		*Limited information available as this study was presented as a conference abstract.*

Unpublished studies:

Study name		***Stannard et al. Unpublished*** ***Working title:*** [redacted]
Size of study groups	***Treatment***	[redacted]
	Control	[redacted]
Study duration	***Time unit***	[redacted]
Type of analysis	***Intention-to-treat/per protocol***	*Draft data does not provide this information.*
Comments		*Summary of results:* [redacted] ***THIS STUDY IS UNPUBLISHED AND CURRENTLY UNDERGOING DATA CLEANING, THEREFORE OUTCOMES REPORTED ARE SUBJECT TO CHANGE.***

7.6.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

Results from both randomised controlled trials and observational studies were included to ensure that conclusions were based upon a complete picture of the available evidence base. Observational results rarely provide an intention-to-treat analysis and therefore the results from other analyses were included. Overall meta-analyses for the key metrics showed that there was generally low heterogeneity between studies, even with the inclusion of studies where an analysis other than intention-to-treat was performed.

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Adverse events were identified from the relevant studies retrieved and appraised in sections 7.1 to 7.6. The wide scope of the search strategy used to identify relevant comparative studies allowed studies to be identified from the initial search.

7.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table B10.

For clarity and transparency, the definition of an adverse event stated by the Medical Device Regulations (The EU Regulation on Medical Devices 2017/745) was adopted. These regulations define an adverse event as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal

laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

Table 15 Adverse events across patient groups

Published journal articles:

Study name	***Hyldig et al 2018***		
	Follow-up period: 30 days post-surgery		
	NPWT – intervention % of patients (n = 432 infection, 410 dehiscence)	***Standard of care - Comparator % of patients (n = 444 infection, 417 dehiscence)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound infection	*4.6% (n=20)*	*9.2% (n=41)*	*Not reported*
Wound exudate	*22.4% (n=92)*	*32.9% (n=137)*	*0.69 (0.55-0.86)*
Wound dehiscence	*15.1% (n=62)*	*16.6% (n=69)*	*0.50 (0.30-0.84)*
Endometritis	*2.0% (n=8)*	*1.9% (n=8)*	*1.02 (0.39-2.68)*
Urinary tract infection	*5.9% (n=24)*	*4.1% (n=17)*	*1.44 (0.78-2.63)*
Mastitis	*4.9% (n=20)*	*4.1% (n=17)*	*1.20 (0.64-2.25)*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Chaboyer et al 2014***		
	Follow-up period: 90 days post-surgery		
	NPWT – intervention % of patients (n = 44)	***Standard of Care - Comparator % of patients (n = 43)***	***Relative risk (95% CI)***
All adverse events reported:			
SSI total	*22.7% (n=10)*	*27.9% (n=12)*	*0.81 (0.39-1.68)*
SSI superficial	*11.4% (n=5)*	*16.3% (n=7)*	*0.70 (0.24-2.03)*
SSI deep	*9.1% (n=4)*	*9.3% (n=4)*	*0.98 (0.26-3.66)*
SSI organ/space	*2.3% (n=1)*	*2.3% (n=1)*	*0.98 (0.06-15.13)*

Wound bleeding	*2.3% (n=1)*	*2.3% (n=1)*	*0.98 (0.06-15.13)*
Wound bruising	*2.3% (n=1)*	*2.3% (n=1)*	*0.24 (0.03-2.10)*
Other wound complication	*9.1% (n=4)*	*2.3% (n=1)*	*3.91 (0.46-33.58)*
Hospital readmission	*2.3% (n=1)*	*2.3% (n=1)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Hickson et al 2015***		
	Follow-up period: 6 weeks post-surgery		
	Intervention % of patients (n = 964)	***Comparator % of patients (n = 1125)***	***Relative risk (95% CI)***
All adverse events reported:			
Surgical site infection	*0.1% (n=1)*	*2.1% (n=24)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Gillespie et al 2015***		
	Follow-up period: 6 weeks post-surgery		
	NPWT - intervention% of patients (n = 35)	***Standard of Care- Comparator % of patients (n = 35)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound infection	*5.7% (n=2)*	*8.6% (n=3)*	*0.67 (0.1-3.7)*
SSI indicators (erythema, swelling, leakage, purulence)	*8.6% (n=3)*	*20.0% (n=7)*	*0.43 (0.1-1.5)*

Complications (bruising, bleeding, haematoma, seroma, dehiscence)	*68.5% (n=24)*	*42.8% (n=15)*	*1.6 (1.0-2.5)*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Karlakki et al 2016***		
	Follow-up period: 6 weeks post-surgery		
	NPWT - intervention% of patients (n = 102)	***Standard of Care- Comparator % of patients (n = 107)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound infection	*1% (n=1)*	*5.6% (n=6)*	*Not reported*
Prolonged discharge	*2% (n=2)*	*3% (n=3)*	*Not reported*
Delayed healing	*1% (n=1)*	*3% (n=3)*	*Not reported*
Haematoma	*0% (n=0)*	*1% (n=1)*	*Not reported*
Cellulitis	*1% (n=1)*	*0% (n=0)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Nodermeyer et al 2016***					
	Follow-up period: Day 5			***Follow-up period: Day 10***		
	Intervention % of patients (n = 10)	***Comparator % of patients (n = 10)***	***Relative risk (95% CI)***	***Intervention % of patients (n = 10)***	***Comparator % of patients (n = 10)***	**Relative risk (95% CI)**
All adverse events reported:						
Adverse event	*No adverse events reported*					
CI, confidence interval						

Adapted from European Public Assessment Reports published by the European Medicines Agency

Study name	***Matsumoto and Parekh 2015***		
	Follow-up period: 4 weeks post-operative		
	PICO % of patients (n = 37)	***Standard % of patients (n = 37)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound healing problem	*2.7% (n=1)*	*24.3% (n=9)*	*Not reported*
SSI total	*2.7% (n=1)*	*8.1% (n=3)*	*Not reported*
Superficial SSI	*0% (n=0)*	*5.4% (n=2)*	*Not reported*
Deep SSI	*2.7% (n=1)*	*2.7% (n=1)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Dingemans et al 2018***		
	Follow-up period: 30 days post-operative		
	Intervention % of patients (n = 53)	***Comparator % of patients (n = 47)***	***Relative risk (95% CI)***
All adverse events reported:			
Infection	*7.5% (n=4)*	*14.9% (n=7)*	*Not stated*
Superficial SSI	*3.8% (n=2)*	*8.5% (n=4)*	*Not stated*
Deep SSI	*3.8% (n=2)*	*6.4% (n=3)*	*Not stated*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Hester et al 2015***		
	Follow-up period: 6 weeks		
	PICO % of patients (n = 18)	***Standard dressing% of patients (n = 18)***	***Relative risk (95% CI)***
All adverse events reported for knee operation patients:			
Wound complications	*7.7% (n=1, out of 13 knees)*	*15.4% (n=2, out of 13 knees)*	*Not reported*
Anterior knee pain	*0% (n=0)*	*15.4% (n=2, out of 13 knees)*	*Not reported*
Blistering	*0% (n=0)*	*0% (n=0)*	*Not reported*
Maceration	*0% (n=0)*	*0% (n=0)*	*Not reported*
Skin tearing	*0% (n=0)*	*0% (n=0)*	*Not reported*
All adverse events reported for hip operation patients:			
Aseptic loosening for the femoral stem	*25% (n=1, out of 4 hips)*	*0 (n=0)*	*Not reported*
Wound complications	*0% (n=0)*	*20% (n=1, out of 5 hips)*	*Not reported*
Blistering	*0% (n=0)*	*0% (n=0)*	*Not reported*
Maceration	*0% (n=0)*	*0% (n=0)*	*Not reported*
Skin tearing	*0% (n=0)*	*0% (n=0)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Adogwa et al 2014***		
	Follow-up period: 90 days post-operative		
	Intervention % of patients (n = 46)	***Comparator % of patients (n = 114)***	***Relative risk (95% CI)***
All adverse events reported:			
Spinal cord/nerve injury	*2.1% (n=1)*	*1.8% (n=2)*	*Not reported*
Durotomy	*12.8% (n=6)*	*19.3% (n=22)*	*Not reported*

CSF leak	*8.5% (n=4)*	*3.5% (n=4)*	*Not reported*
PE/DVT	*8.5% (n=4)*	*2.6% (n=3)*	*Not reported*
UTI	*21.3% (n=10)*	*17.5% (n=20)*	*Not reported*
Pneumonia	*0% (n=0)*	*2.6% (n=3)*	*Not reported*
SSI	*10.6% (n=5)*	*14.9% (n=17)*	*Not reported*
Wound dehiscence	*6.4% (n=3)*	*12.3% (n=14)*	*Not reported*
Return to OR	*12.8% (n=6)*	*10.5% (n=12)*	*Not reported*
30-day readmission	*19.1% (n=9)*	*18.4% (n=21)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Uchino et al 2016***		
	Follow-up period: 4 weeks post-surgery		
	Intervention % of patients (n = 28)	***Comparator % of patients (n = 31)***	***Relative risk (95% CI)***
All adverse events reported:			
Incisional SSI	*10.7% (n=3)*	*3.2% (n=1)*	*Not reported*
Wound bleeding	*0% (n=0)*	*0% (n=0)*	*Not reported*
Entero-cutaneous fistula	*0% (n=0)*	*0% (n=0)*	*Not reported*
Bowel obstruction	*10.7% (n=3)*	*9.7% (n=3)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Selvaggi et al 2014***		
	Follow-up period: 6 weeks post-surgery		
	NPWT – intervention % of patients (n = 25)	***Standard of Care - Comparator % of patients (n = 25)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound infection	*8% (n=2)*	*48% (n=12)*	*Not reported*
Seroma	*8% (n=2)*	*44% (n=11)*	*Not reported*
Anastomotic leak	*4% (n=1)*	*8% (n=2)*	*Not reported*
Postoperative haemorrhage	*8% (n=2)*	*12% (n=3)*	*Not reported*
Intra-abdominal abscess	*4% (n=1)*	*12% (n=3)*	*Not reported*
Stoma complication	*8% (n=2)*	*4% (n=1)*	*Not reported*
Death	*0% (n=0)*	*0% (n=0)*	*Not reported*
Major complications	*20% (n=6 in 5 patients)*	*28% (n=9 in 7 patients)*	*Not reported*
Patients requiring reoperation	*8% (n=2)*	*20% (n=5)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Pellino et al 2014a***		
	Follow-up period: 6 weeks post-surgery		
	NPWT - intervention% of patients (n = 50)	***Standard of care - Comparator % of patients (n = 50)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound infection	*8% (n=4)*	*40% (n=20)*	*Not reported*
Seroma	*6% (n=3)*	*30% (n=15)*	*Not reported*
Major complications (not specified)	*16% (n=8)*	*16% (n=8)*	*Not reported*

Perioperative deaths	*0% (n=0)*	*0% (n=0)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Pellino et al 2014b***		
	Follow-up period: 30 days post-surgery		
	Intervention % of patients (n = 13)	***Comparator % of patients (n = 17)***	***Relative risk (95% CI)***
All adverse events reported:			
Anastomotic leak	*7.7% (n=1)*	*5.9% (n=1)*	*Not reported*
Intra-abdominal abscess	*0% (n=0)*	*17.6% (n=3)*	*Not reported*
Postoperative haemorrhage	*7.7% (n=1)*	*11.8% (n=2)*	*Not reported*
Stoma complication	*7.7% (n=1)*	*5.9% (n=1)*	*Not reported*
Death	*0% (n=0)*	*0% (n=0)*	*Not reported*
Patients requiring reoperation	*7.7% (n=1)*	*11.8% (n=2)*	*Not reported*
Need for stoma during reoperation	*7.7% (n=1)*	*11.8% (n=2)*	*Not reported*
Urinary tract infection	*7.7% (n=1)*	*0% (0)*	*Not reported*
Ileus	*15.4 (n=2)*	*17.6% (n=3)*	*Not reported*
Seroma	*7.7% (n=1)*	*47% (n=8)*	*Not reported*
Serosanguineous discharge	*7.7% (n=1)*	*29.4% (n=5)*	*Not reported*
Superficial SSI	*7.7% (n=1)*	*23.5% (n=4)*	*Not reported*
Deep SSI	*0% (n=0)*	*17.6% (n=3)*	*Not reported*
Organ/space SSI	*0% (n=0)*	*5.9% (n=1)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***van der Valk et al 2017***		
	Follow-up period: Not specified		
	Intervention % of patients (n = 10)	***Comparator % of patients (n = 10)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound complications (Infection)	*70% (n=7)*	*60% (n=6)*	*Not Reported*
Surgical reintervention	*0% (n=0)*	*10% (n=1)*	*Not Reported*
Bedside wound opening	*20% (n=2)*	*20% (n=2)*	*Not Reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Svensson-Bjork et al 2018***		
	Follow-up period: Median 808 days post-surgery		
	PICO % of patients (n = 34)	***ViTri Pad% of patients (n = 34)***	***Relative risk (95% CI)***
All adverse events reported:			
All	*No adverse events reported*	*No adverse events reported*	*Not applicable*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Witt-Majchrzak 2014***		
	Follow-up period: 22 months		
	PICO % of patients (n = 40)	***ViTri Pad% of patients (n = 40)***	***Relative risk (95% CI)***
All adverse events reported:			
Reoperation	*2.5% (n=1)*	*2.5% (n=1)*	*Not reported*

Blood product transfusion	*2.5% (n=1)*	*2.5% (n=1)*	*Not reported*
Total superficial SSIs	*2.5% (n=1)*	*17.5% (n=7)*	*Not reported*
Superficial SSIs treated with antibiotics only	*0% (n=0)*	*10% (n=4)*	*Not reported*
Superficial SSIs requiring wound opening	*2.5% (n=1)*	*7.5% (n=3)*	*Not reported*
Deep SSIs	*0% (n=0)*	*0% (n=0)*	*Not reported*
Sternal instability	*2.5% (n=1)*	*2.5% (n=1)*	*Not reported*
Sterile dehiscence following suture removal	*2.5% (n=1)*	*2.5% (n=1)*	*Not reported*
Healing abnormalities resulting from wound ischemia	*0% (n=0)*	*2.5% (n=1)*	*Not reported*
Wounds with secondary suturing	*5% (n=2)*	*12.5% (n=5)*	*Not reported*
Sternal refixation	*2.5% (n=1)*	*0% (n=0)*	*Not reported*
Signs and symptoms that accompanied wound healing:			
Serious vesicles	*12.5% (n=5)*	*0% (n=0)*	*Not reported*
Marginal necrosis	*0% (n=0)*	*30% (n=12)*	*Not reported*
Ecchymosis	*12.8% (n=5)*	*5% (n=2)*	*Not reported*
Hypertrophic scar	*7.7% (n=3)*	*18.4% (n=7)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			
Study name	***Tanaydin et al 2018***		
	Follow-up period: 7 days post-surgery		
	NPWT - intervention% of patients (n = 32)	***Standard of Care- Comparator % of patients (n = 32)***	***Relative risk (95% CI)***

All adverse events reported:			
Wound dehiscence	*15.6% (n=5)*	*31.3% (n=10)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Galiano et al 2018***		
	Follow-up period: 90 days post-surgery		
	NPWT - intervention% of patients (n = 200)	***Standard of Care- Comparator % of patients (n = 200)***	***Relative risk (95% CI)***
All adverse events reported:			
Dehiscence	*16% (n=32)*	*26% (n=52)*	*Not reported*
SSI	*2% (n=4)*	*3% (n=6)*	*Not reported*
Nipple necrosis	*1% (n=2)*	*0.5% (n=1)*	*Not reported*
Areola necrosis	*0.5% (n=1)*	*0.5% (n=1)*	*Not reported*
Epidermolysis	*0% (n=0)*	*0.5% (n=1)*	*Not reported*
Haematoma	*1% (n=2)*	*1.5% (n=3)*	*Not reported*
Seroma	*0% (n=0)*	*0.5% (n=1)*	*Not reported*
Cellulitis	*0.5% (n=1)*	*1% (n=2)*	*Not reported*
Abscess	*0% (n=0)*	*0% (n=0)*	*Not reported*
Suture abscesses or extrusions	*1.5% (n=3)*	*2% (n=4)*	*Not reported*
Other healing complications	*4.5% (n=9)*	*5% (n=10)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Holt and Murphy 2015***		
	Follow-up period: 12 days post-surgery		
	Intervention % of patients (n = 24)	***Comparator % of patients (n = 24)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound breakdown	*4.2% (n=1)*	*16.7% (n=4)*	*Not reported*
Delayed wound healing	*4.2% (n=1)*	*4.2% (n=1)*	*Not reported*
Fat necrosis	*4.2% (n=1)*	*4.2% (n=1)*	*Not reported*
Re-operation	*4.2% (n=1)*	*4.2% (n=1)*	*Not reported*
Delay to adjuvant therapy	*4.2% (n=1)*	*4.2% (n=1)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Tan et al 2017***		
	Follow-up period: 30 days post-surgery		
	NPWT – intervention % of patients (n = 14)	***Standard of Care - Comparator % of patients (n = 28)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound infection	*0% (n=0)*	*32% (n=9)*	*Not reported*
Wound dehiscence	*N = 3 across study, treatment groups not specified*		*Not reported*
Wound debridement or amputation	*N=21 across study, treatment group not specified*		*Not reported*
Graft thrombosis	*N=8 across study, treatment group not specified*		*Not reported*
Required secondary vascular procedures	*N=26 across study, treatment group not specified*		*Not reported*

Required further wound debride-ment or amputation	*N=21 across study, treatment group not specified*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*		

Study name	***O'Leary et al 2016***					
	Follow-up: Postoperative day 4			***Follow-up Postoperative day 30***		
	PICO % of patients (n = 24)	***Standard dressing % of patients (n = 25)***	***Relative risk (95% CI)***	***Intervention % of patients (n = 24)***	***Comparator % of patients (n = 25)***	***Relative risk (95% CI)***
All adverse events reported:						
Surgical site infection	*4.2% (n=1)*	*8.0% (n=2)*	*Not reported*	*8.3%(n=2)*	*32.0% (n=8)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*						

Study name	***Fleming et al 2018***		
	Follow-up period: Minimum 6 weeks post-surgery		
	PICO % of patients (n = 73)	***Comparator % of patients (n = 78)***	***Relative risk (95% CI)***
All adverse events reported:			
Infection	*2.7% (n=2)*	*6.4% (n=5)*	*Not reported*
Seroma	*1.4% (n=1)*	*7.7% (n=6)*	*Not reported*
Haematoma	*2.7% (n=2)*	*3.8% (n=3)*	*Not reported*
Dehiscence	*1.4% (n=1)*	*1.3% (n=1)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Published conference abstracts:

Study name	***Tuuli et al 2017***		
	Follow-up period: 30 days post-surgery		
	Intervention % of patients (n = 60)	***Comparator % of patients (n = 60)***	***Relative risk (95% CI)***
Class 1 (wound complications)			
Surgical site infection	*5% (n=3)*	*3.3% (n=2)*	*Not reported*
Skin separation	*3.3% (n=2)*	*0% (n=0)*	*Not reported*
Seroma	*0% (n=0)*	*1.7% (n=1)*	*Not reported*
Hematoma	*0% (n=0)*	*0% (n=0)*	*Not reported*
Adverse skin reaction	*3.3% (n=2)*	*0% (n=0)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Kawakita et al 2018***		
	Follow-up period: Assessment time point for adverse events listed below was not reported in the study abstract		
	Intervention % of patients (n = 167)	***Comparator % of patients (n = 592)***	***Adjusted odds ratio (95% CI)***
All adverse events reported:			
Composite wound infection	*9.6% (n=16)*	*7.9% (n=47)*	*1.02 (0.42 – 2.35)*
Endometritis diagnosed before discharge	*1.2% (n=2)*	*1.7% (n=10)*	*0.22 (0.02 – 2.24)*
Endometritis diagnosed after discharge	*0.6% (n=1)*	*1.2% (n=7)*	*1.21 (0.08 – 18.52)*
Deep wound infection	*2.4% (n=4)*	*0.7% (n=4)*	*7.34 (0.85 – 6.12)*

Other severe infections	*1.2% (n=2)*	*1.0% (n=6)*	*Not reported*
Cellulitis	*3.0% (n=5)*	*3.7% (n=22)*	*0.86 (0.20 – 3.17)*
Hematoma or Seroma	*3.6% (n=6)*	*2.0% (n=12)*	*3.07 (0.67 – 12.64)*
Dehiscence	*7.8% (n=13)*	*2.4% (n=14)*	*2.35 (0.73 – 7.33)*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Hackney and McCoubrey et al 2017***		
	Follow-up period: Time-point of assessment of adverse events were not reported within study abstract		
	PICO % of patients (n = 39)	***ViTri Pad% of patients (n = 32)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound complications	*7.6% (n=3)*	*15.6% (n=5)*	*Not reported*
Readmission	*2.6% (n=1)*	*6.3% (n=2)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Zotes et al 2015***		
	Follow-up period: 10 days post-surgery		
	Intervention % of patients (n = 10)	***Comparator % of patients (n = 10)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound complication (any)	*50% (n=5)*	*10% (n=1)*	*RR=5 (Not reported)*
- ***Seroma***	*30% (n=3)*	*0% (n=0)*	*Not reported*
- ***Wound abscess***	*20% (n=2)*	*0% (n=0)*	*Not reported*

- ***Wound dehiscence***	*10% (n=1)*	*20% (n=2) *Note: Possible error but this is what is reported in the abstract*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

Study name	***Irwin et al 2018***		
	Follow-up period: The time-point for assessment of adverse events was not reported in the study abstract		
	Intervention % of patients (n = 102)	***Comparator % of patients (n = 152)***	***Relative risk (95% CI)***
All adverse events reported:			
Wound breakdown	*0% (n=0)*	*5.9% (n=9)*	*Not reported*
Reconstructive failure	*0% (n=0)*	*3.9% (n=6)*	*Not reported*
CI, confidence interval *Adapted from European Public Assessment Reports published by the European Medicines Agency*			

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

A search of reports made to the Manufacturer and User Facility Device Experience (MAUDE) database, maintained by the US FDA, was undertaken for "PICO" NPWT for the period May 2011 to 22nd August 2018 in order to establish the nature and number of adverse events observed for PICO NPWT devices.

MAUDE data dating from the first launch of a PICO device in May 2011 highlights a single case report of a death reported in June 2013. Details of this case narrative are provided below:

Case Report 8043484-2015-00041 (NPWT PICO Sterile)

It was reported that whilst a patient was receiving treatment with PICO, she became very unwell and was admitted to hospital. The patient died in hospital. The cause of death was unknown. The suspected cause of death was reported to be either osteomyelitis or a chest infection.

Table 16 Adverse Events - MAUDE

Categorisation of MAUDE reported injuries from 1st May 2011 to 22nd August 2018.	
System Organ Class/Preferred Term	Number of Adverse Events Reported
Vascular disorders	
Haematoma	2
Haemorrhage	3
Total	5
Injury poisoning or procedural complications	
Skin graft failure	2
Wound complication	16
Total	18
General disorders and administration site conditions	
Device failure	7
Necrosis	3
Device allergy	4
Pain	4
Death	1
Application site inflammation	16
Application site erosion	2
Application site injury	7
Total	44
Skin and subcutaneous tissue disorders	
Decubitus ulcer	1
Skin stripping	4
Burn	1
Blister	19
Cellulitis	2
Dermatitis	7
Skin Reaction	7
Skin Maceration	25
Total	66
Infections and infestations	
Infection	12
Purulent discharge	1
Fungal infection	1
Total	14
TOTAL ADVERSE EVENTS	147

The UK MHRA Website has been searched in relation to any information concerning the subject devices (or non-equivalent products), in order to determine any product non-conformances, field safety notices and/or product withdrawals. A search range from 1st May 2011 – 22nd August 2018 was used. Zero (0) hits were identified relating to "PICO".

[redacted]

[redacted]

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

Based on an assessment of all the available data (manufacturer and published scientific literature) in respect to PICO NPWT systems, and taking account of the risk analyses undertaken for the devices along with post-market surveillance data, it is considered that PICO has an acceptable and positive risk-benefit within the context of the intended indications.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

All fully published clinical studies that were relevant to the scope of this review were assessed for data related to each of the outcome metrics. As stated previously, conference abstracts were excluded from meta-analysis because they often contained incomplete data, lacked details of the methodology used, and were difficult to interpret with the limited information available. However, as part of the sensitivity analysis, conference abstracts were included to determine whether this changed the result.

Meta-analyses were performed in Review Manager (RevMan), Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, using

either a fixed-effect or a random-effects model depending on the presence or absence of significant heterogeneity between studies. For dichotomous outcomes, an odds ratio (OR) with a 95% CI was reported as the summary statistic. For continuous outcomes, we used the mean difference (MD). We used the inverse variance and Mantel–Haenszel methods to combine separate statistics and if p values were less than 0.05, the results were considered statistically significant. Data were analysed separately for RCTs and observational studies; however, the main analysis reported the results of the combined analysis.

Heterogeneity of the included studies was assessed using the I^2 statistic. When the calculated I^2 statistic was less than 50%, a fixed-effect model was used (no substantial heterogeneity) and when it was greater than 50%, a random-effects model was used. A funnel plot was used to qualitatively evaluate reporting biases.

Sensitivity analyses were performed using alternative pooling methods (Peto method vs. Mantel-Haenszel method applicable to dichotomous data). Further sensitivity analyses were the inclusion and exclusion of conference abstracts, and using fixed or random effects models.

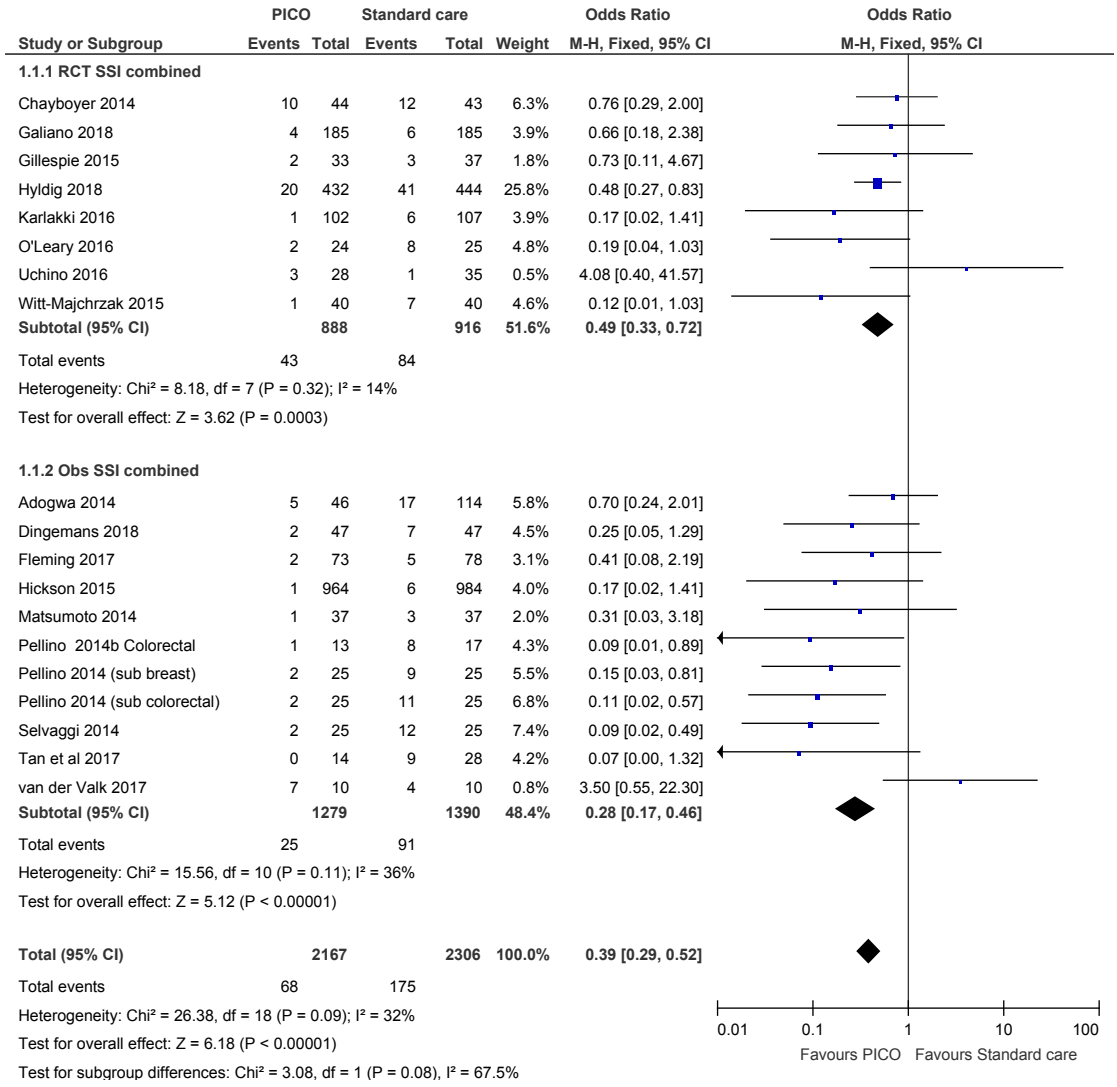
An overview of the results from meta-analyses is shown below:

Main outcomes from meta-analysis of relevant study results					
Outcome or Subgroup	*Studies*	*Participants*	*Statistical Method*	*Effect Estimate*	*p value*
1) Post-surgical wound complications					
1.1 Surgical site infection combined	*19*	*4473*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.39 [0.29, 0.52]*	*<0.0001*
1.1.1 RCT SSI	*8*	*1804*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.49 [0.33, 0.72]*	*0.0003*
1.1.2 Observational SSI	*11*	*2669*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.28 [0.17, 0.46]*	*<0.0001*
1.1.3 With conference abstracts included	*21*	*5352*	*Odds Ratio (M-H, Random, 95% CI)*	*0.43 [0.27, 0.69]*	*0.0004*
1.2 Dehiscence combined	*8*	*1753*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.75 [0.57, 0.99]*	*0.05*
1.2.1 RCT dehiscence	*4*	*1374*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.78 [0.59, 1.05]*	*0.11*
1.2.2 Observational dehiscence	*4*	*379*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.52 [0.21, 1.30]*	*0.16*
1.2.3 With conference abstracts included	*11*	*2652*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.95 [0.55, 1.61]*	*0.84*
1.3 Seroma combined	*7*	*771*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.23 [0.11, 0.45]*	*<0.0001*
1.3.1 RCT seroma	*2*	*440*	*Odds Ratio (M-H, Fixed, 95% CI)*	*2.03 [0.37, 11.14]*	*0.42*
1.3.2 Observational seroma	*5*	*331*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.13 [0.05, 0.31]*	*<0.0001*
1.3.3 With conference abstracts included	*8*	*891*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.23 [0.12, 0.45]*	*<0.001*
1.4 Haematoma combined	*3*	*591*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.88 [0.29, 2.65]*	*0.81*
1.4.1 RCT haematoma	*2*	*440*	*Odds Ratio (M-H, Fixed, 95% CI)*	*1.00 [0.25, 4.07]*	*1.00*
1.4.2 Observational haematoma	*1*	*151*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.70 [0.11, 4.34]*	*0.71*
1.5 Necrosis (only RCTs identified with relevant data)	*2*	*443*	*Odds Ratio (M-H, Random, 95% CI)*	*0.16 [0.01, 4.27]*	*0.27*

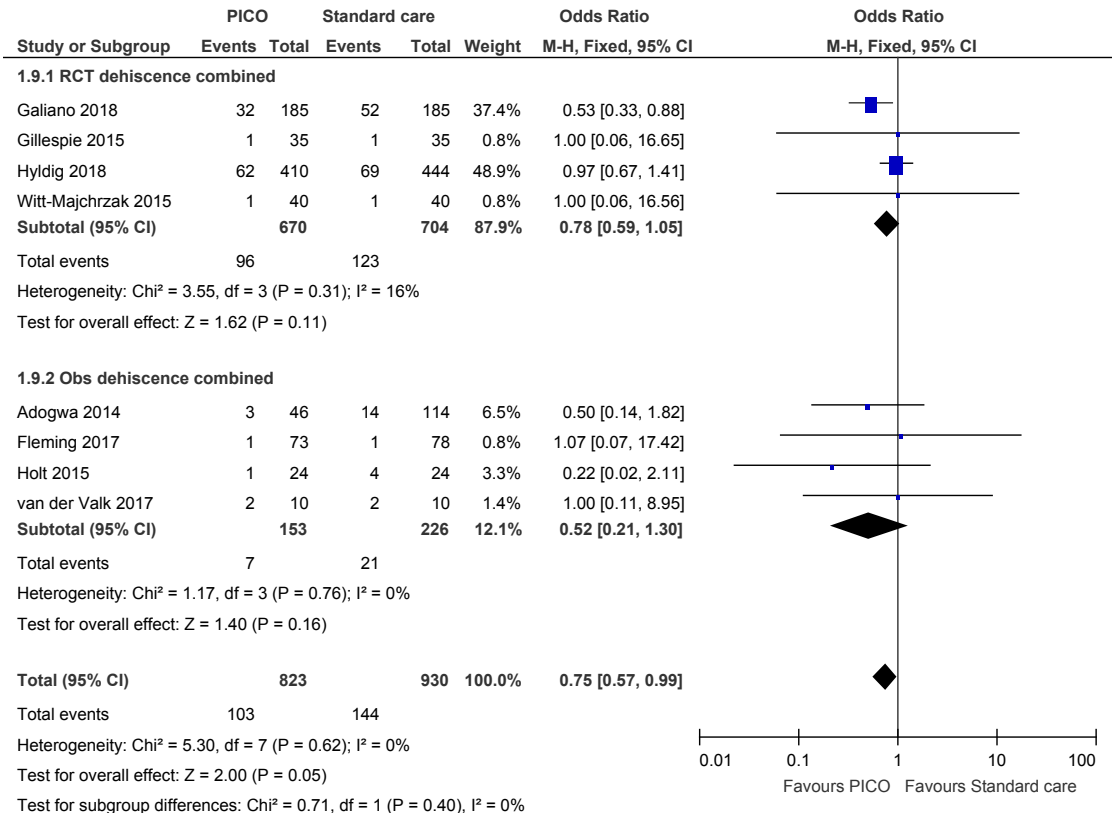
1.6 Abnormal scarring (only one RCT identified with relevant data)	*1*	*80*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.38 [0.09, 1.60]*	*0.19*
1.7 Time to healing (combined)	*3*	*259*	*Mean Difference (IV, Random, 95% CI)*	*-10.83 [-22.91, 1.25]*	*0.08*
1.7.1 RCT time to healing	*1*	*59*	*Mean Difference (IV, Random, 95% CI)*	*-4.10 [-9.64, 1.44]*	*0.15*
1.7.2 Observational time to healing	*2*	*200*	*Mean Difference (IV, Random, 95% CI)*	*-21.07 [-62.49, 20.36]*	*0.32*
1.8 Delayed healing combined	*3*	*627*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.77 [0.51, 1.16]*	*0.21*
1.8.1 RCT delayed healing	*2*	*579*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.77 [0.50, 1.16]*	*0.21*
1.8.2 Observational delayed healing	*1*	*48*	*Odds Ratio (M-H, Fixed, 95% CI)*	*1.00 [0.06, 16.97]*	*1.00*
2) Hospital efficiencies					
2.1 Length of stay (LOS) combined	*11*	*948*	*Mean Difference (IV, Random, 95% CI)*	*-1.75 [-2.69, -0.81]*	*0.00 02*
2.1.1 RCT LOS	*4*	*415*	*Mean Difference (IV, Random, 95% CI)*	*-0.51 [-1.23, 0.21]*	*0.16*
2.1.2 Observational LOS	*7*	*533*	*Mean Difference (IV, Random, 95% CI)*	*-2.78 [-4.90, -0.67]*	*0.01*
2.2 Readmission combined	*9*	*966*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.82 [0.49, 1.38]*	*0.45*
2.2.1 RCT readmission	*3*	*513*	*Odds Ratio (M-H, Fixed, 95% CI)*	*2.02 [0.50, 8.12]*	*0.32*
2.2.2 Observational readmission	*6*	*453*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.70 [0.39, 1.24]*	*0.22*
2.3 Reoperation combined	*10*	*1427*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.87 [0.52, 1.46]*	*0.59*
3) Surgical site infections by surgical speciality					
3.1 Orthopaedic surgery SSI combined	*5*	*607*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.43 [0.21, 0.86]*	*0.02*
3.1.1 RCT orthopaedic SSI	*2*	*279*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.32 [0.08, 1.24]*	*0.10*
3.1.2 Observational orthopaedic SSI	*3*	*328*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.47 [0.21, 1.08]*	*0.08*

3.2 Plastics/Breast surgery SSI combined	*2*	*420*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.36 [0.14, 0.97]*	*0.04*
3.2.1 RCT plastics SSI	*1*	*370*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.66 [0.18, 2.38]*	*0.52*
3.2.2 Observational plastics SSI	*1*	*50*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.15 [0.03, 0.81]*	*0.03*
3.3 Vascular surgery SSI (only observational studies were identified)	*2*	*193*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.22 [0.05, 0.87]*	*0.03*
3.4 Cardio-thoracic surgery SSI (only RCTs were identified)	*1*	*80*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.12 [0.01, 1.03]*	*0.05*
3.5 Mixed surgery SSI (only RCTs were identified)	*1*	*49*	*Odds Ratio (M-H, Fixed, 95% CI)*	*0.19 [0.04, 1.03]*	*0.05*
3.6 Obstetric surgery SSI combined	*3*	*2911*	*Odds Ratio (M-H, Random, 95% CI)*	*0.47 [0.29, 0.74]*	*0.001*
3.6.1 RCT obstetric SSI	*2*	*963*	*Odds Ratio (M-H, Random, 95% CI)*	*0.50 [0.31, 0.80]*	*0.005*
3.6.2 Observational obstetric SSI	*1*	*1948*	*Odds Ratio (M-H, Random, 95% CI)*	*0.17 [0.02, 1.41]*	*0.10*
3.7 Colorectal surgery SSI combined	*4*	*159*	*Odds Ratio (M-H, Random, 95% CI)*	*0.56 [0.07, 4.51]*	*0.59*
3.7.1 RCT colorectal RCT SSI	*1*	*59*	*Odds Ratio (M-H, Random, 95% CI)*	*3.60 [0.35, 36.80]*	*0.28*
3.7.2 Observational colorectal SSI	*3*	*100*	*Odds Ratio (M-H, Random, 95% CI)*	*0.32 [0.03, 3.58]*	*0.35*

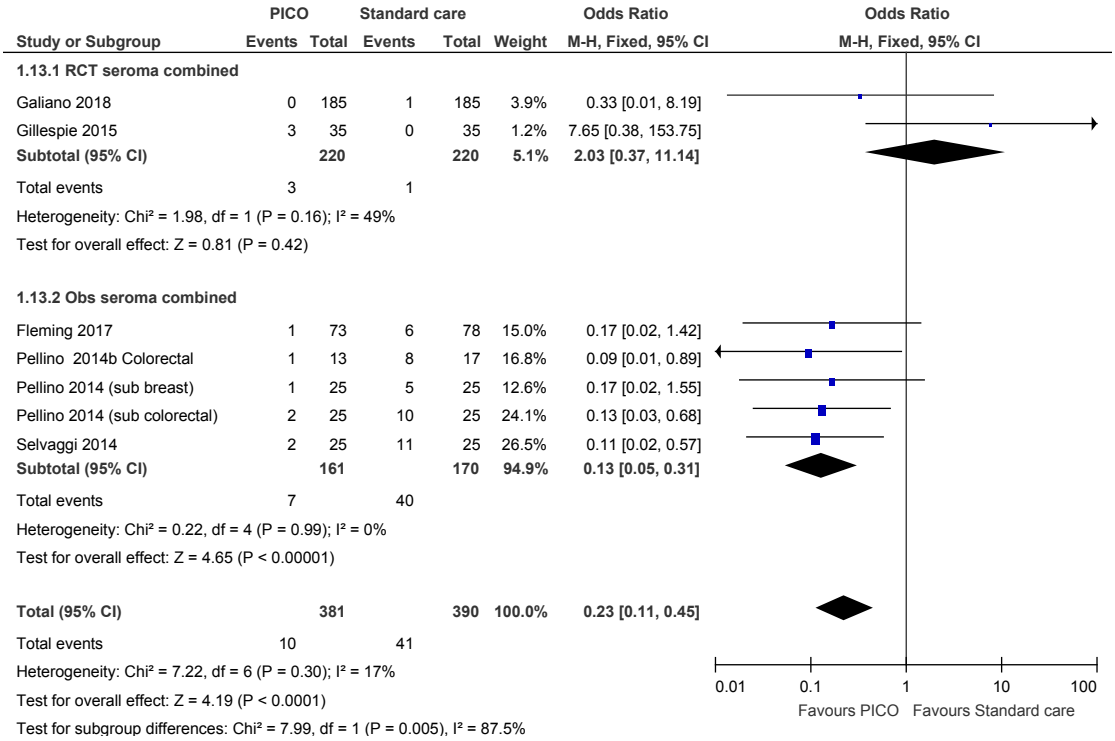
Forest plot of comparison: PICO versus Standard care, all surgeries surgical site infection



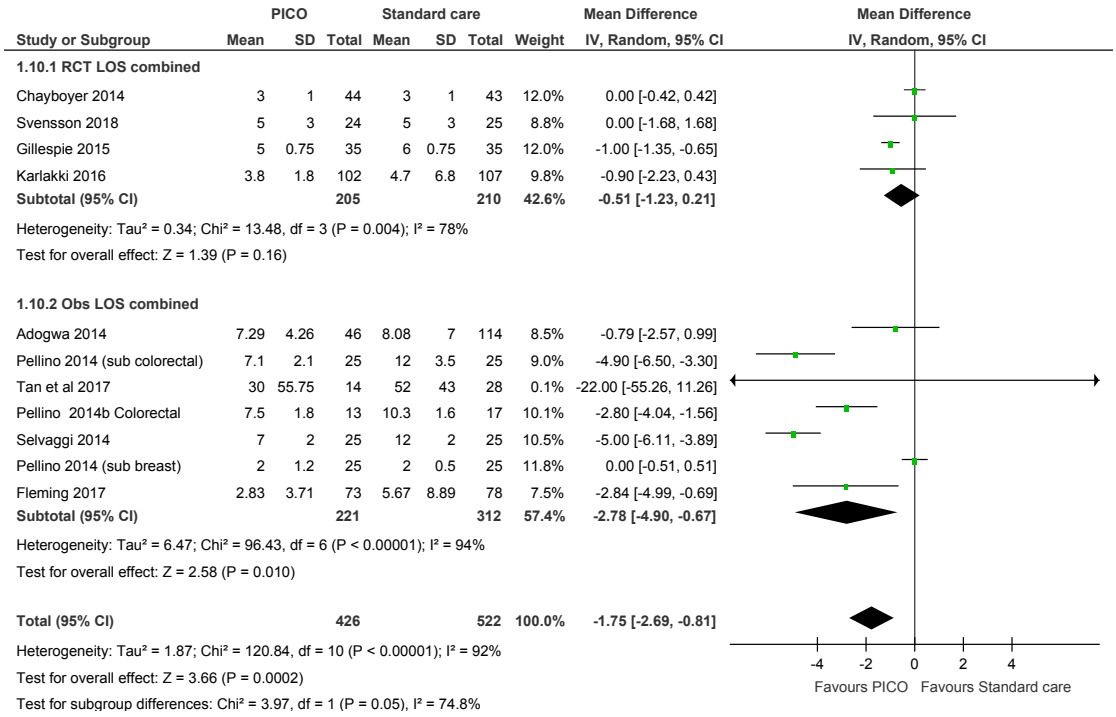
Forest plot of comparison: PICO versus Standard care, all surgeries dehiscence



Forest plot of comparison: PICO versus Standard care, all surgeries seroma



Forest plot for comparison: PICO versus Standard care, Length of stay



7.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Data related to the ease of use of the PICO device was qualitative in nature and could not be included in meta-analyses. Studies that reported on ease of use were Karlakki et al 2016, Pellino et al 2014b, Selvaggi et al 2014, Tanaydin et al 2018, and Galiano et al 2018. Karlakki et al 2016 stated that "the iNPWTd was easy to apply and well tolerated by patients". Selvaggi et al 2014 commented that "the device is safe and easily managed by patients". Pellino et al 2014b claimed that, although one patient experienced a problem with the device that was self-addressed by the patient, "no patients experienced difficulties with PICO requiring unscheduled outpatient visits". Tanaydin et al 2018 stated that "NPWT was easy to use" and Galiano et al 2018 commented that "ease of application, comfort and acceptability during wear were also assessed; SC [standard care] and NPWT were very similar (data not shown)". No other studies commented on the ease of use of the PICO device. Taken together, these comments suggest that the ease of use of the PICO device is at least in-line

with the standard of care. This was also reflected by comments from the clinical advisors supporting this submission.

Only one study formally assessed the time taken by staff to apply the device compared to the standard of care. Nordmeyer et al 2016 found that PICO required less wound care time (p = 0.0005) and fewer gloves were needed for dressing changes (p = 0.0006).

In addition to the above, there was considerable inter-study heterogeneity in how wound exudate was assessed and reported which precluded a meta-analysis from being performed on these data. Hyldig et al 2018 found that wound exudate was reported by fewer PICO patients (22.4% vs 32.9% for standard care), which corresponded to a relative risk of 0.69 (95% CI: 0.55-0.86; p = 0.001). Gillespie et al 2015 noted that there were no reported incidents of leakage in the PICO group (out of 35 patients), compared to two in the comparator group (out of 35 patients). Karlakki et al 2016 performed a more granular analysis and stratified wound exudate by the amount of dressing coverage. They again found that the level and number of peak exudate differed significantly between the groups (p = 0.007), with more PICO patients in the lower exudate grades and fewer patients in the high exudate grades. Other studies quantified the volume of wound exudate: Nordmeyer et al 2016 and Witt-Majchrzak et al 2015 found that volumes were lower in the PICO group (Nordmeyer et al 2016: mean 454mL vs 621mL; Witt-Majchrzak et al 2015: mean 610.8mL vs 632.1mL), although in neither study was this difference statistically significant. The former of these studies also found that there was a significantly lower number of days of wound secretion for the PICO subgroup (p = 0.0055).

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

This systematic literature review with meta-analysis has demonstrated a reduction in several important surgical site complications, including surgical site infections, dehiscence and seroma, compared to the standard of care. With surgical site

infections specifically, this reduction was seen across a range of surgical specialities, including orthopaedics, plastics/breast surgery, vascular surgery and C-Section. In other surgical indications (specifically for colorectal surgery), PICO demonstrated improved outcomes but these failed to reach statistical significance. This can be explained by the presence of multiple small studies within this analysis and potential outliers reporting results which were inconsistent with the broader body of evidence. Such variance between studies is not unusual in trials of medical devices and may be affected by an inability to control all confounding variables, such as user skills and, in this case, the consistent management of the device between acute and sub-acute care settings following discharge. Alternatively, it is possible that this may reflect the contaminated nature of colorectal surgery where many of the closed surgical incisions may be at higher risk of later infections.

In addition to these improvements in SSCs, this review has also shown that PICO has other benefits such as reducing the patient's length of hospital stay, which may be associated with the development of post-operative complications. Based on an assessment of all the available data, both in national regulatory databases of adverse events and published clinical studies, it is considered that PICO has a positive risk-benefit within the context of the intended indications.

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The major strength of the clinical evidence for PICO's use in closed surgical incisions is the depth and breadth of the evidence base. There were 12 randomised controlled trials (excluding two which were only published as conference abstracts) available which were included in the current analyses. Where findings were from studies other than RCTs, the included evidence came from comparative studies that compared PICO to the standard of care through observational study designs. Furthermore, many of these studies were published within the last 24 months, allowing for timely comparison to current standard of care in many cases. Additionally, the clinical studies identified demonstrated that PICO has benefits across a range of surgical specialities and in different geographical locations, thereby increasing the external validity of the

clinical evidence base. There was also a high degree of consistency in study findings both within indications and across indications.

A limitation of the data is that the number of patients included was relatively low in some instances which is not uncommon for studies of novel surgical devices. However, there were many studies included with relevant data that had in excess of 100 patients per treatment arm (Hyldig et al 2018, Hickson et al 2015, Kawakita et al 2018, Karlakki et al 2016, Galiano et al 2018, Irwin et al 2018). Future RCTs with larger patient numbers may refine the clinical benefit of PICO over the standard of care even further.

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

SSCs are burdensome to healthcare systems globally; according to the NICE guideline on preventing and treating surgical site infections [NICE; Clinical Guideline CG74], 20% of health-care associated infections are surgical site infections and approximately 5% of surgical patients develop a surgical site infection. The evidence base for PICO demonstrates clear advantages in reducing the incidence of SSCs when applied to closed surgical incisions, particularly for SSIs, compared to the standard of care. The data also demonstrate reductions in a patient's length of hospital stay, leading to additional resource benefits for the healthcare system. The evidence is strengthened by consistency across several surgical specialities and geographical locations. Furthermore, the patients included in most of the studies were broadly representative of the general surgical population.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

As with all clinical trials, the inclusion and exclusion criteria used for patient selection in the identified studies may influence the external validity of the main findings of this report. However, it was encouraging to see that PICO had demonstrable benefits across a range of surgical specialities and in different geographical locations. Furthermore, the inclusion criteria were generally broad, with the majority of the adult surgical population being potentially eligible for inclusion. Notable common exclusion

criteria were the presence of an existing infection or any evidence of allergy to the dressing material. In some cases, a BMI of ≥30 was used; this was principally for obstetric studies as this sub-group has been identified as being at elevated risk of surgical site complications. In this respect, the inclusion criteria in these studies selected a more challenging group of patients for treatment with PICO. Overall, the evidence demonstrated that PICO had benefits for patients at risk of surgical site complications, whether those were from patient-related risk factors (for example, increased BMI, older age, diabetes, current smoker) or procedure-related risk factors (for example, vascular or emergency surgery). This is illustrated by the subgroup analyses presented by Galiano et al 2018 and Pellino et al 2014a, which demonstrated an increasing benefit of PICO over the standard of care with increasing patient age and BMI.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

From the available clinical evidence, the device may be best suited for use after closed surgical incisions in patients with intrinsic risk factors for increased wound complications, such as high BMI or older age. In addition, PICO is likely to be particularly beneficial in surgical procedures that may have higher risk of surgical site complications and where the patient population may have high underlying incident rates of these risk factors (such as vascular surgery). The benefits of PICO are of particular importance where the consequences of SSI are severe and difficult to treat, such as orthopaedic surgery involving the use of implants.

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

The review of the economic evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA statement (www.prisma-statement.org/statement.htm).

A PDF copy of all included studies should be provided by the sponsor.

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

A systematic review was conducted to identify cost-effectiveness studies of relevant interventions for the prevention of surgical site complications (SSC) following closed surgical incisions. The following electronic databases were searched; PubMed, and Embase. Electronic searches were supplemented by hand searching the following sources; contacting clinical authors, and NICE guidelines. We also searched for unpublished health economic studies (the grey literature) in the Health Economic

Evaluation Database, NHS Economic Evaluation Database and DARE, Tufts Cost-Effectiveness Analysis Registry. We are not aware of best practice guidelines or standard tools for risk of bias assessments in economic evaluations. However there are a number of checklists that are used to assess the quality of the published studies, and we have used the adapted Drummond checklist recommended by NICE.

Full details of the search strategies employed are found in Section 10.3 and inclusion/exclusion criteria are presented in Section 8.1.2 below.

In total, 504 papers were identified through the electronic searches and three were identified through contacting authors. Upon the removal of duplicate papers, 104 titles and abstracts were reviewed of which, 20 were ordered for full paper review. Of the 20 full texts, 8 were excluded, resulting in 12 relevant papers for final inclusion (Figure 1 section 8.1.3). Of the 12 studies, 5 were full economic evaluations, 2 published (Nherera 2017 [45], Heard 2017 [46]) and 3 unpublished obtained through contacts with authors Galiano [47] Nherera [48] and Hyldig [49]. All 5 full economic evaluations evaluated the cost-effectiveness of PICO compared to SC in the prevention of SSC following closed surgical incisions. The remaining seven studies provided information on costing (Bullough 2015 [4], Fleming 2018 [8], Hickson 2015 [14], Jenks 2014 [18], Edwards 2018 [50] and McGeown 2017 [51]) Tanner 2009 [54].

8.1.3 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table 17 Selection criteria used for health economic studies

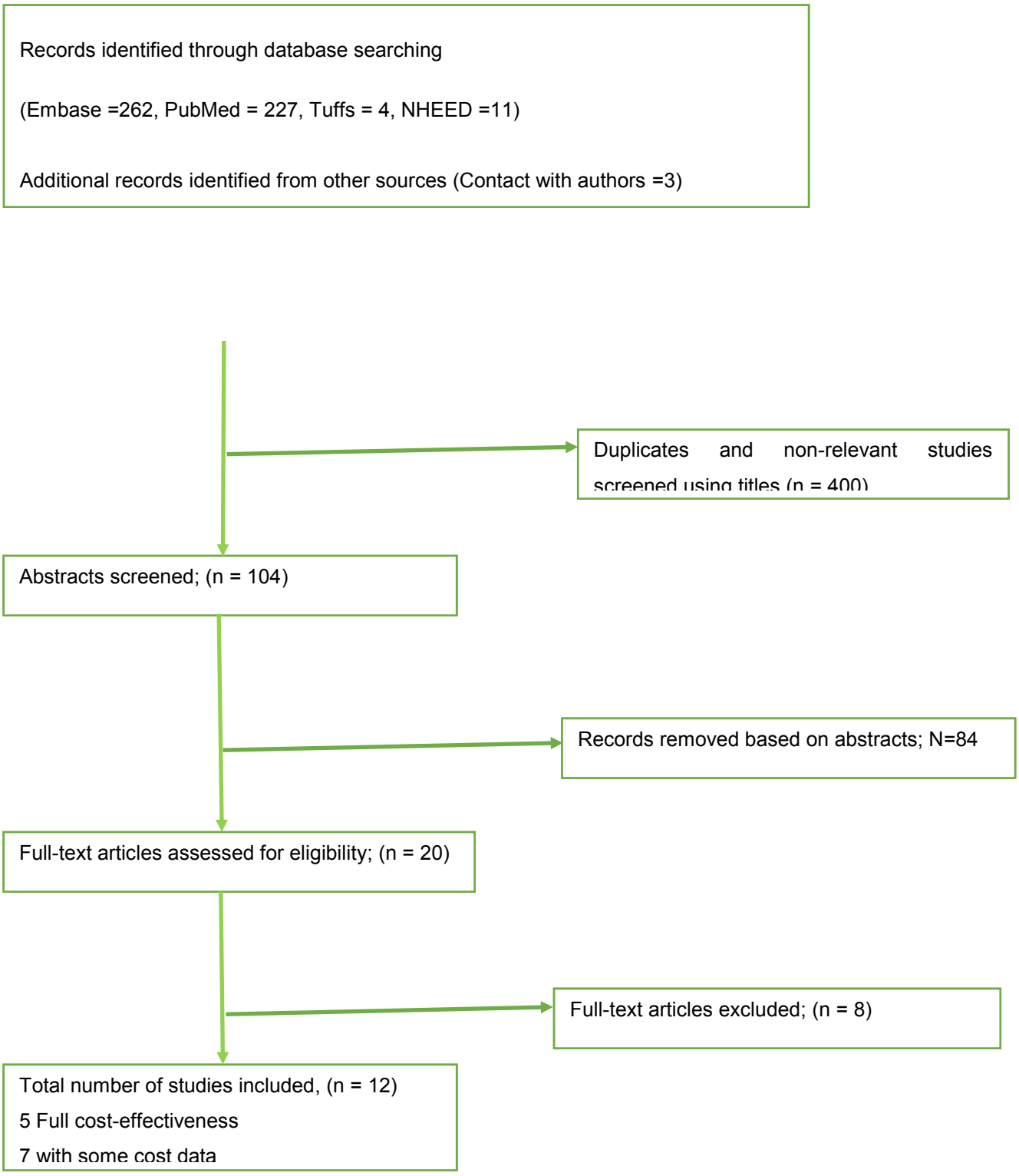
Inclusion criteria	
Population	Patients with closed surgical incisions
Interventions	PICO single-use negative pressure wound therapy system compared to standard of care (traditional post-operative wound dressings)
Outcomes	Cost, QALYs, complications avoided
Study design	CUA, CEA, Cost consequence analysis, Burden of illness, cost of illness or cost evaluation studies Database studies collecting cost data (e.g. claims databases and hospital records)
Language restrictions	English only
Search dates	2011-present
Exclusion criteria	
Population	Chronic wounds
Interventions	Traditional negative pressure wound therapy (non-single use) and other non-PICO negative pressure devices
Outcomes	None
Study design	None
Language restrictions	None
Search dates	Prior to PICO approval (2010 backwards)

8.1.4. Report the numbers of published studies included and excluded at each stage in an appropriate format.

Response

It is recommended that the number of published studies included and excluded at each stage is reported using the PRISMA statement flow diagram (available from www.prisma-statement.org/statement.htm)

Figure 1 presents the PRISMA flow diagram showing flow of studies through the systematic review process.



8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

After full text review a total of 5 articles considered to be full cost effectiveness studies were extracted into Table C2 below for inclusion in this submission (2 from the literature search and 3 studies pending publication identified through direct contact with authors). Three studies used a decision analytic approach and were all probabilistic (Nherera2017 [45], Nherera 2018 [48], Galiano 2018 [47]) and two were conducted alongside clinical trials (Heard 2017 [46], Hyldig 2018 [49]). The studies were conducted in UK, Germany, USA, Australia and Denmark. All the studies used clinical data from single RCTs in each case. A number of other studies considered the cost implications of use of PICO on closed surgical incisions but not in a structured framework for economic evaluation (Bullough 2015 [4], Fleming 2018[8], Hickson 2015 [14], Edwards 2018 [50] and McGeown 2017[51]). These studies concluded that PICO was cost saving, due to savings from the avoidance of complications exceeding the acquisition costs of the device. These studies were not considered to be full cost effectiveness studies and as such are not included in the synthesis of evidence below. The other two studies were not PICO specific, Jenks 2014 [18] and Tanner 2009 [54] but were detailed costing studies relevant to the NHS and management of surgical site complications. These two studies were used as the source of cost data that was applied in the model.

Figure 2 Summary list of full economic evaluations (published and unpublished)

Study name (year)	**Location of study & study type**	**Summary of model and comparators**	**Patient population *(key characteristics, average age)***	**Costs *(intervention and comparator)***	***Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)***	***Results (annual cost savings, annual savings per patient, incremental cost per QALY)***
Nherera (2017) [45]	UK *Both cost-effectiveness and cost utility analysis using a probabilistic decision analytic model*	sNPWT Standard of care (dressing of clinician's choice)	Patients undergoing primary hip and knee replacement Mean age = 69	Standard care £6,713 ($9,559) *Standard care £6,740 ($9,585)* sNPWT £5,602 ($7,954) *sNPWT £5,692 ($8,083)*	SC, Complications avoided 0.92 SC, QALY gained 0.115 *SC, Complications avoided 0.92* *SC, QALY gained 0.116* sNPWT, Complications avoided 0.98 sNPWT QALY gained 0.116 *sNPWT, Complications avoided 0.97 sNPWT QALY gained 0.117*	Difference in complications = 0.07 *Difference in complications = 0.059* Difference in QALYs = 0.0014 *Difference in QALYs = 0.0012* Incremental cost difference = £1,132 sNPWT savings £1,132 ($1,607) *Incremental cost difference = £1,132* *sNPWT savings £1,049 ($1,490)*

Heard (2017) [46]	Australia *Both cost-effectiveness and cost utility analysis conducted alongside a pilot RCT*	Pilot RCT 1:1 ratio using simple randomisation; NPWT PICO™ or standard care which consisted of Comfeel Plus® dressing	Obese women undergoing elective caesarean section with a pre-gestational BMI ≥30 kg/m2	sNPWT AU$ 5,887.21 Standard dressing AU$ 5754.04 Difference AU$ 133.17	sNPWT, Incidence of SSI = 25% SC, Incidence of SSI = 34.89% Difference = 9.88% sNPWT QALYs 0.069 SC, QALYs = 0.066 Difference = 0.0031	ICER AU$ 1347 per SSI prevented AU$ 42,339.87 per QALY
Nherera (2018) in press [48]	Germany *Both cost-effectiveness and cost utility analysis using a probabilistic decision*	sNPWT Standard of care	Patients undergoing coronary artery by-pass (CABG) surgery Mean age = 65 years	Standard care €20,572 sNPWT €19,986 BMI	SC, Complications avoided 0.952 SC, QALY gained 0.7934 sNPWT, Complications avoided 0.989 sNPWT QALY gained 0.8219 SC, Complications avoided 0.838 sNPWT, Complications avoided 0.989	Savings for base case Incremental cost difference = -€586 Savings for sub-group BMI Incremental cost difference = -€1,586

	analytic model			Standard care €21,572 sNPWT €19,986 Diabetes Standard care €21,356 sNPWT €19,986 Smoking Standard care €21,284 sNPWT €19,986	SC, QALY gained 0.7073 sNPWT QALY gained 0.8219 SC, Complications avoided 0.863 sNPWT, Complications avoided 0.989 SC, QALY gained 0.7259 sNPWT QALY gained 0.8219 SC, Complications avoided 0.871 sNPWT, Complications avoided 0.989 SC, QALY gained 0.7321 sNPWT QALY gained 0.8219	Savings for sub-group Diabetes Incremental cost difference = -€1,370 Savings for sub-group Smokers Incremental cost difference = -€1,298
Hyldig (2018) in press [49]	Denmark *Both cost-effectiveness and cost utility analysis*	sNPWT Standard of care (post-operative dressings)	Women undergoing caesarean section with a pre-gestational BMI ≥30 kg/m2 Mean age =32±5	Complete case analysis Standard care €5,624.70	SC, Incidence of SSC = 9.23% sNPWT, Incidence of SSC = 4.63% Difference = 4.6% SC, QALY gained = 43.437	Complete case analysis Cost per SSI avoided €902 Complete case analysis

	conducted alongside a RCT			sNPWT €5,667.10 Difference €42 Excluding the outlier Standard care €5,624.70 sNPWT €5,544.90 Difference = €79.80 Sub groups BMI ≥35 SC €5,952.70 sNPWT €5,844.90 Difference = €107.80	sNPWT QALY gained 43.814 Difference = 0.377	ICER €112/QALY Excluding the outlier Cost saving €79.80 BMI ≥35 Cost saving €107.80
Galiano (2018) in preparation [47]	US *A cost-effectiveness*	sNPWT Standard of care	Patients undergoing reduction mammaplasty	Standard care $3,106 sNPWT	SC, Expected incidence of dehiscence per patient [redacted]	[redacted]

	analysis using a probabilistic decision analytic model		Mean age- 35.7 (18–65)	$2,463 Scenario analysis Assuming that patients used 2 sNPWT (4 devices per patient) Standard care $3,106 sNPWT $2,903 Scenario analysis Assuming correlation of the left and right incisions Standard care $1,789 sNPWT $1,541	sNPWT, Expected incidence of dehiscence per patient [redacted]	[redacted]

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Table 18 Quality assessment of health economic studies

Study name: Nherera 2017 [45]		
Study design	CUA	
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	As reported in the clinical paper, any dressing of clinician choice which makes results generalisable
5. Were the alternatives being compared clearly described?	Yes	Mentioned in the abstract
6. Was the form of economic evaluation stated?	Yes	In the title
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Short term follow up of less than a year
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	RCT by Karlakki (10)
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Single study
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	Study conducted from the payer's perspective
15. Was the relevance of productivity changes to the study question discussed?	N/A	Study conducted from the payer's perspective
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	Time horizon less than a year
24. Was the choice of rate justified?	N/A	

25. Was an explanation given if cost or benefits were not discounted?	Yes	Time horizon less than a year
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and		

Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Study name Heard 2017 [46]		
Study design CUA		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Australian health payer
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Pilot RCT by the same authors
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Single study

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	Time horizon less than a year
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	Yes	Time horizon less than a year

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Hyldig 2018 (In press) [49]		
Study design CUA		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	RCT by the same authors
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Single study
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	

12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	Were deemed too small and therefore excluded
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	Time horizon less than a year
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	Yes	Time horizon less than a year
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	

28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	The study should have excluded the outlier patient from the main analysis, doing so would have led to a cost-saving conclusion
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Nherera 2018 (In press) [48]		
Study design CUA		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	As reported in the clinical paper, any dressing of clinician choice which makes results generalisable
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	In the title
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Short term follow up of less than a year
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	RCT by Witt-Majchrzak (20)
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Single study

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	Study conducted from the payer's perspective
15. Was the relevance of productivity changes to the study question discussed?	N/A	Study conducted from the payer's perspective
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	Time horizon less than a year
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	Yes	Time horizon less than a year

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Galliano 2018 (Manuscript in preparation) [47]		
Study design CUA		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Not clear	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Short term follow up of less than a year
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	RCT by Galliano
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Single study
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	

12. Were the methods used to value health states and other benefits stated?	Yes	Cost-effectiveness analysis with data from the a single RCT
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Cost-effectiveness analysis with data from the a single RCT
14. Were productivity changes (if included) reported separately?	N/A	Study conducted from the payer's perspective
15. Was the relevance of productivity changes to the study question discussed?	N/A	Study conducted from the payer's perspective
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	Time horizon less than a year
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	Yes	Time horizon less than a year

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

The included studies were of moderate to good quality. They all showed that PICO was a cost-effective intervention in preventing SSC. Three studies (Nherera 2017, Galiano 2018 (unpublished), Nherera 2018 (in press) concluded that PICO was cost saving. Heard 2017 and Hyldig 2018 concluded that PICO was cost-effective in obstetric surgery. In Hyldig study the result was cost-saving once an outlier was removed from the analysis. The overall conclusions from these studies is that PICO provides value for money to the healthcare payers and patients.

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

The scope requires an evaluation of the costs and resource consequences associated with the use of PICO sNPWT to the NHS. Due to the absence of economic evidence encompassing all the different surgical areas considered in the scope, a de novo cost analysis has been developed to capture resource use and estimate expected costs in relevant surgical indications from the NHS perspective.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

The base case analysis considered the population in the UK who attend hospital and have a surgical procedure of any type in line with scope issued by NICE. In addition to looking at the overall population at risk of SSC, we also considered the following sub-groups by surgery type:

- *Obstetric surgery patients*
- *Colorectal surgery patients*
- *Orthopaedic surgery patients*

- *Cardiothoracic surgery patients*
- *Plastic/breast surgery patients*
- *Vascular surgery patients*

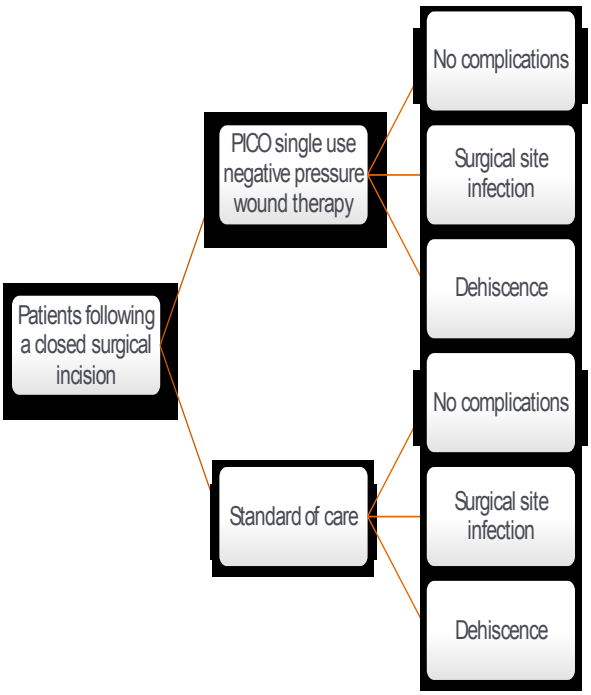
Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

The intervention is PICO single use negative pressure wound therapy. The technology has been described in Section 2.1-2.2. The comparator is standard of care (conventional post-surgical wound care dressings) as determined in the scope.

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.



9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

Response

A de novo cost consequence analysis was developed using Excel to explore the costs and health outcomes associated with the use of PICO sNPWT and standard care (standard post-operative dressings) for a cohort of 1000 patients undergoing surgery using a decision analytic approach.

The model is similar to previously published cost effectiveness analysis but allows for analysis of a total population as well as sub-groups undergoing specific surgical procedures. This addresses the shortcomings in the available published evidence.

Following a discussion with clinical experts, clinical outcomes in the model were limited to surgical site infections and dehiscence. We restricted the analysis to these surgical site complications because they are associated with the most significant remedial resource use. Other outcomes such as haematoma and seroma are therefore excluded, meaning that a conservative approach has been adopted.

The model adopts a short-term time horizon on the basis that most surgical complications occur relatively soon after surgery, although it is recognised that some dehisced surgical wounds can become chronic in nature and require long-term care following discharge, again meaning that a conservative approach has been adopted. As a result of the short time horizon, no discounting was necessary.

The perspective of the model is the NHS, thereby considering costs and outcomes which are incurred in both acute and community care following discharge. Whilst patients and employers may incur costs these are excluded, again as a conservative measure and in line with guidance for manufacturer submissions.

Consider how the model structure captures the main aspects of the condition for patients and the NHS. What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Cross-reference to section 3.3.

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

The majority of the baseline data on the rate of complications and the costs of treating complications are derived from a UK based study by Jenks 2014 [18]. The baseline SSI rates reported in this study are derived from observational, non-investigative data and are therefore assumed to be representative of standard practice in the UK.

Cost data were also derived from Jenks 2014. The mean attributable cost of an SSI reported was estimated to be £9,654.75, based on infections which occurred during the in-patient stay or resulted in readmissions for all surgical procedures that are of interest for this submission (See table C 3.1). For the purposes of our analysis we converted the relevant surgical specialities median costs to means using the following formula by Hozo 2005 [52]. Hozo et al found that for sample sizes greater than 25, the median is the best estimator of the mean for both normally distributed and skewed data.

*[=IF(N ≤ 25,(L+2*M+U)/4,M)].*

Where
N= number of patients
M= median cost
LB= minimum value
UB= maximum value

This cost was then inflated to 2016/17 using the hospital and community health services index [53].

In a further adjustment to the costs reported in Jenks [18] and Tanner 2009 [54], we sought to acknowledge that SSI can be treated in both acute and post-acute care settings, with very different resource impacts. To reflect this, we sought to estimate the proportion of complications that occur in acute and post-acute care settings and apply different costs. Both Jenks 2014 and Tanner 2009 report that around 15% of the attributable cost of SSI were incurred in the community.

We therefore derived weighted mean costs of SSI based on the proportions treated in acute and community settings and the application of different unit costs. The unit cost of an acute SSI was derived directly from Jenks 2014 for the majority of surgical specialties with the exception of colorectal which was derived from Tanner 2009. The unit cost of a community SSI was estimated to be 15% of the total acute care cost, based on the data reported in Jenks 2014 and Tanner 2009. When combined with the rates, we were able to derive a weighted mean cost for SSI and each surgical speciality as shown in Table C3.1.

Table 19 1, Conversion of median to mean SSI cost from Jenks 2014 [18]

Procedure type	**Median**	**Minimum value (a)**	**Maximum value (b)**	**Number of patients**	**Estimated mean**
Breast surgery	£1,469	£1,123	£4,058	3	£2,178.48
Vascular surgery	£2,480	-£757	£9,209	5	£3,598.69
Hip replacement	£3,214	£657	£17,040	11	£6,473.19
Knee replacement	£2,356	£2,356	£2,356	6	£2,528.63
Caesarean section	£3,716	£894	£4,905	25	£3,550.12
Cardiothoracic	£11,003	£8,517	£15,395	43	£11,809.24
Colorectal	£10,523*			69	£12,414.68
All surgeries	=SUMPRODUCT(numbers x corresponding mean)/ (162)			**162**	**£9,654.75**
*Data from Tanner 2009, otherwise all data is from Jenks 2014					

For each surgical procedure, we calculated the weighted cost for example in Breast surgery calculation

- *Firstly convert the median to mean costs using the formula [=IF(N ≤ 25,(LB+2*M+UB)/4,M)].*
- *Median £1,469, minimum value £1,123, maximum value, £4,058 and there were 3 patients (n), inflated by 7%. The estimated mean was £2,178.48*
- *Proportion of SSI that are in patient = 43.8%*
- *Community costs =15% of inpatient costs = (0.15*2178.48)*
- *Weighted Breast surgery cost in the model =inpatient costs + community costs = (0.438*2178.48)+ 0.15*2178.48*(1-0.438)=* ***£1,136.89***

This approach is considered to be conservative – it would have been less complex to simply apply the acute care cost to all cases – but more realistic of real practice where SSI in the community are likely to incur lower costs, primarily nurse time, dressings and medications.

No reliable data were identified on the cost of dehiscence. As a result, we applied the same unit costs as SSI. Given that dehiscence often requires additional surgery to close the wound this is again considered to be a conservative assumption as an observational colorectal study in Sweden by Zoucas [66] showed that the costs of wound disruption/dehiscence were higher than that of SSI. In sensitivity analysis we assumed there were no costs associated with dehiscence, and considered only infections as an extreme value analysis.

The cost of PICO was the weighted average of the different dressing sizes obtained from the list price. We assumed one PICO kit was used per patient (i.e. 7 days treatment), which consists of two dressings and therefore two dressing changes were also factored into the cost.

The cost of standard care was obtained from the list price and we used the cost of the commonly used surgical dressings. We assumed that standard care dressings were changed daily (5 times per week) in accordance with advice received from clinicians. No discounting was applied as the time horizon was short, 90 days post-surgery.

Effectiveness data on the impact of PICO were obtained from the meta-analysis conducted for the submission as reported in Section 7.8.1. These data were available for SSI, dehiscence and LOS.

The base case analysis considered the impact of PICO across all surgical procedures in line with the scope issued by NICE. We then considered the impact of PICO on individual surgery types where data were available for SSI (Orthopaedic, Colorectal, C-Section, Vascular, Cardiothoracic and Plastics/Breast surgery). Dehiscence and LOS was reported for combined surgeries only due to limited data.

Response

9.1.7 Define what the model's health states are intended to capture.

The model does not include health states per se. The health outcomes included in the model were SSI and dehiscence. As such, a patient with a closed surgical incision can experience no complications, SSI or dehiscence following surgery.

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table 20 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	90 days	This is the time that SSI/C manifest themselves especially the superficial and deep infections and is in line with the CDC definition.	European CDC [55]
Discount of 3.5% for costs	No discounting	Short time horizon less than 12 months	NICE methods guide
Perspective (NHS/PSS)	NHS	Scope of the review was NHS	Scope
Cycle length	N/A	N/A	N/A
NHS, National Health Service; PSS, Personal Social Services			

9.2 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical evidence section of the submission (section 7). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis

Baseline rates of infection and dehiscence were derived from literature (SSC, LOS,). The probability of SSI/Cs occurring with PICO sNPWT was based on effectiveness data from the meta-analyses reported in the clinical Section 7.8.1. Odds ratios (OR) for complications following treatment with PICO were applied to the baseline event rates. The base case model applies the combined Odds Ratios for all surgery types.

A sub-group analysis was conducted for each surgery type using effectiveness data from the meta-analysis. Within the surgery type we further considered risk factors such as BMI≥30, diabetes, ASA score ≥3 and smoking which are known

to affect the baseline and post-operative SSC risk. This was done in order to identify the sub-group of patients that would most benefit from PICO treatment.

In addition, if transition probabilities have been used in the model, explain how they were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here. If the (transition) probabilities vary over time for the condition or disease, state how this has this been included in the evaluation and if it has not been included, provide an explanation of why it has been excluded. If transition probabilities have not been used, explain how the results of the clinical evidence were incorporated into the model.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

No extrapolation was done due to the short time horizon considered in our analysis of 90 days.

In particular, consider what assumption was used regarding the longer term difference in effectiveness between the technology and its comparator.

Were any assumptions and/or techniques used for the extrapolation of longer term differences in clinical outcomes between the technology and its comparator?

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

N/A

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

No adverse events associated with the use of PICO (rather than as a result of the underlying surgery) were considered. Adverse events are rare and relatively minor (e.g. blistering). These would typically be treated through modification of analgesia, which patients typically receive as part of their recovery. As such, these are deemed to have little impact on the costs or clinical outcomes.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Response

The parameters in the model were derived from literature and the meta-analysis that was reported in Section 7.8.1. Clinicians were consulted to comment on the model structure and data inputs. Clinical input was sought from healthcare professionals with sufficient experience in the use of PICO to understand the decision problem. We also sought to identify experts from different clinical areas (infection prevention and different surgical specialities). We e-mailed clinicians from the company's contact list and for those that replied and shown interest, we scheduled telephone interviews describing the project and time needed to read the document. In total we contacted 10 clinicians and 5 responded and agreed to provide feedback.

- *Darly Mathew – Consultant Obstetrician & Gynaecologist , Chesterfield Royal NHS Trust*
- *Mr Anthony Kawesha - Consultant Colorectal and General Surgeon, Dudley Group NHS, West Midlands*
- *Heidi Caisley – ANP, Brighton & Sussex University NHS Trust*
- *Prof Edward Davis – Consultant Orthopaedic Surgeon, Royal Orthopaedic NHS Trust, Birmingham*
- *Mr Ben Ollivere – Consultant Orthopaedic Surgeon, Queen Medical Centre NHS Trust, Nottingham*

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

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

Details should also include the values used, range (and distribution) and source

Table 21 Summary of variables applied in the cost model

Incidence of SSI and dehiscence for various surgery types

Incidence of SSI				
Surgery type	**Mean**	**Total patients**	**Number of events**	**Source**
All surgeries	5.10%	14300	729	Jenks 2014 [18]
Orthopaedic	5.60%	107	6	Karlakki 2016 [19]
Colorectal	17%	105	18	Tanner 2009 [54]
C-Section	10%	4107	394	Wolch 2012 [42]
Breast surgery	5%	1016	49	Tanner 2011[56]
Vascular	7%	401	28	Jenks 2014 [18]
Cardiothoracic	11%	1672	180	Jenks 2014 [18]
Incidence of dehiscence				
All surgeries	6.90%	34096	2363	Calculated
Orthopaedic	3.60%	749	27	Krishnan 2016 [57]
Colorectal	8.60%	24232	2075	Cong 2014 [58]
C-section	6.50%	398	26	Subramaniam 2014 [59]
Breast surgery	4.60%	1324	61	Piper 2016 [60]
Vascular	9.00%	245	22	Biancari 2010 [61]
Cardiothoracic	2.10%	7148	152	Tarzia 2014 [62]

Proportion of SSI that occur inpatient

Surgery type	Inpatient SSI	Source
All surgeries	37.30%	Jenks 2014 [18]
Orthopaedic	33.30%	Karlakki 2016 [19]
Colorectal	68.80%	Tanner 2009 [54]
C-Section	11.20%	Wolch 2012 [42]
Breast surgery	43.80%	Tanner 2011[56]
Vascular	24.10%	Jenks 2014 [18]
Cardiothoracic	42.90%	Jenks 2014 [18]

Risk factors for SSI by surgery type - odds ratio of SSI

Surgical procedure	BMI≥35	Diabetes	ASA≥3	Smoking	Source
C-Section	2.01	1.63	1.61	-	Wolch 2012 [42]
Colorectal	1.88	1.12	1.07	-	Tanner 2009 [54]
Orthopaedic	2.78	3.33	3.84	-	Karlakki 2016 [19], Nherera 2017 [45]
Breast surgery	2.09	-	1.59	1.99	Tanner 2011 [56]
Cardiac		2	1.97	1.23	NICE CG74 [64]
Cardiothoracic	3.36	2.85	-	2.68	Olsen 2002 [65]

Effectiveness of PICO on rates of complications derived from the meta-analysis (Odds ratios, 95% CI)

Outcome	**Mean**	**Lower value**	**Upper value**	**Standard error**
All surgeries	0.39	0.29	0.52	0.149
Orthopaedic	0.43	0.21	0.86	0.36
Colorectal	0.56	0.07	4.51	1.063
C-Section	0.47	0.29	0.74	0.239
Breast surgery	0.36	0.14	0.97	0.494
Vascular	0.22	0.05	0.87	0.729
Cardiothoracic	0.12	0.01	1.03	1.182
Dehiscence	0.75	0.57	0.99	0.141

Reduction in length of stay in days from the meta-analysis - days

Outcome	**Mean**	**Lower value**	**Upper value**	**Standard error**
LOS reduction (days)	1.75	0.81	2.69	0.306

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

Costs of SSC are incurred across the primary and secondary care NHS settings. In acute care, where SSI results in extended LOS this is absorbed into the cost of the initial hospital stay. Where complications result in readmission within 30 days, this should not result in any incremental payment to the hospital, although in some cases additional procedure codes may be raised by hospitals to treat complications. In primary care, the majority of the care is provided by community nursing teams, to manage dressing changes, and general practitioners through prescription medications.

Provide Healthcare Resource Groups (HRG) and PbR codes and justify their selection.

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

There are no relevant HRGs or OPCS directly associated with the technology as it applied prophylactically following surgery to prevent SSC. As such it is considered part of the procedure rather than a standalone procedure per se.

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

A systematic review for evidence on the cost effectiveness of PICO identified a number of relevant studies that were utilised to populate the model. However, given the time available to prepare the submission, it was not possible to undertake a second systematic review for resource use and cost data. Rather, a purposive search was

undertaken starting with known economic studies of PICO and two known studies of the costs of SSI, notably Jenks 2014 and Tanner 2009. These two studies provided a detailed cost analysis of costs attributable to SSI following different surgical procedures. Furthermore, both studies adopted an NHS perspective and reported costs in UK£. Both were also based on observational analyses, rather than trials, and as such, are considered to be broadly representative of NHS practice. Data from these two studies were deemed relevant and were therefore used for the denovo cost analysis. The cost data were adjusted for inflation and weighted to reflect that a proportion of costs are incurred in hospital and the community. Data from Jenks 2014 [18] and Tanner 2009 [54] was presented in Table C3.1 in Section 9.1.6. Table C5.1 below shows the data extracted from the PICO specific studies.

Table 22 1, PICO specific costing studies

Study name (year)	**Location of study**	**Summary of model and comparators**	**Patient population *(key characteristics, average age)***	**Costs *(intervention and comparator)***	***Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)***	***Results (annual cost savings, annual savings per patient, incremental cost per QALY)***
Hickson (2015) [14]	US	Patients were separated into either a high-risk or low-risk category. Body-mass index (BMI) in excess of 35 kg/m^2 were placed in the higher risk category. Standard post-operative dressings were used (2007) Traditional negative pressure wound therapy (tNPWT)	The mean BMI of patients over the 5-y period was 35 (±7) kg/m^2 and the mean age was 28 (±6) y.	Cost for managing a low-risk patient was $32.94 (2007) Cost of incisional bolstering with traditional NPWT (Non-PICO device) required by a high-risk patient is $348.62 (2008-2011) High-risk patient with incisional	SSI in (2007) 2.13% SSI in (2012) 0.10% Absolute decrease (2007-2012) 2.03% Prior to 2011 standard post-operative dressings were used (soft cloth adhesive dressings and absorbent cotton gauze dressings)	Ninety-two caesarean SSIs were prevented since implementing the bundle. Yielding an approximate cost savings of $5,000,000 (based upon a historic average of $50,000 per readmission).

		was used on high-risk patients (2008–2011). The single-use NPWT system (2012). In 2012 tNPWT was replaced with the single-use NPWT system in the formal high-risk dressing bundle implemented in 2012.		bolstering with the single-use negative pressure device (PICO) is $245.30 (2012) (A savings of $103.32 per patient compared with tNPWT)		
McGeown (2017) [51]	Northern Ireland	Standard dressing PICO (NPWT)	34 year old woman who had received 71 days of standard daily dressing changes following day 4 dehiscence of a post-op breast	62X standard dressings = £930 (£15 each) 62 visits from practice nurse =£1,550 (£25 per visit) % Review visits= £500 (£100 each) Total= £2980 3X PICO dressings= £360 (£120 each)	The breast care nurse specialist (BCN) reported that the PICO dressing was easy to apply, was delighted with the speed of wound healing and reduction of pain due to fewer dressing changes. Additionally, the patient's quality of life was reported to	Potential savings of £2,445 if PICO system had been applied post-operatively on day 4 when dehiscence occurred.

			abscess wound	3X Breast Care Nurse Specialist visits =£75 (£25 per visit) 1 Review visit= £100 Total=£535	have greatly improved as was the patient's mood and satisfaction with breast care service.	
Edwards (2018) [50]	UK	Retrospective, longitudinal review was conducted in 2017, on all plastic surgery patients' who received a PICO™ device for wound management. Data from 2012-2017	Plastic surgery wounds Median patient age: 50 years Even gender divide	Total PICO cost over review period £60,606.20 Nurse resource cost £9,6023.20 Total cost of bed day released £146,800	Number of bed days released 367	Total cost efficiency savings £76,591.60
Bullough (2015) [4]	UK	In all cases, the NPWT system was applied in theatre onto closed wounds, following suturing. PICO therapy was applied in theatre immediately following the	Patients having C-section Average age: 30.2 33.5% of patients had BMI>=40	PICO £11,476 Previous protocol £0 Readmissions with PICO £0	In women with BMI>35 treated with PICO (n = 239), only one patient developed a wound infection (0.4%). The patient who developed an infection had gestational diabetes	Annual savings £122,300

		operation and was left in situ for one week only BMI>35	About 35% had 2 or more C-sections	Readmissions with previous protocol £133,776	and was having her second Caesarean section. The infection was superficial in nature and the patient was not readmitted to hospital for treatment.	
Fleming 2018 [8]	Ireland	Six week study for patients who had peripheral vascular Surgery in Ireland	151 patients who had peripheral vascular surgery were analysed PICO 73 standard care 78 Mean age 71	Cost of dressings €20,880 Cost of 17 bed days @ €814 =€13,838 PICO total costs €34,718 Cost of 85 bed days @€814 Standard care €69,190	Wound complications PICO 6/73 SC 15/78 Re-admission LOS (days) PICO 3/50 SC 6/4 Total bed days PICO 17 SC 85 Cost per bed day €814	Savings from PICO €34,472

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[1].

Response

Given the short timelines for submission it was not possible to conduct any formal Delphi panels or consensus based approaches to validating the model inputs. We identified healthcare professionals with relevant expertise in the use of PICO and management of SSCs. However, a number of clinicians were consulted as part of the model development, as detailed earlier in Section 9.2.5.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

PICO Dressing size	Unit cost
10cm x 20cm	£128.09
10cm x 30cm	£127.45
10cm x 40cm	£146.86
15cm x 15cm	£127.45
15cm x 20cm	£127.45
15cm x 30cm	£146.86
20cm x 20cm	£146.86
25cm x 25cm	£146.86
15cm x 20cm	£126.88
20cm x 25cm	£145.48

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

£130 per kit– weighted average by sales volume and cost of different sizes

A rationale must be provided for the choice of values used in the cost model. All prices should be referenced. Any uncertainty around prices should be

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

addressed by sensitivity analysis. All costs must be cross-referenced to other sections of the submission if possible.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

When completing tables C6 and C7 the price of the technology should refer to the list price stated in 9.3.4 unless a justification for using an alternative price has been provided in 9.3.5. If a technology is not for single use and consumables are needed to provide a treatment, these must be itemised and a breakdown of prices presented.

For all costs presented a source of the data must be stated.

Table 23 Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	£130 (2 dressings per pack) x 1 kit per week =£130 per week	Drug Tariff (July 2018) and volume data

Table 24 Costs per treatment/patient associated with the comparator technology in the cost model

Items	Value	Source
Cost of the comparator per treatment/patient	£2.50 (1 dressing) x 5 dressing changes per week =£12.50	Weighted average cost (foam dressings)- 2016/17 IMS Health by volume and cost per dressing
Dressing change costs	The cost is included in the calculated cost of SSC inpatient and outpatient costs	See sec 9.1.6 for dressing changes assumption

Health-state costs

If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in

section 9.1.7. Provide a rationale for the choice of values used in the cost model.

The model does not have health states per se. However, the costs associated with SSI/C in the different surgical areas are presented in table C8

Table 25 List of health states and associated costs in the economic model

SSI cost used in the model	Weighted SSI cost	Lower 95% CI	Upper 95% CI	SE	Source
Orthopaedic	£2,201.76	£1,651	£2,752	£281	Jenks [18]
Colorectal	£7,842.79	£5,882	£9,803	£1,000	Tanner [54]
C-Section	£869.51	£652	£1,087	£111	Jenks [18]
Breast surgery	£1,136.89	£853	£1,421	£145	
Vascular	£1,850.75	£1,388	£2,313	£236	
Cardiothoracic	£4,187.91	£3,141	£5,235	£534	
All surgeries	£4,505.55	£3,379	£5,632	£575	Calculated
Abbreviations: CI; confidence interval, SE; standard error We assumed that costs will be ±25% of the mean cost to derive the 95% CI					

Adverse-event costs

9.3.8 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Table 26 List of adverse events and summary of costs included in the cost model

No adverse events costs were included in the model. As described earlier, adverse events are typically minor (e.g. blistering) and managed through adjustment to standard analgesia.

Miscellaneous costs

9.3.8 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Only direct costs to the NHS are considered in the model. Whilst there may be savings to patients and employers as a result of faster recovery, no attempt is made to quantify these.

9.3.9 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Response

The occurrence of surgical site complications creates unpredictability about hospital length of stay and in the worst cases can create bed-blocking or unplanned readmissions. Using PICO to reduce complications can help avoid both.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

One way and probabilistic sensitivity analysis were implemented.

Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied, and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

A range of one way sensitivity analyses were performed for the modelling analyses to consider the variation in the incremental cost when plausible ranges of parameter values were independently considered. A probabilistic SA was implemented. The rationale for the ranges tested are as follows:

- ***Efficacy parameters*** *(OR and baseline probabilities of events): Base case OR were adjusted based on 95% confidence intervals from the analysis of the Meta Analysis.*
- ***Dressing costs****: Variations in dressing costs were derived from alternative dressing sizes as reported by the Drug Tariff (highest and lowest prices). Only PICO costs were varied as the standard care costs were considered insignificant.*
- *Cost per surgical procedure were varied by ±25% which was considered sufficient variation to capture relevant uncertainty as there were no standard errors reported.*
- *Analysis by surgery type was done and we also considered the risk factors for SSI to establish patients that will benefit most*
- *A probabilistic sensitivity analysis was implemented*

9.4.2 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table 27 Variables used in one-way scenario-based deterministic sensitivity analysis

Baseline incidence of SSI and dehiscence

Variable	Base case	Lower value	Upper value	Source
SSI	0.051	0.015	0.18	Jenks 2014 [18], CG74 [64]
Dehiscence	0.069	0.013	0.093	World Union [63]

Effectiveness of PICO from the meta-analysis – odds ratio

Variable	Base case	Lower value	Upper value	Source
SSI	0.39	0.29	0.52	Meta-analysis
Dehiscence	0.75	0.57	0.99	Meta-analysis

Cost data

Variable	Base case	Lower value	Upper value	Source
PICO	£130	£128	£147	Drug Tariff
Standard of care	£2.50			Weighted average cost (foam dressings)-2016/17 IMS Health by volume and cost per dressing
SSC cost	£4,505.55	£3,379	£5,632	Calculated

Table 28 Variables used in multi-way scenario-based sensitivity analysis

Variable	*Parameter 1*	*Parameter 2*	*Parameter 3*
Base case			
Scenario 1			
Scenario 2			

N/A

Table 29 Variable values used in probabilistic sensitivity analysis

Baseline incidence SSC values

Variable	Base case	N	Events (alpha)	No events (beta)	Distribution
SSI	0.051	14300	729	13571	Beta
Dehiscence	0.069	34096	2363	31733	Beta

Effectiveness of PICO from the meta-analysis – odds ratio

Outcome	Mean	Lower value	Upper value	Standard error	Distribution
SSI	0.39	0.29	0.52	0.149	Log normal
Dehiscence	0.75	0.57	0.99	0.141	Log normal

Cost data

Item	Mean	Lower value	Upper value	Standard error	Distribution
PICO	£130	£128	£147	£5	Gamma
Standard care	£2.50				Not varied
SSC cost	£4,506	£3,379	£5,632	£575	Gamma

9.4.3 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

N/A

It is acknowledged that some model parameters may be excluded from sensitivity analysis considerations, for example, because they can be considered 'constant' or because evidence exists about unbiased and accurate measurement.

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.4.4 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

Table 30 Base-case results

The model was run for a cohort of 1000 patients for all surgeries combined

Results	PICO	Standard care	Difference
Total cohort costs	£453,806	£554,537	-£100,731
Total cost per patient	£453.81	£554.54	-£100.73

9.4.5 Report the total difference in costs between the technology and comparator(s).

-£100.73 per patient, in favour of PICO treated patients, see table C12 for detailed breakdown of the costs. That is, the incremental cost of PICO is more than offset by savings accrued as a result of fewer surgical site complications.

9.4.6 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Table 31 Summary of costs by category of cost per patient

Item	Cost *PICO*	Cost *Standard care*	Increment
Technology cost	£130	£12.50	£117.50
Mean total treatment cost	£323.81	£542.04	-£218.23
Total	£453.81	£554.54	**-£100.73**
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee (Modified version)			

9.4.7 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

N/A

Table 32 Summary of costs by health state per patient

N/A

9.4.8 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

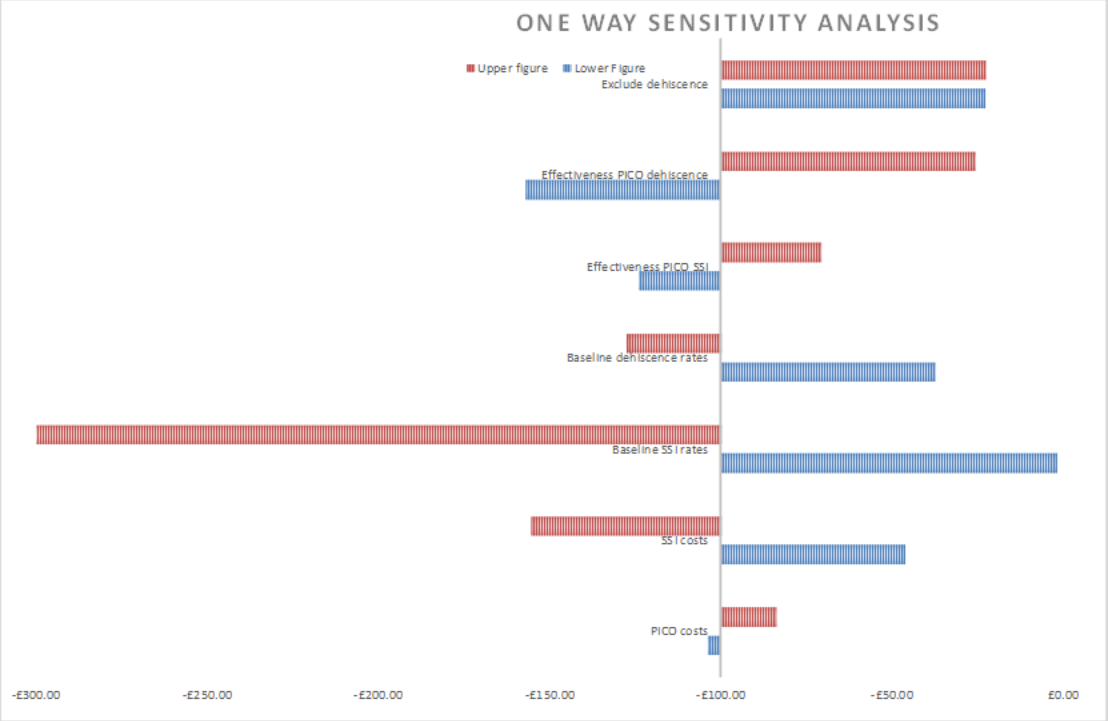
Table 33 Summary of costs by adverse events per patient

N/A

Sensitivity analysis results

Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

One way sensitivity analysis Tornado diagram



One way sensitivity analysis showed that the results were robust with PICO remaining cost saving even at extreme values. The findings were most sensitive to changes in the baseline rate and costs of surgical site complications. However, even with uncertainty around the main variables considered, PICO should be considered to be a cost saving intervention.

9.4.9 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

N/A

9.4.10 Present results of the probabilistic sensitivity analysis described in table C10.3.

Results of probabilistic sensitivity analysis (scatter plot)

We conducted PSA and ran 2000 simulations. The results showed that in 100% of the 2000 simulations, PICO was cost saving when compared with standard care and the difference in costs was statistically significant. The mean cost savings per patient were £326, this corroborates the findings from one way sensitivity analysis and the base case which showed PICO to be cost saving.

9.4.11 What were the main findings of each of the sensitivity analyses?

PICO remained cost-saving when various inputs were changed individually as well as in the probabilistic analysis. The findings were robust to changes in all key parameters, including extreme values. The exclusion of any treatment costs associated with dehiscence, thereby considering only infection as an adverse outcome, did not change the model conclusions and PICO remained cost saving. It should be emphasised that these results are achieved with a number of conservative assumptions in the model.

What are the key drivers of the cost results?

The baseline risk of SSI and cost of SSI are the major drivers.

Miscellaneous results

9.4.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

Response N/A

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

The base case model considered all surgical specialities together. In sub group analyses we considered surgery types that were identified in the scope and had data available in literature. However, it should be acknowledged that in doing so it was necessary to base some inputs on relatively small samples so some caution should be taken in interpreting the findings of the sub-groups.

We also considered patients with known risk factors for SSI. In practice these patients are often identified as those most able to benefit from treatment with PICO. We adopted a conservative assumption that patients will have one risk factor at a time, we note in practice patients are likely to make multiple risk factors for instance diabetes and BMI≥30 are likely to occur at the same time. As such, some caution should be taken in interpreting the results.

Consider if these subgroups were identified on the basis of a hypothesised expectation of differential clinical benefit or cost because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors.

9.6.2 Define the characteristics of patients in the subgroup(s).

Patients undergoing surgical specialties including orthopaedic surgery, colorectal surgery, breast surgery, C-section surgery, vascular surgery and cardiothoracic surgery.

The following risk factors were used to identify patients at elevated risk of surgical site complications:

ASA score ≥3

Diabetes

BMI ≥30

Smoking

9.6.3 Describe how the subgroups were included in the cost analysis.

Data on the rate of SSCs in the surgical specialties were derived from literature and used as a basis for the analysis. Odds ratios for SSC based on the presence of known risk factors were applied to the baseline rates to reflect the increased risk of SSI these populations.

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis)

Results by surgery type

Across surgical specialties, PICO remains the dominant treatment option for colorectal, cardiothoracic and vascular surgery. In the other indications, which are typically associated with shorter hospital stays, fewer infections and lower SSI cost, PICO is marginally cost additive when used across all patients. However, some caution should be taken in interpreting these findings given the small sample sizes used to derive some of the inputs.

Subsequent analyses will consider more targeted use in high-risk patients in these indications. Results by surgery type are shown in Table C13.1

Table 34 Sub-group by surgery type

Orthopaedic surgery				
Intervention	**Intervention costs**	**Consequence costs**	**Total cost per patient**	**Cost difference**
Standard Care	£12.50	£202.83	£215.33	
PICO	£130.00	£112.62	£242.62	£27.28*
Colorectal surgery				
Standard Care	£12.50	£2,020.54	£2,033.04	
PICO	£130.00	£1,259.10	£1,389.10	-£643.94
C-Section surgery				
Standard Care	£12.50	£140.22	£152.72	
PICO	£130.00	£81.81	£211.81	£59.09*
	Breast surgery			
Standard Care	£12.50	£107.21	£119.71	
PICO	£130.00	£59.02	£189.02	£69.31*
Vascular surgery				
Standard Care	£12.50	£295.42	£307.92	
PICO	£130.00	£153.07	£283.07	-£24.85
Cardiothoracic surgery				
Standard Care	£12.50	£539.91	£552.41	
PICO	£130.00	£120.89	£250.89	-£301.51
*PICO was marginally cost additive				

Impact of commonly risk factors for individual surgery types

When limited to patients at elevated risk of surgical site complications, PICO remained dominant in orthopaedic, cardiothoracic, vascular and colorectal surgery. In the case of breast surgery and C-Section PICO was marginally cost

additive in some high-risk patient groups. This stems from lower costs attributable to surgical site infection in these patient groups. Some caution should be taken in interpreting sub-group analysis as the derivation of some variables was based on small studies. Furthermore, we made a simplifying assumption that co-morbidities were independent whereas in practice, patients may experience one or more risk-factors.

This may explain the dissonance from previously published studies in C-sections and breast surgery which have previously reported cost savings as a result of PICO.

Table C13.2 shows the results by surgery type and commonly reported risk factors.

Table 35 Sub-group by surgery type and risk factors

Orthopaedic surgery			
Risk factors	**PICO**	**Standard care**	**Cost difference**
ASA≥3	£393.39	£565.97	-£172.58
Diabetes	£366.31	£503.00	-£136.69
BMI≥30	£337.12	£435.10	-£97.98
C-Section surgery			
	PICO	Standard care	Increment
ASA≥3	£235.72	£203.60	£32.12
Diabetes	£236.51	£205.27	£31.24
BMI ≥35	£316.48	£375.44	-£58.95
Breast surgery			
	PICO	Standard care	Increment
ASA≥3	£200.67	£152.06	£48.61
BMI≥30	£210.54	£179.48	£31.06
Smoking	£208.57	£173.99	£34.57
Colorectal surgery			
	PICO	Standard care	Increment
ASA≥3	£1,441.98	£2,127.47	-£685.49
Diabetes	£1,479.75	£2,194.92	-£715.16
BMI≥30	£2,053.87	£3,220.13	-£1,166.26
Vascular surgery			
ASA≥3	£310.65	£433.27	-£122.62
Diabetes	£311.50	£437.15	-£125.65
Smoking	£289.61	£337.64	-£48.03
Cardiothoracic surgery			
BMI≥30	£378.57	£1,616.41	-£1,237.84
Diabetes	£350.98	£1,386.48	-£1,035.50
Smoking	£341.78	£1,309.84	-£968.05

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

It was only possible to identify data to support sub-group analysis of patients with some risk factors for surgical site complications. Data at a specialty level also limited some analyses.

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The technical validity of the model was quality assured by doing the following

- *Testing whether all sheets and other items were in working order*
- *Changing inputs to determine whether they function as expected*
- *Manually calculating the cost impact and correlating with model to ensure the formulas are correct*
- *Two Health Economists looked at the model separately to check for errors*
- *Two external advisors Professor Michael Drummond University of York and Professor Francis Fatoye of Manchester Metropolitan University commented on the model and the results*

  Probabilistic and one way sensitivity analysis was implemented to test different data assumptions.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Our results were comparable from those reported in published literature. Studies by Nherera in orthopaedics and one in cardiothoracic surgery (in press) concluded that PICO was cost-saving.

In C-section, one previously published study concluded that PICO was cost-effective (Heard 2017) which used data from a pilot study and a second study by Hyldig 2018 concluded that PICO was cost-saving when data from an outlier was removed from the analysis. The outlier was an obese woman BMI>40 whose cost was 3 times higher than the second most costly patient and contributed over €120 to the mean total costs. Our analysis shows that women who undergo a C-section and have BMI>30 benefit most from PICO treatment.

A study by Galliano 2018 for breast surgery concluded that PICO was cost saving in the US. This differs from our current analysis which showed PICO resulted in a marginal increase in costs in this patient group. This may be due to the use of conservative assumptions that we adopted for our analysis. Galiano considered dehiscence alone and the unit costs per case of dehiscence in his model was $US 6,777 compared to our weighted cost of £1137.

In higher risk and higher cost surgeries such as colorectal, cardiothoracic and vascular surgery, PICO was always found to be cost saving. This finding is not surprising given the high cost of surgical complications for these surgeries.

Our analysis used data from a robust meta-analysis and we used costs that were relevant to the NHS. The base case analysis showed that PICO is cost-saving when compared to standard care. The savings are more pronounced when the baseline risk for SSI is higher as was evident when risk factors were considered. This was also the case when surgery types that are associated with higher risk of infection such as colorectal surgery has higher savings.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

Yes, the analysis considers all surgery types and where data permitted, we considered some individual surgery types in isolation.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Strengths:

The technology is underpinned by strong and robust clinical evidence from both randomised and observational evidence. Costs were derived from detailed studies that were conducted in NHS hospitals by Jenks 2014 and Tanner 2009. A wide range of sensitivity analyses were conducted to test key model assumptions, and the base case results are robust. Both one way and PSA results corroborates the base case findings that using PICO prophylactically following surgical procedures saves money for the NHS.

The model and the write up was validated externally by well-respected health economists and academics Professor Michael Drummond University of York and Professor Francis Fatoye of Manchester Metropolitan University.

Weaknesses:

A number of simplifying assumptions were made in an attempt to provide analyses relevant to the decision problem and account for the limitations in the data. These are listed below:

- *Dehiscence was assumed to have the equivalent cost to SSI, in the absence of detailed data. In practice, dehiscence can result in the need for additional surgery or lengthy ongoing care and as such may result in excess treatment costs. We did stress the model by eliminating the costs and outcome of dehiscence and the model remained cost-saving although the savings were lower than the base case.*
- *Furthermore, dehiscence and SSI were assumed to be independent. The relationship between dehiscence and SSI is somewhat complicated as some SSI are due to dehiscence and vice-versa.*
- *Exclusion of all other surgical site complications, such as haematoma and seroma, despite evidence suggesting that PICO may reduce their incidence;*
- *Limiting the time horizon to 90 days which was intended to capture the incidence of complications but may not capture longer-term costs associated with these;*

- *Adjusting the reported cost per SSI to a weighted cost per SSI in an attempt to reflect the resources used to treat these in acute and community care settings;*
- *Assuming that risk factors of SSI are independent, when in reality patients often present with multiple morbidities;*
- *Excluding all costs that are incurred beyond the NHS, including productivity costs, which may be significant;*
- *Excluding intangible costs, such as patient pain, recovery and concerns over cosmetic outcomes.*

Whilst these are all limitations of our model, the approach adopted in every case was considered conservative and as such, may under-estimate the savings associated with PICO. Sensitivity analysis provides an indication of the scale of potential savings above the base case assumptions.

What further analyses could be undertaken to enhance the robustness/completeness of the results?

None, we believe we have done all the necessary analysis with the available data.

References

1. Adogwa O, Fatemi P, Perez E, Moreno J, Gazcon GC, Gokaslan ZL, Cheng J, Gottfried O, Bagley CA. Negative pressure wound therapy reduces incidence of postoperative wound infection and dehiscence after long-segment thoracolumbar spinal fusion: a single institutional experience. *Spine J* 2014;14(12):2911-7.

2. Andersson A, Bergh I, Karlsson J and Nilsson K. Patients' experiences of acquiring a deep surgical site infection: An interview study. *American Journal of Infection Control* 2010;38: 711-717.

3. Bullough L, Wilkinson D, Burns S and Wan L. Changing Woundcare protocols to postoperative caesarean section infection and readmission. *Wounds UK* 2014. Vol 10, No 1.

4. Bullough L. Reducing C-section wound complications. *The Clinical Services Journal* 2015a; 43-47.

5. Bullough, L. Incision management with negative pressure wound therapy : a new mode of action? *Wound Essentials* 2015b: Vol 10;1:14-18.

6. Chaboyer W, Anderson V, Webster J, Sneddon A, Thalib L, Gillespie BM. Negative pressure wound therapy on surgical site infections in women undergoing elective caesarean sections: a pilot RCT. *Healthcare (Basel)* 2014;2(4):417-28.

7. Dingemans SA, Birnie MFN, Backes M, de Jong VM, Luitse JS, Carel Goslings J, Schepers T. Prophylactic negative pressure wound therapy after lower extremity fracture surgery: a pilot study. *Int Orthop* 2018;42(4):747-53.

8. Fleming CA, Kuteva M, O'Hanlon K, O'Brien G, McGreal G. Routine use of PICO dressings may reduce overall groin wound complication rates following peripheral vascular surgery. *J Hosp Infect* 2018;99(1):75-80.

9. Galiano RD, Hudson D, Shin J, van der Hulst R, Tanaydin V, Djohan R, Duteille F, Cockwill J, Megginson S, Huddleston E. *Plast Reconstr Surg Glob Open* 2018;6(1):e1560.

10. Gillespie BM, Rickard CM, Thalib L, Kang E, Finigan T, Homer A, Lonie G, Pitchford D, Chaboyer W. Use of negative-pressure wound dressings to prevent surgical site complications after primary hip arthroplasty: a pilot RCT. *Surg Innov* 2015;22(5):488-95.

11. Gray D. Assessment, diagnosis and treatment of infection. *Wounds UK* 2011. Vol 7, No.2.

12. Hackney L, McCoubrey A. The effect of negative pressure dressings (PICO) on wound complications, readmission rates and length of stay. *Colorectal Disease* 2017;19(Suppl 2):60.

13. Hester T, Mahmood S, Moftah F. Is single use portable incisional negative pressure wound therapy system suitable for revision arthroplasty? *Advances in Orthopedic Surgery* 2015;247324.

14. Hickson E, Harris J, Brett D. A journey to zero: reduction of post-operative caesarean surgical site infections over a five-year period. *Surg Infect (Larchmt)* 2015;16(2):174-7.

15. Holt R, Murphy J. PICO incision closure in oncoplastic breast surgery: a case series. *Br J Hosp Med (Lond)* 2015;76(4):217-23.

16. Hyldig N, Vinter CA, Kruse M, Mogensen O, Bille C, Sorensen JA, Lamont RF, Wu C, Heidemann LN, Ibsen MH, Laursen JB, Ovesen PG, Rorbye C, Tanvig M, Joergensen JS. Prophylactic incisional negative pressure wound

therapy reduces the risk of surgical site infection after caesarean section in obese women: A pragmatic randomised clinical trial. *BJOG* 2018. doi:10.1111/1471-0528.15413 [Epub ahead of print].

17. Irwin G, Highton L, Murphy J. Negative pressure dressings significantly decrease rates of wound breakdown and may reduce implant loss rates in prepectoral breast reconstruction. *European Journal of Surgical Oncology* 2018;44:910.

18. Jenks et al. Clinical and economic burden of surgical site infection (SSI) and predicted financial consequences of elimination of SSI from an English hospital. Journal of Hospital Infection. 2014. 86, 24-33

19. Karlakki SL, Hamad AK, Whittall C, Graham NM, Banerjee RD, Kuiper JH. Incisional negative pressure wound therapy dressings (iNPWTd) in routine primary hip and knee arthroplasties: A randomised controlled trial. *Bone Joint Res* 2016;5(8):328-37.

20. Kawakita T, Iqbal SN, Desale S, Overcash RT. Negative pressure wound therapy (PICO) in morbidly obese women after caesarean delivery compared with standard dressing. *American Journal of C-Section & Gynecology* 2018;218(1 Suppl):S323.

21. Kirkland K, Briggs PJ and Trivette S. The impact of surgical site infections in the 1990s: Attributable mortality, excess length of hospitalisation and extra costs. *Journal of Infection Control* 1999; Vol 20;11: 725-730.

22. Matsumoto T, Parekh SG. Use of negative pressure wound therapy on closed surgical incision after total ankle arthroplasty. *Foot Ankle Int* 2015;36(7):787-94.

23. NICE Quality Standard49 Surgical Site Infection https://www.nice.org.uk/guidance/qs49/chapter/Introduction

24. NICE PICO MIB149
https://www.nice.org.uk/advice/mib149

25. Nordmeyer M, Pauser J, Biber R, Jantsch J, Lehrl S, Kopschina C, Rapke C, Bail HJ, Forst R, Brem MH. Negative pressure wound therapy for seroma prevention and surgical incision treatment in spinal fracture care. *Int Wound J* 2016;13(6):1176-9.

26. O'Leary DP, Peirce C, Anglim B, Burton M, Concannon E, Carter M, Hickey K, Coffey JC. Prophylactic negative pressure dressing use in closed laparotomy wounds following abdominal operations: a randomized, controlled, open-label trial: The P.I.C.O. trial. *Ann Surg* 2017;265(6):1082-6.

27. Pellino G(a), Sciaudone G, Candilio G, De Fatico GS, Landino I, Della Corte A, Guerniero R, Benevento R, Santoriello A, Campitiello F, Selvaggi F, Canonico S. Preventive NPWT over closed incisions in general surgery: does age matter? *Int J Surg* 2014;12 Suppl 2:S64-8.

28. Pellino G(b), Sciaudone G, Candilio G, Campitiello F, Selvaggi F, Canonico S. Effects of a new pocket device for negative pressure wound therapy on surgical wounds of patients affected with Crohn's disease: a pilot trial. *Surg Innov* 2014;21(2):204-12.

29. Rodden D and Taylor R. NPWT: Incision management in high risk Cardiothoracic patients – reducing surgical site infection and length of stay. *Case Series Poster* 2011

30. Scalise A, Calamita R, Tartaglione C, Pierangeli M, Bolletta E, Gioaccheni M, Gesuita R and Di Benedetta G. Improving wound healing and improving surgical site infections of closed surgical incisions: a possible role of incisional negative pressure wound therapy. A systematic review of the literature. *International Wound Journal* 2015: doi:10.1111/iwj.12492

31. Selvaggi F, Pellino G, Sciaudone G, Corte AD, Candilio G, Campitiello F, Canonico S. New advances in negative pressure wound therapy (NPWT) for surgical wounds of patients affected with Crohn's disease. *Surg Technol Int* 2014;24:83-9.

32. Shanmugam K, Fernandez S, Evans K, McNish S, Banerjee A, Couch K, Mihrie Mete N, and Shara N. Postoperative wound dehiscence: predictors and associations. *Wound Repair Regen* 2015; 23(2): 184-190.

33. Svensson-Bjork R, Hasselmann J, Acosta S. Evaluation of inguinal vascular surgical scars treated with closed incisional negative pressure wound therapy using three-dimensional digital imaging-A randomized controlled trial on bilateral incisions. *Wound Repair Regen* 2018;26(1):77-86.

34. Tan KW, Lo ZJ, Hong Q, Narayanan S, Tan GWL, Chandrasekar S. Use of negative pressure wound therapy for lower limb bypass incisions. *Ann Vasc Dis* 2017;10(4):386-90.

35. Tanaydin V, Beugels J, Andriessen A, Sawor JH, van der Hulst RRWJ. Randomized controlled study comparing disposable negative-pressure wound therapy with standard care in bilateral breast reduction mammoplasty evaluating surgical site complications and scar quality. *Aesthetic Plast Surg* 2018;42(4):927-35.

36. Tuuli MG, Martin S, Stout MJ, Steiner HL, Harper LM, Longo S, Cahill AG, Tita AT, Macones GA. Pilot randomized trial of prophylactic negative pressure wound therapy in obese women after caesarean delivery. *American Journal of C-Section & Gynecology* 2017;216 (1 Suppl):S245.

37. Uchino M, Hirose K, Bando T, Chohno T, Takesue Y, Ikeuchi H. Randomized controlled trial of prophylactic negative-pressure wound therapy at ostomy closure for the prevention of delayed wound healing and surgical site infection in patients with ulcerative colitis. *Dig Surg* 2016;33(6):449-54.

38. Van der Valk MJM, de Graaf EJR, Doornebosch PG, Vermaas M. Incisional negative-pressure wound therapy for perineal wounds after abdominoperineal resection for rectal cancer, a pilot study. *Adv Wound Care (New Rochelle)* 2017;6(12):425-9.

39. Webster J, Scuffham P, Sherriff KL, Stankiewicz M and Chaboyer WP. Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention (Review). *Cochrane Database of Systematic Reviews* Issue 4: CD 009261

40. WHO Guidelines: Global Guidelines on the Prevention of Surgical Site Infection. http://www.who.int/gpsc/ssi-guidelines/en/

41. Witt-Majchrzak A, Zelazny P, Snarska J. Preliminary outcome of treatment of postoperative primarily closed sternotomy wounds treated using negative pressure wound therapy. *Pol Przegl Chir* 2015;86(10):456-65.

42. Wloch C. et al. Risk factors for surgical site infection following caesarean section in England: results from a multicentre cohort study. BJOG 2012

43. World Union of World Healing Societies: Consensus document http://www.wuwhs2016.com/files/WUWHS_SI_consensus_Web.pdf

44. Zotes V, Mier JM, Cortes G. Negative pressure wound therapy in a potentially infected wound after empyema surgery. *Interactive Cardiovascular and Thoracic Surgery* 2015;21(Suppl 1):S51.

45. Nherera, L. M., Trueman, P. and Karlakki, S. L. Cost-effectiveness analysis of single-use negative pressure wound therapy dressings (sNPWT) to reduce surgical site complications (SSC) in routine primary hip and knee replacements; Wound Repair Regen;2017; 25(3): 474-482

46. Heard, C., Chaboyer, W., Anderson, V., Gillespie, B. M. and Whitty, J. A. Cost-effectiveness analysis alongside a pilot study of prophylactic negative pressure wound therapy; Journal of Tissue Viability;2017; 26(1): 79-84

47. Galiano RD et al; The cost-effectiveness of single-use negative pressure wound therapy (PICOTM) vs standard care for the prevention of wound dehiscence in patients undergoing bilateral reduction mammaplasty in the USA (Manuscript under preparation)

48. Nherera L, Trueman P, Schmoeckel M, Fatoye FA; Cost-effectiveness analysis of single use negative pressure wound therapy dressings (sNPWT) compared to standard of care in reducing surgical site complications (SSC) in patients undergoing coronary artery bypass grafting surgery; Journal of Cardiothoracic Surgery JCTS-D-18-00184 (In Press)

49. Hyldig N, Joergensen JS , Wu C, Bille C, Vinter CA, Sorensen JA, Mogensen O, Lamont RF, Kruse M; Cost-effectiveness of incisional negative pressure wound therapy compared to standard care after caesarean section in obese women (In press)

50. Edwards D, Bourke N, Murdoch J, Verma S; Using portable, single-use, canister-free, negative-pressure wound therapy for plastic surgery wounds. Wounds UK . 2018, 14 (3): 56-62.

51. McGeown, E. The use of PICO negative pressure wound therapy system for a patient following incision and drainage of breast abscess: A case study that shows the cost benefit of the PICO system for this patient and a Breast Care Nurse Specialists perspective; European Journal of Surgical Oncology;2017; 43(5): S43

52. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005 Apr 20;5:13.

53. Curtis, Lesley A. and Burns, Amanda (2017) Unit Costs of Health and Social Care 2017. Personal Social Services Research Unit, University of Kent, 260 pp. ISBN 978-1-911353-04-1.

54. Tanner J, Khan D, Aplin C, Ball J, Thomas M, Bankart J. Postdischarge surveillance to identify colorectal surgical site infection rates and related costs. J Hosp Infect 2009;72:243e250.

55. European Centre for Disease Prevention and Control. Surveillance of surgical site infections in Europe 2010–2011. Stockholm: ECDC; 2013.

56. Tanner J, Khan, D; Ball, J; Aplin, C; Pickard, J; Bankart J; The rate, risk factors and cost of surgical site infections in primary breast surgery. Journal of Infection Prevention. Infection Prevention, 2011, 12 (5); 204-209.

57. Krishnan R, MacNeil SD, Malvankar-Mehta MS. Comparing sutures versus staples for skin closure after orthopaedic surgery: systematic review and meta-analysis. BMJ Open. 2016, 20;6(1):e009257. doi: 10.1136/bmjopen-2015-009257.

58. Cong Z, Hu L, Xing J, Bian Z, Fu C, Yu E. Incidence and mortality of anastomotic dehiscence requiring reoperation after rectal carcinoma resection. Int Surg 2014;99 (2):112–119 [doi: 10.9738/INTSURG-D-13-00059].

59. Subramaniam A, Jauk VC, Figueroa D, et al. Risk factors for wound disruption following cesarean delivery. J Matern Fetal Neonatal Med 2014; 27(12): 1237–40.

60. Piper ML, Esserman LJ, Peled AW. Outcomes following oncoplastic reduction mammoplasty: a systematic review. Ann Plast Surg 2016; 76 (suppl 3): S222–26.

61. Biancari F, Tiozzo V. Staples versus sutures for closing leg wounds after vein graft harvesting for coronary artery bypass surgery. Cochrane Database Syst Rev 2010; 5L CD008057.

62. Tarzia V, Carrozzini M, Bortolussi G, et al. Impact of vacuum-assisted closure on outcomes of sternal wound dehiscence. Interactive Cardiothor Thorac Surg 2014; 19: 70–75.

63. World Union of Wound Healing Societies (WUWHS) Consensus Document. Surgical wound dehiscence: improving prevention and outcomes. Wounds International, 2018. Available at https://www.woundsinternational.com/resources/details/surgical-wound-dehiscence-improving-prevention-and-outcomes Accessed 18 September 2018

64. National Collaborating Centre for Women's and Children's Health (UK). Surgical Site Infection: Prevention and Treatment of Surgical Site Infection. London: RCOG Press; 2008 Oct. (NICE Clinical Guidelines, No. 74.) 3, Definitions, surveillance and risk factors. Available from: https://www.ncbi.nlm.nih.gov/books/NBK53724/

65. Olsen MA, Lock-Burkley P, Hopkins D, Polish L, Sundt TM, Fraser; VJ. The risk factors for deep and superficial chest surgical-site infections after coronary artery bypass graft surgery are different; J Thorac Cardiovasc Surg 2002; DOI: https://doi.org/10.1067/mtc.2002.122306

66. Zoucas E, Lydrup, ML. Hospital costs associated with surgical morbidity after elective colorectal procedures: a retrospective observational cohort study in 530 patients. Patient Safety in Surgery, 2014, (8);2.

10 Appendices

10.1 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

A search of four electronic bibliographic databases was performed. Medline and Medline In-Process were searched using PubMed. Embase was searched using the Embase.com web interface. The Cochrane Library, which includes the Cochrane Central Register of Controlled Trials, was searched using the CochraneLibrary.com/central web interface.

10.1.2 The date on which the search was conducted.

The date searches were performed on were:

- *PubMed: August 1st 2018*
- *Embase: August 15th 2018*
- *The Cochrane Library: August 16th 2018*

10.1.3 The date span of the search.

Searches were performed with the following date spans:

- *PubMed – January 1st 2011 to August 1st 2018*
- *Embase – January 1st 2011 to August 15th 2018*
- *The Cochrane Library – January 1st 2011 to August 1st 2018*

10.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

To enhance the sensitivity of searches, search terms were left open and did not include words related to specific outcomes, patient populations or adverse events. The following search terms were used in all database searches:

#	Search term
1	*Negative pressure wound therapy*
2	*NPWT*
3	*PICO*
4	*Topical negative pressure*
5	*1 OR 2 OR 3 OR 4*

For Embase and PubMed, the search terms were limited to searches of the title and abstracts of studies.

10.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Reference lists of included studies were searched for further relevant studies – this identified no additional references not already captured through database searches. Additional publications were sought from internally held reference lists related to PICO – this identified one additional reference not already captured through database searches (Hester et al 2015).

10.2 The inclusion and exclusion criteria.

The inclusion and exclusion criteria for studies are listed below:

Inclusion criteria	
Population	*Patients of any age with closed surgical incisions. Patients with any risk factors for complications were also included*
Interventions	*PICO (single-use NPWT) compared with standard care (any non-NPWT dressing) applied post-operatively on a closed surgical incision. Participants undergoing any type of operation were eligible and both prophylactic and reactive usage of PICO was included.*
Outcomes	*Surgical site infections, dehiscence, oedema, seroma, haematoma, skin/fat necrosis, length of hospital stay, reoperation rates*
Study design	*Randomised controlled trials or retrospective/prospective observational studies with at least 10 patients in each treatment arm*
Language restrictions	*English*
Search dates	*Studies published from 01/01/2011 to 01/08/2018*
Exclusion criteria	
Population	*Patients with open surgical incisions or any non-surgical wound*
Interventions	*Other forms of NPWT (i.e. not PICO) were excluded.*
Outcomes	*N/A*
Study design	*Case reports, case-series, studies with less than 10 patients in each treatment arm, letters, commentaries, notes, reviews and editorials*
Language restrictions	*Not in English*
Search dates	*Studies published before 2011*

10.1.6 The data abstraction strategy.

All abstracts were screened by at least two individuals experienced in performing literature reviews. Where there was disagreement regarding the inclusion or exclusion of a particular study, a third reviewer made the final decision.

After the final list of relevant studies was compiled, data were extracted from included studies by one reviewer using a standardised data extraction form. All extracted data were checked by a second reviewer for accuracy. Data were gathered on the design, methodology, participants, and results of the studies.

10.3 Appendix 2: Search strategy for adverse events (section 7.7.1)

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The wide scope of the search terms included in the original searches used to identify relevant clinical evidence allowed for the identification of all comparative studies related to the use of PICO compared to standard care. These studies, identified from four databases (Medline, Medline In-Process, Embase and the Cochrane Library), were used to assess adverse events.

10.3.2 The date on which the search was conducted.

As described in section 10.1.2.

10.3.3 The date span of the search.

As described in section 10.1.3.

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

As described in section 10.1.4.

10.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Reference lists of included studies were searched for further relevant studies – this identified no additional references not already captured through database

searches. Additional publications were sought from internally held reference lists related to PICO – this identified one additional reference not already captured through database searches (Hester et al 2015).

In addition to this, searches of national regulatory databases such as those maintained by the MHRA and FDA (MAUDE) were performed to capture additional information on adverse events.

10.3.6 The inclusion and exclusion criteria.

As described in section 10.1.6.

10.3.7 The data abstraction strategy.

As described in section 10.1.7.

10.4 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

A systematic review was conducted to identify cost-effectiveness studies of interventions for the prevention of surgical site complications (SSC) following closed surgical incisions. The following electronic databases were searched; NHS EED, Embase. Electronic searches were supplemented by hand searching the following sources; Cost-Effectiveness Analysis (CEA) Registry,

contacting clinical authors, and NICE guidelines. We also search for unpublished health economic studies (the grey literature) in the Health Economic Evaluation Database, NHS Economic Evaluation Database and DARE, Tufts Cost-Effectiveness Analysis Registry. We are not aware of best practice guidelines or standard tools for risk of bias assessments in economic evaluations and therefore, this review will not assess risk of bias in the included studies

10.4.2 The date on which the search was conducted.

20 August 2018

10.4.3 The date span of the search.

January 2011 to 20 August 2018

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

#	Search term
1	Negative pressure wound therapy
2	NPWT
3	PICO
4	Topical negative pressure
5	1 OR 2 OR 3 OR 4
6	Economics*
7	Cost*
8	6 OR 7
9	5 AND 8

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

We contacted authors of the clinical studies to see if they had pending cost-effectiveness papers

10.5 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

The following information should be provided.

10.5.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

See Section 10.3 above

10.5.2 The date on which the search was conducted.

See Section 10.3 above

10.5.3 The date span of the search.

See Section 10.3 above

10.5.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See Section 10.3 above

10.5.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See Section 10.3 above

10.5.6 The inclusion and exclusion criteria.

Inclusion criteria	
Population	Patients undergoing closed surgical incisions
Interventions	PICO single-use negative pressure wound therapy system compared to standard of care (traditional post-operative wound dressings)
Outcomes	Cost, QALYs, complications avoided
Study design	CUA, CEA, Cost consequence analysis, Burden of illness ,cost of illness or cost evaluation studies Database studies collecting cost data (e.g. claims databases and hospital records)
Language restrictions	English only
Search dates	2011-present
Exclusion criteria	
Population	Chronic wounds
Interventions	Traditional negative pressure wound therapy (non-single use) and other non-PICO negative pressure devices
Outcomes	None
Study design	None
Language restrictions	None
Search dates	Prior to PICO approval (2010 backwards)

10.5.7 The data abstraction strategy.

Response

11 Related procedures for evidence submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.
- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any

information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

11.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

NICE National Institute for Health and Care Excellence

Expert adviser collated comments table

MT390 PICO negative pressure wound therapy for closed surgical incision wounds

The below experts agreed to advise NICE and were sent a number of questions by the external assessment centre during the production of the EAC assessment report. The questions sent and their subsequent responses have been collated in the table below.

Expert #1	Ms Pauline Whitehouse, Consultant General and Colorectal Surgeon, Worthing Hospital (Western Sussex Hospitals NHS Foundation Trust)
Expert #2	Dr Fania Pagnamenta, Nurse Consultant (Tissue Viability), Newcastle upon Tyne Hospitals NHS Foundation Trust
Expert #3	Ms Caryn Carr, Lead tissue viability nurse, Southern Health Foundation Trust
Expert #4	Mr Sudhir Karlakki, Consultant Orthopaedic Surgeon, Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry
Expert #5	Mr Thomas Pinkney, Senior Lecturer and Consultant Colorectal Surgeon, Academic Department of Surgery, University of Birmingham

#	Question	Expert responses	
1	What are the main clinical guidelines in the UK relevant to closed surgical incision wound management? Do these align with the clinical pathway? Is there local variation?	Expert #1:	NICE guidance: Surgical Site Infections: prevention and treatment. 2008 updated 2017 World union of Wound Healing Societies Consensus Document WHO recommendations https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(16)30402-9/fulltext Local Trust Policy: this does vary for each specialty. For general surgery/colorectal the Trust has modified the NICE guidance to – keep dressing on for 5 days unless there is a suspicion of wound infection. NICE suggests using tap water to clean wounds after 48 hours. Local policy is to continue using sterile saline.

			The use of adjuncts, such as NPWT, is not mandated within the Trust, but with a continued education and audit protocol is adhered to in the main.
		Expert #2:	The only one available is the NICE guidance, which you will already be familiar with.
		Expert #3:	As far as I'm aware there is local variation. In my community location we have no guidelines for closed incisions or pathways
		Expert #4:	Although there are several publications, recently published NICE publications on PICO are probably the only Clinical Guidelines as such
		Expert #5:	The NICE guidelines CG74. WHO have also put out some recent guidelines (but they are not often taken up in the UK). Some of the NICE guidelines are standard practice now, but most are not. Applied variably in different hospitals. CG74 is currently going through an update at present – with the public consultation phase due to start next month.
2	How would you assign someone to a high risk population for SSCs (and SSIs in particular?)?	Expert #1:	We use established risk factors such as those used by Public Health England https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/666465/SSI_annual_report_NHS_hospitals_2016-17.pdf These are in line with the USA National Nosocomial Infection Surveillance (NNIS) system risk index, which is based on a combination of ASA, wound class and duration of operation. For our local audit we used the risk factors and grading system described by Stannard et al (**Use of negative pressure therapy on closed surgical incisions: a case series**. *Ostomy Wound Manage*. 2009;**55**(8);58-66) For GI surgery, emergency surgery is a key risk factor.
		Expert #2:	This will be procedure-dependent, but commonalities will be diabetes, High BMI and 're-do' (going through the same incision line).

		Expert #3:	We follow local guidance if high risk
		Expert #4:	In my practice, I use NPWT in patients undergoing. 1. All Revision Hip and Knee Replacements - The reason being the wound complications in this group is between 15-20%, surgery often is extensive, long, larger exposure, through previous scar tissues and considerably long. 2. Primary Hip and Knee Replacement, in patients with Significant subcutaneous Adipose tissues (generally higher BMI patients >35BMI but not always) Poor quality soft tissues (often influenced by patients age and comorbidities in other words Elderly Patients and ASA Grade 3) Uncontrolled diabetes and Type I Diabetic patients
		Expert #5:	By operation type (target organ) and contamination level – e.g. clean, clean-contaminated, contaminated, dirty. There is also the NNIS system which also takes into account the operation duration and ASA grade – but I have literally never seen this used in clinical practice.
3	How variable are the rates of SSC (and SSI in particular) e.g. across demographic populations and surgical procedures?	Expert #1:	As published by PHE SSI rates vary between different specialties. GI tract have the highest rates of SSIs as would be expected as at the very best wounds are clean contaminated, but often contaminated or dirty. However, it is estimated that rates published by PHE for non-mandatory operations is an underestimate of the true rate of SSI. This is evidenced when comparing to global publications on SSIs.
		Expert #2:	Mostly unknown, unless there is a national requirement for data collection, for instance in hip replacement, data have been collected for years.
		Expert #3:	Sorry unable to comment as within community we don't collate this data
		Expert #4:	The true incidence is not known, the SSI data from department of Public health captures SSI for inpatient and readmission data for a quarter of the year.

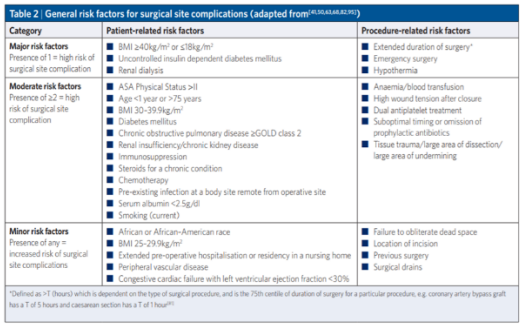
			The rates certainly vary depending on types of surgery i.e. increased SSI in emergency abdominal surgery to relatively low risk in elective hip surgery. The PROMS data indicate that the SSI in Hips and knees post discharge form hospital to be about 5-6% and wound complications between 9-11%, this information is based on 20-25% f the patients returning their PROMS questionnaire. Most of these complications are dealt in the community therefore the true incidence of wound complication perhaps is around 10%, in our retrospective audits of Hip and Knee replacement we found 6% complication and in our RCT the wound complications were 9%. I am afraid as to other surgical procedures. It's a long answer and requires researching.
		Expert #5:	Hugely. From 0.5% in elective orthopaedic surgery to 30-40% in emergency abdominal surgery with peritonitis.
4	What wound dressings are conventionally used in the NHS for closed surgical incision wounds? Would you take into account the level of exudate in the decision of which dressing to choose (e.g. low/moderate?)	Expert #1:	Most closed incisions have a low level of exudate. Therefore, dressings such as skin glue or mepore are commonly used. For incisions with a more moderate exudate, dressings such as Aquacel and Leukomed can be considered. This list is not exhaustive. For wounds where a large volume of exudate is expected it would be common place to use negative pressure wound therapy.
		Expert #2:	Post-operative dressings, ideally waterproof, bacterial proof but at times surgeons still use gauze-based post-operative dressings. NICE guidance are not specific enough to guide clinicians due to lack of research in the field (however, we are waiting for the BELL trial to conclude to see what is the best way to close a surgical wound and that will aid decision-making regarding post-operative dressings).
		Expert #3:	Presently we follow our local formulary and SIGN checker guidance
		Expert #4:	Highly variable between hospitals and surgical specialities. The commonly used dressings are Mepore, Tegaderm or similar dressings. Hydrocolloid dressings like Aquacel are increasingly gaining popularity predominantly because the dressings are left untouched for a week. In my practice, any hip and knee wound apart from those which mentioned earlier in question 2 get a PICO dressing if the wound remains oozy or leaking beyond 48 hours.
		Expert #5:	We looked into this in the Bluebelle trial, which is now published. Almost all operations get a simple dressing (pad and sticky border). More recently, people

			might take into account SSI risk and/or predicated exudate levels and modify their dressing choice. But only in a tiny proportion of operations overall.
5	What is the most important outcome measure for a study investigating closed surgical incision wound management?	Expert #1:	Incidence of SSI. However, I believe the use of negative pressure may reduce the severity of the SSI even when they occur and this has a big impact for the patient, hospital stay and cost. This is perhaps not an easy thing to measure. Length of hospital stay due to SSI and cost of post-operative wound management.
		Expert #2:	SSI, as wound dehiscence usually occurs in the presence of infection.
		Expert #3:	The wound remains closed and healing with signs of infection
		Expert #4:	Wound discharge beyond 48 hours and superficial surgical site infection.
		Expert #5:	SSI rate, as defined by the CDC criteria.
6	What is the time horizon for SSCs to occur, most studies have used 3-4 weeks (min 3 weeks, max 6 weeks) follow-up for SSCs to occur, is that enough?	Expert #1:	The time for an SSI to occur is specific to the specialty. For example, in large bowel surgery, the SSI often manifests itself on the initial admission. However, with enhanced recovery and shorter hospital stays the SSIs may present in the community. In my experience, it would seem that 6 weeks is a more than adequate time span. An SSI related to a prosthesis is considered to be up to a year from placement.
		Expert #2:	Wound infection occurs within 48h (primary) or after 10 days (secondary). It depends if the SSI is deep or superficial. Within hip replacements for instance, the collected data pertain to deep infections. No one knows how many times patients go to their GP for minor signs of infection such as redness/ low exudate due to superficial infection, as superficial data collection are not mandatory.
		Expert #3:	This sounds sensible.
		Expert #4:	To measure SSC, ideally the studies need to incorporate weekly review of patients for the first 2 weeks and thereafter between 4-6 weeks. Late complications such as

			deep infection through superficial SSI may not be obvious until a year later or in some cases many years later in Hip and Knee Replacements.
		Expert #5:	By definition, an SSI must occur within 30 days. Unless an implant is left, in which case this window extends to 1 year. As such, for non-implant trials the primary outcome should be measured at 30-45 days. Most SSIs occur between day 5 and 11, we think. But this varies according to operation sire and pathogen.
7	How transferable would PICO clinical trial results be between different surgical populations (such as orthopedics and obs/gynae)? What are the highest risk surgical procedures?	Expert #1:	As above – GI operations have the highest rate of SSIs. However, some operations, such as cardiac surgery or orthopaedics using a prosthesis may have a lower rate of SSI but when they occur they may have more severe consequences and therefore are equally important to reduce. The principles of PICO clinical trial results are transferable between different procedures. NPWT on closed incisions is effective due to a number of different modes of actions, many of which are still poorly understood. Therefore, the efficacy of PICO in different specialties may be due to different modes of action.
		Expert #2:	Highest risks are orthopedics surgery (where SSI can be catastrophic to the patient outcome). Cardio-thoracic too, for obvious reasons. The evidence for PICO is very limited as of yet, it is therefore really not yet transferable.
		Expert #3:	Very transferable. As not acute unable to comment on highest risk procedure
		Expert #4:	In my view the outcomes are very transferable for SSC. The risk of SSC varies between procedures even within the specialities and best commented by those within the specialities.
		Expert #5:	We do not know how transferrable results are. Thankfully, there are currently loads (40+?) trials of PICO being undertaken in many surgical fields. Highest risk of SSI is probably emergency abdominal surgery. Our current SUNRRISE trial is in this field.
8	In the UK, do you use the CDC definitions of SSIs for superficial vs. deep incisional SSIs? Is dehiscence associated primarily with deep incisional SSIs as stated by the CDC definition?	Expert #1:	The CDC definitions are essentially the same but we use the Public Health England protocol (see page 22) - for a UK audience using UK guidelines rather than USA is better really. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/633775/surgical_site_infections_protocol_version_6.pdf
		Expert #2:	Yes, we do – surveillance teams keep data on specific surgical procedures, such as hip and they keep data on deep incisional SSI. It depends how deep is the dehiscence. Full deep dehiscence is associated with deep SSI.

		Expert #3:	Not acute (community) so not used.
		Expert #4:	I am not an expert in surgical site infection nor am I am expert in epidemiology of SSI. I am an orthopaedic surgeon with an interest in preventing infection especially deep prosthetic infection from superficial surgical site infection and the precursor for it in orthopaedic settings is prolonged wound discharge secondary to extent of surgery, bleeding, hematoma, further compounded by patient factors as set out in your table that delay wound healing where negative pressure wound therapy dressings ca help improve wound healing. This is where my expertise lies. I am afraid you would have direct your questions 8, 9 & 10 to a microbiologist with an interest in SSI, however here is something you can look up Regards to SSI, lot of this information is available from the PHE (Public Health of England Website) SSIs are monitored in the UK by PHE and the data collection and methodology is based on the publication and they use CDC definition. 1. Public Health England. Protocol for the surveillance of surgical site infection. Version 6 June 2013. Public Health England. 2013 2. CDC/NHSN Surveillance definition of healthcare-associated infection and criteria for specific types of infection in the acute care setting. 2013. Centers for Disease Control and Prevention. http://www.cdc.gov/nhsn/PDFs/pscManual/17pscNosInfDef_current.pdf
		Expert #5:	Yes and yes. Although dehiscence is a poorly used terminology – some people use it (probably correctly) to mean when the muscles and fascia come apart and the wound opens right up. Others talk about dehiscence as being when the skin edges come apart – which is just confusing.

9	In a UK setting, do you use the USA National Nosocomial Infection Surveillance (NNIS) system risk index for assigning a risk score for SSIs?	Expert #1:	We do not use the NNIS as a risk score but we have used that when doing audit and writing up data so this has educated us but we do not routinely use this (however it is quoted in the PHE surveillance feedback).
		Expert #2:	Not to my knowledge.
		Expert #3:	Not acute (community) so not used.
		Expert #4:	See answers in Q8.
		Expert #5:	No. As per Q8.
10	The World Union of Wound Healing Societies (WUWHS) Closed Surgical Incision Management Consensus Document requires the presence 2 or moderate risk factors for assigning a high-risk status for SSCs (please see table below). To this end will the following patient populations be classified as high risk in a UK setting?	Expert #1:	We use the same criteria as WUWHS (however we were using these criteria prior to the publication of WUWHS which are based on Stannard/NNIS criteria as previously stated).
		Expert #2:	Each team in each hospital is using a different definition and in the UK, we have not adopted this table as a national guidance as of yet (but we should).
		Expert #3:	I would agree with this.
		Expert #4:	Don't quite understand your question, but I would agree with the criteria set out in the table

	 **Table 2 | General risk factors for surgical site complications (adapted from[41,50,63,68,82,95])** **Category** / **Patient-related risk factors** / **Procedure-related risk factors** **Major risk factors** (Presence of 1 = high risk of surgical site complication): BMI ≥40kg/m² or ≤18kg/m²; Uncontrolled insulin dependent diabetes mellitus; Renal dialysis — Extended duration of surgery*; Emergency surgery; Hypothermia **Moderate risk factors** (Presence of ≥2 = high risk of surgical site complication): ASA Physical Status >II; Age <1 year or >75 years; BMI 30–39.9kg/m²; Diabetes mellitus; Chronic obstructive pulmonary disease ≥GOLD class 2; Renal insufficiency/chronic kidney disease; Immunosuppression; Steroids for a chronic condition; Chemotherapy; Pre-existing infection at a body site remote from operative site; Serum albumin <2.5g/dl; Smoking (current) — Anaemia/blood transfusion; High wound tension after closure; Dual antiplatelet treatment; Suboptimal timing or omission of prophylactic antibiotics; Tissue trauma/large area of dissection/ large area of undermining **Minor risk factors** (Presence of any = increased risk of surgical site complications): African or African-American race; BMI 25–29.9kg/m²; Extended pre-operative hospitalisation or residency in a nursing home; Peripheral vascular disease; Congestive cardiac failure with left ventricular ejection fraction <30% — Failure to obliterate dead space; Location of incision; Previous surgery; Surgical drains *Defined as >T (hours) which is dependent on the type of surgical procedure, and is the 75th centile of duration of surgery for a particular procedure, e.g. coronary artery bypass graft has a T of 5 hours and caesarean section has a T of 1 hour[41]	Expert #5:	Yes probably. But I've never used thus before and doubt how clinically useful it would be.
11	Would you consider dehiscence and infection to be the most common serious complications following surgery?	Expert #1:	No. Deep organ space infection, especially following anastomotic leak, would be the most serious surgical complication, although many patients are elderly and have other systemic complications which are very serious, such as chest infection and renal failure. It depends if you mean dehiscence associated with infection, full dehiscence as in the deep layers (this is often technical and if occurring early might be resutured), or deep superficial infection with dehiscence of skin and to but not including the fascial layer. Deep incisional infections do require more input than superficial infections. You might need to be clearer in your question if that hasn't answered it as I am not sure whether you are using dehiscence in the true sense of full all layer breakdown.
		Expert #2:	Yes the more common, but also respiratory distress and complications relating to the anaesthesia rather than the surgery and pain and associated complication of medicating. Medium-long term, you need to consider 'loss of function'; 'adherence', hernia (see repair of aortic aneurysm); and more soft outcomes, such as reduced quality of life, self-esteem and so for.
		Expert #3:	Probable but as not in acute care. In the community these are the patients we see but those who have healed will not have been reviewed. Common cause to see a practice nurse is surgical wounds and it would be for these reasons.

		Expert #4:	Deep prosthetic infection is one of the serious complication following joint replacement but not necessarily the most serious complication, superficial SSI is not a serious complication neither is wound dehiscence, if identified early and dealt adequately.
		Expert #5:	Depends on the surgery. But no, the most serious complication is death!
12	Would you consider the typical resource implications (e.g. additional length of stay) of these two complications to be similar?	Expert #1:	No. See the answer to the Q11.
		Expert #2:	Not necessarily, because you can send somebody home with a dehiscence (albeit in the very deep dehiscence, this can be challenging for DNs to manage at home but feasible and we have done so with the help of TNP (not PICO!); if somebody has a deep infection, they will be systemically unwell and increase hospital stay. If deep infection results in deep dehiscence, this is a double problem and that would increase hospital stay.
		Expert #3:	Delayed healing. Cost of dressings. Time from health professionals, Travelling time if housebound. Requirement of equipment and resource implications. Delayed hospital discharge. Bed stay. Antibiotics and the resulting impact. Staffing knowledge and skill mix to support management.
		Expert #4:	NO, for reasons as explained above (Q11).
		Expert #5:	Depends on what you mean by dehiscence (as above in Q11).
13	After surgery, and when using a standard dressing, how often would the dressing be changed during post-operative stay (e.g. daily)?	Expert #1:	When using a standard dressing OUR local policy is keeping it on for 5 days unless there is excess soiling or possibility of wound infection. This is NOT NICE guidance - they suggest washing with normal water after 48 hours. For elective patients we often use skin glue so you can see the wound anyway. We try and avoid daily dressing changes as it is more likely infection will be introduced.
		Expert #2:	NICE recommends that a post-operative dressings should be left in situ for 2 days post-operatively and generally, this is the guidance that we use. However, I do question that if we understand the healing process (arrival of microphages to the wound and so forth), it would therefore be helpful to leave it in situ for 5 days –

			however, there is no evidence to this. If low exudate, one dressing is sufficient (2-5 days); it also depends what post-operative dressing is used [again NICE does not stipulate what type (film backed dressing or gauze - they use the term 'modern' which is not very specific. We take 'modern' to mean film backed dressing, which is showerproof and bacterial proof)], if film-backed, then it does not need to be changed if there is a bit of exudate visible and it is preferable to leave it in situ for 2-5 days.
		Expert #3:	Apologies, I do not work in the acute environment to answer this question. Although some patients will be day case surgery and will be told to see their practice nurse- but couldn't tell you time period.
		Expert #4:	The dressings for clean incisional surgical wounds are preferably left undisturbed, if they are clean and not much bleeding or exudate from the wound. The idea is to keep the surgical wound to keep dry (to prevent skin maceration) and free from contamination. Typically in a hospital setting, dressing is changed at 48 hours (this is traditional to inspect the wound) and a new dressing is applied and changed again at a week and until the sutures/staples come out. The tradition of early change of dressing purely for wound inspection should be avoided and this is now being recognised as good practice. Newer dressings like Aquacel are designed to left alone for a week even in the presence of surgical site bleed and wound ooze. These dressings are passive, in other words a covering on the surgical wound, NPWT dressings differ by actively promoting wound sealing and healing.
		Expert #5:	Very variable. Some surgeons/units will stipulate that dressings must not be touched for xx days. Others will mandate that they must be removed after 24, or 48, or 72 hours – and not replaced at all unless there is significant discharge. In UK practice most dressings are changed when they need to be in terms of 'strike-through' (i.e. soakage of the dressing) or when the wound is inspected a new one will be placed afterwards as the original one won't re-stick. But there really is no standard answer to this question I'm afraid.
14	How long would you expect a patient to be treated with PICO, for a week or until their	Expert #1:	N/A

	discharge from hospital? How likely are patients to require a second PICO device?	Expert #2:	N/A
		Expert #3:	N/A
		Expert #4:	N/A
		Expert #5:	If we put one on, we tend to say that it should stay on for the recommended duration of 7 days. If they are still an inpatient at day 8 or 9 we wouldn't necessarily take it off When they go home, we tend to remove it and either give normal dressings or, more likely, nothing at all and let the air get to the wound. Likelihood of needing 2nd PICO dressing is directly related to the likelihood of SSI So in high risk operations (e.g. emergency abdominal operations) the risk is quite high of needing the second dressing. This used to come in the pack anyway, so was cost-neutral (i.e. one battery pack and 2 dressings) but in the updated PICO dressings I believe this may not be the case
15	Given that 1 PICO system comes with 2 dressings, how many systems do you use per patient, on average, if they do not develop any SSCs? How likely is it that you will use more than 1 PICO system in patients without complications?	Expert #1:	This is based on our local experience for laparotomy. I expect orthopaedics is quite different. We tend to use 1 system. The wound has either healed or it has not in that time. It is not necessary to use both dressings but we tend to remove the first at 3-4 days for a wound check. However if there is no suspicion of wound infection one dressing could remain on for the 7 days. We just feel we like the opportunity to have a look and check.
		Expert #2:	Best practice is that TNP should be applied for 7 days – having to change the dressing half-way introduces possible infection to the wound. This is because PICO does not have a canister like other TNP system have and this is the reason why they have to supply two dressings. In my clinical experience, PICO requires changing as it does not hold the exudate, does not provide enough negative pressure (80mmHg versus 125mmHg in other brands) and requires therefore more than 7 days treatment.
		Expert #3:	You can now obtain PICO 7. This will allow 1 dressing kit, 2 dressing kits or a Multipack of 5 dressings. I would expect that with a closed wound with no complications 1 dressing/system for the week. Might only be required for a week.

			Unlikely as closed wound.
		Expert #4:	N/A
		Expert #5:	N/A
16	What happens when a patient that uses PICO develops a SSC? Do you stop using PICO? Are there cases that you will use PICO for therapeutic use (i.e. after the development of a SSC)?	Expert #1:	If there is a minor wound infection with shallow defect then another PICO could be used as treatment rather than prophylaxis, and continued in the community if appropriate.
		Expert #2:	I would never use PICO in the treatment of SSI. Mostly, presence of SSI increases exudate levels and as I have already reservations on the ability of PICO to manage light exudate, it would certainly not be the product of my choice in this.
		Expert #3:	No this is the ideal treatment option and in theory, using this should reduce complications. Evidence I have seen supports this. If the wound exudate is too much then the patient would be moved from a PICO to a more robust TNP therapy i.e. larger pump. This would occur if the wound opens up and you have more than 1cm depth. Yes I have seen this used with the same answer as the last question (Q15).
		Expert #4:	N/A
		Expert #5:	N/A

National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT390 PICO negative pressure wound therapy for closed surgical incision wounds

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
Clinical evidence section	**Initial questions sent to manufacturer 10.09.18** **1.** In the 'Ongoing studies' section (5.1-5.2) the sponsor mentions 12 ongoing scientific studies and 3 real world audits. Are these separate to the 11 unpublished studies listed in table B4 in section 7.3.1? If so, can the sponsor provide more details on the 12 ongoing scientific studies and 3 real world audits, such as preliminary results or expected publication dates? **2.** In the appendix, the sponsor mentions that they searched the MHRA and FDA MAUDE databases for adverse events – were any adverse events found in these databases? **3.** Pg 12, table A2 – our understanding is that table A2 shows 3 types of PICO dressing (PICO, PICO 7 and PICO 7Y) included in 7 bundles which include different dressing sizes. Are all 3 versions currently on the market? Could you clarify the difference between these 3 versions? Have there been previous versions? Could you clarify what is	**Responses received from manufacturer during the TC 13.09.18 (see appendix 1a)** **1.** The sponsor answered that these are two different sections. There are 12 studies in the section of Ongoing Studies and 11 studies in the clinical section. The reason for that discrepancy is that for the clinical section, Smith & Nephew used a systematic way to identify the studies (11 ongoing studies where PICO was used were identified in searches), whereas the studies in section 5 were identified after discussions with clinical trial colleagues who made us aware of the studies. As a result, there are nine studies in total that do not overlap. All of those studies were led by the investigators and the company has no access to their data until that the final report for publication is ready. Smith & Nephew has access to data for only one of them. For the rest of those studies, Smith & Nephew was not in position to ask for the results as the studies were produced independently. If KiTEC contacts the authors separately, some of the data might be made available to the EAC, but some of them are in very early stages. **2.** The sponsor responded that there were. For MDA MAUDE search, they came across several adverse events detailed in the document sent in the section 7.7.3. From MHRA no hits were identified, from MUADE 147 adverse events were found, regardless if these were attributed to the device or not. **3.** The sponsor answered that there are 3 different PICO systems in the UK: PICO, PICO7 and PICO7Y. All of them use the same dressing and they all have the same clinical applications to the patient. In terms of differences: - PICO – original pump - PICO7 – upgraded version of PICO where mechanism is completely unchanged; new pump with improved functionality - a few changes were made to the pump (additional power added) to make it more efficient to better manage air leakage,

	meant by small or large multi-site dressing? Is there a single-site dressing? Summary of technology (pg 12) says "includes a multisite dressing of up to 20 cm × 25 cm". Table A2 doesn't include this dimension – the largest dressing is 25x25cm – could you clarify?	especially when applying the dressing in the difficult-to-heal areas. Another benefit of PICO7 is the inclusion of the belt click that allow the patient to transport the device more easily. - PICO7Y – this can be used on two different dressings; the sponsor mentioned an example of hernia incision or reconstructive breast surgery, where two dressings can be managed by one pump to make it easier for the patient. There is also a change indicator feature in this version, which helps to better-manage the dressing so that it is not changed unnecessarily. PICO dressings are available in different sizes: singe site and multi-site. The multi-site means that it is best to apply in various difficult-to-dress areas, i.e. areas with body contour. The sponsor mentioned couple of examples for applications of multi-site PICO dressings, e.g. C-section requires long, thin dressing to cover the incision, diabetic foot ulcer or toe amputation where square or rectangular dressing is not sufficient. KiTEC asked if there are two different sizes of dressing: 20 x 25 cm and 25 x 25 cm. The sponsor confirmed that both exist, in square and rectangular shapes.
	4. Pg 13 (section 2.2) – to confirm, the key difference outlined between PICO and conventional NWPT is that the PICO has: - a perforated silicone wound layer across the length of the dressing - AND covers substantial peri-wound skin as well as the wound itself	**4.** The sponsor agreed with the statements and mentioned the change indicator as additional difference, which serves as reassurance to nurses when the wound needs redressing. The main difference however is with regard to the pump, as NWPT are large devices to carry around, whereas PICO pump has always had a small portable design. KiTEC asked if the change indicator was introduced only for the latest version (2018). The sponsor confirmed it. KiTEC concluded that all the evidence available would not include change indicator function and also asked about the instructions for usage of the change indicator. The sponsor answered that it is detailed in IFU.
	5. Pg 19 (section 3.3) – says "In the hospital, PICO single-use NPWT system should be utilised in place of conventional post-surgical wound dressings to prevent or treat SSIs in closed surgical incision wounds with low to	**5.** The sponsor answered that it is used predominantly in the prevention of SSCs. If wound reopens following discharge and the wound needs to be closed again, PICO can be used as well.

	moderate exudate level." In hospitals, is PICO used to treat SSIs only or all SSCs?	
	E-mail sent to manufacturer 01.10.18 We are hoping that you can provide the RevMan file that includes the data and analysis of the meta-analysis results included in your clinical submission. Would it be possible? **E-mail sent to manufacturer 03.10.18** Can we also ask you to provide the IFUs for all 3 PICO versions and let us know if there any contraindications for using PICO?	**Response from manufacturer 02.10.18 (see below and appendix 2a)** Please find the RevMan file attached. **Response from manufacturer 05.10.18 (see below and appendix 2b)** Please find attached the requested IFUs, with the exception of PICO 7Y (it's too large to send via email). […] I need to upload PICO 7Y via this portal as it's too large to send even when zipped, via email.
Economic evidence section	**E-mail sent to manufacturer 05.10.18** Following your economic submission, we noticed that you have included 5 studies, out of which Nherera 2018, Hyldig 2018 & Galiano 2018 are either in press or preparation. Is it possible to make these available to us?	**Response from manufacturer 05.10.18 (see below and appendix 2c)** Please find attached 2/3 studies you require – I will send on Nherera's paper as soon as I receive it. **Response from manufacturer 05.10.18 (see below and appendix 2c)** Please find attached the Nherera paper.
Clinical evidence section	**E-mail sent to manufacturer 09.10.18** Could you please let us know the following: based on which risk factors you have categorised the	**Response from manufacturer 12.10.18 (see appendix 2d)** Please find attached a document in response to your queries around risk factors for the various studies, please let me know if you need anything in addition to this. I would like to emphasise that although these studies don't exclusively focus on high risk patients, that

	following study populations as high-risk and subsequently included in your submission? · Holt 2015 · Matsumoto 2015 · Pellino 2014a · Hackney 2017 · Tanaydin 2018 · Irwin 2018 In addition, could you please provide the thresholds (when applicable) you used for your inclusion/exclusion criteria for the studies included in your submission? For example did you use a BMI>30 or >40?'	they have a large proportion of patients with risk factors that increase the likelihood of a wound complication arising. I'm awaiting the papers you requested (Hyldig and Galiano) from my Scientific & Medical Affairs team, but I've sent a chase email so I'll send as soon as I receive them. **Response from manufacturer 15.10.18 (see appendix 2e)** Please find the papers you requested attached.
Clinical evidence section	**E-mail to study author (Thomas Hester) 13.09.2018** My team is doing an evaluation on PICO for NICE and came across your publication from 2015. https://www.hindawi.com/journals/aos/2015/247324/ I was trying to clarify if the included population falls under the description of 'Patients having closed surgical incisions with low to moderate levels of exudate who are considered to be **at high risk of developing** a surgical site complication particularly SSI and dehiscence'.	**Response from study author 13.09.18** You are entirely correct, closed high risk surgical wounds.

Appendix 1

a) Minutes of teleconference with sponsor 13.09.18:

MT390
PICO_sponsor TC_13

Appendix 2

a) Attachments received in e-mail from sponsor dated 02.10.18:

PICO NICE submission.rm5

b) Attachments received in e-mail from sponsor dated 05.10.18:

PICO Dressings RoW English FINAL

PICO 7 RoW English IFU FINAL 2(

09691_PICO 1.6 user manual_30.06.1

c) Attachments received in e-mail from sponsor dated 05.10.18:

Hyldig 2018 prophylactic incisior

Galiano et al 2018.pdf

Nherera 2018.pdf

d) Attachments received in e-mail from sponsor dated 12.10.18:

NICE PICO MT390 Submission_clinical

e) Attachments received in e-mail from sponsor dated 15.10.18

Hyldig 2018 C-section economic

Galiano 2018 Breast CE.PDF

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

PICO negative pressure wound therapy for closed surgical incision wounds

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from King's Technology Evaluation Centre External Assessment Centre (EAC), to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **1 November 2018** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

29 October 2018

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table1, Cost analysis Section 2.2 Table 1	The analysis matches the scope (Yes)	The EAC notes that the sponsor did not address number of PICO used. We assumed that one PICO (comprising one pump and two dressings which is sufficient for one week of therapy) is sufficient to treat the majority of closed surgical incisions. Based on the EAC analysis, the mean number of PICO used in the studies was 1.09.	See answer to Issue 9.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Hard to heal wounds Section 2.2 Table 1	These were not addressed	Sponsor and NICE agreed in a pre-submission call that the remit was closed surgical incisions. Whilst PICO can be used to manage open, chronic wounds, this is considered a different patient population/indication with a distinct evidence base.	Thank you for your comment. We address deviations from the final scope as published by NICE in this section. The final scope does include hard to heal wounds as a subgroup and we had to refer to the submission not including any evidence for this subgroup. I have added a line to clarify that this subgroup was not relevant to the submission as follows:

			'' The sponsor did not address the latter as the focus of the submission was closed surgical wounds.''

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Use of Evidence Section 3.8.2 Table 14	We suggest that both RCT and Observational evidence be used in the base case clinical and economic analysis	We note that the EAC has excluded observational studies from the meta-analysis used in the economic evaluation of all surgeries. However, this is inconsistently adopted in the evaluation of individual specialties. We acknowledge that there may be inherent weaknesses of observational evidence and that they are subject to bias. However, we would recommend that the prevailing approach should be to make best use of all relevant evidence. We note that the NICE methods guidance for MTEP is intended to be pragmatic and recommends that all sources of evidence should be considered, MTEP PMG33 Methods Guide Section 6.2.1. Although PICO is atypical of medical devices, in that there are a number of well-designed RCTs	The EAC regards evidence from meta-analysis of trial data to constitute a less biased source of data on effectiveness and to preferred, where available. The EAC would have applied this approach to each of the six sub-specialties of surgery examined if sufficient data in each of the six sub specialties had been available. It was not. In such cases observational data provides a substitute.

		available to illustrate performance, this should not lead to exclusion of non-randomised data sources. We would argue that non-randomised studies often have higher external validity that RCTs, which is particularly important in surgical specialties to illustrate that trial outcomes can be reproduced in practice. As such, we would recommend that observational studies are included in the meta-analysis. A sensitivity analysis considering only RCT evidence should be a secondary analysis.	

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Included studies Section 4.1	Hyldig 2018 is in press and Galiano 2018a is in preparation	The EAC reported these incorrectly.	The EAC will update the reference to these studies in the report.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Comparators Section 4.2	Evidence to support this was obtained from clinical experts consulted by the sponsor.	The EAC noted that the evidence to support this assumption is not provided. See Section 9.1.6 of the	The EAC will amend the report to note the basis of this assumption.

		submission, we state that we were advised by clinicians.	

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Role of expert advisors Section 4.2	Expert advisors commented on the model structure and data inputs.	See section 9.2.5 of the sponsor's submission, we make this clear	The EAC did not have access to the comments made by the expert advisers and it is unclear if any changes were made following their advice. The EAC accepts the comment is misleading. The EAC will revise this comment as follows: The advisors commented on the model and the source of parameters. It is unclear whether the model was revised following this consultation.

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Reproducing the proportions of SSI in and out of hospitals Section 4.2, resource identification	This is consistent with Jenks paper	Table 1 in Jenks paper provides data for in patients, readmissions and post discharge SSI. We took post discharge to reflect outpatient while inpatient and readmission reflected inpatient SSI. For example Vascular 5 inpatient + 7 on readmission =12 SSI	P203 of the sponsor's submission reports a proportional of inpatient SSI for vascular surgery of 24.1%. Jenks reports 12 inpatient episodes out of 28 – 42.9% (as identified in the comment). The sponsor's table reports a proportion of 42.9% for cardiothoracic surgery – Jenks reports 43 admissions out of 180 episodes or 23.9%. The EAC assumes that data for the two sub specialties have

		16 SSI post discharge Total SSI =28 Inpatient =43% and outpatient 57%	been inadvertently swapped in the table. A value of 42.9% (correct) has been applied for vascular surgery in the sponsor's model. However, the value of 24.1% has been applied for cardiothoracic surgery – the true value from Jenks is 23.9%.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Risk factor ASA	Replace ASA >2 with ASA≥3	We assessed ASA≥3 as a risk factor, see text in the submission Section 9.2.6 Table 21 and 9.6.4 Table 35	The EAC regards the two expressions, which are mathematically equivalent, to be the same. However, the EAC will update the description in the final report.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Assuming PICO is used for the duration of hospital stay and therefore is a function of length of stay Section 4.3	1.09 PICOs are used.	It would be incorrect to assume that PICO is used for the entire duration of the hospital stay. Management of the closed incision is only one determinant of length of stay – other factors such as underlying health status, ability to discharge etc could also influence this.	The EAC noted the lack of evidence on the duration of PICO use. The EAC noted that it has made this assumption to estimate PICO use. The EAC has described the methods it used to derive a figure of 1.09 PICOs, which the sponsor appears to be in agreement with. The EAC will add an additional statement.

		On balance, we concur with the EAC finding that on average 1.09 PICO/pt is applied as the base case. This concurs with anecdotal feedback from clinical experts which suggests in most cases one week of therapy (1 PICO) is required, with a second week required in a minority of cases.	The EAC notes that some patients may have extended stay in hospital for reasons unrelated to wound closure, and that for these patients PICO may not be used for the entirety of their stay. To the extent that factors unrelated to wound closure extend LOS, the EAC's calculation will have overestimated the number of PICOs used.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Using cost data from all 19 surgical sub specialties	Data used from 6 surgical sub specialties	It would seem logical to apply cost data relating to the surgical specialties under consideration, rather than adopting a mean across all surgical procedures reported in the Jenks paper.	The EAC does not agree with the sponsor's statement. The EAC believes that data from all of the surgeries reported in Jenks 2014 provides a better estimate of the overall cost of SSI than the selection of six of the sub specialties with data from the remaining 13 discarded. The EAC notes that several of the sub specialties reported in Jenks 2014 but not included in the sponsor's submission included a large number of procedures undertaken by the hospital: reduction long bone fracture – 1503; repair neck of femur – 598; cranial 896; spinal – 1827.

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Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Sensitivity analysis interpretation	PICO was cost saving in the base case and the majority of the sensitivity analyses, suggesting that on balance it is cost saving with a small likelihood of being cost additive.	The exec summary and conclusions state that on balance is it likely to be cost effective – rather than cost saving. This appears to contradict the EAC's own findings and is potentially misleading. The EAC's own SA (11/17 ie 65%) and the sponsor SA shows that PICO is cost saving in the base case and the majority of sensitivity analyses. EAC notes that PICO is insensitive to the majority of parameters when 11 of the 17 parameters varied PICO remained cost saving. The main sensitivities relate to the price of PICO and the effectiveness derived from the meta-analysis. As indicated above, using all relevant data in the meta-analysis results in PICO remaining cost saving even in the extreme values analysis. It only becomes – marginally – cost additive when the EAC meta-analysis excluding observational data is applied. Similarly, PICO only becomes cost additive at an extreme price level of £195 – 50% above the list price. This is an unrealistic assumption	The EAC does not agree with the sponsor's inference from the EAC's sensitivity analysis. The EAC found PICO to be cost saving in the base case. Hence it is only to be expected that when parameters used in that analysis were varied across a range spanning the point estimate the result would be cost saving at one end of the range. The point of the sensitivity analysis was to examine whether the inference that PICO was cost saving is robust as the parameter is varied across the range examined. The data indicate that inference was robust for only two parameters: standard dressing cost and the risk of SSI in primary care. For the other six parameters inference on whether PICO is cost saving changes as the parameter is varied across its range. The EAC accepts it is unlikely that PICO would cost £195 and has noted this in its interpretation of the results: 'However, the EAC notes that the cost of PICO is determined by the manufacturer and uncertainty in this parameter relates to future pricing strategy rather than sampling uncertainty.'

		and does not reflect prices charged to the NHS.	The evidence on effectiveness of PICO is a key source of uncertainty. The EAC believes that it is important to obtain the least biased estimate of effectiveness of PICO and regards the value determined from meta-analysis of trial data to be less likely to be biassed than that obtained with the inclusion of observational data.

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Clinical evidence conclusions Sec 5.1 and remove the word ***wide*** confidence interval at the end of the section	Pooled estimate of effect for PICO (combining RCT and observational) is (OR 0.37 95% CI 0.24, 0.57). When data from 8 RCTs including all medical specialties, the use of PICO reduces the rate of SSIs (OR 0.49, 95%CI 0.33-0.72, p=0.0003). The pooled analysis of the 11 observational studies confirmed this result (OR 0.28, 95%CI 0.17-0.46, p <0.0001). However, it should be noted that given the variability of risk factors in clinical practice and the number of studies, some caution should be exercised in estimating the size of the effect for each surgical procedure separately	In line with the methods guidance, we recommend that all relevant data are used in the meta-analysis base case. A sensitivity analysis, considering just RCT data, should be considered a secondary analysis.	Please see previous response in issue 3. Data from observational studies can be used to support the decision problem when there is a lack of RCTs. Observational studies, especially when conducted as before, and after studies overestimate the size of the effect. However, they can be used to support the direction of the effect and as part of sensitivity analysis. As a result we don't believe that the pooled estimated from combining data from observational and RCT studies provides an accurate estimation of the effect (Please see chapter 13 of the Cochrane Handbook for Systematic Reviews of Interventions for more details on this).

			Finally, the Cochrane guidance for the use of non-randomised in meta-analysis provides the following statement: “Broadly, the NRSMG considers that there are three main reasons for including NRS in a Cochrane review: a) To examine the case for undertaking a randomized trial by providing an explicit evaluation of the weaknesses of available NRS. The findings of a review of NRS may also be useful to inform the design of a subsequent randomized trial, e.g. through the identification of relevant subgroups. b) To provide evidence of the effects (benefit or harm) of interventions that cannot be randomized, or which are extremely unlikely to be studied in randomized trials. In these contexts, a disinterested (free from bias and partiality) review that systematically reports the findings and limitations of available NRS can be useful. c) To provide evidence of effects (benefit or harm) that cannot be adequately studied in randomized trials, such as long-term and rare outcomes, or outcomes that were not known to be important when existing, major randomized trials were conducted.’’ None of the above reasons is justifiable in the sponsor’s submission.

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Conclusions from the economic analysis section 5.2	The estimate was not sensitive to the majority of the parameters - 11 of the 17 scenarios PICO remained cost saving. Based on the data reported in Jenks 2014 PICO was cost saving across all surgical specialties considered, cost saving in 3 specialities (cardiothoracic, vascular and colorectal) and marginally cost additive in the other 3 (orthopaedic, C-section and breast surgery). However, caution should be taken interpreting these findings at a specialty level. The analysis undertaken by the EAC suggests that PICO is cost saving for highly invasive surgery; for surgery commonly undertaken on healthier patients such as C-section and orthopaedic surgery PICO is likely to be cost neutral and possibly cost saving in those with additional risk factors such as BMI or diabetes.	The EAC concludes that on balance PICO is more likely to be cost additive than cost saving. This contradicts the sensitivity analysis. Across surgical specialities the EAC concludes that the **majority** of surgical specialities were not cost saving. This is not consistent with their own analysis which showed that 3 sub specialities were cost saving and 3 were not. EAC and sponsor sensitivity analysis shows that PICO is at worst cost neutral and likely cost saving when additional risk factors are taken into account for orthopaedic, C-section and breast surgery. Indeed, it may be more appropriate to argue that on balance PICO is cost neutral – in all sensitivity	The EAC does not agree with the sponsor's interpretation of the evidence. The sponsor has incorrectly interpreted the evidence from the table on sensitivity analysis. The finding that PICO is cost saving was sensitive to 6 of the 8 parameters varied. The EAC has noted that the use of PICO is likely to be cost saving across all surgeries. The EAC reports in section 5.2 'The EAC estimated a very modest saving from the use of PICO across all surgeries.' The EAC chose to undertake analysis of PICO across all sub specialties for which data on more than 100 patients is reported in Jenks 2014. This included 17 of the 19 sub specialties. The EAC found PICO to be cost saving in gastric and small bowel surgery, in addition to colorectal, vascular, and cardiothoracic surgery, 5 of the 17 sub specialties examined. The EAC undertook analysis of patients in elevated risk groups undergoing orthopaedic surgery, breast surgery, and C-section (OR 1.95). The EAC did not find PICO to be cost saving for patients

		analyses the cost difference is close to zero. Given the uncertainty around various parameter estimates and conservative assumptions (e.g. such as exclusion of nurse time associated with dressings) it may be more realistic to state that on balance PICO is expected to be cost neutral or at best cost saving.	with elevated risk of SSI undergoing these three procedures.

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Summary conclusions	The EAC notes that the evidence of effectiveness of PICO indicates the likelihood of a health benefit. The overall analysis shows a cost saving result and this was shown in 3 sub-specialities. The other 3 sub-specialities showed that PICO may be cost incurring and therefore cost-effective. On the balance of evidence there is a higher likelihood that PICO is cost saving as shown in the sensitivity analysis of the sponsor and EAC.	The EAC SA shows that the majority of parameters varied result in cost savings, the sponsor one way and PSA shows a similar result. We suggest the EAC present the results of their own PSA which we believe will show that PICO is cost saving the majority of the iterations	The EAC does not agree with the sponsor's interpretation of the evidence. The finding that PICO is cost saving was sensitive to the majority of parameters varied in one-way sensitivity analysis. The EAC has noted that PICO is likely to be cost saving in gastric and small bowel surgery in addition to the three sub specialties identified by the sponsor. The EAC evidence suggested that PICO was cost incurring across the other sub specialties for which sufficient evidence is presented in Jenks 2014. While it remains possible that PICO is cost-effective in these sub-specialties after consideration of patient outcomes, and

			the EAC has noted this, cost-effectiveness has not been evaluated and remains uncertain.

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 8 –study figures	Witt 2015 – the p value should be 0.0339 not 0.34 (there is a significant difference). There is also no mention of the SSI results (where there is also a significant difference).	Misrepresentation of figures and result	Thank you for spotting this. We have changed the p-value to 0.034. We try to present in table 8 only essential information for each study as the table is otherwise difficult to read through. Table 13 lists the rate of SSIs for this publication.

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 8 –study figures	Galiano 2018 - Dehiscence p value should be <0.001 rather than 0.01. Skin necrosis should be PICO 2, control 7 (p = 0.008)	Misrepresentation of figures	Thank you for spotting we have revised accordingly.

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 8 –study figures	Selvaggi 2014 – Seroma data needs to be added: PICO 2 (8%) vs SC 11 (44%), p = 0.008.	Relevant figures have not been included	Please see previous comment about trying to present only essential information in table 8. This study was not powered to detect differences in seroma rates between the 2 groups and the detected statistically significant difference does not add significant information to the decision. We have however, added a line stating the different rates between the 2 groups.

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 8 –study figures	Van der Valk 2017 – Wound complications should be 70% vs 40%	Misrepresentation of figures	Thank you for spotting we have changed this accordingly.

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
MIB 149 citation	It could be used in an inpatient setting, to prevent SSC perioperatively, with treatment continuing in an outpatient department. Or it could be used in a community setting for treating postoperative SSC.	The wording on page 9 of the EAC document refers to only one type of complication and doesn't describe in full the intended treatment group	A MIB is advice and not guidance. As a result it is misleading to present information reported in MIB 149 about the potential use of PICO as guidance. We have listed the relevant section from MIB 149 that lists were in the current pathway a NPWT device may be used based on existing guidance. We don't believe that the section that reflects the sponsor's intended use is information that can be used to inform the relevant guidance section of the assessment report.

Issue 20

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Summary conclusions	PICO has been indicated for the duration of one week (7 days) in the majority of clinical studies.	In the case of closed surgical incisions, one PICO (1 pump and 2 dressings providing 1 week of therapy) is typically sufficient for the	Please see previous response to issue 9.

		management of closed surgical incisions. In a small number of cases a second week of therapy may be required, as reflected in the EAC analysis which indicated an average number of 1.09 PICOs per patient.	

Issue 21

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Summary conclusions from study selection 3.2	A majority of the PICO surgical incision studies were not Smith & Nephew instigated, rather Investigator Initiated.	The majority of studies were independent investigator initiated studies, in some cases supported financially by Smith & Nephew. In these instances, Smith & Nephew has no influence over the study design and execution. The benefit of this approach is the evidence should be considered as independent of the manufacturer. The disbenefit is the degree of variance in the study design, population and methods, creating heterogeneity in the studies.	The EAC has addressed the funding sources, where relevant, for each study in the critical appraisal paragraphs in section 3.3.

Issue 22

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Statement on reporting Galiano 2018 – Scar reporting	Further evidence to support claim	An additional paper has been prepared with the results of the scars assessment. For the N=200 patients scar quality as measured by POSAS, showed a significant difference in favor of NPWT compared to fixation strips both at day 42 (-4.0 units ($p<0.001$, 95% confidence interval -5.0 to -2.5) and at day 90 (- 2.5 units, $p<0.001$, 95% confidence interval -3.0 to -1.5).	Thank you for the additional information. Unfortunately only published evidence or evidence that have been submitted to the EAC in the form of academic in confidence or commercial in confidence can be included in the assessment report. In addition, Galiano 2018 was not powered to report differences in scar quality, therefore, this additional information is of little relevance to the decision.

Issue 23

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Funding on Hyldig 2018	Explanation of funding arrangements	The sponsoring of this and all other IISs is made under the form of unrestricted grants. Authors retain the whole responsibility for the performing of the study, they also have full freedom on the publication of results, when, what and where is their responsibility. The only requirement is that they effectively publish the results whatever they had been.	Thank you for clarifying. As part of our methodological quality assessment we need to highlight if studies have received support by the sponsor. The nature of the funding does not change the possibility of added bias. We haven't made further changes to the assessment report based on this comment.

Issue 24

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Nordmeyer 2016	Clinical insignificant	Five years in age is not a clinically significant difference. I agree age is a risk factor for wound healing, However that is more relevant in the population >65	We ned to highlight possible imbalances in the baseline characteristics between the two groups. Since age is a risk factor any imbalance between the 2 groups can lead to differences in outcomes. Unfortunately the authors do not report if this difference was statistically significant. The clinical relevance remains unknown.

Issue 25

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 6 incorrect patient numbers	Correct number is 60 in ITT and 53 in PP	Incorrect recording	Thank you we have changed this accordingly to 53.