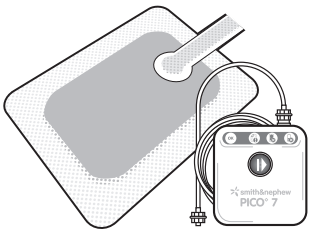
Summary of clinical evidence on the use of PICO for the reduction of incidence of Surgical Site Complications



smith&nephew

PICO◇ Family of products

Single Use Negative Pressure
Wound Therapy System
User Manual

CLINICAL EVIDENCE SUMMARY

1. Clinical Data

A systematic literature review and associated meta-analyses were used to support the safety and effectiveness of the PICO Family over closed incisions in reducing the incidence of surgical site infections (SSIs), seromas and dehiscence versus conventional wound dressings.

Database search and study selection:
A comprehensive review of published PICO Family literature identified relevant articles to support a reduction in SSI, seroma, and dehiscence. Three databases (PubMed, EMBASE and the Cochrane Library) were used to identify published clinical studies. The exact search terms used for each of the three databases are detailed in **Table 1**. Registered studies at ClinicalTrials.gov were also reviewed using the same search terms for completed and terminated studies with results available **(Table 1).**

Table 1. Search strings and filters used for each of the database searches.

Database	Search query	Filters / Limits	Search hits
PubMed	("Negative Pressure Wound Therapy"[All Fields] OR "NPWT"[All Fields] OR "PICO"[All Fields] OR "Topical Negative Pressure"[All Fields]) AND (2011/1/1:2021/4/19[pdat])	Date: 01/01/2011 to 19/04/2021 Searched: All Fields	6581
EMBASE	('negative pressure wound therapy' OR 'npwt' OR 'pico' OR 'topical negative pressure') AND [1-1-2011]/sd NOT [20-4-2021]/sd	Date: 01/01/2011 to 19/04/2021 (Date added to EMBASE) Searched: All Fields	7711
Cochrane Library	("Negative Pressure Wound Therapy" OR "NPWT" OR "PICO" OR "Topical Negative Pressure") (Word variations have been searched)	Date: Jan 2011 to Apr 2021 Searched: All Text	852
ClinicalTrials.gov	"Negative Pressure Wound Therapy" OR "NPWT" OR "PICO" OR "Topical Negative Pressure"	Date: 01/01/2011 to 19/04/2021 'Results available'	139

Two (2) independent reviewers performed the study selection. Abstracts that met the search criteria were screened and assessed against inclusion and exclusion criteria provided in **Table 2**. If either reviewer deemed an article as potentially relevant, then the article progressed to full text screening. In case of disagreement a third reviewer made the final decision after reading the full text paper or conference abstract. Included studies detailed outcomes following the use of PICO compared to standard care for closed surgical incisions. The standard of care was defined as the use of standard non-NPWT dressings.

1. Clinical Data (continued)

Table 2. Inclusion and Exclusion Criteria.

Inclusion Criteria		Exclusion Criteria
Population	Patients of any age with closed surgical incisions. Patients with any risk factors for complications were also included.	Patients with open surgical incisions or any non-surgical wound.
Intervention	PICO (single-use NPWT) applied post-operatively on a closed surgical incision. Participants undergoing any type of operation were eligible.	Other forms of NPWT (i.e. not PICO) were excluded.
Comparator	Standard care (any non-NPWT dressing).	Non-standard care.
Outcome	Surgical site infections or seroma or dehiscence.	N/A
Study design	Randomised controlled trials or prospective observational studies with at least 10 patients in each treatment arm.	Retrospective observational studies, case reports, case-series, studies with less than 10 patients in each treatment arm, letters, commentaries, notes, reviews and editorials.
Language restrictions	English	Not in English
Search dates	Studies published from 01 Jan 2011 to 19 Apr 2021	Studies published before 2011

Data extraction and quality assessment:
Data were extracted from included studies by one reviewer using a predefined and standardized data extraction form and checked by a second reviewer for accuracy. Extracted data included descriptions of study design, location of study, the number of patients, patient demographic data, and the type of surgery. Outcomes pertaining to SSI, seroma and dehiscence in closed surgical incisions were also extracted and evaluated. Quality assessment of studies was made according to two well-established guidelines. Randomized controlled trials were assessed according to the quality criteria from the Centre for Reviews and Dissemination (CRD) guidelines[1]. Prospective observational studies were assessed according to adapted criteria from the Critical Appraisal Skills Programme (CASP)[2].

Summary of the clinical data identified:
Ultimately, twenty-five (25)[3-23,27-30] articles were deemed to be relevant to the systematic literature review and used for the meta-analysis for SSI, seroma and dehiscence characterization. This consisted of seventeen (17) randomized controlled trials and eight (8) prospective observational studies. A total of up to 5,673 evaluable patients were included in these meta-analyses with 2,737 in the PICO Family therapy (treatment) group and 2,936 in the SOC (control) group. A summary of the articles identified in the review and those eligible for meta-analysis is provided in **Figure 1** and **Figure 2**.

Figure 1: Study Selection for the Meta-Analysis of Reduction of Wound Complications: Infection, Seroma and Dehiscence

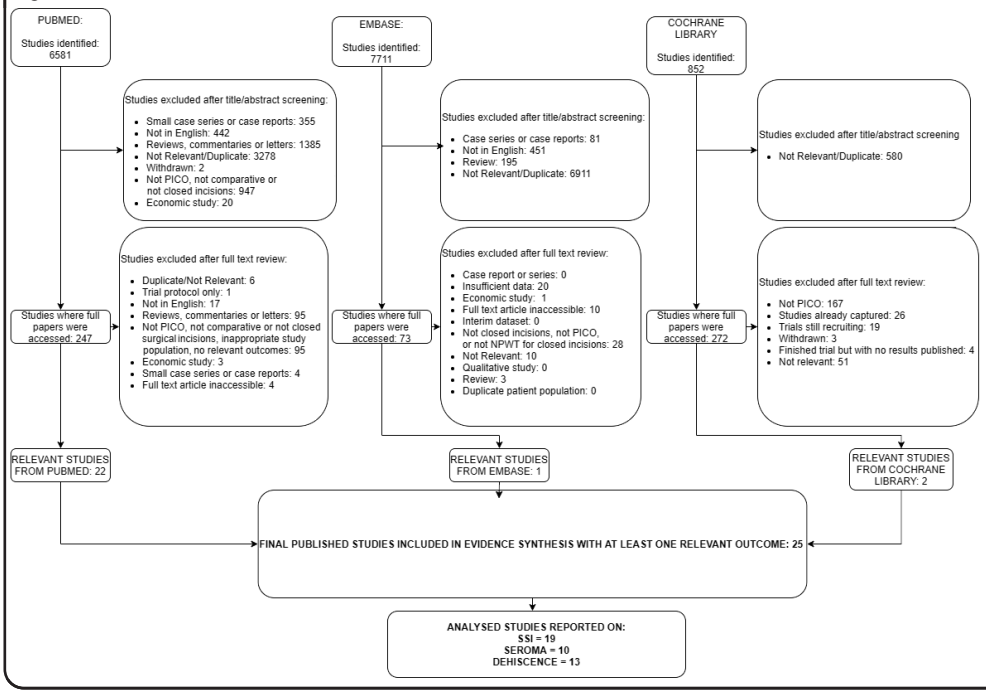
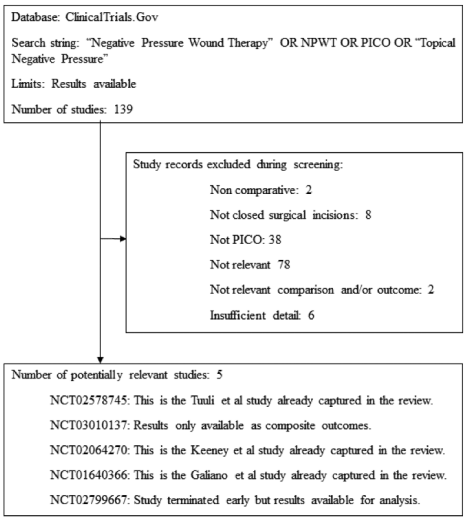


Figure 2: Study Selection from the ClinicalTrials.gov database



2. Surgical Site Infection (SSI)

A systematic literature review is included to demonstrate that the PICO Family can reduce the incidence of surgical site infections in closed surgical incisions in high risk patients in Class I and Class II wounds. Clinical studies which followed-up patients for at least 30 days (as defined by CDC guidelines[24]) were included in the analysis. A study was considered to contain 'high risk' patients if the majority (> 50%) of patients treated with PICO in that study presented with at least one 'intrinsic' or 'extrinsic' risk factor, as defined by the American College of Surgeons (ACS) and Surgical Infection Society's Surgical Site Infection Guidelines[25].

Literature Support (Reduction in SSI for High Risk Patients)

Meta-analysis of the seventeen (17) studies relevant to SSI demonstrates a statistically significant reduction in the odds of developing an infection when using PICO Family therapy in comparison to standard surgical dressing (SOC). Of the seventeen (17) prospective studies included in the meta-analysis for infection:

- Twelve (12) studies were randomized controlled trials and considered Level I evidence
- Five (5) studies were considered Level II evidence, which are non-randomized prospective observational studies

See **Table 3** below for a complete description of these studies.

Table 3. Published Studies Evaluating Reduction in Infection for High Risk Patients

Study	Study design	Surgical Procedure	Identified potential risk factors for surgical site infections	Study duration	Incisional dressings used	No. of Subjects	Treatment duration
Gillespie *et al* 2015	RCT	Elective primary hip arthroplasty patients	The majority of patients had a ASA score of ≥2	6 weeks	PICO dressing	35	5 days
					Comfeel™ dressing reinforced with 2 absorbent dressings, and then with a self-adhesive, non-woven tape	35	Left intact and patients were discharged with their original dressing
Hyldig *et al* 2018	RCT	Elective and emergency caesarean section patients	Inclusion criterion of BMI ≥30kg/m^2	30 days	PICO dressing	432	5 days
					Standard postoperative dressing	444	The dressing was left *in situ* for at least 24 hours
Karlakki *et al* 2016	RCT	Patients undergoing elective hip and knee arthroplasty	The majority of patients had a raised BMI and ASA score. The mean age of participants was >65 years old	6 weeks	PICO dressing	102	4 days or longer
					Comfeel™ dressing	107	Dressing was left on for 4 days, or longer if drainage continued, unless soiled or dislodged.
O'Leary *et al* 2017	RCT	Laparotomy patients who received open abdominal surgery	The majority of patients had a raised BMI and ASA score Type of surgery	30 days	PICO dressing	24	4 days
					Transparent waterproof dressing (Smith & Nephew)	25	4 days
Uchino *et al* 2016	RCT	Patients with ulcerative colitis undergoing elective ileostomy closure	All patients had a raised ASA score; inclusion criterion of patients with ulcerative colitis	Patients visited the clinic 4 weeks after the discharge, and every 4 weeks thereafter if they presented with complications	PICO dressing	28	Continued for 2 weeks, with exchange every 3–4 days
					Simple adhesive plaster	31	Not Reported
Witt-Majchrzak *et al* 2015	RCT	Patients undergoing coronary artery bypass grafting surgery	The majority of patients had a raised BMI and co-morbidities; Prolonged duration of surgery	6 weeks	PICO dressing	40	Applied for up to 6 days. Dressing changed on day 2 or 3 and removed on day 5 or 6 after surgery
					Conventional dressing	40	Dressings changed daily
Hasselmann *et al* 2019	RCT	Patients undergoing elective open vascular surgery with inguinal incisions	The majority of patients had pre-existing co-morbidities	90 days	PICO dressing	78	The PICO device and dressing was left in place for seven days post-operatively, after which patients were instructed to remove it
					Vitri Pad; ViTri Medical, Saltsjo¨-Boo, Sweden or OPSITE Post-Op Visible; Smith and Nephew, London, UK	80	Unless an unplanned change had to be conducted, the standard dressing was left in place for at least 48 hours, although changes due to moisture build-up was an issue on the standard dressing side and dressing changes did sometimes happen prior to 48 hours post-operatively
Keeney *et al* 2019	RCT	Patients undergoing primary or revision lower extremity TJA	43.0% of hip patients and 55.5% of knee patients had a BMI > 35 kg/m^2	35 days	PICO dressing	185	Initial period of 7 days
					Non-adherent incisional cover (Adaptic™ or Xeroform™ gauze)	213	Dressings were changed on postoperative day 2 with subsequent dressing changes performed at 3- to 5-day intervals until the incision was dry
Dingemans *et al* 2018	Prospective and historical controlled	Patients with foot or ankle fractures	Type of surgery	30 days	PICO dressing	47	7 days
					Conventional surgical dressings	47	For the control arm of the study, patients received a pressure bandage with gauze placed underneath, usually for three days duration.
Pellino *et al* 2014a	Prospective observational study	Patients (50 undergoing breast surgery, 50 colorectal surgery)	Type of surgery Prolonged duration of surgery	3 months	PICO dressing	50	7 days
					Basic wound contact absorbent dressings	50	Sterile removal for control after 48 h. On post-operative day 3, gauzes were removed sterilely and wounds left exposed if no complications occurred.
Pellino *et al* 2014b	Prospective observational	Crohn's disease patients undergoing small bowel resection	Type of surgery The majority of patients had co-morbidities and raised ASA score	3 months	PICO dressing	13	7 days
					Basic wound contact absorbent dressings	17	Sterile removal for control after 48 h. On postoperative day 3, gauzes were removed sterilely and wounds left exposed if no complications occurred.
Selvaggi *et al* 2014	Prospective observational study	Crohn's disease patients undergoing abdominal surgery	Type of surgery The majority of patients had co-morbidities	3 months	PICO dressing	25	7 days
					Basic wound contact absorbent dressings	25	Sterile removal for control after 48 h. On postoperative day 3, gauzes were removed sterilely and wounds left.
Tuuli *et al* 2017	RCT / Conference Abstract	Caesarean section patients	Inclusion criterion of a BMI ≥30kg/m^2	30 days	PICO dressing	60	Removed at discharge (usually on day 4)
					Standard wound dressing	60	The dressing was removed after hours

2. Surgical Site Infection (SSI) (continued)

Study	Study design	Surgical Procedure	Identified potential risk factors for surgical site infections	Study duration	Incisional dressings used	No. of Subjects	Treatment duration
Martin and O'Neil 2020	RCT / Conference Abstract	Patients undergoing hepatectomy and pancreatectomy.	The average age among all participants was 60.82 years and BMI was 31.7.	1 year	PICO dressing	20	For the PICO arm of the study, the PICO device was left in place for a total of 7 days.
					Sterile island dressing	20	For the control arm of the study, the length of time the dressing was left in place for was a median on 5 days (range 2-5 days).
Helito *et al* 2020	Prospective and historical controlled	Patients undergoing total knee arthroplasty	The majority of patients (51.7%) had at least one risk factor for surgical wound complications	12 months	PICO dressing	97	Applied with an intentional duration of 7 days.
					Conventional surgical dressings	199	Applied with an intentional duration of 7 days.
Costa *et al* 2020	RCT	Patients undergoing surgery for lower limb fractures associated with major trauma	Type of surgery	6 months	PICO dressing	770	Applied according to surgeon's normal practice and the manufacturer's instructions (up to 7 days of treatment).
					Sterile dressings (varied by treatment centre – details not given)	749	Varied based on routine local care.
Masters *et al* 2021	RCT	Patients undergoing surgery for hip fractures associated with trauma	Type of surgery, median age (>84 years)	120 days	PICO dressing	232	Applied according to surgeon's normal practice and the manufacturer's instructions (up to 7 days of treatment).
					Sterile dressings (varied by treatment centre – details not given)	230	Varied based on routine local care.
Bueno-Lledo *et al* 2020	RCT	Patients undergoing incisional hernia repair	Obese patients undergoing incisional hernia repair (BMI > 30; total pop: n=37/150)	30 days	PICO dressing	72	Applied with an intentional duration of six days.
					Conventional sterile dressing (MEPORE pro; Molnlycke, Goteborg, Sweden)	74	Applied with an intentional duration of six days.
Andrianello *et al* 2020	RCT	Patients undergoing pancreatic resection	Type of surgery	90 days	PICO dressing	46	Applied with an intentional duration of seven days
					Sterile gauze until post-op day 3, then sterile island dressing (OPSITE Post-Op Visible; Smith & Nephew)	49	Dressing (OPSITE) was changed according to clinical judgement.

Together, the seventeen (17) studies contained 1,354 evaluable patients receiving the PICO Family (treatment group) and 1,516 patients receiving conventional wound dressings (control group). The conventional wound dressings used in each study can be seen in **Table 3** and ranged from standard transparent dressings to basic wound contact absorbent dressings. The endpoint in the studies was the incidence of infection in the treatment group compared to the control group, with follow-up of patients for at least 30 days following surgery as per CDC guidance. The treatment effect for each study was summarized using odds ratio (OR), which was calculated using the following formula:

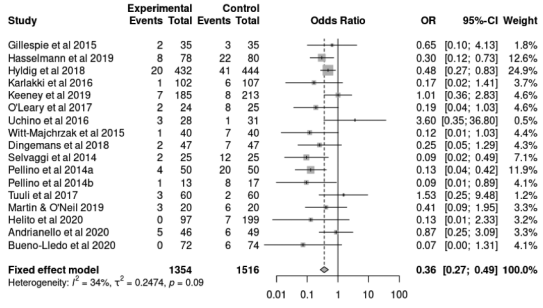
OR = AD/BC, where

- A = the number of subjects with Infection events for the treatment group
- B = the number of subjects without Infection events for the treatment group
- C = the number of subjects with Infection events for the control group
- D = the number of subjects without Infection events for the control group

An OR of less than 1 suggests a favorable effect by the treatment in reducing the incidence of infection in high risk patients, whereas an OR greater than 1 suggests a favorable effect by the conventional wound dressings. The 95% confidence interval (95% CI) for the odds ratio is calculated based on the standard error of Log(OR).

As demonstrated in **Figure 3**, there is an observable trend supporting a favorable effect by the PICO Family in reducing the incidence of infection compared to the control group.

Figure 3: Forest plot showing Infections in patients treated with PICO compared to SOC



Adverse events (AEs) or other potential device-related problems, ranging from patient reported noise concerns and vacuum failure to reports of pain and adverse skin reactions, were detailed in fifteen (15) of the seventeen (17) studies included in the meta-analyses.

Literature Supports Reduction in Infection for Class I and II Wounds
To analyze the effect of the PICO Family on infection in wounds of different degrees of contamination, a wound classification designation was applied following the Center for Disease Control and Prevention (CDC) guidelines[24].

Literature Support: Reduction in Superficial and Deep Surgical Site Infection (Infection Depth)
The definitions of "superficial" and "deep" incisional surgical site infections (SSIs) utilized within this analysis are based on the established and recognized definitions provided by the Centers for Disease Control and Prevention (CDC). According to the latest recommendations[24], superficial and deep incisional SSIs are briefly defined as follows:

- A superficial incisional SSI involves only skin and subcutaneous tissue of the incision and occurs within 30 days after any NHSN operative procedure.
- A deep incisional SSI involves deep soft tissues of the incision (for example, fascial and muscle layers) and occurs within 30 or 90 days after the NHSN operative procedure.

Meta-analysis of appropriate studies from Class I or Class II wound studies show a reduction in infection for superficial and deep infection when using the PICO Family compared to standard surgical dressing (SOC). Specifically, to analyze the effect of the PICO Family on infections of different depths, subgroup analyses were performed using studies where the authors stated the use of the CDC criteria discussed above for superficial and deep SSIs[26].

Meta-analyses of the relevant studies show a statistically significant reduction in infection for both superficial and deep incisional infections for class I/II wounds when comparing use of the PICO Family to SOC (**Figures 4 and 5**). The meta-analysis for superficial SSI includes eight (8) studies (5 RCTs, 3 prospective observational) containing a total of 723 evaluable patients, of which 356 received the PICO Family (treatment group) and 367 received conventional wound dressings (control group). The deep SSI analysis includes six (6) studies (4 RCTs, 2 prospective observational) containing a total of 2,284 evaluable patients, of which 1,146 received the PICO Family (treatment group) and 1,138 received conventional wound dressings (control group). The conventional wound dressings used in each study can be found in **Table 3** and range from standard transparent dressings to simple adhesive plasters. The endpoint in the studies was the incidence of SSI (superficial and/or deep) in the treatment group compared to the control group.

Figure 4: Forest plot showing superficial SSI defined in patients treated with PICO Family compared to SOC

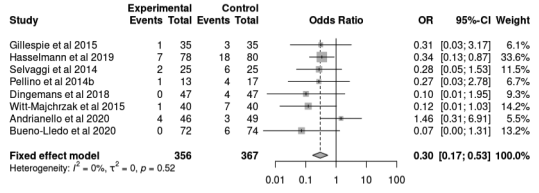
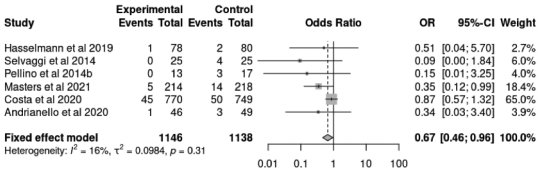


Figure 5: Forest plot showing deep SSI defined in patients treated with PICO Family compared to SOC



3. Post-Operative Seroma

A review of literature is included to demonstrate that the PICO Family is intended to reduce the incidence of post-operative seroma for closed surgical incisions. Studies assessing seroma were only included if they had at least 10 days of follow-up time (see **Table 4**).

Literature Review

A meta-analysis of ten (10) studies demonstrated a statistically significant reduction in the odds of developing a seroma when using PICO in comparison to standard of care (SOC). Of the ten (10) prospective studies included in the meta-analysis for seroma:

- Seven (7) studies were randomized controlled trials and considered Level I evidence.
- Three (3) studies were considered Level II evidence, which are non-randomized prospective observational studies.

See **Table 4** below for a complete description of these studies.

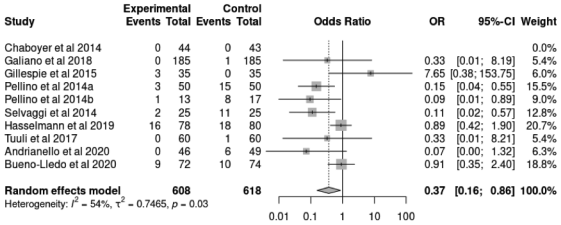
The ten (10) studies contained 608 evaluable patients receiving the PICO Family (treatment group) and 618 patients receiving conventional wound dressings (control group). The conventional wound dressings used in each study can be found in **Table 4** and range from standard transparent dressings to basic wound contact absorbent dressings. The endpoint in the studies was the incidence of post-operative seroma in the treatment group compared to the control group for at least 10 days following surgery.

As demonstrated in **Figure 6**, there is an observable trend supporting a favorable effect by the PICO Family in reducing the incidence of seroma.

Table 4. Published Studies Evaluating Reduction in Seroma.

Study	Study design	Surgical Procedure	Follow up period	Incisional dressings used	No. of Subjects	Treatment duration
Chaboyer *et al* 2014	Randomized Controlled Trial (RCT)	Elective caesarean section patients	6 weeks	PICO dressing	44	4 days or more
				Comfeel™ dressing	43	Dressing was left on for 4 days, or longer if drainage continued, unless soiled or dislodged
Galiano *et al* 2018	RCT	Bilateral reduction mammoplasty patients	21 days (90 days)	PICO dressing	185	The overall duration of PICO treatment was a median of 7 days
				3M STERI-Strip (3M Health Care, St. Paul, Minn.).	185	Not reported
Gillespie *et al* 2015	RCT	Elective primary hip arthroplasty patients	6 weeks	PICO dressing	35	5 days
				Comfeel™ dressing reinforced with 2 absorbent dressings, and then with a self-adhesive, non-woven tape	35	Left intact and patients were discharged with their original dressing
Hasselmann *et al* 2019	RCT	Patients undergoing elective open vascular surgery with inguinal incisions	90 days	PICO dressing	78	The PICO device and dressing was left in place for seven days post-operatively, after which patients were instructed to remove it.
				Vitri Pad (ViTri Medical, Saltsjo¨-Boo, Sweden or OPSITE Post-Op Visible; Smith and Nephew, London, UK)	80	The standard dressing was left in place for at least 48 hours, although changes due to moisture build-up was an issue on the standard dressing side and dressing changes did sometimes happen prior to 48 hours post-operatively.
Pellino *et al* 2014a	Prospective observational study	Patients (50 undergoing breast surgery, 50 colorectal surgery)	3 months	PICO dressing	50	7 days
				Basic wound contact absorbent dressings	50	Sterile removal for control after 48 h. On post-operative day 3, gauzes were removed sterilely and wounds left exposed if no complications occurred.
Pellino *et al* 2014b	Prospective observational	Crohn's disease patients undergoing small bowel resection	3 months	PICO dressing	13	7 days
				Basic wound contact absorbent dressings	17	Sterile removal for control after 48 h. On post-operative day 3, gauzes were removed sterilely and wounds left exposed if no complications occurred.
Selvaggi *et al* 2014	Prospective observational study	Crohn's disease patients undergoing abdominal surgery	3 months	PICO dressing	25	7 days
				Basic wound contact absorbent dressings	25	Sterile removal for control after 48 h. On post-operative day 3, gauzes were removed sterilely and wounds left exposed if no complications occurred.
Tuuli *et al* 2017	RCT / Conference Abstract	Caesarean section patients	30 days	PICO dressing	60	Removed at discharge (usually on day 4)
				Standard wound dressing	60	The dressing was removed 24 to 48 hours
Bueno-Lledo *et al* 2020	RCT	Patients undergoing incisional hernia repair	30 days	Conventional sterile dressing (MEPORE pro; Molnlycke, Goteborg, Sweden)	74	Applied with an intentional duration of six days
				PICO dressing	72	Applied with an intentional duration of six days
Andrianello *et al* 2020	RCT	Patients undergoing pancreatic resection	90 days	Sterile gauze until post-op day 3, then sterile island dressing (OPSITE Post-Op Visible; Smith & Nephew)	49	Dressing (OPSITE) was changed according to clinical judgement.
				PICO dressing	46	Applied with an intentional duration of seven days

Figure 6: Forest plot showing Seroma in patients treated with PICO compared to SOC



Device related adverse events (AEs) or other potential device-related problems, ranging from sealing issues to reports of pain and adverse skin reactions, were reported in eight (8) of the ten (10) studies included in the meta-analysis.

4. Dehiscence

A review of literature is included to demonstrate that the PICO Family is intended to reduce the incidence of dehiscence in closed surgical incisions. Studies assessing dehiscence were only included if they had at least 10 days of follow-up time (see **Table 5**).

Literature Support

In accordance with the literature review process described above, seven (7) prospective studies demonstrated a statistically significant reduction in developing dehiscence when using PICO in comparison to standard of care. Of the seven (7) studies included in the meta-analysis for dehiscence:

- Six (6) studies were randomized controlled trials and considered Level I evidence.
- One (1) study was considered level II evidence, which are non-randomized prospective observational studies.

See **Table 5** below for a complete description of these studies.

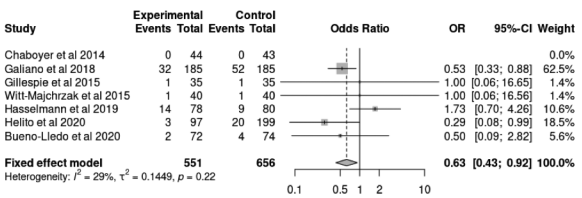
The seven (7) studies contained 551 evaluable patients receiving the PICO Family (treatment group) and 656 patients receiving conventional wound dressings (control group). The conventional wound dressings used in each study can be found in **Table 5** and range from standard sterile dressings to fixation strips. The endpoint in the studies was the incidence of dehiscence in the treatment group compared to the control group for at least 10 days following surgery.

As demonstrated in **Figure 7**, there is an observable trend supporting a favorable effect by the PICO Family in reducing the incidence of dehiscence.

Table 5. Studies Evaluating Reduction in Dehiscence in Closed Surgical Incisions.

Study	Study design	Surgical Procedure	Follow up period	Incisional dressings used	No. of Subjects	Treatment duration
Chaboyer *et al* 2014	Randomized Controlled Trial (RCT)	Elective caesarean section patients	6 weeks	PICO dressing	44	4 days or more
				Comfeel™ dressing	43	Dressing was left on for 4 days, or longer if drainage continued, unless soiled or dislodged
Galiano *et al* 2018	RCT	Bilateral reduction mammoplasty patients	21 days (90 days)	PICO dressing or 3M STERI-Strip (3M Health Care, St. Paul, Minn.).	185	The overall duration of PICO treatment was a median of 7 days
					185	Not Reported
Gillespie *et al* 2015	RCT	Elective primary hip arthroplasty patients	6 weeks	PICO dressing or Comfeel™ dressing reinforced with 2 absorbent dressings, and then with a self-adhesive, non-woven tape	35	5 days
					35	Left intact and patients were discharged with their original dressing
					417	The dressing was left in situ for at least 24 hours
Witt-Majchrzak *et al* 2015	RCT	Patients undergoing coronary artery bypass grafting surgery	6 weeks	PICO dressing	40	Dressing changed on day 2 or 3 and on day 5 or 6 after surgery
				Conventional dressing	40	Dressings changed daily
Hasselmann *et al* 2019	RCT	Patients undergoing elective open vascular surgery with inguinal incisions	90 days	PICO dressing	78	The PICO device and dressing was left in place for seven days post-operatively, after which patients were instructed to remove it.
				(Vitri Pad; ViTri Medical, Saltsjo¨-Boo, Sweden or OPSITE Post-Op Visible; Smith and Nephew, London, UK)	80	The standard dressing was left in place for at least 48 hours, although changes due to moisture build-up was an issue on the standard dressing side and dressing changes did sometimes happen prior to 48 hours post-operatively.
				Sterile island dressing	20	Not Reported
Helito *et al* 2020	Prospective and historical controlled	Patients undergoing total knee arthroplasty	12 months	PICO dressing	97	Applied with an intentional duration of 7 days.
				Conventional surgical dressings	199	Applied with an intentional duration of 7 days.
Bueno-Lledo *et al* 2020	RCT	Patients undergoing incisional hernia repair	30 days	Conventional sterile dressing (MEPORE pro; Molnlycke, Goteborg, Sweden)	74	Applied with an intentional duration of six days
				PICO dressing	72	Applied with an intentional duration of six days

Figure 7: Forest plot showing dehiscence in patients treated with PICO compared to SOC



Device related adverse events (AEs) or other potential device-related problems, ranging from sealing issues to reports of pain and adverse skin reactions, were reported in five (5) of the seven (7) studies included in the meta-analysis.

5. Limitations of the Clinical Evidence

There can be many inherent limitations to meta-analyses, such as publication bias, selection bias, and varying quality of the underlying studies. Efforts were made in the study identification and selection process to reduce potential biases by selecting higher quality level I and level II studies. The criteria used to assess quality within the identified studies is detailed earlier in the methodology of the systematic literature review (**Section 1** and **Table 2**). Another potential bias affecting studies included in meta-analyses is publication bias, whereby studies with statistically significant results are more likely to be published. This may also occur in the context of selective outcome reporting in which only significant outcomes are reported at study publication. To address this, searches were also conducted on ClinicalTrials.gov to check for completed trials with results available that had not been published.

Most studies (16/25) included in the systematic literature review were at higher risk of bias or the risk for bias was unclear. Specifically, many level I studies failed to include an intention to treat (ITT) analysis and often only reported on the per protocol (PP) analysis. Deficiencies in level II prospective observational studies included a lack of reporting of confidence intervals or p-values. Additional sources of bias included the variability between studies in the length of follow-up time for assessment of surgical site complications such as SSI. While inclusion for analysis required a follow-up period of at least 30 days post-operatively (as per CDC definitions), some studies exceeded this threshold sometimes by a few weeks. As a result, this may have impacted on the number of detected SSIs during the specified clinical endpoint. Some studies (Van der Valk *et al* 2017; Dingemans *et al* 2018; Helito *et al* 2020) included in the analysis used a historical cohort group as the control arm. There can be problems with interpreting data based on historical comparators. Namely, clinical practice, such as the use of technologies, procedures or care pathways, may have changed over time since the original data was collected meaning that any clinical improvement in the intervention arm may be attributable to these medical advances, rather than just the intervention alone. The systematic literature review also only included studies published in the English language. As such, there is the possibility of excluding valid data published in a different language.

Although these limitations should be considered when examining the results from these meta-analyses, the depth and breadth of the evidence provided gives reassurance to the conclusions reached for each of the outcomes assessed for the proposed Indications For Use. In addition, by the very nature of the inclusion criteria used for the systematic literature review, only studies considered methodologically robust (i.e., prospective and comparative) were selected for these analyses.

The device has not been demonstrated to be effective in reducing the incidence of surgical site infection, seroma, and dehiscence in all surgical procedures and patient populations; therefore, the device may not be recommended for routine use to reduce surgical site infection, seroma, and dehiscence. Surgeons should continue to follow the 'Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection'[31] and the 'American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines'[25] for best practices in preventing surgical site infection.

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