NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

V.A.C. VERAFLO Therapy System for acute infected or chronic wounds that are failing to heal

External Assessment Centre report

Produced by: Newcastle External Assessment Centre

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Date completed: 28//07/2020

Updated following public consultation.

Contains confidential information: Yes

Number of attached appendices: None

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None

Acknowledgements

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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.

Contents

Abbreviations

Term	Definition
AWC	Advanced wound care
CASP	Critical Appraisal Skills Programme
CFU	Colony forming unit
CI	Confidence interval
DRG	Diagnosis-related group
DSA	Deterministic sensitivity analysis
EAC	External Assessment Centre
HES	Hospital episode statistics
HRG	Healthcare resource group
IPG	Interventional procedures guidance
IQR	Interquartile range
ITT	Intention to treat
KoL	Key opinion leader
LoS	Length of [hospital] stay
LoT	Length of treatment
MAUDE	Manufacturer and User Facility Device Experience
MeSH	Medical subject headings
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
MTG	Medical technologies guidance
MIB	Medtech innovation briefing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPWT	Negative pressure wound therapy
NPWTi	Negative pressure wound therapy with instillation
PP	Per protocol
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
RCT	Randomised controlled trial
SD	Standard deviation
STSG	Split-thickness skin graft
VAS	Visual analogue scale
Vs	Versus

Executive summary

V.A.C. VERAFLO is an automated system that combines negative pressure wound therapy (NPWT) and wound instillation with topical solutions (NPWTi). Following a systematic literature search, 19 studies were identified that were considered by the EAC to be in scope of the assessment. These included 9 comparative studies, of which 2 were RCTs of limited relevance (Kim *et al.*, 2015, Yang *et al.*, 2017), and 6 were observational studies (Chowdhry and Wilhelmi, 2019, Deleyto *et al.*, 2018, Gabriel *et al.*, 2014, Goss *et al.*, 2012, Kim *et al.*, 2014, Omar *et al.*, 2016). One unpublished, directly relevant RCT was also identified, and has since been published (Kim *et al.*, 2020). Ten single-armed observational studies identified were of limited utility.

The EAC considered evidence from the recently published RCT was the most robust (Kim *et al.*, 2020). It compared NPWTi with NPWT in patients with acute and chronic wounds (n = 181) and reported no significant difference in its primary endpoint, the number of follow-on surgical debridements: 1.1 (95% confidence interval [CI] 0.93 to 1.30) for NPWTi compared with 1.1 (95% CI 0.85 to 1.18) for NPWT (p = 0.68). The RCT reported that NPWTi was associated with a significant reduction in bacterial bioburden (p = 0.02), but other secondary outcomes were found to have no significant differences.

The observational comparative studies were generally retrospective and of limited methodological quality. Common issues included poor reporting of patient selection; small sample sizes; use of historical control groups without adequate description of how these were selected; lack of statistical matching; and a lack of confidence in how endpoints were measured, recorded and reported. The EAC considered that these limitations, taken together, meant that causal associations between NPWTi and clinical outcomes had not been established. Additionally, the heterogeneity of the study populations and variance in patient pathways meant the data could not be generalised to the UK NHS. Thus the evidence that NPWTi improves healing or reduces hospital length of stay (LoS) compared with NPWT was equivocal. There was not enough data published to make a meaningful comparison with advanced wound care (AWC).

No useful published economic studies were identified. The company reported a *de novo* economic model that compared NPWTi, NPWT and AWC. This was a cost calculator of cost consequences. Three variables in the model determined overall costs; these were LoS; length of treatment (LoT, direct costs associated with each technology); and repeat surgical debridement costs. The model was informed from selected comparative observational studies identified in the clinical literature. Four scenarios were reported (“lower limb”, “mixed wound”, “prosthetic implant” and “surgical infection”), and these were combined into a base case scenario, based on aggregated data from the

informing studies. Deterministic and probabilistic sensitivity analyses (DSA and PSA) were reported.

The company reported that in the base case, NPWTi was cost saving by £3,251 compared with NPWT, and by £8,312 compared with AWC. The principal driver of the cost savings was the reduction in LoS, as shown by DSA. The company reported that NPWTi was cost-saving in all 4 scenarios and in 3 of these, PSA indicated that the probability of NPWTi being cost saving was ≥ 94%.

The EAC had concerns with the *de novo* model. Firstly, the company's study selection was subject to potential bias. Secondly, the EAC considered the causality between the intervention and the reported outcomes had not been established with enough certainty. Thirdly, some parameter inputs had been derived using data transformation from two unrelated studies. Fourthly, the informing studies were based on heterogeneous case mixes of patients that could not be generalised to NHS population, and there were further issues with the generalisability of patient pathways. Fifthly, the method of reporting the base case results was not directly based on appropriate empirical data and was not accordingly weighted to reflect this. Finally, the EAC considered that the scale of the structural and parameter uncertainty in the model meant that the sensitivity analyses used were not meaningful.

The EAC replicated the company's *de novo* model and changed some assumptions and inputs in an attempt to improve the model's accuracy and internal consistency. The main change was to use data from the Kim *et al*. (2020) RCT to inform the base case. The best EAC estimate using PSA was that NPWTi was cost neutral with respect to NPWT, with a point estimate of £471 cost incurring (95% credibility interval [CrI] -£1085 to £2015). However, this estimate was also subject to several assumptions which were not directly evidenced. Thus, the EAC considers the cost-saving potential of NPWTi cannot currently be confirmed. An important caveat to these findings is that an absence of clinical benefit is not evidence of absent benefit. NICE clinical experts were unanimous the technology is clinically beneficial, and potentially cost-saving, in appropriately selected patients. Further clinical research would be required to confirm and quantify this benefit, and which patients will benefit most.

1 Decision problem

Changes to the decision problem made by the company, with EAC comments, are reported in Table 1.1.

Table 1.1. *Description of decision problem.*

Decision problem	Scope	Proposed variation in company submission	EAC comment
Outcomes	• Length of stay in hospital • Rates of partial and complete wound closure (which may vary depending on wound type, location, depth and size) • Mean time to partial or complete wound closure • Mean time to healing • Number of dressing changes • Number of follow on treatments and visits to hospital • Number of surgical debridements • Number of amputations or skin grafts • Staff time and use of other consumables • Colonisation with antimicrobial resistant pathogens	<u>Remove mean time to healing</u> Only 3 studies collected mean time to healing data and whilst 1 showed very high statistical significance p=0.0000 the majority of studies focussed upon wound closure rates and the associated timescales. NPWTi is used to prepare a wound bed for closure, it is not designed to heal wounds and we suggest it is not an appropriate outcome. This may explain why this data was not collected. <u>Remove number of amputations</u> Only 4 studies collected amputation data, 3 of which had no comparator. <u>Modify colonisation with antimicrobial resistant pathogens to colonisation with pathogens</u> Whilst many of the studies record the presence of pathogens, whether or not they were	The EAC considered there was no reason not to report this outcome, in studies that report it. NICE clinical experts confirmed the technology has several use cases, including use as a bridging procedure to surgical repair and as a standalone procedure (EAC External correspondence log, 2020). The EAC considered there was no reason not to report this outcome, in studies that report it. The EAC concurs that colonisation with any pathogens is the relevant measure. The implications for microbial resistance can be inferred from this. The EAC considers that this is potentially

	• Antibiotic use • Health-related quality of life • Patient satisfaction and acceptability • Patient-related outcomes such as pain scores	microbially resistant was not usually documented. <u>Remove antibiotic use</u> The majority of studies documenting antibiotic use prescribed them systemically for all patients or for all those who had an infected wound. Data collection in studies more often focussed on pathogen types and colonisation levels. <u>Remove HRQOL</u> None of the studies selected in the systematic review presented any data related to patient's QOL.	a relevant outcome where it is reported. The lack of HRQoL data reported is relevant and will be documented in the Assessment Report.

The EAC has made the following clarifications on other aspects of the scope.

1.1. Population

The population described in the scope is "Patients with acute infected or chronic wounds that are failing to heal" (NICE, 2020). This is a very broad population that signifies the versatility of the V.A.C. VERAFLO system in treating wounds of varying aetiologies and anatomical locations, as well as reflecting the heterogeneous nature of study population described in the literature. The company has commented that the population is appropriate because the mechanism of action of the technology is applicable to most wounds, regardless of the aetiology (EAC External correspondence log, 2020). Nevertheless, the breadth of the population makes generalisation of results challenging (see Section 8).

1.2. Intervention

The intervention is the V.A.C. VERAFLO system, in its entirety. This system features the following components:

- Negative Pressure Wound Therapy device with instillation option, namely the V.A.C. ULTA™ with VERAFLO Therapy (launched 2011) OR the V.A.C.ULTA™ 4 Therapy System (launched 2019).

- Specific, bespoke dressings for use with the system, namely the V.A.C. VERAFLO™ Dressing (2011), V.A.C. VERAFLO CLEANSE Dressing (2011), OR the V.A.C. VERAFLO CLEANSE CHOICE Dressing (2016).

- An approved instillation fluid (including Dakin's solution, Prontosan, and normal saline).

The V.A.C. VERAFLO also has other additional features that are bespoke to the system (canisters, cassettes, and drapes). However, these are rarely reported in published studies, and will not directly affect the technology's efficacy, so have not been considered further. The predecessor technology to the V.A.C. VERAFLO system was V.A.C. Instill™ system, which differs from V.A.C. VERAFLO in some potentially important ways, such as the use of gravity assisted instillation rather than active instillation of controlled volumes of fluid through pumps and software control.

Following discussion with the company (EAC External correspondence log, 2020), the EAC accepts that the V.A.C. VERAFLO system is likely to represent an incremental improvement over the predecessor system (VAC Instill). It is noted that V.A.C. VERAFLO was licenced in the United States under the 510k pathway via its predicate system and will likely result in at least equivalent, if not better, outcomes. This is mainly due to expected system benefits accrued collectively from the components of the technology. However, because many of the innovative aspects of the technology are specific to the V.A.C. VERAFLO system (discussed in Section 2 of the company's clinical submission), the EAC maintains studies of predecessor systems, or technologies from other companies, would not fully capture the operational effectiveness of the V.A.C. VERAFLO system. Therefore the studies reporting on the predecessor system, or other systems, were excluded from clinical assessment. However, some excluded studies were included in the company's economic assessment, to inform model inputs. These have been necessarily included, but limitations have been noted (Section 9.2.3).

For simplicity, the V.A.C. VERAFLO system in this report is referred to as negative wound pressure therapy with instillation (NPWTi).

1.3 Comparator

Two comparators are listed in the scope (NICE, 2020). These are standard advanced wound dressings and negative pressure wound therapy without instillation (NPWT). The company has illustrated the possible position of NPWTi in the patient pathway in Section 3 of the clinical submission (using diabetic foot ulcer as an example). The EAC considers that, because the population is patients with "wounds that are failing to heal", this is indicative

that usually NPWTi would be used as second-line treatment to standard care dressings, and as such, NPWT is the most appropriate comparator. This was confirmed by clinical experts (EAC External correspondence log, 2020). However, the company has suggested that earlier use of NPWTi, for instance at the stage in wound care where dressings are used, could lead to better outcomes in the longer-term (EAC External correspondence log, 2020).

1.4 Outcomes

The EAC notes that the clinical management outcomes listed in the scope were generally proxy measurements of healthcare resource use rather than actual clinical outcomes. The EAC notes that there is an absence of standard wound healing endpoints (Driver *et al.*, 2019), such as percentage area reduction in 4 to 8 weeks, reflecting the fact that NPWTi is an intervention that may reduce the time until wound closure, rather than the longer-term outcome of wound healing. See Section 9.2.3.

The EAC noted that outcome assessment is problematic in this medical field, due to population and setting heterogeneity; use of non-standardised definitions and measurement; and use of observational data that is often retrospective. These issues have been confirmed by NICE clinical experts (EAC External correspondence log, 2020) as well as the principal author of an important RCT on the technology. In particular, there are difficulties measuring and interpreting hospital length of stay (Section 5.3.1).

2 Overview of the technology

The V.A.C. VERAFLO Therapy system (3M + KCI) is an automated system that combines negative pressure wound therapy (NPWT) and wound instillation with topical solutions for wound healing. The therapy system delivers automated cycles of wound cleansing (instillation), dissolution and removal of infectious material and exudate (dwell time), and NPWT (completing the cycle). Collectively, this process is known as negative pressure wound therapy with instillation (NPWTi).

During NPWTi, a VeraFlo dressing foam is applied to the wound bed, available in a variety of sizes. A VAC Advance drape is then placed over the wound with a 3 cm margin to make sure there is full adhesion, with a small hole cut into the drape surface. The VAC VERATRAC Pad can then be attached to the drape, using a stabilisation layer to ensure complete contact. The pad is then connected to the VeraFlo Therapy system. This collects fluid and substances produced by the body in response to tissue damage from the wound into a single-use 500 ml or 1000 ml canister. The VAC system fill assist tool is used to determine and ensure an appropriate instillation volume has been applied and the SEAL CHECK leak detector is designed to minimise potential leaks.

The VeraFlo Therapy system is primarily used for patients with open, infected wounds or chronic wounds which are failing to heal. The company has described the technology in Section 2 of the clinical submission. In 2019, international consensus guidelines were published which advised on appropriate settings for the technology (Table 2.1).

Table 2.1 *Recommended settings for NPWTi with V.A.C. VERAFLO system.*

Parameter	**Recommended by consensus (≥80% positive response)**
Instillation fluid*	Hypochlorous acid solution (examples: Vashe, Puracyn, NeutroPhase)
	Sodium hypochlorite solution (Dakin's solution 0.125%)
	Acetic acid solution (0.25% to 1.0%)
	Polyhexamethylene biguanide (0.1%) + betaine (0.1%) (Prontosan)
NPWT cycle time	2.0 to 3.0 hours
NPWT pressure	-125 mmHg
Dwell time	10 minutes
Abbreviations: NPWT, negative pressure wound therapy * Normal saline recommended as first-line treatment. Solutions with antiseptic or anti-microbial actions recommended in some instances (e.g. highly infected wounds). Data from (Kim *et al.*, 2019)	

3 Clinical context

3.1 Clinical guidelines

The company describes the clinical context in which NPWTi is intended to be used in Section 3 of the clinical submission. Because the scope of the population is very broad (Section 1.1), it is not possible to place the technology in a specific part of the patient pathway. In general, however, it may be considered as an alternative or adjunct to NPWT (Section 1.3).

The EAC identified two relevant NICE clinical guidelines which are applicable to this technology (as they make recommendations on NPWT). These were:

- *Pressure ulcers: prevention and management* (CG179) (NICE, 2014b). Recommendation 1.4.13 states "Do not routinely offer adults negative pressure wound therapy to treat a pressure ulcer, unless it is necessary to reduce the number of dressing changes (for example, in a wound with a large amount of exudate)".

- *Diabetic foot problems: prevention and management* (NG19) (NICE, 2015). Recommendation 1.5.9 states "Consider negative pressure wound therapy after surgical debridement for diabetic foot ulcers, on the advice of the multidisciplinary foot care service". The evidence base for NPWT itself is generally poor, with no firm conclusions on the effectiveness of the procedure being able to be drawn. Table 3.1 summarises the conclusions from Cochrane systematic reviews.

Several NICE Interventional Procedures Guidance (IPG). Medical Technology Guidance (MTGs), and Medtech Innovation Briefings (MIBs) have been published which are concerned with the management of wounds that are difficult to heal or chronic infected wounds. The most relevant of these are

- Negative pressure wound therapy for the open abdomen (IPG467) (NICE, 2013).

- *PICO negative pressure wound dressings for closed surgical incisions* (MTG43) (NICE, 2019a).

- *The MIST Therapy system for the promotion of wound healing* (MTG5) (NICE, 2011)

- *The Debrisoft monofilament debridement pad for use in acute or chronic wounds* (MTG17).(NICE, 2014a)

- *Prevena incision management system for closed surgical incisions* (MIB173) (NICE, 2019b)

- *The Versajet II hydrosurgery system for surgical debridement of acute and chronic wounds and burns* (MIB1) (NICE, 2014c).

The two former technologies (subject of MTG43 and MTG5) listed may be regarded as comparators in some patient populations; whereas the latter two (MTG17 and MIB173) technologies may be used in conjunction with NPWTi. In all instances, these technologies might impact on the economics of wound healing (Section 9).

3.2 Use of debridement in wound healing

Debridement is the removal of devitalised, contaminated or foreign material from the surface of an acutely infected or chronic wound. The purpose of debridement is to promote wound healing and as such it is a fundamental component of the management of poorly healing wounds. There are several methods of debriding wounds, each mechanistically distinct, and each with their own advantages and disadvantages. These are (Wounds UK, 2013):

- Autolytic debridement. This is a naturally occurring process in which the body's own enzymes and moisture rehydrate, soften and liquify hard eschar and slough. This can be aided by use of appropriate dressings and can be undertaken in community, generalist or specialist settings.

- Mechanical debridement. This is removal of non-viable material using a specialised monofilament such as Debrisoft (NICE, 2014a). It can be used in a generalist or specialist setting.

- Larval therapy (biosurgical) debridement. The larvae of green bottle fly (*Lucilia sericata*) are used to remove moist devitalised tissue from the wound. It can be used in a generalist or specialist setting.

- Ultrasonic debridement. Use of direct ultrasound or atomised solution to debride tissue. An example of this is MIST therapy (NICE, 2011). Used in specialist settings only (not routinely available).

- Hydrosurgical debridement. Removal of devitalised tissue using a high energy fluid beam as a cutting implement, for example Versajet (NICE, 2014c).

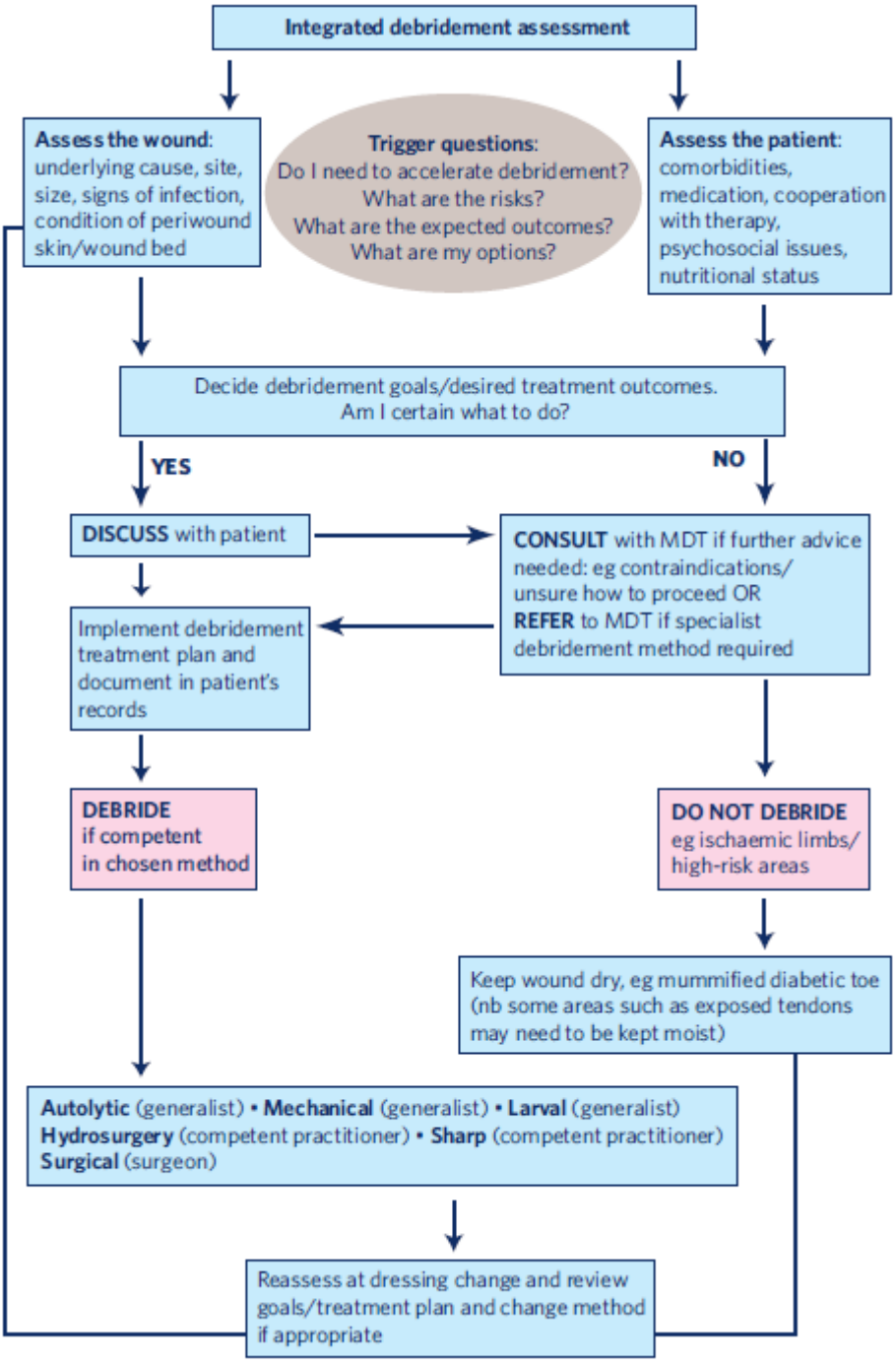
- Sharp debridement. This is removal of dead or devitalised tissue using a scalpel, scissors and/or forceps to just above the viable tissue level. It is undertaken in conjunction with other therapies (e.g. autolytic

debridement). Analgesia is not normally required and it can be done at the bedside. However, complete removal of devitalised tissue is not always possible and it is not without risk. This is a specialist competency undertaken by specialist nurses or podiatrists.

- Surgical debridement. This is excision or wider resection of non-viable tissue, including the removal of healthy tissue from the wound margins, until a healthy bleeding wound bed is achieved. It is suitable for use on large wounds and requires anaesthesia and theatre time. It is a specialist procedure.

There are consensus guidelines published on debridement (Wounds UK, 2013). Patient pathways from initial assessment are published in Figure 3.1.

Figure 3.1. *Flow chart illustrating debridement pathways. Taken from (Wounds UK, 2013)*



3.3. Negative pressure wound therapy.

As discussed in Section 1.3, NPWT might be considered as the main comparator to NPWTi, with the introduction of instillation being considered an adjunctive treatment to this (with advanced dressings having been used

earlier in the pathway, and/or subsequent to either type of NPWT, to progress towards complete healing) (EAC External correspondence log, 2020). However, the evidence base for NPWT itself is generally poor, with no firm conclusions on the effectiveness of the procedure being able to be drawn. Limitations in the evidence base included a general lack of robust, vigorous RCTs, and issues with generalisability. Table 3.1 summarises the conclusions from Cochrane systematic reviews (citations given in the table).

Table 3.1 *Summary of the conclusions of Cochrane systematic reviews reporting on NPWT as the intervention.*

Population of interest	Reference	Number of studies identified	Comparator	Outcomes reported	Summary of conclusion
Partial thickness burns	(Dumville *et al.*, 2014)	1 RCT (interim report on n=23 patients) in patients with bilateral thermal hand burns.	Silver sulphadiazine	Primary outcomes: • Time to complete healing • Rate of change in wound area • Proportion of wound completely healed within the trial period Secondary outcomes: • Incidence of wound infection • Adverse events • Measures of satisfaction or patient preference • Quality of life	"There was not enough evidence available to permit any conclusions to be drawn regarding the use of NPWT for treatment of partial-thickness burn wounds".
Open traumatic wound	(Iheozor-Ejiofor *et al.*, 2018)	7 RCTs (n=1388) 4 studies including open fracture wounds and 2 studies (one with three arms) including open traumatic wounds (not involving a broken bone)	Standard care Different NPWT pressure settings	Primary outcomes: • Complete wound healing (time to complete wound healing, the proportion of wounds healed). • Wound infection • Adverse events Secondary outcomes: • Proportion of wounds closed or covered with surgery • Time to closure or coverage surgery	"There is moderate-certainty evidence for no clear difference between NPWT and standard care on the proportion of wounds healed at six weeks for open fracture wounds."

Population of interest	Reference	Number of studies identified	Comparator	Outcomes reported	Summary of conclusion
				• Participant health-related quality of life/health status • Wound recurrence • Mean pain scores • Within-trial cost effectiveness analysis comparing mean differences in effects with mean cost differences between two arms	
Surgical wounds healing by secondary intention	(Dumville *et al.*, 2015b)	2 RCTs (n=69); one study in open infected groin wounds, one study of excised pilonidal sinus.	Alginate dressing Silicone dressing	<u>Primary outcomes:</u> • Complete wound healing (time to complete wound healing, proportion of wounds healed) • Adverse events <u>Secondary outcomes:</u> • Participant health-related quality of life/health status • Wound infection • Mean pain scores • Resource use • Costs • Complete fascia closure • Proportion of wounds closed or time to wound closure	"There is currently no rigorous RCT evidence available regarding the clinical effectiveness of NPWT in the treatment of surgical wounds healing by secondary intention as defined in this review".
Surgical wounds healing by	(Webster *et al.*, 2019)	30 Intervention trials (n=2957) and two	Standard surgical dressings varied amongst studies	<u>Primary outcomes:</u> • Morality	"Despite the addition of 25 trials, results are consistent with our earlier review, with the evidence judged to be of low or very low

Population of interest	Reference	Number of studies identified	Comparator	Outcomes reported	Summary of conclusion
primary closure		economic studies nested in trials; surgeries included abdominal and colorectal (5 studies), caesarean section (5 studies), knee or hip arthroplasty (5 studies), groin surgery (5 studies), fractures (5 studies), laparotomy (1 study), vascular surgery (1 study), sternotomy (1 study), breast reduction mammoplasty (1 study), mixed (1 study).	(including standard gauze, sterile gauze secured with perforated stretchable cloth tape, non-adhesive silicone layer, bacteriostatic single silver layer, absorbent adhesive dressing, Steri-strips and sterile gauze and Tegaderm transparent film dressing)	• Surgical site infection (SSI) • Dehiscence <u>Secondary outcomes:</u> • Reoperation • Readmission to hospital within 30 days for a wound-related complication • Seroma • Haematoma • Skin blisters • Pain • Quality of life • Dressing-related costs (including the cost of the dressing and healthcare professional time) • Resource use • Quality-adjusted life year gained • Incremental cost-effectiveness ratio	certainty for all outcomes. Consequently, uncertainty remains about whether NPWT compared with a standard dressing reduces or increases the incidence of important outcomes such as mortality, dehiscence, seroma, or if it increases costs".

Population of interest	Reference	Number of studies identified	Comparator	Outcomes reported	Summary of conclusion
Leg ulcers	(Dumville *et al.*, 2015a)	1 RCT (n=60) in patients with recalcitrant ulcers (venous arteriolosclerotic and venous/arterial in origin) that had not healed after treatment over a six-month period.	Standard care with dressings and compression until 100% granulation. Participants also received a punch skin-graft transplant and then further treatment with standard care as in-patients until healing occurred.	Primary outcome: • Complete wound healing (time to complete wound healing, the proportion of ulcers healed) • Adverse events Secondary outcomes: • Participant health-related quality of life/health status • Resource use • Costs • Wound recurrence • Wound infection • Mean pain scores • Proportion of wounds closed with surgery of time to preparation for surgery	"There is limited rigorous RCT evidence available concerning the clinical effectiveness of NPWT in the treatment of leg ulcers. There is some evidence that the treatment may reduce time to healing as part of a treatment that includes a punch skin graft transplant, however, the applicability of this finding may be limited by the very specific context in which NPWT was evaluated. There is no RCT evidence on the effectiveness of NPWT as a primary treatment for leg ulcers".
Pressure ulcers	(Dumville *et al.*, 2015c)	4 RCTs (n=149)	Two studies compared with dressings, one study compared with a series of gel treatments and one study with moist wound healing.	Primary outcomes: • Complete wound healing (time to complete wound healing, the proportion of ulcers healed) • Adverse events Secondary outcomes: • Change (and rate of change) in wound size with adjustment for baseline size	"There is currently no rigorous RCT evidence available regarding the effects of NPWT compared with alternatives for the treatment of pressure ulcers. High uncertainty remains about the potential benefits or harms, or both, of using this treatment for pressure ulcer management".

Population of interest	Reference	Number of studies identified	Comparator	Outcomes reported	Summary of conclusion
				• Participant health-related quality of life/health status • Wound infection • Mean pain scores • Resource use • Costs • Wound recurrence	
Foot wounds in diabetics	(Liu *et al.*, 2018)	11 RCTs (n=972); two studies included post-amputation wounds, the other studies included foot ulcers in people with diabetes mellitus (DM).	Ten studies compared NPWT with dressings, one study compared NPWT delivered at 75 mmHg with NPWT delivered at 125 mmHg.	<u>Primary outcomes:</u> • Complete wound healing (time to wound healing, number of wounds completely healed during follow-up) • Amputation (major amputation, minor amputation) <u>Secondary outcomes:</u> • Proportion of wounds closed or covered with surgery • Time to closure or coverage surgery • Participant health-related quality of life/health status • Other adverse events • Within-trial cost-effectiveness analysis comparing mean differences in effects with mean cost differences between two arms	"There is low-certainty evidence to suggest that NPWT, when compared with wound dressings, may increase the proportion of wounds healed and reduce the time to healing for postoperative foot wounds and ulcers of the foot in people with diabetes mellitus……The limitations in current RCT evidence suggest that further trials are required to reduce uncertainty around decision-making regarding the use of NPWT to treat foot wounds in people with diabetes mellitus".

Population of interest	Reference	Number of studies identified	Comparator	Outcomes reported	Summary of conclusion
				• Wound recurrence	
Abbreviations: NPWT, negative wound therapy; RCT, randomised controlled trial.					

3.4 Special considerations, including issues related to equality

In section 1 of the clinical submission, the company identified older or physically disabled people as being more likely to suffer chronic and complex wounds. Additionally, diabetes is a known risk factor for poor wound healing, and this condition is associated people of some ethnicities.

No specific equality issues were identified by the EAC for this technology.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The company search strategy was critiqued using the PRESS tool. The strategy did not utilise any database subject headings, so MeSH headings and their equivalent were added to the updated search. The company had used a limited selection of databases; particularly no nursing databases had been used, which was considered important for wound care, so CINAHL was added to the updated search. Access to QUOSA was not available to EAC information specialists so this was not included in the update search. The search strategy is described in detail in Appendix A.

Following the literature search, studies were sifted according to the final published scope (NICE, 2020) on the basis of title and abstract alone by one reviewer (KK). At this stage, sensitivity was maximised to minimise exclusion of relevant papers. Studies identified as potentially relevant were retrieved and selected during a second sift by a second reviewer (IW). At this stage, specificity was maximised so studies considered out of scope were excluded. In particular, studies were excluded if they did not feature the V.A.C. VERAFLO system as the intervention (Section 1.2). The study selection process is illustrated as a PRISMA diagram in Figure A1.

4.2 *Included and excluded studies*

The company identified 30 fully published studies from their literature search. Additionally, the company reported on 1 abstract and 1 ongoing study as relevant to the evidence base. This study has since been fully published in a peer reviewed journal. The fully published studies are listed in Table 1 of the submission, stratified by anatomical location of the wound or wound type (aetiology).

The EAC performed its own literature search (Section 4.1). All the studies identified by the company were identified with the exception of those excluded on the basis of publication date. Sixty six papers were identified as potentially relevant to the decision problem from the title and abstract alone, and full papers associated with these were retrieved. Studies were excluded if they did not fit the scope, including the specific intervention (Section 1.2); if they were published in abstract form only; if they were not published in English; or if they were a case series with n < 10. Following further consideration on these criteria, 48 papers were rejected, mainly because the intervention did not match the scope (see Figure A1). The EAC identified 19 studies it considered to be relevant. Of these studies, 17 had been identified and included by the company, and 2 additional studies were identified by the EAC (one of which, published in April 2020, was identified during the search for

economic papers, see Section 9.1.1). The EAC excluded 15 of the studies included by the company from the clinical evidence review (see Table 4.1).

Table 4.1. *Studies included by the company and the EAC.*

Study	Company inclusion?	EAC inclusion?
Lower limb		
(Kim *et al.*, 2015)	☑	☑
(Kim *et al.*, 2014)	☑	☑
(Yang *et al.*, 2017a)	☑	☑
(Yang *et al.*, 2015)	☑	☒*
(Goss *et al.*, 2008)	☑	☑
(Omar *et al.*, 2016)	☑	☑
(Brinkert *et al.*, 2013)	☑	☑
(Milcheski *et al.*, 2017)	☑	☑
(Blalock, 2019)	☑	☑
(Gabriel *et al.*, 2008)	☑	☒
(Davis *et al.*, 2019)	☑	☒
(Zelen *et al.*, 2011)	☑	☒
Mixed wounds		
(Latouche and Devillers, 2020)	☒	☑*†
(Fluieraru *et al.*, 2013)	☒	☑
(Gabriel *et al.*, 2014)	☑	☑*
(Ludolph *et al.*, 2018)	☑	☑
(McElroy, 2019)	☑	☑
(Timmers *et al.*, 2009)	☑	☒
Prosthetic implants		
(Garcia-Ruano *et al.*, 2016)	☑	☒
(Deleyto *et al.*, 2018)	☑	☑
(Eckstein *et al.*, 2019)	☑	☑
(Lehner *et al.*, 2011)	☑	☒
(Hehr *et al.*, 2020)	☑	☑
(Morinaga *et al.*, 2013)	☑	☒
(Chen *et al.*, 2018)	☑	☒
(Huang *et al.*, 2020)	☑	☒
(Qiu *et al.*, 2019)	☑	☒
(Ikeno *et al.*, 2019)	☑	☒
Surgical site infections		
(Jurkovic *et al.*, 2019)	☑	☒
(Chowdhry and Wilhelmi, 2019)	☑	☑
(Jain *et al.*, 2018)	☑	☒
(Téot *et al.*, 2017)	☑	☑

Unpublished studies		
(Powers *et al.*, 2013) [Abstract]	☑	☒
(Kim *et al.*, 2020)‡	☑	☑
* Economic studies that are discussed in Section 9.1.2. † Identified through economic literature search. ‡ One study was unpublished and academic in confidence at the time of the company's clinical submission and earlier drafts of this assessment report. However, it has since been published in full (Kim *et al.*, 2020).		

The reasons the EAC excluded the company studies are reported in Table 4.2. The principal reason was that the intervention did not match the scope; that is the NPWT device was not a VAC Ulta device; V.A.C. VERAFLO dressings were not used (VERAFLO, VERAFLO CLEANSE, or VERAFLO CLEANSE CHOICE); or the study did not explicitly state that V.A.C. VERAFLO therapy or system was used, and this could not be confirmed by the company (EAC External correspondence log, 2020). The use of compatible instillation fluids, cycle lengths, and dwell times, were not considered for the purposes of including or excluding studies. Nine of the studies were comparative, or nominally comparative (Table 4.3), and ten were single-armed studies (Table 4.4).

Table 4.2. *Reasons for excluding company studies (N = 15).*

Study name and location	Design	Population	Intervention (and comparator)	EAC comments
	Key: ☑ aspect of study in scope; ☑☒ aspect of study partially in scope, or elements of this are not in scope; ☒ aspect of study not in scope.			
(Huang *et al.*, 2020) China	Retrospective single-armed observational study. ☑	Patients with implant infection/exposure in titanium mesh cranioplasty. n = 21 patients ☒	NPWTi system was not specified, but the company confirmed it was not the V.A.C. VERAFLO system. The instillation fluid used was chemotrypsin, which is not an approved solution for V.A.C. VERAFLO. ☒	The intervention is out of scope (not V.A.C. VERAFLO). It is a complex intervention combining a specific surgical treatment with NPWTi, thus the population is highly specific and not generalisable.
(Davis *et al.*, 2019) United States	RCT (3 armed) ☑	Patients with a chronic or traumatic wound, subacute or dehisced wound, partial-thickness burn, ulcer (such as a diabetic or pressure ulcer), flap or graft of the foot. n = 90 patients ☑	None of the three arms of the RCT utilised V.A.C. VERAFLO. This has been confirmed by the company. ☒	The aim of the study was to compare the use of NPWT with NPWTi with saline, but is excluded because the V.A.C. VERAFLO system was not used.

Study name and location	Design	Population	Intervention (and comparator)	EAC comments
(Ikeno *et al.*, 2019) Japan	Retrospective single-armed observational study ☑	Patients undergoing aortic surgery via a median sternotomy, who developed a deep sternal wound infection. n = 18 ☒	The system used was not V.A.C. VERAFLO, and included use of Mepilex dressings. This has been confirmed by the company. ☒	This study was focused on a complex surgical intervention and did not use V.A.C. VERAFLO. It is not generalisable to a broader population.
(Qiu *et al.*, 2019) China	Retrospective single-armed observational study ☑	Patients with severe oral, maxillofacial, and cervical infections. n = 73 ☑	The device and dressings used were not the V.A.C. VERAFLO system. ☒	Excluded because the intervention was not V.A.C. VERAFLO. Additionally, the technique and patients operated on were highly selected and not generalisable.
(Chen *et al.*, 2018) China	Retrospective single-armed observational study ☑	Patients with post-operative infection following spinal surgery. n = 18 ☑	NPWTi system used was not V.A.C. VERAFLO. This was confirmed by the company. ☒	Exclusion on basis of out-of-scope intervention.
(Jain *et al.*, 2018) United States	Retrospective single-armed observational study ☑	Patients receiving girdlestone orthopaedic operations. n = 10 ☑☒	The study used the V.A.C. VERAFLO system, but combined with an orthopaedic intervention. ☑☒	Excluded because the intervention formed part of a more complex surgical procedure. Data not generalisable.

Study name and location	Design	Population	Intervention (and comparator)	EAC comments
(Garcia-Ruano *et al.*, 2016) Spain	Retrospective comparative cohort study. ☑	Patients who suffered abdominal wall wound dehiscence with mesh exposure. ☑	Intervention: NPWTi using "VAC-instillation therapy". Including use of GranuFoam dressings. ☒ Comparator (historical control): Conventional treatment comprised saline-soaked gauze dressings, antiseptic solutions and open lavage, determined by the judgment, experience, and training. ☑	This study reported on the same patients as an economic study included by the company (Deleyto *et al.*, 2018). As it did not report on additional clinical outcomes, this study was excluded on the basis of duplication.
(Yang *et al.*, 2015) United States	Retrospective economic analysis	Patients with massive venous leg ulcer n = 7 patients ☑☒	Intervention V.A.C. VERAFLO system prior to STSG Instillation fluid: Dakin's solution. 10 minutes dwell time 1 hour cycle time	Excluded on basis of intervention (includes STSG) and patient numbers (n < 10).
(Morinaga *et al.*, 2013) Japan	Retrospective single-armed observational study ☑	Patients with mediastinitis. n = 46 ☒	The device used was Mera Sakume MS-008, not the VAC Ulta. This was confirmed by the company ☒	Excluded because the intervention was not V.A.C. VERAFLO. Additionally, the patient population had mediastinitis arising from open heart surgery, which

Study name and location	Design	Population	Intervention (and comparator)	EAC comments
				may be an off-label use of the technology.
(Lehner *et al.*, 2011) Germany	Prospective observational study ☑	Patients with infected implants (knee, hip, other osteosynthesis material) ☑	VAC Instill wound therapy ☒	Excluded because the intervention was not V.A.C. VERAFLO.
(Zelen *et al.*, 2011) United States	Prospective observational study ☑	Diabetic patients with chronic non-healing foot ulcers. n = 20 ☑	The NPWT system used was the instructions Svedman Wound Treatment System; the company has confirmed the V.A.C. VERAFLO system. ☒	Excluded because the intervention was not V.A.C. VERAFLO.

Abbreviations: NPWT, negative pressure wound therapy; NPWTi, negative wound therapy with instillation; RCT, randomized controlled trial; STSG, split thickness skin graft.

Note. Two studies were excluded because they were published before the search date of the EAC's literature search (Timmers *et al.*, 2009, Gabriel *et al.*, 2008). This indicates they were not reporting on the V.A.C. VERAFLO system (Section 1.2). One study was excluded because it was it was not published in English (Jurkovic *et al.*, 2019). The study by Powers *et al.* (2013) was excluded on the basis it was available as an abstract only.
* The study by Yang *et al.* (2015) reported economic outcomes briefly discussed in Section 9.1.2.

Table 4.3. *Characteristics of comparative studies (N = 9)*.

Study name, design, and location	Participants and setting	Intervention	Comparator	Outcomes
Key: ☑ aspect of study in scope; ☑☒ aspect of study partially in scope, or elements of this are not in scope; ☒ aspect of study not in scope.				
(Chowdhry and Wilhelmi, 2019) Retrospective comparative observational study. USA ☑	Patients undergoing reconstructive surgery by a single surgeon for sternal wound complications. Recruitment June 2015 to October 2017. n = 30 ☑	NPWTi with V.A.C. VERAFLO using VeraFlo Cleanse Choice dressings. Instillation fluid: 1/8th strength Dakin's solution*. Dwell time: 20 minutes NPWT (-125 mm Hg). Dressings changed every 72 hours. n = 15 ☑	Treatment with wet-to-moist dressings soaked in 1/8th strength Dakin's* solution. Dressings changed every 6 hours. n = 15 ☑	• Time to wound closure. • Number of therapy days. • Number of excisional debridements. • Drainage duration. • Complications. ☑
(Deleyto *et al.*, 2018) Retrospective observational study with economic analysis Spain ☑	Patients diagnosed with abdominal wall wound dehiscence and presenting with abdominal mesh exposure. Recruitment January 2010 to December 2013. n = 45	NPWTi with V.A.C. VERAFLO Instillation fluid: hypertonic saline Dressings changed every 3 days n = 11 ☑	Conventional dressings n = 34 ☑	• Number of hospitalization episodes • Number of additional surgeries • Length of hospital stay • Cost analysis ☑

Study name, design, and location	Participants and setting	Intervention	Comparator	Outcomes
	☑			
(Yang *et al.*, 2017b) RCT United States, single-centre ☑	Patients with a leg or foot ulcer > 40 cm^2 that would usually be treated with NPWT and the patient would be hospitalized. Recruitment January 2014 to November 2014. n = 20 ☑	NPWTi using the VAC Ulta device (assumed V.A.C. VERAFLO mode). Instillation fluid: ¼ strength Dakin's solution*. Volume of 0.2 mL per cm^2 wound area. Dwell time: 10 minutes. Cycle length: 60 minutes NPWT (-125 mm Hg). Sharp debridement and wound irrigation repeated at day 7. n = 10	NPWT using the VAC Ulta device. Negative pressure of -125 mm Hg. Sharp debridement and wound irrigation repeated at day 7. n = 10 ☑	• Bacterial bioburden. ☑
(Omar *et al.*, 2016) Prospective observational study with historical cohorts Germany, single centre ☑	Patients with acute wounds of the lower limb (infected or traumatic). Prospective consecutive recruitment between January and July 2014. n = 20 ☑	NPWTi with V.A.C. VERAFLO system. Instillation fluid: saline Dwell time: 15 minutes Cycle length: 4 hours n=10 ☑	NPWT using VAC Ulta without instillation n = 10 ☑	• Surgeries required • Time to wound closure (days) • Length of hospital stay • Wound size (cm^2) ☑

Study name, design, and location	Participants and setting	Intervention	Comparator	Outcomes
(Gabriel *et al.*, 2014) Retrospective observational study with historical controls. Economic analysis. United States ☑	Patients with infected or critically colonized extremity and trunk wounds. Recruitment January 2010 to May 2013. n = 82 ☑	NPWTi with V.A.C. VERAFLO Therapy. V.A.C. VERAFLO dressing. Instillation fluid: Prontosan** or saline. Dwell time: 1 to 60 seconds. Cycle length: 1-2 hours NPWT (-125 mm Hg). Dressing changes occurred every 2 to 3 days. n = 48 ☑	NPWT with VAC. GranuFoam Dressing or VAC. GranuFoam Silver Dressing -125 mm Hg Dressing changes occurred every 2 to 3 days n = 34 ☑	• Number of surgical debridements • Length of hospital stay • Length of therapy • Time to wound closure • Cost analysis ☑
Kim *et al.* (2015) RCT*** United States, single centre NCT01939145 ☑	Patients admitted to a tertiary wound referral academic hospital with an infected wound requiring surgical debridement in an operating room. n = 100 ☑	NPWTi using Prontosan** as the instillation fluid. Received NPWTi with VAC ULTA NPWT system with VeraFlo. Dwell time: 20 minutes. Cycle length: 2 hours NPWT	NPWTi using 0.9% saline as the instillation fluid. Received NPWTi with VAC ULTA NPWT system with VeraFlo. n = 49 ☒	Primary • Number of operating room visits (primary) Secondary • Length of hospital stay in days • Time to final surgical procedure during the admission in days.

Study name, design, and location	Participants and setting	Intervention	Comparator	Outcomes
		n = 51 ☒		• Proportion (percentage) of wounds closed/covered during the admission • Proportion (percentage) of wounds that remained closed or covered approximately30 days after hospital discharge ☑
(Kim *et al.*, 2014) Retrospective cohort study United States, single centre ☑	Patients with infected wounds requiring admission with at least 2 operative debridements and who have received either NPWT or NPWTi application at the time of the initial operation. n = 142 ☑	NPWTi with V.A.C. VERAFLO system. Instillation fluid: Prontosan**. Dwell time: 6 minutes (n=34) Cycle length: 3.5 hours NPWT (-125 mm Hg) Dwell time: 20 minutes (n=34)	NPWT using Info VAC Therapy System (historical controls for the same 6 month period separated by exactly 1 year). −125 mm Hg continuous negative pressure n = 74 ☑	• Number of operating room visits • Length of hospital stay • Time to final surgical procedure • Wound closure • Wound closed at 1 month • Culture improvement with Gram-negative, Corynebacterium, and yeast excluded ☑

Study name, design, and location	Participants and setting	Intervention	Comparator	Outcomes
		Cycle length: 2 hours NPWT (-125 mm Hg) ☑		
(Goss *et al.*, 2012) Prospective comparative cohort study Italy ☑	Patients with chronic lower extremity wounds demonstrating significant bioburden. Recruitment October 2012 to October 2013. n = 13 (16 wounds) ☑	NPWTi (confirmed as V.A.C. VERAFLO by company). Instillation fluid: Dakins solution (1/4 strength)*. Dwell time: 10 minutes. Cycle length: 60 minutes NPWT (-125 mmHg). n = 7 (1 patient received both NPWTi and NPWT) ☑	NPWT 125 mmHg n = 7 ☑	• Bacterial load ☑
(Kim *et al.*, 2020) RCT United States NCT01867580	Inpatients with open wounds (>4 cm) requiring debridement and appropriate for conventional NPWT. Most wounds were chronic (71.8%), with 43.1% being diabetic ulcers.	NPWTi with the V.A.C. VERAFLO system (VAC Ulta with V.A.C. VERAFLO dressings. Instillation fluid: Prontosan**	Continuous NPWT using the VAC Ulta device with GranuFoam dressings. Dressings changed every 3 days. n = 88 (ITT)	Primary • Number of inpatient operating room debridements Secondary • Difference in Total Bacterial Counts Measured in Colony

Study name, design, and location	Participants and setting	Intervention	Comparator	Outcomes
☑	Recruitment December 2012 to November 2015. n = 183 (randomised) ☑	Dwell time: 20 minutes, Cycle length: 3.5 hours continuous NPWT. Dressings changed every 3 days. n = 93 (ITT) ☑	☑	Forming Units (CFU) as Determined by Quantitative PCR Analysis • Time until wound closure/coverage • Proportion of wounds closed • Wound complications ☑

Abbreviations: ITT, intention to treat (group); NPWT, negative pressure wound therapy; NPWTi, negative wound therapy with instillation; RCT, randomized controlled trial.

* Dakin's solution is sodium hypochlorite solution. Full strength is around 0.5%. It is an approved solution for use with the the V.A.C. VERAFLO system.
** Prontosan is a proprietary wound irrigation solution consisting of polyhexamethylene biguanide (0.1% an antimicrobial compound) and betaine (0.1%, a surfactant). It is an approved instillation agent for the V.A.C. VERAFLO system.
*** This study was an RCT that used the V.A.C. VERAFLO system; however, because the comparison being made in the RCT was not relevant to the decision problem, data reported from the study must be considered as a single-armed study. Results which are comparisons are not applicable.

Table 4.4. *Characteristics of single-armed studies (N = 10).*

Study name, design, and location	Participants and setting	Intervention	Outcomes
Key: ☑ aspect of study in scope; ☑☒ aspect of study partially in scope, or elements of this are not in scope; ☒ aspect of study not in scope.			
(Latouche and Devillers, 2020) Retrospective case series France ☑	Patients with pressure ulcers (PUs), postoperative wounds or trauma wounds. Recruitment between October 2015 and March 2018. n = 15 ☑	NPWTi with the V.A.C. VERAFLO system using V.A.C VERAFLO dressings. Instillation fluid: norma saline (0.9%) Dwell time: 10 minutes Pressure: -75 to -125 mmHg Cycle time: 2 to 3 hours Dressing changes: 2 to 3 days ☑	• Patient characteristics. • Duration of treatment • Number of dressing changes • Mean costs of treatment ☑☒
(Blalock, 2019) Retrospective case series United States ☑	Patients with complex wounds. Mixed aetiologies (surgical, trauma, ulcers (pressure and non-pressure). Recruitment between January 2017 and November 2017. n = 19 ☑	NPWTi with the V.A.C. VERAFLO system, using V.A.C. VERAFLO CLEANSE dressings. Instillation fluid: saline or 0.025% Dakin's solution. Dwell time: 1-10 minutes. Cycle length: 2-3.5 hours NPWT (-125 mm Hg). Dressings changed every 2-3 days. ☑	• Patient characteristics. • Duration of therapy ☒
(Eckstein *et al.*, 2019) Retrospective case series	Patients with septic wounds of the head and neck area.	V.A.C. VERAFLO system.	• Procedural success • Leukocyte concentration • CRP

Study name, design, and location	Participants and setting	Intervention	Outcomes
Germany ☑	Recruitment between September 2015 and September 2016. n = 15 ☑	Instillation fluid: polyhexanide 0.04%. Dwell time: 10 minutes. Cycle length: 3 hours NPWT (-125 mm Hg). ☑	• Bacterial loads • Wound size (cm^2) • Pain ☑
(Hehr *et al.*, 2020) Retrospective case series. United States ☑	Patients with open wounds revealing exposed hardware. Recruitment between April 2016 and October 2018. n = 28 ☑	V.A.C. VERAFLO system with VeraFlo or Cleanse Choice dressings. Instillation fluid: Dakin's solution* or Prontosan**. ☑	• Patient characteristics • Initial debridement bacterial culture. • Time to wound closure ☒
(McElroy, 2019) Retrospective case series. United States ☑	Patients with at least one complex wound (including pressure injuries, necrotising fasciitis, diabetic foot ulcers, surgical wounds). Recruitment between September 2016 and October 2017. n = 14 ☑	V.A.C. VERAFLO system with Cleanse Choice dressings. Instillation fluid: normal saline, acetic acid or hypchlorous solution Dwell time: 10 minutes. Cycle length: 0.5-4 hours NPWT (-125 mm Hg). Dressing changes every 2-3 days.	• Patient characteristics • Number of debridements • Return to operating room • Duration of therapy • Improved granulation ☒

Study name, design, and location	Participants and setting	Intervention	Outcomes
		☑	
(Ludolph *et al.*, 2018) Prospective single-armed observational study Germany ☑	Patients with "with wounds of different origins at various body sites" (including different types of ulcers, chronic, acute and trauma-related). Recruited between January 2013 and November 2017. n = 111 ☑	NPWTi, the company has confirmed this was V.A.C. VERAFLO therapy. Instillation fluid: 0.4% polyhexanide solution (Lavasept, not an approved solution) Dwell time: 20 minutes Cycle length: 2 hours NPWT (-125 mm Hg) ☑☒	• Patient characteristics • Microbial colonization. ☑☒
(Milcheski *et al.*, 2017) Prospective observational study Brazil ☑	Patients with infected or contaminated complex wounds. Recruitment between March 2016 and August 2016. n = 10 ☑	V.A.C. VERAFLO system. Instillation fluid: normal saline. 2 hour cycle NPWT (-125 mm Hg), 20 minutes dwell time. ☑	• Patient characteristics • Time to wound closure • Qualitative cultures in each surgical procedure • Number of surgical procedures performed • Length of hospital stay ☒
(Téot *et al.*, 2017) Retrospective case series France	Patients with large complex chronic wounds with viscous wound exudate that contained substantial areas of devitalized tissue (including pressure ulcers,	V.A.C. VERAFLO system. Dressing VeraFlo Cleanse Choice. Instillation fluid: normal saline. Dwell time: 10 minutes	• Patient characteristics • Pain • Number of dressing changes • Surgical debridement (type and frequency) • Wound granulation.

Study name, design, and location	Participants and setting	Intervention	Outcomes
☑	burns, necrosis after skin excision). Recruitment between January 2016 and July 2016. n = 21 ☑	Cycle length: 3.5 hours NPWT (-125 mm Hg). Dressing changes every 3 days. ☑	☑☒
(Brinkert *et al.*, 2013) Prospective observational case series France ☑	Patients with infected wound or wound at risk of infection (including open fracture, infected haematoma, pressure ulcer, non-healing postoperative dehiscence, diabetic foot ulcer, necrotizing fasciitis, limited exposure to osteosynthetic hardware, leg ulcer. Recruited between January 2012 and December 2012. n = 131 ☑	NPWTi with V.A.C. VERAFLO therapy. Dressing: V.A.C. VERAFLO (reticulated open cell). Instillation fluid: normal saline. Dwell time 20 or 30 seconds, soak time 10 minutes. Cycle length: 4 to 12 hours NPWT (-125 mmHg) Average dressing change every 3 days. ☑	• Patient characteristics (including previous treatment) • Length of therapy • Need for NPWT after NPWTi • Surgical closure ☑☒
(Fluieraru *et al.*, 2013) Retrospective case series	Patients receiving NPWTi recruited between January to December 2012. Patients had	NPWTi using V.A.C. VERAFLO dressings (unclear if Ulta sysem was used).	• Patient characteristics (including previous treatment) • Adverse events

Study name, design, and location	Participants and setting	Intervention	Outcomes
France ☑	infected wounds or poor granulation. Recruitment between January 2012 and December 2012. n = 24 ☑	Instillation fluid: normal saline Dwell time 30 seconds, soak time 10 minutes. Cycle length: 4 hours NPWT (-125 mm Hg)Dressings changed every 3 days. ☑☒	• Number of cycles per day • Closing technique ☒

Abbreviations: CRP, C-reactive protein; NPWTi, negative wound therapy with instillation; RCT, randomized controlled trial.

* Dakin's solution is sodium hypochlorite solution. Full strength is around 0.5%. It is an approved solution for use with the the V.A.C. VERAFLO system.
** Prontosan is a proprietary wound irrigation solution consisting of polyhexamethylene biguanide (0.1% an antimicrobial compound) and betaine (0.1%, a surfactant). It is an approved instillation agent for the V.A.C. VERAFLO system.

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

Three of the comparative studies (Table 4.3) were randomised controlled trials (RCTs). However, although it used the V.A.C. VERAFLO NPWTi system, one of the RCTs (Kim *et al.*, 2015) compared two instillation fluids (Prontosan compared with 0.9% saline), which did not inform the decision problem. Data derived from this study was considered as a single-armed analysis. One study was reported as a small RCT (n = 19) which compared NPWTi with NPWT (Yang *et al.*, 2017a). The remaining RCT (Kim *et al.*, 2020) also compared NPWTi with NPWT. This study had not been peer-reviewed or published at the time of the company's clinical submission or final drafts of this Assessment Report prepared prior to the covid-19 pandemic. However, it has subsequently been published in *International Wound Journal*. Because of its relative quality and relevance to the scope, the EAC considered this the most informative study overall.

The other comparative studies were described as retrospective (Chowdhry and Wilhelmi, 2019, Gabriel *et al.*, 2014, Kim *et al.*, 2014) or prospective (Goss *et al.*, 2012, Omar *et al.*, 2016). All the studies compared the use of NPWTi with NPWT, with the exception of Chowdry and Wilhelmi (2019) and Deleyto *et al.* (2017), which reported comparison with wet wrap dressings or conventional dressings, respectively. The comparative studies were set in a broad-range of populations overall, with some studies describing a relatively specific wound type as inclusion criteria, and other covering a wide spectrum of wound aetiology. One study was primarily an economic analysis, but was also considered in the clinical evidence review as it reported relevant clinical outcomes (Deleyto *et al.*, 2018).

The single-armed studies were mainly retrospective, with three studies being described as prospective (Brinkert *et al.*, 2013, Ludolph *et al.*, 2018, Milcheski *et al.*, 2017). Most of the studies were descriptive, sometimes on an individual level (case series), and meaningful aggregated data were often not reported. A wide-range of wound type and patient groups were reported on, including acute infected bio-hardware prostheses, surgical infections, pressure ulcers. and chronic diabetic foot ulcers.

In total, there were 636 patients enrolled into comparative studies (of any methodology), of which 365 received NPWTi, 222 received NPWT, and 49 received dressings. In the single-armed studies, 373 patients were enrolled. Thus there was very little data on patients receiving dressings in particular. None of the included studies were set in the NHS or reported on UK populations. Some clinical experts expressed concern that NHS treatment pathways might vary substantially from those used in other countries; for

instance the use of culture to guide requirement for debridement is not practised in the UK (EAC External correspondence log, 2020).

5.2 *Critical appraisal of studies and review of company's critical appraisal*

5.2.1 RCTs

The included RCTs were critically appraised using the *Cochrane Collaboration's tool for assessing risk of bias in randomised trials* (Higgins *et al.*, 2011). These appraisals are reported fully Appendix B (Tables B1 to B3), and summarised in Table 5.1.

The EAC considered the most informative study was the RCT by Kim (2020). This was because it was within scope, made a relevant comparison, had a relatively large sample size (n = 183 randomised), and had relatively high methodological quality. This study enrolled patients with acute or chronic wounds of varying aetiology, with the most common causes being diabetic ulcers, pressure ulcers, and infected surgical wounds (dehisced or non-dehisced). Patients were randomised to receive NPWTi with Prontosan anti-septic fluid or NPWT. Randomisation and allocation concealment were reported, and selection bias was likely to be minimal. However, the study was not blinded, leading to potential performance and detection bias, and had a high attrition rate, with inadequate description of which results reflected *intention to treat* (ITT) or *per protocol* (PP) analysis. The study was powered to detect a reduction in the number of operative debridements (primary outcome: 3.6 in control and 1.6 in treatment, requiring 164 patients, 82 in each arm), which was appropriate. Reporting of secondary outcomes was limited and could have been selective, although there is no evidence of this. However, correction for multiple testing was not applied. There was no information on financial disclosures. In terms of generalisability, the heterogeneous nature of the study population, with relatively small patient numbers for each type of wound, makes interpretation to specific patient groups difficult.

The RCT by Yang *et al.* (2017) also compared NPWTi with NPWT. However, this study was small (n = 19) and of low methodological quality, with potential bias in all domains. In particular, although it was described as an RCT, it is likely randomisation was not employed; instead a consecutive alternating method was used to select the study arms. Only one outcome, bacterial burden, was reported. The generalisability of this study is low because of the very small sample size and mixed aetiologies of the wounds in the study. The RCT by Kim *et al.* (2015) was also of low methodological quality, and had the potential for bias in most domains. Its comparative results were not relevant to the decision problem.

Table 5.1. *Summary of critical appraisal of RCTs.*

Study	Potential source of bias						
	Random allocation sequence	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
(Kim *et al.*, 2020)	☺	☺	☹	☹	☹	☹	?
(Yang *et al.*, 2017a)	☹	☹	☹	☹	☹	☹	?
(Kim *et al.*, 2015)†	☺	☹	☹	☹	☺	☹	☹
Key: ☺ Low risk of bias; ☹ High risk of bias; ? Unclear risk of bias (poor reporting or not ascertainable). * This RCT was provided in draft (academic in confidence), but has since been published. † The comparison the RCT was making was not in scope.							

5.2.2 Comparative observational studies

The comparative observational studies were appraised using the Critical Appraisal Skills Programmes (CASP, 2020) cohort study checklist. These are reported in Appendix B (Tables B4 to B9). All the studies were of poor methodological quality in most domains. In general, there was little reporting about how the control groups, which were usually historical, were selected. Historical control groups are inherently confounded by the passage of time (and improvements in overall healthcare management), whereas in groups where prospective selection is employed, a major confounding factor is that the underlying reason for the patient to be managed with the intervention or comparator is not usually known or controlled. Descriptions of wound characteristics were usually absent, and the patient populations consisted of heterogeneous case mixes. This meant there was high degree of potential for selection bias. None of the studies attempted to identify or control for confounding variables, and the retrospective nature of the outcomes cast some doubt on their robustness. Statistical adjustment for multiple comparisons was not undertaken in any study and in some cases statistical comparative analysis was incorrectly applied (see Table C2). In summary, it was not possible to attribute causality of the intervention to the reported outcomes with confidence.

5.2.3 Single-armed observational studies

The single-armed studies could not be formally appraised, and did not report results that could be meaningfully interpreted. This was because the nature of the intervention did not allow for analysis of a longitudinal effect size (i.e. “before and after” effect). Thus effectiveness results could not be contextualised. Furthermore, several of the studies were restricted to purely descriptive “outcomes” (e.g. description of patient characteristics), or did not

report aggregated data at all (i.e. were case series). These issues were compounded by the heterogeneous case mix of the populations under investigation, which were not generalisable to broader populations. In short, the EAC did not consider any of the single-armed studies provided data that could reliably inform treatment pathways in the NHS.

5.3 *Results from the evidence base*

The company reported results by study in Section 4 (Table 4), and in a narrative format in Section 8. In general, data from the studies were not extracted in a quantitative manner, with sections cut and pasted from the relevant papers without specific context to the outcomes listed in the scope. The EAC has therefore independently reported the results directly from the primary studies. Results are presented on an outcome by outcome basis as listed in the scope. A summary of these are provided in Table 5.2.

5.3.1 Clinical outcome measurements

Several of the comparative studies reported on clinical outcome measures. In general, very little data of this nature was reported by the single-armed studies.

Length of stay in hospital

Length of hospital stay associated with NPWTi compared with NPWT was reported by several comparative observational studies (Gabriel *et al.*, 2014, Kim *et al.*, 2014, Omar *et al.*, 2016). Kim *et al.* (2014) reported a mean length of hospital stay of 14.92 ± 9.2 days in the NPWT group. This was significantly longer than the length of stay (LoS) associated with NPWTi with a 20 minute dwell time (11.4 ± 5.1 days, p = 0.03) and longer than NPWTi with a 6 minute dwell time (11.9 ± 7.8 days), although the latter value was not significant (p = 0.10). Gabriel *et al.* (2014) reported a mean length of hospital stay of 8.1 days in the NPWTi group, compared with 27.4 days in the NPWT group (p < 0.0001). Omar *et al.* reported the median length of hospital stay associated with NPWTi was 21.5 days (interquartile range [IQR] 15.5 to 32.0 days). This was not significantly different from those treated with NPWT (26.5 days, IQR 18.5 to 33.3 days, p = 0.43).

The RCT by Kim *et al.* (2015) reported mean length of hospital stay was 13.6 days and 14.5 days in patients receiving saline and Prontosan respectively (no significant difference between groups, p = 0.68). Although it was measured, the RCT by Kim *et al.* (2020) did not report differences of LoS overall [redacted]. However, the LoS was reported as an outcome in *post hoc* subgroup analysis in patients with surgical dehisced wounds (n = 23). Length of stay was reported as being significantly shorter in patients receiving NPWTi compared with NPWT (9.3 days compared with 21.8 days, p = 0.05).

The economic study by Deleyto *et al.* (2017) reported a mean length of hospital stay of 69.1 ± 33.6 days for patients receiving NPWTi, compared with 88.2 ± 77.1 days for those receiving conventional dressings; this difference was not significant (p = 0.745).

None of the single-armed studies included this outcome.

Note: there are inherent problems in assessing and interpreting LoS data in wound care studies due to study heterogeneity. This is an important consideration because LoS informed the economic model (see Section 9.2.3).

Wound healing

This is a summary of the three outcomes listed in the scope: rates of partial and complete wound closure; mean time to partial or complete wound closure; and mean time to healing.

The most robust evidence for these outcomes was reported in the RCT comparing NPWTi with NPWT (Kim *et al.*, 2020). This study reported the mean time until the wound was deemed ready for closure/coverage was 6.8 days for NPWTi compared with 6.3 days for NPWT. This difference was not significant (p = 0.71). There was also no statistical difference in the proportion of wound closure/coverage by day 56 (± 8 days) between patients receiving NPWTi (68/71, 95.8%) compared with those receiving NPWT (64/66, 97.0%, p = 1.00). No significant differences in healing outcomes were observed for subgroups of patients with high bacteria counts or who had at least one debridement.

The retrospective comparative study by Kim *et al.* (2014) reported 62% of wounds were successfully closed. The closure rate in patients receiving NPWTi with 6 minutes dwell time was significantly improved at 94% (p = 0.0004). For 20 minutes dwell time, the improvement was not significantly different (80%, p = 0.08). The proportion of wounds that remained closed at 1 month was not different between the groups. Gabriel *et al.* (2014) reported a mean time to wound closure of 4.1 days in patients receiving NPWTi compared with 20.9 days in those receiving NPWT (p <0.0001). Omar *et al.* (2016) reported patients receiving NPWTi had a median time to wound closure of 9.0 (IQR 7.0 to 19.3) days compared with12.5 (IQR 7.8 to 23.3) days in those receiving NPWT. This difference was not significant (p = 0.36). The RCT by Kim *et al.* (2015) reported that 85.7% of wounds treated with NPWTi with saline achieved complete closure. This compared with 92.2% in those receiving the Prontosan fluid instillation (p = 0.35).

One study comparing NPWTi with wet wrap dressings reported that the mean time to primary wound closure was 7.9 ± 2.3 days (median 8 days) in the NPWTi group compared with 13.9 ± 3.2 days (median 15 days) (Chowdhry and Wilhelmi, 2019). This difference was significant (p < 0.0001). The population enrolled in this study was specific to sternal wounds that were difficult to heal. Deleyto *et al.* (2018) reported a significantly reduced time to recovery in patients treated with NPWTi compared with those receiving

conventional dressings (mean time of 2.4 months compared with 31.3 months, p < 0.001).

None of the single-armed studies reported on these outcomes.

Number of dressing changes

One single-armed study reported that the mean number of dressing changes in patients receiving NPWTi (with V.A.C. VERAFLO Cleanse Choice dressings) was 2.9, over the course of 8.7 days (Téot *et al.*, 2017). Patients in this study (n = 21) featured a heterogeneous case mix of wounds and comorbidities.

Number of follow on treatments and number of surgical debridements

This section combines the outcomes of number of follow on treatments and visits to hospital, and number of surgical debridements.

The most robust evidence for these outcomes is reported in the RCT comparing NPWTi with NPWT (Kim *et al.* 2020), which had "number of inpatient Operating Room debridements required during the initial inpatient stay after the initial debridement until the wound was deemed ready for closure or coverage by the Investigator" as the primary outcome (and the study was powered to show superiority in this outcome). In patients receiving NPWTi, there was a mean of 1.1 debridements required (95% confidence interval [CI] 0.93 to 1.30). The corresponding number in the NPWT group was also 1.1 (95% CI 0.85 to 1.18) with no significant difference observed between the groups (p = 0.68).

The primary outcome of the observational comparative study by Kim *et al.* (2014) was the number of visits to the operating room following commencement of treatment. In the NPWT this was 3.0 ± 0.9 (SD). There were significantly fewer return visits in patients treated with NPWTi with 6 minute dwell time (2.4 ± 0.9, p = 0.04) or 20 minute dwell time (2.6 ± 0.9, p = 0.003). In the study by Gabriel *et al.* (2014), the mean number of surgical debridements in the NPWTi group was 2.0 compared with 4.4 in the NPWT group (p < 0.0001). Omar *et al.* (2016) reported that patients receiving NPWTi required a median of 3.0 surgical interventions following treatment with NPWTi (IQR 2.0 to 4.3). This was the same as for those receiving NPWT (3.0, IQR 2.8 to 5.3, p = 0.65).

The RCT comparing NPWTi instillation fluids (Kim *et al.*, 2015) reported a mean number of operations of 2.5 ± 0.9 (SD) in patients receiving normal saline and 2.8 ± 0.9 in those receiving Prontosan (p = 0.19).

One study reported data comparing the use of NPWTi with wet dressings (Chowdhry and Wilhelmi, 2019). This study reported the mean number of

surgical debridements was 1.8 ± 0.7 (SD) in patients receiving NPWTi compared with 3.1 ± 1.0 in patients receiving dressings only. This difference was statistically significant (p = 0.0011). One study that compared NPWTi with conventional dressings reported an average of 0.82 ± 0.75 (SD) additional surgeries in the NPWTi group compared with 2.29 ± 2.11 in the control group (p = 0.009) (Deleyto *et al.*, 2018). The same study reported reduced hospitalisation episodes with NPWTi (mean 1.64 vs. 3.59, p = 0.003).

None of the single-armed studies reported on these outcomes.

Number of amputations or skin grafts

The single-armed study of Brinkert *et al.* (2013) reported 58% of patients had closure delivered by skin graft. A flap was used in 17% of patients and 25% achieved closure through primary suturing.

Staff time and use of other consumables

Two single-armed studies reported on the number of dressing changes associated with NPWTi. One study reported a mean of 6.6 ± 6.8 (SD) changes over 19.4 ± 20.8 days treatment (Latouche and Devillers, 2020). This compared with a mean number of 2.9 dressing changes over a mean duration of NPWTi therapy of 9.7 days in another study (Téot *et al.*, 2017).

Colonisation with antimicrobial resistant pathogens

The company requested that this outcome was broadened to include all bacterial pathogens, not just ones which were resistant to antimicrobial drugs. The EAC concurred that this was logical. Several studies reported on the broader outcome, and inferences can be drawn from this data on antimicrobial resistant pathogens.

The best evidence for the potential of NPWTi to reduce bacterial burden is reported in the comparative RCT by Kim *et al.* (2020). Microbiological evaluation of results showed a significant decrease in mean total bacterial counts between time of initial surgical debridement and first dressing change in NPWTi treated patients (n=69, PP analysis) subjects compared with NPWT treated patients (n=63). The values were -0.18 Log_{10} CFU/g [colony forming units per gram tissue] for NPWTi compared with 0.6 Log_{10} CFU/g for NPWT (p = 0.02).

Another RCT, with a small sample size (n = 19) and of low methodological quality (Yang *et al.*, 2017a), reported on the concentration of planktonic and biofilm bacteria following treatment as its only endpoint. In the patients receiving NPWTi (using ¼ strength Dakin's solution as the instillate), there were 10.5 x 10^5 CFU/g ± 15.1 x 10^5 CFU/g planktonic bacteria. This compared with 12.3 x 10^5 CFU/g ± 28.6 x 10^5 CFU/g in patients receiving NPWT alone. There was no statistical difference between groups (p = 0.86).

There was also no initial difference in biofilm-protected bacteria concentrations (8.6 x 10^3 CFU/g ± 8.8 x 10^3 CFU/g compared with 12.9 x 10^3 CFU/g ± 12.5 x 10^3 CFU/g, p = 0.48). The authors reported that following 7 days treatment with NPWTi there was a significant reduction in bacteria (43%, p < 0.05), whereas in the NPWT there was non-significant increase (14%, p = 0.46). However, there was no difference between the groups (p = 0.11).

One comparative observational study reported on bacterial bioburden as its sole outcome (Goss *et al.*, 2012). The authors reported that there was a mean of 3 ± 1 (SD) types if bacteria in the wounds, with most common being *Staphylococcus aureus*, Corynebacterium, and *Pseudomonas aeruginosa.* After 7 days treatment with NPWTi (with Dakin's solution as the instillate) or NPWT alone, the mean absolute reduction in bacteria in the NPWTi was 10.6 x 10^6 per gram of tissue compared with a mean absolute *increase* of 28.7 x 10^6 bacteria per gram of tissue in the NPWT group. This was a significant decrease in bioburden associated with NPWTi (p = 0.016).

The observational study by Kim *et al.* (2014) reported "an overall culture improvement" of 38% in the NPWT group, compared with 59% in patients receiving NPWTi with 6 minutes dwell time, and 50% in patients receiving NPWTi with 20 minutes dwell time. These differences were not significant. However, patients in the 6 minute dwell time group did have significant culture improvement when Gram-negative bacteria, Corynebacterium, and yeast were excluded.

One single-armed observational study reported bacterial loads did not significant decrease over the course of NPWTi therapy (Eckstein *et al.*, 2019).

Antibiotic use

No studies reported on antibiotic use.

5.3.2. Patient outcomes (including adverse events)

The patient outcomes listed in the scope were "Health-related quality of life"; "Patient satisfaction and acceptability"; and "Patient-related outcomes such as pain scores". Only one single-armed study reported on any Patient Related Outcome Measure (PROM). This was the single-armed study by Eckstein *et al.*, (2018), whose authors stated "The course of the pain value determined via the NRS [Numeric rating scale] was highly variable but at the end of the therapy all but 1 patient obtained pain relief". Without quantitative data, it is not possible to qualify or interpret this statement.

The RCT by Kim *et al.* (2020) reported significantly lower pain scores in patients with dehisced surgical wound receiving NPWTi compared with NPWT. In the NPWTi group, the maximum visual analogue score [VAS] pain

score was 52.0, compared with 79.0 in the NPWT group (p = 0.03). However, overall pain scores for the whole cohort were not reported. Additionally, no statistical adjustments for multiple comparisons were made.

The RCT by Kim *et al.* (2020) reported on potential device-related adverse events. More patients experienced at least one treatment-related adverse event in the NPWTi group (20/93, 21.5%) compared with the control group (11/88, 12.5%). The statistical significance of this difference was not reported. The most common adverse event were skin and subcutaneous tissue disorders (skin macerations, rash, dermatitis), which occurred in 18/93 (19.4%) of the NPWTi group compared with 9/88 (10.2%) in the NPWT group. There were 3 deaths in the NPWTi group compared with 1 death in the NPWT group, but none of these were considered to be treatment-related. It was noted the company did not report these adverse events in the submission.

In one observational study comparing NPWTi with wet wrap dressings (Chowdhry and Wilhelmi, 2019), no complications were reported in the NPWTi. Three patients had seromas in the dressings group. This difference was not significant (p = 0.22).

Further discussion of adverse events is in Section 6.

Table 5.2. *Summary of outcomes reported by the included studies.*

	Outcome	Comparative evidence from experimental studies (RCTs, NPWTi vs. NPWT)	Evidence from observational studies (comparative and single-armed)	EAC comment on validity of the evidence*
Clinical Management Outcomes	Length of stay in hospital	One RCT reported significantly reduced LoS associated with NPWTi in a subgroup of patients with surgically dehisced wounds (Kim *et al.*, 2020).	Two comparative observational studies reported NPWTi was associated with reduced length of hospital stay (Gabriel *et al.*, 2014, Kim *et al.*, 2014). One study reported no difference compared with NPWT (Omar *et al.*, 2016). One study reported no difference compared with conventional dressings (Deleyto *et al.*, 2018)	Weak evidence that NPWTi is associated with reduced length of hospital stay compared with in certain patient populations.
	Wound healing	One RCT reported no significant difference in the time until wound healing associated with NPWTi (Kim *et al.*, 2020).	Two studies reported improved wound healing associated with NPWTi (Gabriel *et al.*, 2014, Kim *et al.*, 2014). One study reported no difference (Omar *et al.*, 2016). One study reported improved healing associated with NPWTi compared with wet wrap dressings (Chowdhry and Wilhelmi, 2019).	There is equivocal evidence that NPWTi is associated with improved wound healing parameters. The strongest evidence, from an RCT, did not identify this effect. Non-randomised evidence was largely of poor methodological, particularly regarding patient selection, and might not be generalisable.
	Number of dressing changes	No evidence reported on this outcome.	No comparative evidence reported on this outcome.	No conclusions can be drawn

	Outcome	Comparative evidence from experimental studies (RCTs, NPWTi vs. NPWT)	Evidence from observational studies (comparative and single-armed)	EAC comment on validity of the evidence*
	Number of follow on treatments and number of surgical debridements	One RCT reported there was no difference in the number of operating room debridement between patients receiving NPWTi or NPWT (Kim *et al.*, 2020).	Two studies reported a reduced rate of debridements associated with NPWTi compared with NPWT (Gabriel *et al.*, 2014, Kim *et al.*, 2014). One study reported no significant difference (Omar *et al.*, 2016). One study reported the use of NPWTi was associated with a significantly reduced rate of surgical debridement compared with wet wrap dressings (Chowdhry and Wilhelmi, 2019). One study reported significantly reduced additional surgeries and hospitalisation episodes with NPWTi compared with conventional dressings.	The evidence that NPWTi is associated with reduced requirement for debridement or other follow on treatments compared with NPWT is equivocal, with the most robust evidence not identifying any difference.
	Number of amputations or skin grafts	No evidence reported on this outcome.	No comparative evidence reported on this outcome.	No conclusions can be drawn
	Staff time and use of other consumables	No evidence reported on this outcome.	No comparative evidence reported on this outcome.	No conclusions can be drawn
	Colonisation with antimicrobial resistant pathogens	One RCT reported that NPWTi was associated with significantly reduced bacterial counts compared with NPWT (Kim *et al.*, 2020).	One study reported NPWTi was associated with a decrease in bacterial load compared with NPWT alone (Goss *et al.*, 2012).	The available evidence suggests that NPWTi reduces bacterial bioburden compared with NPWT alone. However, the significance of this on clinical outcomes is

	Outcome	Comparative evidence from experimental studies (RCTs, NPWTi vs. NPWT)	Evidence from observational studies (comparative and single-armed)	EAC comment on validity of the evidence*
		One small RCT identified a trend for decreased bacterial counts in patients receiving NPWTi compared with NPWT (Yang *et al.*, 2017a).		unclear. Additionally, this effect may be dependent on the type of instillation fluid used.
Patient Outcomes	Health-related quality of life	No evidence reported on this outcome.	No comparative evidence reported on this outcome.	No conclusions can be drawn
	Patient satisfaction and acceptability	No evidence reported on this outcome.	No comparative evidence reported on this outcome.	No conclusions can be drawn
	Patient-related outcomes such as pain scores	One RCT reported NPWTi was associated with significant reductions in pain compared with NPWT in a subgroup of patients with surgical dehiscence (Kim *et al.*, 2020).	One study narratively reported that NPWTi reduces pain (Eckstein *et al.*, 2019).	No conclusions can be drawn There is insufficient evidence reported to assess the pain-relieving potential of NPWTi.
	Adverse events	One RCT reported an adverse event rate of 21.5% for NPWTi compared with 12.5% for NPWT (Kim *et al.*, 2020).	One study reported three patients treated with wet wrap dressings had seroma, compared with none who received NPWTi (Chowdhry and Wilhelmi, 2019).	No conclusions can be drawn It is possible that NPWTi is associated with an increased risk of adverse events compared with NPWT, but statistical evidence has not been reported.

Abbreviations: NPWT, negative wound therapy; NPWTi, negative wound therapy with instillation (V.A.C. VERAFLO).

* This is the EAC's subjective judgement on the quality of evidence available to inform conclusions. Objective grading of this level of evidence was not possible, as, for instance, it was not compatible with GRADE methodology (Guyatt *et al.*, 2008).

5.3.3. Subgroups

Five subgroups for special consideration were considered in the scope (NICE, 2020). These were diabetic ulcers, pressure ulcers, surgical site infections, venous leg ulcers, and wounds containing prosthetic implants.

Diabetic ulcers

The company did not report separately on this subgroup, nor were studies any identified which reported specifically on diabetic foot ulcers. However, many studies included patients with diabetic ulcers in their study populations. In the RCT by Kim *et al.* (2020), diabetic ulcers made up 78/181 (43.1%) of the population. However, results were not reported by subgroup, with the exception of surgical dehisced wounds.

Pressure ulcers

The company identified one study included by the EAC that reported mainly on pressure ulcers (Téot *et al.*, 2017). In this study, 18/21 (85.7%) had pressure ulcers, with the remainder having burns or tissue necrosis. In the RCT by Kim *et al.* (2020), pressure ulcers made up 31/181 (17.1%) of the population, the second largest grouping by wound aetiology. However disaggregated data on these patients was not reported.

Surgical site infections

The company identified 2 studies that were specifically on surgical site infections. The study by Jurkovic (2019) was excluded by the EAC on the basis it was published in a foreign language and reliable translation was not available. Additionally, this study was based on a predecessor device (VAC Instill). The study by Chowdry and Willhelmi (2019) was in people with sternal wound complications following reconstruction. It compared NPWTi with wet dress wrappings.

Venous leg ulcers

This subgroup was not specifically addressed by the company. No studies were identified that specifically reported on this condition. The RCT by Kim *et al.* (2020) included 5/181 (2.8%) of people with venous leg ulcers.

Prosthetic implants

Wounds associated with prosthetic implants were the subject of several studies included by the company. Several of these were excluded by the EAC (see Table 4.1). The studies included by the EAC were in patients presenting with abdominal mesh exposure (Deleyto *et al.*, 2018) and patients with open wounds revealing exposed hardware (Hehr *et al.*, 2020). The study by Eckstein *et al.* (2019) was in patients with head and neck reconstructive surgery, but did not report these patients had prosthetic implants.

6 Adverse events

The company summarised adverse events (AEs) from their literature searches in Section 6 of their evidence submission as follows:

- "Garcia-Ruarno. 12 patients who had presented with abdominal mesh exposure developed hernias, 7, reappearance of mesh and 3 an enterocutaneous fistula. No outcomes were given.

- Kim *et al.* (2020). 1 patient developed an infection and another an undefined problem. No outcomes were given".

The EAC considered that the adverse events reported in Garcia-Ruarno (2016) did not appear to be device related. The study by Kim (2020) reported a higher number of skin reactions in the NPWTi group (with Prontosan instillation fluid) compared with the NPWT group, but the clinical significance of this was not stated.

The company also searched the FDA Manufacturer and User Facility Device Experience (MAUDE) database for the terms "V.A.C. VERAFLO DRESSING", "V.A.C. VERAFLO THERAPY", "VERAFLO"," VERAFLOW", "VERAFLO CLEANSE CHOICE" and "ODP", for reports dated from 01/01/2005 to 31/02/2020 (sic). Eight MAUDE reports were summarised by the company as 2 cases of device malfunction, 5 relating to the treatment of patients and 1 with insufficient information to determine reason for the report.

The EAC repeated the company search of the MAUDE database on 16/04/2020 for reports dated from 01/01/2000 to 31/03/2020. Some additional searches were undertaken, to check for any relevant reports registered under the "VAC ULTA" brand name, referring to the relevant pump used in VeraFlo therapy, rather than the dressing terms. Obvious variant spellings were also checked, including "V.A.C.", "V.A.C", and "ULTRA". In total, the EAC MAUDE searches found 29 records. The EAC reviewed each of the narrative reports and removed 17 which did not state that the event report related to a VeraFlo therapy procedure. The remaining 12 reports related to 9 unique MAUDE report numbers with event dates ranging from 03/09/2013 to 18/12/2019. The 9 unique events were categorised as 7 injuries and 2 malfunctions. The EAC review of each narrative report found that 4 of the 9 were events of VeraFlo dressings crumbling or adhering to the wound with either haemorrhage or wound deterioration and malodour being reported as a consequence by the user. In each of these cases, the manufacturer response in MAUDE attributed cause as possible user error, with aspects of the treatment going against the device instructions for use (IFU). Two more reports were of a Cleanse Choice and a VeraFlo dressing being left in the wound, both of which were attributed as possible user error by the manufacturer, as regular monitoring of the

dressing is required in the device IFU. One further report of wound deterioration and malodour was not attributed to the VeraFlo therapy by the manufacturer, after tests on the ULTA system found it met expected specifications. The final 2 of the 9 reports were a fire in the power pack plugged into the wall and an event where the power cord came apart. Neither of these had a manufacturer response in MAUDE.

It is important to note that the FDA states that their medical device report data alone "cannot be used to establish rates of events, evaluate a change in event rates over time or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices." The fact that there is no denominator figure of total procedures undertaken means these MAUDE reports cannot be set in context of all patients treated with V.A.C. VERAFLO therapy in the USA.

The EAC agrees with the company in their submission that there are no VeraFlo adverse event reports in the MHRA database.

The NICE Expert Advisors did not raise any specific safety concerns; although one emphasised the skills required and therefore potential for human error. This expert would encourage more research to produce evidence-based data on the correct amount of fluid for soaks/washes, rather than relying upon trial and error to get this right.

The EAC considers that the few injury reports in the FDA MAUDE database, which were predominantly attributed to possible human error, tend to align with the NICE Expert Advisor's opinion on the skills required for administering VeraFlo therapy. Evidence from one RCT suggested that NPWTi using antiseptic instillation fluid may be associated with increased risk of skin reactions, although the importance of this was not clear. In summary, the EAC did not identify any significant safety concerns for the technology.

7 Evidence synthesis and meta-analysis

No evidence synthesis was reported by the company. This was appropriate because of the heterogeneous nature of the studies in terms of methodology, study populations, and outcomes reported.

8 Interpretation of the clinical evidence

The evidence base for NPWTi is dominated in number by observational studies and there are few well-designed and conducted studies of the comparative effectiveness with NPWT. Thus, the quantity and quality of evidence is lacking.

The most robust evidence was from an RCT, which enrolled patients with mixed wound aetiologies which were either acute (30.1%) or chronic in nature (69.9%) (Kim *et al.*, 2020). Although this was also the largest study (n = 181), the heterogeneity of the study population meant that the sample size of individual wound types were small, and did not allow for extensive subgroup analysis. In this study, NPWTi was *not* shown to be superior to NPWT. Outcomes included wound healing and requirement for debridement, which are important economic parameters.

The results of the Kim *et al.* (2020) RCT were contradicted by some, but not all, the observational studies, such as the relatively large (n = 142) retrospective cohort study by Kim et al. (2014). This study also had broad inclusion criteria in common with the later RCT. In contrast, many of the other observational studies had highly selected populations, but these invariably had small sample sizes and the selection of control groups was poorly reported, with statistical matching not performed, and often patient and wound characteristics were under-reported. This made interpretation and contextualisation of results difficult. It was not possible to meaningfully interpret the single-armed studies, which reported few relevant outcomes. There was also not enough data to make any judgement of NPWTi compared with conventional dressings, but this might not be the most relevant comparator (Section 1.3).

It was noted that no study has published HRQoL or PROM outcomes, and this is a substantial omission in the evidence base. Additionally, the evidence for the superiority of NPWT itself over standard care is equivocal in most conditions (Table 3.1), and NICE clinical guidelines have made only limited recommendations for this intervention (Section 3.1).

It should be stressed that a lack of overall evidence is not evidence of no effect. The technology is plausible in its mechanism, and likely represents an incremental improvement over its predecessor, offering clear system benefits through programming and automation. NICE clinical experts who used the technology or were aware of it, were unanimous that judicious use of NPWTi was likely to be effective in selected patients (EAC External correspondence log, 2020). Generally, the patients thought most likely to benefit had complex wounds that were not responding to conventional therapies. The issue is to date are there have been few high-quality experimental studies that have clearly demonstrated this benefit. The recently published RCT by Kim *et al.* (2020) was likely to be underpowered, as were all the other studies, and there were issues with outcome assessment due to the multicentre nature of the study and the heterogeneity of patients included. Furthermore, given these issues with complexity and the heterogeneity of the population the technology is indicated in, future research is likely to be challenging (Section 12).

Nevertheless, in the opinion of the EAC, the claimed benefits of NPWTi were not unequivocally supported by the current evidence base. These claims are summarised in Table 5.3.

Table 5.3. *EAC interpretation of the evidence for the claimed benefits of NPWTi. The first 3 columns are taken directly from the claimed benefits made by the company (page 9 of the clinical submission). The fourth column reflects the EAC's opinion on whether these claims have been adequately substantiated.*

	Claimed benefit	Supporting evidence*	Company Rationale	EAC opinion
Patient benefits	Reduced Hospital Length of Stay	Kim 2014, Gabriel 2014~~, Gabriel 2008, Timmers.~~ Kim 2015, Omar, Deleyto~~, Garcia-Ruano~~ , ~~Powers and Davis~~.	The first four of these studies showed statistically significant reductions in patient's length of hospital stay when NPWTi use was compared to either NPWT or conventional wound care. The remaining studies showed shorter, but non-statistically significant reductions. Patients benefit from reduced LoS as it allows them an earlier return to their home and families and activities of daily living. It also removes them from a hospital environment where they may be vulnerable to hospital acquired infection. Please note the Davis study used an alternative company's product.	**<u>Claim not unequivocally proven</u>** The included studies which reported reduced LoS were observational studies incorporating retrospective patient selection. It is not possible to interpret results from these studies with confidence. One RCT reported NPWTi reduced length of stay in a subgroup analysis (of patients with surgically dehisced wounds). However, results for the cohort as a whole were not reported (Kim *et al.*, 2020).
	Reduced number of surgical debridements	Kim 2014, Gabriel 2014, ~~Garcia-Ruano~~, Choudhry, ~~Timmers, Powers~~	The first of these 6 studies showed statistically significant reductions in the number of surgical debridements required when NPWTi use was compared to either NPWT or conventional wound care. This means that patients have to undergo fewer	**<u>Claim not unequivocally proven</u>** The observational studies reporting this outcome were of limited methodological quality and it was not possible to interpret results with confidence. In particular, there were issues with the generalisbility of this outcome with NHS pathways (Section

	Claimed benefit	Supporting evidence*	Company Rationale	EAC opinion
		~~Jurkovic~~, Kim 2015, Omar, Goss, Kim 2020)	painful procedures and the risk of an anaesthetic.	This was listed as the primary outcome in the study by Kim *et al.* (2020). There was no significant difference reported between NPWTi and NPWT (1.0 vs 1.1, respectively; p = 0.68).
	Higher rates of surgical implant retention	Lehner, ~~Garcia-Ruano~~. Deleyto, Ikeno, Eckstein, ~~Morinaga~~, ~~Huang~~	The first 2 of these studies showed statistically significant retention of surgical implants. The remaining studies recorded either high rates of retention when compared with conventional wound dressings, but without documenting significance, or they reported ranges of retention from 90-100%. Implants documented included life-saving cardiovascular grafts or orthopaedic implants that are essential to allowing patients to maintain their independence. Please note the Ikeno, Morinaga and Huang studies used an alternative company's products.	**Claim not unequivocally proven** This claim was not made in the final scope (NICE, 2020). The studies reporting these outcomes were generally of limited methodological quality and it was not possible to interpret their results into NHS pathways with confidence. Several studies did not report on the V.A.C. VERAFLO device.
	Reduced time to wound closure	Gabriel 2014, ~~Gabriel 2008~~, ~~Qui~~, ~~Garcia-Ruano~~, Choudhry ~~Jurkovic~~, Omar, ~~Morinaga~~, ~~Davis~~ and Kim 2020	The first 5 of these studies showed statistically significant reductions in mean time to complete or partial wound closure when NPWTi was compared with NPWT or conventional wound care.	**Claim not unequivocally proven** The listed studies that were included by the EAC were regarded as being of limited quality and interpretation of results could not be made with confidence, due to the heterogeneous nature of the populations

	Claimed benefit	Supporting evidence*	Company Rationale	EAC opinion
			The remaining studies showed shorter mean times to wound closure but these were not found to be significant. Patients living with open wounds are subject to increased pain and risk of infection. Please note the Qui, Morinaga and Davis studies used an alternative company's products.	studied and lack of generalisability with NHS clinical pathways. One RCT reported no significant difference between NPWTi and NPWT in terms of the proportion of successful wound closure or time until wound closure (Kim *et al.*, 2020).
	Reduced Pain	Eckstein, Kim 2020 Teot, Milcheski, ~~Qui~~, Gabriel 2014, ~~Chen~~	A number of papers referenced reduced pain levels for patients using NPWTi. The first 2 reported statistical significance in pain reduction post treatment with NPWTi The remaining stated pain reduction during and following NPWTi but did not publish statistical analysis. Please note the Qui and Chen studies used an alternative company's products. Nurses using NPWTi in the NHS completed a short survey with 13 patients in February and March 2020. Removal No pain or discomfort = 8 Some pain or discomfort = 5 A lot of pain or discomfort = 0	**Claim not proven** This claim was not made in the final scope (NICE, 2020). The RCT by Kim (2020) only presented analysis of pain outcomes as a *post hoc* subgroup analysis. It was not possible to interpret the results from Eckstein *et al.* with confidence. The survey results provided was not formally part of the submission.

	Claimed benefit	Supporting evidence*	Company Rationale	EAC opinion
			Application No pain or discomfort = 9 Some pain or discomfort = 4 A lot of pain or discomfort = 0	
	Patients discharged more quickly	Kim 2014, Gabriel 2014, ~~Gabriel 2008~~, ~~Timmers~~. Kim 2015, Omar 2016, Deleyto 2017, Garcia-Ruano , ~~Powers~~ and ~~Davis~~.	The papers supporting reductions in LoS have been documented in the Patient Benefit Section of this table. When patients are discharged from hospital more quickly, they release capacity to the NHS for additional patients to receive care. This may include admitting patients who have been subject to long waits in A&E departments. Please note the Davis study used an alternative company's product.	**Claim not proven** The EAC considers the claims for reduced length of stay were equivocal. Thus, so are claims of earlier discharge.
	Higher rates of wound closure	Kim 2014, ~~Garcia-Ruano~~ and ~~Powers~~. Kim 2015, Brinkert, ~~Zelen~~, Yang, ~~Gabriel 2008~~,Eckstein, Hehr~~,~~ ~~Jain~~, ~~Morinaga~~, ~~Davis~~	The first 3 of these studies showed statistically significant higher rates of complete wound closure when NPWTi was compared with NPWT or conventional wound care. The remaining papers showed non-significant differences between NPWTi and comparative care or recorded only closure rates for NPWTi. These ranged from 64 to 100%.	**Claim not unequivocally proven** The evidence for higher rates of wound closure is equivocal. The most robust study, the RCT by Kim *et al.* (2020) did not identify improvements in the rate of wound closure.

	Claimed benefit	Supporting evidence*	Company Rationale	EAC opinion
			Higher wound closure rates are a contributory factor to early hospital discharge, reductions in the number of debridements, dressing changes and skin grafts required as well as reducing the numbers of consumables used and staff time caring for patients.	
System benefits	Reduced follow on treatments	Deleyto, ~~Garcia-Ruano~~, ~~Chen~~, ~~Davis~~	Deleyto was the only paper to document a statistical significance for patients requiring fewer follow on treatments. Patients requiring follow on treatments, in the remaining 3 papers that recorded this data, ranged from 16% to 54% although this higher % was matched with 94% of control patients in this study requiring further treatment. Avoidance of follow on treatments release both physical and clinical capacity to the NHS to offer care to other patients. As fewer consumables will be required too, these factors are likely to reduce overall costs of care for these patients. Please note the Chen and Davis studies used an alternative company's products.	**Claim not unequivocally proven** This claim was not made in the final scope (NICE, 2020). The claim is not proven because the study by Deleyto was a retrospective cohort study that did not match patients or describe adequately how outcomes were reported. Note this study was conducted in a specific population (45 people, selected from 202, with an abdominal mesh) and is not generalisable to other conditions. There therefore remains considerable uncertainty in the interpretation of this paper. The study by Garcia-Ruano reported on the same patients as Deleyto and had the same limitations (as well as double counting patients).
	Reduced colonisation with pathogens	~~Jurkovic~~, Goss, Yang 2017, ~~Garcia-Ruano~~, ~~Timmers~~, Ludolph Kim 2020	The first 7 of these studies showed statistically significant higher rates of reduction in pathogen colonisation when	**Claim proven** This claim was not made in the final scope (NICE, 2020).

	Claimed benefit	Supporting evidence*	Company Rationale	EAC opinion
		Kim 2014, Powers,	NPWTi was compared with NPWT, or conventional wound care. The remaining 2 papers recorded higher rates of reduction by a % although, statistical significance was not reported. Patients with significant pathogenic colonisation are more likely to require additional treatment to achieve wound closure. This may involve longer hospitalisation periods, repeated surgical intervention, removal of implants and long term antibiotic therapy all of which will place demands on clinical time and consume other resources.	Data from the RCTs Yang *et al.* (2017) and Kim *et al.* (2020) substantiate claims that V.A.C. VERAFLO reduces colonisation rates with pathogens. This is also mechanistically plausible. However, the association between this outcome and clinical outcomes has not been proven.
	Overall reduction in staff and resource use	~~Chen~~ Gabriel 2014, Kim 2014, ~~Garcia-Ruano Qui~~, Choudhry, ~~Timmers~~, ~~Powers~~, Kim 2015, ~~Gabriel 2008~~	Chen was the only paper to directly report a significant reduction in clinical and nurse time although this was not quantified. Other papers referenced here relate to reductions in dressing changes, treatment duration, fewer days to final surgical procedure, fewer debridements, length of therapy and shorter mean times to wound closure. For each of these statistically significant differences were reported between cohorts of patients who had access to NPWTi and control groups	**Claim not proven** The study by Chen *et al.* (2018) was excluded on the basis it was not on the V.A.C. VERAFLO device. The other studies did not report on this outcome.

	Claimed benefit	Supporting evidence*	Company Rationale	EAC opinion
			Please note the Chen and Davis studies used an alternative company's products.	
Cost benefits	Reduction of costs	Gabriel 2014, Jurkovic, Deleyto	Each of these papers considered the cost of NPWTi therapy alongside total hospitalisation costs. As a result 2 suggested that that whilst the costs of using NPWTi were significantly higher the total hospitalisation costs did not differ significantly. Deleyto reported that when NPWTi was used as an alternative to conventional wound dressing the mean costs of NPWTi were €2,000 lower. Detailed costs will be modelled in part 2 of this submission.	**Claims considered in Section 9.1.2**
Sustainability	Reduction of consumables	Lehner, ~~Garcia-Ruano~~. Deleyto, Ikeno, Eckstein, ~~Morinaga~~, ~~Huang~~ Gabriel 2014, ~~Jurkovic~~,	Each of these papers referenced high rates of surgical implant retention or fewer dressing changes. Both of these factors would contribute to sustainability. Please note the Ikeno, Morinaga and Huang studies used an alternative company's products.	**Claim not proven** A reduction in consumables, overall, has not been evidenced by these studies.

Abbreviations: NPWT, negative pressure wound therapy; NPWTi, negative wound therapy with instillation; RCT, randomized controlled trial.

* Studies with strike through annotation were not included by the EAC (see Table 4.2).

8.1 *Integration into the NHS*

None of the included studies were undertaken in the UK. The available evidence may not be generalisable to well-defined populations within the NHS. A further issue is the optimal use of the technology in individual wound types is not fully known, concerning the selection of instillation fluids, dwell times, and cycle times, although there is some consensus guidelines on this (Kim *et al.*, 2019).

There are no significant barriers to adoption. NHS providers already providing NPWT with the VAC Ulta or Ulta 4 pump could adopt NPWTi without any substantive change to procedures. Additionally, NPWTi potentially offers system benefits such as improving reproducibility of treatment through automation, and having a user-friendly interface. The company has stated they offer free training, with successful completion of training is signed off using a competency assessment framework.

8.2 *Ongoing studies*

The company did not identify any ongoing studies in their clinical submission (Table 3 of Section 4 was left unpopulated).

The EAC searched the following databases for ongoing studies: Clinicaltrials.gov, and ISRCTN registry (International Standard Randomised Controlled Trial Number, now expanded to include observational studies). The EAC identified one ongoing study (NCT04026334). One completed study was also identified but peer-reviewed publication of results relating to this study were not found (NCT02266771). Additionally one terminated study (due to difficulty enrolling) was identified (NCT02621073) which aimed to compare V.A.C. VERAFLO with Prontosan with NPWT without instillation (using the VAC Ulta Therapy System) in patients with infected lower extremity status-post open reduction and internal fixation. This has not been included. The identified studies (one ongoing, one completed) are reported in Table 8.1. The EAC considered neither of the studies would be likely to significantly add to the evidence base if published. This is due to their small sample sizes and lack of overall generalisability.

Table 8.1. *List of relevant ongoing studies identified by the EAC*.

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
Evaluation of V.A.C. VERAFLO CLEANSE CHOICE dressing using normal saline to promote increased healthy wound bed tissue (NCT04026334)	Recruiting Study Completion : June 2020	Single-arm (n=15) in patients aged 22 years and older, with full thickness wound (such as chronic, acute, traumatic, sub-acute, and dehisced wounds and/or ulcers) measuring ≥ 4 cm in length and ≥ 4 cm in width (before removal of eschar at the bedside) excluding undermining/tunnelling, has no more than 2/3 of the visible wound bed surface area considered to be clean, healthy and viable.	Percentage change in wound bed surface area (cm^2) of clean, healthy, viable tissue [baseline to day -9]	Percent change in total wound volume (cm^3) [Baseline to day 6-9]; Percent change in total wound area (cm^2) [Baseline to day 6-9]; Physician assessment of the need for surgical debridement [day 6-9]
Impact of V.A.C. VERAFLO Therapy in wounds requiring debridement within orthopaedic practice (NCT02266771)	Completed * Study completion: Dec 2017	Randomised (n=20) in patients aged 18 years and older, requiring surgical debridement for wounds with exposed hardware and/or bone, traumatic wounds, dehisced wounds, post-surgical wounds, and pressure ulcers/sores requiring debridement.	Number of days between the initial and final surgical procedure [6 months]	Length of hospital stay [6 months]; Number of days until wound closure [6 months]; Number of operative debridements [6 months]; Recurrence of wound post discharge [30 days]; Wound related readmission [30 days]

9 Economic evidence

9.1 *Published economic evidence*

9.1.1 Search strategy and selection

The company did not perform a dedicated literature search to identify economic studies. The company did not list any economic study as being relevant in their own right, and instead stated “Due to no economic studies reviewing NPWTi vs the comparator within the scope, we have included below the evidence studies used in our cost consequence model”. These studies were used to inform the parameters of the *de novo* model, rather than reported as economic studies in their own right.

9.1.2 Published economic evidence review

The EAC performed dedicated literatures searches on HTA/NHS, EED/DARE, and IDEAS/RePEc databases (Appendix D), with 51 studies being identified. These were sifted and combined with results from the clinical literature search. Four study protocols were identified. Three were studies that reported economic outcomes already identified from the clinical literature search (see Section 4). An additional study was identified through the economic search. These were of border-line relevance and were not considered by the EAC to be of adequate quality to undergo formal critical appraisal, but are briefly described for completeness.

The study by Deleyto *et al.* (2017) was included by the company in both the clinical and economic sections. This was a retrospective observational study comparing patients with abdominal wall dehiscence following mesh implantation, receiving either NPWTi (n = 11) or conventional wound dressings (n = 34). Cost was calculated using diagnosis-resource groups (DRGs) combined with hospital stay (days). Costs in both groups were compared using the Mann-Whitney U test.

The study by Gabriel *et al.* (2014) was a retrospective comparative observational study that reported economic outcomes. It was included by the company in both the clinical and economic sections. It compared patients with infected or critically colonized wound receiving NPWTi (n = 48) with patients receiving NPWT (n = 34). Costs were calculated by calculating the daily cost of treatment and multiplying this by the length of hospital stay. Groups were compared using the 2-sided Wilcoxon ranked sum test.

One study that reported cost outcomes was included by the company, but excluded by the EAC on the grounds it only reported on 7 patients, who received both NPWTi and split-thickness skin grafts (STSG) (Yang *et al.*, 2015). This was a retrospective observational study that enrolled patients with massive venous leg ulcers (> 100 cm^2). This was compared with the

estimated costs associated with use of compression bandages, although the methodologies behind these estimates were not clearly reported.

The study identified in the economic search was a retrospective case series (Latouche and Devillers, 2020). It reported data on 15 patients with hard-to-heal wounds with or without infection who were treated with NPWTi using the V.A.C. VERAFLO system.

9.1.3 Results from the economic evidence

The study by Deleyto *et al.* reported that in the NPWTi group, the mean average total costs (n = 11) were €15,093 (95% CI €11,170 to €19,017). Most of these costs were associated with hospital stay (€13,504) rather than treatment costs (€1589). The mean total costs were substantially higher in the conventional wound therapy group (n = 34, €29,614; 95% CI €20,422 to €38,805). For the NPWTi group, total costs were €15,093 (95% CI €11,170 to €19,017). The difference in total overall costs were €14,520 (95% CI €4459 to €24,581)

In the study by Gabriel *et al.* (2014), total therapy costs were less with NPWTi compared with NPWT ($799 compared with $2217, difference $1418). This was mainly because of a reduction in the number of debridement required (2.0 for NPWTi compared with 4.0 for NPWT). Daily cost of therapy was marginally higher for NPWTi ($195 compared with $106, difference $89), due to increased costs associated with dressings and canisters.

The study by Yang *et al.* (2015) reported total costs of $27,792 for compression therapy compared with $27,152 for NPWTi combined with STSG, a difference of $640 favouring the intervention. It is not clear how these results were calculated.

The study by Latouche and Devillers (2020) reported that the mean cost of treatment with NPWTi was €1643 ± €1709 (SD). The range was €747 to €7470. No information was reported on how these data were calculated. No comparative data was reported.

The results from all these studies should be treated with caution. Clinical parameters were mainly derived from small retrospective cohort studies or studies with historical controls, with questionable selection of patients and measurement of outcomes. Analysis was performed using simple costing calculations with no statistical matching or sensitivity analysis. Costs were derived from foreign healthcare services, not the NHS, and were reported in euros or US dollars. Overall the reporting quality of these studies was lacking and they do not provide robust economic data.

9.2 *Company de novo cost analysis*

The company reported developed an economic model using a cost consequence analysis (CCA) framework, which was appropriate and consistent with the Medical Technologies Evaluation Programme (MTEP) methodology (NICE, 2017). The model did not include any clinical outcomes, clinical states, PROMs, or HRQoL outputs. The model is described and critiqued in the following sections.

9.2.1 Economic model structure

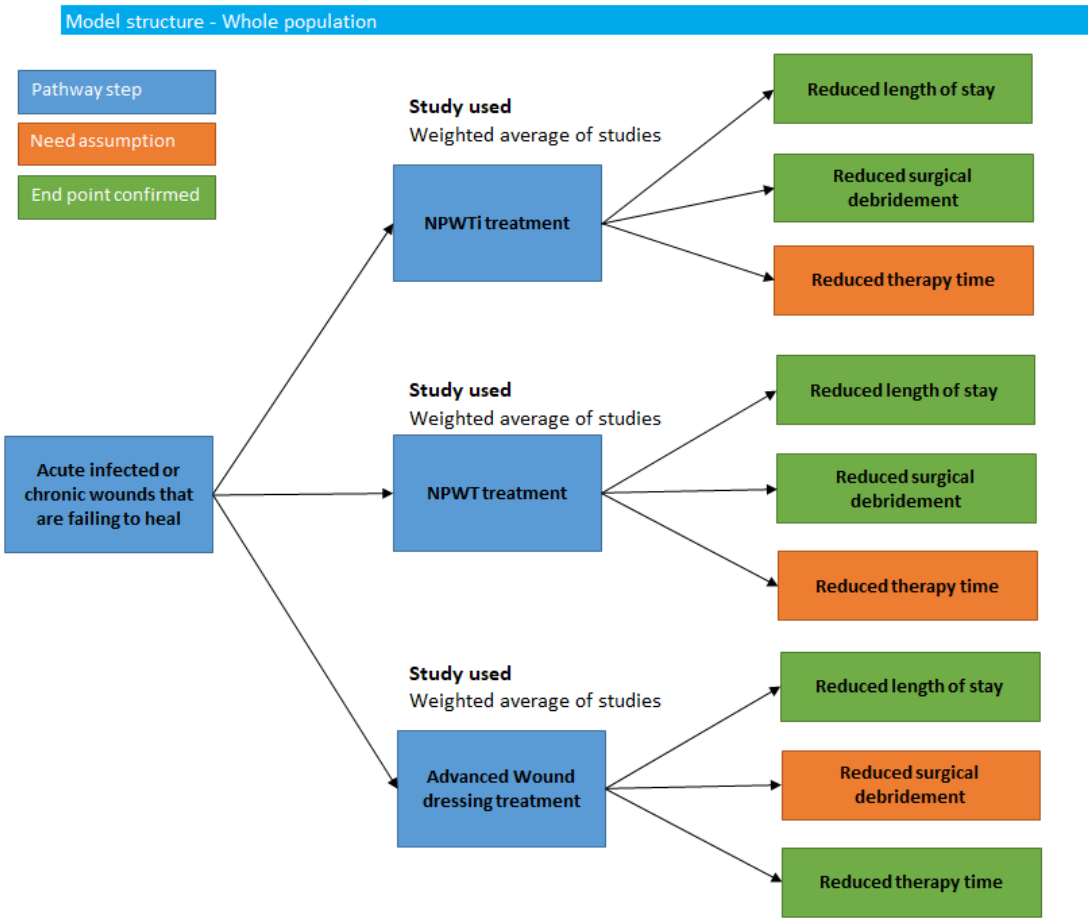
The model was a cost calculator, provided in an executable Excel spread sheet across 23 worksheets. The layout of the spread sheet was generally clear, although the spread sheet was not entirely transparent. For example, some input cells did not contribute to calculations or outputs, and the rationale behind some calculations was not always evident. A series of embedded Macros in the model were used to generate Tornado diagrams (univariate deterministic sensitivity analysis [DSA]) and run probabilistic sensitivity analysis (PSA).

The model incorporated four scenarios, namely that of lower limb; mixed wounds; prosthetic implant; and surgical site infections. Results from these scenarios were aggregated to give an overall cost estimate, which might be regarded as a *de facto* "base case" representing the whole population (this is an unusual method of establishing a base case, see Section 9.2.3).

The model estimated the costs associated with NPWTi compared with NPWT and advanced wound care (AWC). Three costs were accounted for in the model: therapy costs, the length of hospital stay, and the number of surgical debridements required during that stay. The model structure for the base case is reported in Figure 9.1.

The EAC questioned NICE clinical advisors regarding the structure of the model (EAC External correspondence log, 2020). In general, the advisors did not believe the pathways were representative of NHS practice for many patient groups. For instance, the model assumes that there is a requirement for surgical debridement following treatment, but this is often not the case, with patients being discharged and being treated using less intensive nurse-led forms of debridement in clinics.

Figure 9.1. *Structure of the de novo model. Note: The outcomes listed are not all "reduced". Reductions between treatment modalities are relative to each other.*



The company listed the assumptions in the model in Table 2 of the submission. The EAC has critiqued this in Table C1. In the opinion of the EAC, several of the assumptions made by the company could not be justified. The EAC considered there were two principal concerns with the model. These were issues with:

- Structural uncertainty, relating to the scope used in the model and how well this reflected clinical reality, in particular in terms of the population and patient pathways. These issues are further discussed in this section.

- Parameter uncertainty, relating to the clinical effectiveness data that were used to inform the model. This is further discussed in Section 9.2.3.

Population

The population was not clearly defined in the company's economic submission, so the population is assumed to be the same as the scope, namely "patients with acute infected or chronic wounds that are failing to heal" (NICE, 2020). The usual approach to economic analysis would be to use the broader population that is in scope as the base case, and perform scenario analysis to estimate costs in different subgroups. Instead, the company used a different approach, by developing separate scenarios for different subgroups of patients, and combining the data from these to estimate an aggregated total of costs, that it claimed reflected the whole population.

The EAC considered this approach was counter-intuitive and fundamentally unsound, for the following reasons:

- The scenario populations described in the model were lower limb; mixed wounds; prosthetic implant; and surgical site infections. These described mixed concepts and were not clearly defined. For instance, "lower limb" wound is an anatomical description, whereas "mixed wounds" implies it is based on aetiology (both acute and chronic) but this was not explained. Thus, the populations were not mutually exclusive and likely to overlap in an undefined way. Furthermore, these populations did not match the subgroups described in the scope, which were diabetic ulcers; pressure ulcers; surgical site infections; venous leg ulcers; and wounds containing prosthetic implants (NICE, 2020).

- Even though the scenario populations were envisioned to represent more clearly defined cohorts of patients, they still represented broad, heterogeneous cohorts of patients. For instance, there are many possible types of lower limb wounds. Mixed wounds by definition are a heterogeneous concept, and similarly prosthetic implants and surgical site infections include many types of wound and patient groups.

- The populations enrolled in the clinical studies that informed the scenarios did not reflect those of the scenario. Issues with study identification, extraction and extrapolation of key parameters, and the representativeness of key populations are discussed in Section 9.2.3.

- The company claimed that the data informing the whole population ("base case") was weighted. However, this was not the case. Instead the parameters were calculated using simple averages without weighting by study sample size or underlying population prevalence. Thus, even allowing for the limitations of the informing data, the EAC had additional concerns over the aggregated costs.

The EAC notes that one study reflected the population of the scope well. This was the RCT by Kim *et al.* (2020) which enrolled people with both acute (30%) and chronic (70%) wounds. However, this study was not included in the economic analysis. This omission is discussed further in Section 9.2.3. The EAC also notes the contention from the company that the mechanism of action of NPWTi is common to all indicated conditions, and therefore results from these populations may be reasonably aggregated (EAC External correspondence log, 2020). However, the EAC considered that a common mechanism of action would not necessarily mean the benefits would be equivalent in different populations; in fact, this would be highly unlikely. Therefore the EAC did not adopt this approach in its own analysis (see Section 9.2.7).

Intervention

As discussed in Section 1.2, the EAC excluded studies that did not specifically include NPWTi with the V.A.C. VERAFLO device. However, three of the seven studies that the company used to inform the economic model used the predecessor device (VAC Instill). For the purpose of economic modelling, the EAC accepted these studies. However, inclusion of these studies added an extra source of uncertainty into the model, and therefore the results reported (see Section 9.2.3).

Comparator

The EAC accepted clinical data for NPWT from any technology, although the costing used in the economic modelling was restricted to the VAC Ulta device. There was very little evidence on which to base analysis of AWC dressings, and the use of dressings is likely to be very variable depending on the underlying condition as well as on local practice within the NHS. Additionally, AWC may not be an appropriate comparator as NPWT and NPWTi may be used second-line to this in some scenarios (Section 1.3). This meant there was particular uncertainty regarding economic data comparing NPWTi with AWC. This was verified by NICE clinical experts, some of whom considered AWC would be used before or after NPWTi, but was not an appropriate direct comparator (EAC External correspondence log, 2020).

Outcomes

Three outcomes informed the relative costs of the technologies (NPWTi, NPWT, and AWC). These were the frequency of surgical debridement, length of hospital stay (LoS) and length of treatment (LoT).

Surgical debridement.

It was assumed that *post-treatment* surgical debridement would be required in all the scenarios. Reduced requirement for surgical debridement would result in reduced costs relative to the comparator technology. However, the model assumed that all repeat debridement procedures would be surgical, when in fact this is the most invasive option and may be regarded as a third-line option in many patients (see Section 3.2), with less invasive forms of debridement being carried out in community or day clinic settings. One NICE clinical expert stated "the NHS is not set-up to support repeated surgical debridement every 48hrs to negative microbiology, as has been used in trials described in this briefing. Therefore a trial comparing use to standard care within the NHS, including health economic evaluation, would be useful" (EAC External correspondence log, 2020).

Length of hospital stay

The major driver of cost savings in the model was reduction in length of hospital stay, in which it was assumed that there was a causal association between the wound treatment technology and length of hospital stay. However, there are several other factors that could be associated with LoS, such as the underlying condition, and the availability of the necessary social care to allow for discharge. The studies that reported on LoS were not experimental and thus could only infer, rather than prove, causal reductions in this outcome. Furthermore, the studies were all conducted in non-UK settings, and management and discharge pathways might not reflect those of the NHS.

The EAC explored the potential for NPWTi to reduce LoS with the NICE clinical experts (EAC External correspondence log, 2020). There was unanimous agreement that in certain patients and settings, NPWTi had the potential to reduce LoS and consequently reduce healthcare resource use and costs. However, there remained key uncertainties regarding this. One issue was that in the NHS, NPWTi must be performed as an inpatient procedure, meaning it could lead to paradoxical increases in LoS by preventing earlier discharge to community care. Additionally, LoS is frequently not solely related to wound care, but may also be dependent on the underlying condition, comorbidities, and the availability of suitable social care allowing for discharge. In all cases, this outcome is difficult to quantify due to the diverse nature of wounds, even in similarly indicated patients in the same setting. These issues were supported following dialogue with the principal investigator of the RCT (Kim *et al.*, 2020), who, referring to the non-significant difference in LoS between arms of the RCT, stated "[redacted]".

Length of treatment

Length of treatment with the technology was multiplied with the daily cost of that therapy (Section 9.2.4), to establish the overall cost of treatment. Clinical management costs outside this window and upon discharge were not considered. There were concerns about the generalisability of the data reported in the literature when applied to NHS settings.

Time horizon

The model was a cost calculation rather than decision tree, and as such did not have a set time horizon. Instead, costs were calculated based on the length of treatment and length of hospital stay; this was usually measured over the course of days or weeks, depending on the informing study (and therefore scenario). It was thus appropriate not to included discounting.

9.2.2 Validation of the economic model

Company validation

The company described its model validation procedure in the economic submission (page 62). Two modellers were employed to build the model, and the model parameters were reviewed externally by two sources:

- Two tissue viability nurses were used to "gather their view of the resource, the clinical and cost assumptions included [in the model". The names and details of the tissue viability nurses were not reported.

- Two company clinical experts, or Key opinion leaders (KoLs), consisting of a consultant plastic surgeon and a consultant vascular surgeon, were used to allow for the "opportunity to feedback on all elements of the model including resource, pathway, subgroup population levels and the current outputs". This included review of the cost data used as well as review of the informing studies. No formal elicitation process was used.

Given the nature of the uncertainty relating to the model, which related to both the model structure and inputs, the EAC considers the validation process was probably inadequate. Preferably, more KoLs should have been enrolled covering more specialities, particularly considering the broad nature of the intended population. Ideally, formal expert opinion for qualitative evidence (e.g. model structure) and expert elicitation techniques for quantitative (for estimation of model parameters) could have been used to improve the robustness of the model (Peel *et al.*, 2018). However, the EAC appreciates these approaches are difficult to undertake within the timeframe of MTEP assessment, and especially so in the case of this submission (March 2020, during covid 19 pandemic). Nevertheless, there remains a lack of confidence in the validity of the model (Section 9.2.1 and 9.2.3).

EAC validation

The EAC validated the company's base-case and scenario analysis by independently reproducing it in Excel. This highlighted errors in therapy cost associated with NPWTi and NPWT arms in Table 9 of the company's written economic submission where therapy costs of scenario analysis were included instead of base-case therapy cost (these errors were confirmed by the company) (EAC External correspondence log, 2020). Due to the small impact on results (the company submission stated therapy costs for the whole population as £914 and £662 for NPWTi and NPWT respectively, however these should have been £919 and £716), the company was not asked to update the narrative or table 9 of their report. The EAC also validated the

company's PSA by independently reproducing using programming language R (R Core team, 2020).

Due to concerns over the validity and generalisability of the model's inputs, the EAC asked specific questions from the NICE expert advisors regarding these. A full record of questions and responses can be found in the EAC communication log.

9.2.3 Economic model parameters

The key economic model parameters related to measurement of LoS, LoT, and number of surgical debridements for each technology. These were multiplied by unit costs estimated through micro-costing; these values are discussed in Section 9.2.4.

Study selection

The clinical parameters that informed the outcomes were derived from seven comparative studies identified in the clinical evidence section of the submission (Table 4.3). Four studies identified were not included to inform the economic analysis. The EAC noted the small RCT by Yang *et al.* (2017) did not report relevant clinical outcomes, and the larger RCT by Kim *et al.* (2015) did not report on a relevant comparison, and so could not contribute to the economic model. However, it was noted that the RCT by Kim *et al.* (2020) and the prospective observational study by Omar *et al.* (2016) did publish outcomes that were relevant to the model. The company did not report a rationale for the exclusion of these studies in the submission, but in dialogue with the EAC clarified that the study by Kim *et al.* (2020) was excluded because at the time it was not a published peer-reviewed paper (at that time), and additionally that LoS and duration of therapy were not reported for the whole cohort (EAC External correspondence log, 2020).

The key economic results for the omitted studies are reported in Table 9.1. Both studies reported that there was no statistical difference in the key results that could inform the economic model. As with all the studies identified for NPWTi, these studies had considerable limitations. Kim *et al.* (2020) had incomplete reporting of outcomes. Omar *et al.* (2016) was small (10 patients in each cohort) and was not an experimental study. However, both studies were in scope and were relatively well reported, and used appropriate statistical analysis, so in the opinion of the EAC should have been included. Their omission suggests that a degree of cherry picking of studies may have occurred. Both these studies have been included by the EAC in scenario analysis (Section 9.3.4).

Table 9.1. *Relevant economic outcomes reported in omitted studies.*

Outcome	Study	
	(Kim, 2020)	(Omar *et al.*, 2016)
Type	RCT, unpublished (NWTi vs. NPWT)	Prospective observational study with historical controls (NWTi vs. NPWT)
Population	Patients with chronic and acute wounds (n = 181)	Patients with acute wounds of the lower limb (infected or traumatic). (n = 20)
Length of hospital stay	Not reported *.	Median with (IQR) (days) NPWTi: 21.5 (15.5 to 32.0) NPWT: 26.5 (18.5 to 33.3) Wilcoxon rank-sum test (p = 0.43)
Length of treatment**	Mean (days) NPWTi: 6.8 NPWT: 6.3 Log-rank test (p = 0.71)	Median with (IQR) (days) NPWTi: 9.0 (7.0 to 19.3) NPWT: 12.5 (7.8 to 23.3) Wilcoxon rank-sum test (p = 0.36)
Number of debridements (or "surgeries)	Mean (95% CI) NPWTi: 1.1 (0.93 to 1.30) NPWT: 1.0 (0.85 to 1.1*) Wilcoxon rank-sum test (p = 0.68)	Median with (IQR) (days) NPWTi: 3.0 (2.0 to 4.3) NPWT: 3.0 (2.8 to 5.3) Wilcoxon rank-sum test (p = 0.65)

Abbreviations: IQR, inter-quartile range; NPWT, negative pressure wound therapy; NPWTi, negative pressure wound therapy with instillation; SD, statistical deviation.

*The EAC clarified with the lead author of the RCT that this outcome was measured, but not reported, and that the differences between arms (full cohorts) were non-significant. Subgroup analysis of patients with dehisced wounds (n = 23) reported mean LoS was 9.3 days in the NPWTi arm vs. 21.8 days in NPWT arm (p = 0.05).

** Data derived from "Proportion of patients with closed wounds and time to readiness for closure/coverage" (Kim *et al.*, 2020) and "Time to wound closure" (Omar et al, 2016).

Data extraction and parameter calculation (from included studies)

A description of the included studies that informed the economic parameters is reported in Table C2. The EAC had several concerns about these studies and how they were used to inform economic parameters. These were:

- The studies were retrospective observational studies with inherent methodological limitations, for instance concerning patient selection, small sample sizes, and low generalisability. There were particular issues with the selection of control groups and, in some studies, inappropriate statistical analysis. In summary, the EAC considered these studies did not demonstrate a causal association between the interventions and their reported outcomes with any certainty (Section 5.2.2).

- Some of the studies were considered to be out of scope by the EAC because they reported on the predecessor technology (Gabriel *et al.*, 2008, Jurkovic *et al.*, 2019, Timmers *et al.*, 2009). These have not been fully appraised by the EAC.

- Some studies did not enrol patients that were entirely consistent with the scenario described. For instance, the studies by Kim *et al.* (2014) and Gabriel *et al.* (2008), used to inform the "lower limb" scenario, enrolled patients trunk and arm wounds. In the case of other studies, there was insufficient information to determine whether the population was reflective of the described scenario, for instance Gabriel *et al.* (2014) in the "mixed wound" scenario. This scenario also utilised data from Timmers *et al.* (2009) which only enrolled patients with osteomyelitis and related tissue infections. In other instances, such as in the prosthetic implants scenario (Deleyto *et al.*, 2018) and the surgical site infection scenario (Jurkovic *et al.*, 2019, Chowdhry and Wilhelmi, 2019), the population enrolled in the studies was highly selective and did not necessarily represent the study population as a whole.

- Because not all the studies reported the three outcomes necessary to inform the model, the company combined data from two studies to estimate some model parameters. This was done by calculating the ratio between two parameters of interest (a scaling factor) and then applying this to a second study. The EAC considered this was inappropriate, because the studies were performed in different populations, and sometimes different comparators, and could not be directly compared. This data manipulation added a further layer of uncertainty that could not be adequately addressed using sensitivity analysis.

Summary

The EAC considers that an important weakness of the economic model is that the clinical parameters were not sufficiently robust and were subject to high levels of uncertainty. This was due to a combination of how the studies were selected; the quality of the studies selected; and the way data was extracted and manipulated from these studies.

9.2.4 Resource identification, measurement and valuation

Resource use (costs) in the model was broadly described in the company's economic submission and detailed costs were reported in the model itself. The following costs were included.

- Direct costs associated with the interventions themselves.
- Debridement costs associated with repeated surgical debridement following commencement of treatment.
- Hospital stay costs associated with excess bed stay in hospital before discharge.

Direct costs

The company derived direct costs from the NHS Supply Chain. Costs for NPWTi included average costs for dressings (V.A.C. VERAFLO™, V.A.C. VERAFLO CLEANSE™, and V.A.C. VERAFLO CLEANSE CHOICE™) in various sizes (small, medium, or large), as well as costs of the V.A.C. VERALINK™ Canister and V.A.C. VERALINK™ Cassette. In addition, a £16 daily rental charge associated with the V.A.C. Ulta NPWT device was included. The costs of instillation fluids (including normal saline, Prontosan, or Dakin's solution) were not included. The EAC checked these costs, and concluded that, due to the small cost of these relative to the total costs, it was acceptable to exclude these from the model. The EAC also identified from NHS Supply Chain potential costs associated with additional tubing (ELZ414: Negative Pressure Wound Therapy Accessories Duo tubing set for use with instillation unit), which may be used alongside V.A.C. VERAFLO, but does not appear in the economic model. The company confirmed that this product is used on some large wound dressings and certain types of wounds to support the increased fluid exchange. However it was clarified that it is rarely used in the UK and therefore was considered; the EAC accepted this (EAC External correspondence log, 2020). It was assumed most consumables would be changed 3 times per week. The daily cost of VAC VERAFLO use was thus calculated as £75.16 (£14.60 for canisters, £8.30 for cassettes, £36.26 for dressings, and £16.00 for daily rental of the Ulta NPWT device, see Table C4).

Cost associated with NPWT (without instillation) were based on costs of unit rental (the V.A.C. Ulta device), NPWT canisters, and medium foam kit. Costs associated with AWC were based on Aquacel and Alleyvn dressings. All costs were verified by the EAC and, where found to be incorrect, they were updated or changed for the EAC's base case model (see Table C4). However, because these technology costs were low compared with the other costs in

the model, further work on micro-costing of comparator technologies was not undertaken.

Debridement costs

All debridement were assumed to be surgical requiring theatre time (the EAC does not agree with this assumption, see Section 9.2.1). Theatre costs were based on Public Health Scotland average theatre costs per hour by speciality This is inclusive of staff, utility, and infrastructure costs (Public Health Scotland, 2019). There is no equivalent data for the NHS of England and Wales. The duration of debridement (17.7 minutes) was estimated using data from an RCT (n = 41) that compared Versajet Hydrosurgery System with conventional surgical debridement (Caputo *et al.*, 2008). This was multiplied by the theatre cost per minute (£13.37) to give a cost of £237 per surgical debridement. This cost was fixed regardless of the intervention.

The EAC revised the theatre costs, using the most up-to-date data averaged across all relevant specialities, which slightly increased the theatre cost to £16.46 per minute (Table C4). The duration of surgery time was not challenged. One NICE clinical expert considered that the surgical debridement cost was likely to be a substantial underestimate (EAC External correspondence log, 2020), and this reflected the general consensus of NICE clinical experts. Therefore, the cost of surgical debridement used in the model is likely to be conservative, but this is based on the premise this outcome is relevant to the NHS in most patient groups which the EAC considered is unlikely to be true (Section 9.2.1).

Length of stay costs

The estimated the unit costs of LoS using excess bed days as reported by NHS Reference Cost (2017/2018) (NHS Improvement, 2018). The company used subchapter healthcare resource groups (HRGs) for mixed wounds and prosthetic implants, whereas the other scenarios (lower limb and surgical site infections) used national average costs. The EAC considered that this approach wasn't justified given the paucity of data, and simplified the model by applying national average costs to all groups (Table C4).

Excess bed days are not an ideal surrogate measure of cost of hospital stay as they only cover bed, food, accommodation, utilities, and management costs. However, even within an HRG the complexity of patient clinical needs vary, as well as the availability of social care on discharge, as sometimes medically fit patients cannot be discharged due to delays in setting up support packages. Nevertheless, the cost applied (£431) was broadly consistent with

other NICE MTGs utilising LoS as an economic outcome. It should be noted that because the costs associated with a day of LoS were roughly twice as costly as one surgical debridement procedure, and because LoS was significantly higher in comparator groups compared with NPWTi in most scenarios, this parameter was the main driver of the model.

9.2.6 Sensitivity analysis

Sensitivity analysis was applied by the company in several ways. Firstly, separate scenarios were reported on, which were combined in a bottom up manner to report an aggregated *de facto* base case. Secondly, extensive univariate deterministic sensitivity analysis (DSA) was performed to create Tornado diagrams, from which the key drivers of the model could be identified. And thirdly, probabilistic sensitivity analysis (PSA) was employed in an attempt to quantify the level of uncertainty between the model input and outputs (YHEC, 2016b).

Scenario analysis

The EAC had serious concerns regarding the combination of distinct and separate scenarios to inform the base case. These principal concern was the scenarios were poorly defined and that evidence from the informing studies was not sufficiently robust, and not generalisable, to inform the key parameters. These issues are discussed in Section 9.2.1 and 9.2.3.

Deterministic sensitivity analysis

For univariate sensitivity analysis, the company used the upper and lower bounds of the 95% confidence intervals (CIs) where these data were available, which was appropriate. Where these could not be calculated, the company assumed the standard error was 20%.The EAC considered this value was arbitrary unlikely to cover the feasible range of variability in poorly evidenced parameters, thus it did not usefully inform the degree of uncertainty in the model (Briggs *et al.*, 2012).

Probabilistic sensitivity analysis

One thousand runs of the model were performed by applying random draws to parameter distributions for each scenario and the base case scenario. Most of the model parameters were subject to PSA, using beta or gamma distributions as appropriate (listed in the economic submission, pages 49 to 52). The data from the PSA was used to report median probabilistic estimates of cost savings, as well as the probability NPWTi was cost saving in each scenario.

The EAC considered that whilst PSA can be a valuable tool in understanding second order (parameter) uncertainty, by reflecting the level of precision of

point estimate, it does not address issues concerning the validity of the point estimate itself. It does not replace the application of evidence-based best practice, for instance seeking to incorporate all available evidence, rather than selectively picking single sources and using best-practice methods to avoid potential biases (Briggs *et al.*, 2012). Furthermore, PSA is not useful in understanding the structural uncertainty or heterogeneity present in the model (Briggs *et al.*, 2006).

The EAC retained the PSA, primarily to report credibility intervals in the revised model. However, parameters which the EAC considered should be fixed, such as technology costs, were not included in the PSA (Section 9.2.7).

9.2.7 EAC changes to model

The EAC made two sets of changes to the model. Firstly, as the EAC did not accept the company's method of estimating key clinical parameters (primarily LoS and LoT) through combining data from very heterogeneous studies, the EAC instead only used data reported within a single study. This had two implications:

- The scenarios reported by the EAC are applicable to the population described in that study only. However, because of the observational nature of the informing studies, the generally small sample sizes, and the lack of generalisability to the NHS, these scenarios were still subject to very high levels of uncertainty.

- Not all studies reported all the informing parameters. In the absence of data, crude assumptions were made, namely that LoS was the same as LoT. This assumption disbenefits NPWTi, as the assumption in the model is that, whilst NPWTi is more costly than its comparators, it introduces savings by reducing LoS.

The EAC also included scenarios using data from two studies that were not included by the company. Of these, the study by Kim *et al.* (2020) was regarded the most robust and was the closest that could be considered a "base case". This was because this was a relatively high quality experimental study, it was conducted in a well-defined population (case mix of patients with acute and chronic wounds), and it was the largest study (n = 181). Data from the small observational study by Omar *et al.* (2106), which reported on patients with acute wounds of the lower limb (n = 20) was also included. The revised parameter estimates are list in Table C3a (versus NPWT) and Table C3b (versus AWC).

Secondly, the EAC modified some of the inputs concerning resource use and rounding techniques. This was to improve the accuracy and internal consistency of the model. Additional procedural costs that the company included for "prosthetic implant subgroup" (simple wound closure, debridement and closure, mesh removal, mesh replacement), from data reported in the Deleyto study (2018) were also excluded. This was because, in the opinion of the EAC, the data reported in this study, and the application of costs through HRG codes, were not sufficiently robust to support these assumptions. These changes are reported in Table C4.

9.3 *Results from the economic modelling*

9.3.1 Company's base case results

The company's base case results were reported in Table 9 of the company's submission. The EAC independently reproduced the company base case and cross-referenced results reported in the submission which highlighted errors in the tabulated results of the NPWT comparison included company's written submission (these errors were confirmed by the company). The corrected results are reported in Table 9.2a (NPWTi vs. NPWT) and 9.2b (NPWTi vs. AWC).

Table 9.2a. *Corrected base case results of company's economic analysis for comparison of NPWTi and NPWT.*

	NPWTi	NPWT	Mean cost saving per patient
Length of stay	£5,741	£8,880	-£3139
Therapy	£919	£716	£203
Debridement	£505	£820	-£316
Total	£7,165	£10,416	**-£3,251**

Table 9.2b. *Base case results of company's economic analysis for comparison of NPWTi and AWC.*

	NPWTi	AWC	Mean cost saving per patient
Length of stay	£12,309	£20,623	-£8,314
Therapy	£1,136	£149	£986
Debridement	£534	£1,519	-£984
Total	£13,979	£22,291	**-£8,312**

The key results of the company's base case analysis, based on aggregated data from 3 studies (NPWT) or 4 studies (AWC) indicated that NPWTi incurred additional treatment costs compared with both comparators, but these were outweighed by cost savings associated with reduced LoS and requirement for surgical debridement.

9.3.2 EAC's base case results

The EAC's base case results are reported in Table 9.3. Restricting the analysis to the data reported by Kim (2020), NPWTi was found to be cost-expending compared to NPWT in the three cost domains, with an overall cost of £480. The EAC did not consider there was data of sufficient quality to

inform a base case cost analysis of NPWTi versus AWC. This was also considered to be a less suitable comparator (see Section 1.3).

Table 9.3. *EAC base case results of company's economic analysis for comparison of NPWTi and NPWT.*

	NPWTi	NPWT	Mean cost saving per patient
Length of stay	£2555	£2386	£169
Therapy	£526	£258	£268
Debridement	£260	£237	£23
Total	£3342	£2862	**£480**

9.3.2 Sensitivity analysis results

The company reported results from the individual disaggregated scenarios. These are reported in Table 9.4a (NPWTi vs. NPWT) and 9.4b. (NPWT vs. AWC). As can be seen, NPWTi was found to be cost-saving in all these scenarios, with cost-savings ranging from £300 (Jurkovic *et al.*, 2019) to £13,403 (Timmers *et al.*, 2009).

Table 9.4a. *Results of scenarios comparing NPWTi with NPWT.*

Subgroup (study used for clinical parameters)	**NPWTi**	**NPWT**	**Mean cost saving per patient**
Lower Limb (Kim 2014)	£6,427	£7,657	-£1,230
Mixed Wounds (Gabriel 2014)	£3,890	£12,113	-£8,223
Surgical Site infection (Jurkovic 2019)	£11,179	£11,479	-£300

Table 9.4b. *Results of scenarios comparing NPWTi with AWC.*

Subgroup (study used for clinical parameters)	**NPWTi**	**AWC**	**Mean cost saving per patient**
Lower Limb (Gabriel 2008)	£7,915	£18,934	-£11,018
Mixed Wounds (Timmers 2009)	£15,478	£28,880	-£13,403
Prosthetic Implant (Deleyto 2018)	£29,234	£36,957	-£7,723
Surgical Site infection (Chowdry 2019)	£3,289	£4,394	-£1,105

The company also performed extensive one-way DSA. In general, the model was not sensitive to these analyses (that is, varying individual parameters did not change the direction of results). In all cases, the model was most sensitive to parameter or cost changes in LoS. In the case of the surgical site infection scenario, applying changes to these did change the direction of results (versus NPWT).

The company performed PSA on the base case results and all the scenarios, which the EAC replicates. In the base case, the company reported 100% of simulations found that NPWTi was cost saving compared with NPWT or AWC. Probabilistic sensitivity analysis was also employed in the contributing scenarios, with all reporting ≥ 94% probability of NPWTi being cost saving,

with the exception of the surgical site infection scenario (informed by Jurkovic *et al.*, 2008), where 58% of simulations reported cost savings in favour of NPWTi.

The EAC considered that although the DSA and PSA performed by the company were extensive, it did not address the underlying structural and parameter uncertainties present (Section 9.2.6).

9.3.4 EAC sensitivity analysis

A comparison of the differences in cost savings estimated by the company and the EAC is reported in Table C5a and C5b. The parameter and resource use changes introduced by the EAC did not greatly affect the results of NPWTi compared with NPWT (ranging from -£76 to £225). There were greater differences in the estimates when NPWTi was compared with AWC (range -£25 to £4673). The larger difference in the Deleyto estimate was largely due to stripping several assumptions out of this scenario (Section 9.2.7).

The EAC has reported the economic results from its scenarios, with a breakdown in costs, in Table 9.5. Using scenario analysis, other than the base case analysis (using data from Kim 2020, resulting in a £480 cost expenditure for NPWTi), all the recalculated scenarios reported cost-savings associated with NPWTi. Costs saving were predominantly due to savings in LoS, which accounted for 70% to 95% of the reductions in cost. Conversely, technology costs and costs associated with repeat debridement were relatively low. It is notable in the model that the cost of an overnight stay (average cost £407) was almost double the cost of a surgical debridement (£237), and there were more excess overnight stays than excess debridement procedures.

The EAC performed adjusted PSA on the data at a scenario level (Section 9.2.6). The EAC reported the results as 95% credibility intervals (95% CrI). These are broadly synonymous with confidence intervals, and predict the probability the true cost values will fall within the range (95%) (YHEC, 2016a). These results of this analysis are reported in Table 9.6. The results show that, using the company analysis, 4/7 scenarios reported that NPWTi resulted in significant cost savings; whereas in 3/7 scenarios there was uncertainty because the 95% CrI range crossed zero. In the revised EAC estimate, 3/9 scenarios, based solely on the populations reported by the informing studies, indicated cost saving associated with NPWTi were highly likely, whereas there was considerable uncertainty in 6/9 scenarios.

However, the EAC considered that PSA did not address the fundamental limitation and uncertainties of the economic model (see Section 9.2.6).

Table 9.5: *Breakdown of total costs for intervention and comparator arms for each modelled scenario: length of therapy (LOT), length of stay (LOS) and number of debridements (nOR).*

		Intervention (NPWTi)				Comparator (NPWT/AWC)				
	Study	LoS (%)	LoT (%)	nOR (%)	**Total costs**	LoS (%)	LoT (%)	nOR (%)	**Total costs**	**Δ costs**
NPWT	Kim 2020*	£2555 (76%)	£526 (16%)	£260 (8 %)	**£3342**	£2367 (83%)	£258 (9%)	£237 (8%)	**£2862**	**-£480**
	Kim 2014	£5129 (76%)	£1020 (15%)	£568 (9%)	**£6717**	£6431 (83%)	£581 (8%)	£710 (9%)	**£7722**	**£1,005**
	Gabriel 2014	£3044 (79%)	£356 (9%)	£473 (12%)	**£3873**	£10,297 (85%)	£775 (6%)	£1041 (9%)	**£12,113**	**£8,240**
	Jurkovic 2019	£9051 (82%)	£1578 (14%)	£473 (4%)	**£11,103**	£9913 (86%)	£856 (7%)	£710 (6%)	**£11,479**	**£376**
	Omar 2016	£9267 (87%)	£696 (7%)	£710 (7%)	**£10,673**	£11,422 (90%)	£501 (4%)	£710 (6%)	**£12,632**	**£1,959**
AWC	Gabriel 2008	£6323 (88%)	£850 (12%)	£0 (0%)	**£7173**	£16,895 (99%)	£173 (1%)	£0 (0%)	**£17,068**	**£9,895**
	Timmers 2009	£13,528 (80%)	£2785 (17%)	£544 (3%)	**£16,857**	£27,433 (97%)	£347 (1%)	£568 (2%)	**£28,347**	**£11,490**
	Deleyto 2018	£27,057 (83%)	£5261 (16%)	£106 (0%)	**£32,424**	£34,545 (97%)	£419 (1%)	£510 (1%)	**£35,474**	**£3,050**
	Chowdry 2019	£2327 (71%)	£510 (16%)	£426 (13%)	**£3263**	£3620 (82%)	£40 (1%)	£734 (17%)	**£4394**	**£1,131**

Abbreviations: AWC, advanced wound care; LoS, length of stay; LoT, length of treatment; nOR, number of debridements; NPWT, negative pressure wound therapy; NPWTi, negative pressure wound therapy with instillation.

Table 9.6 *Company and EAC PSA applied to all scenarios.*

	Study	**Company estimate**	**EAC estimate**	**EAC estimate (PSA changes applied)***
		Median cost (NPWTi-comparator) [95% CrI]	**Median cost (NPWTi-comparator) [95% CrI]**	**Median cost (NPWT-comparator) [95% CrI]**
Vs. NPWT	Kim 2020	N/A	£491 [-£1037, £2031]	£471 [-£1085, £2015]
	Kim 2014	-£795 [-£2041, £209]	-£1011 [-£2831, £557]	-£1079 [-£2907, £567]
	Gabriel 2014	-£7968 [-£14,293, -£3966]	-£7759 [-£14,252, -£3775]	-£7960 [-£14,125, -£3887]
	Jurkovic 2019†	-£219 [-£3664, £2631]	-£269 [-£3521, £2644]	-£359 [-£3468, £2809]
	Omar 2016	N/A	-£1905 [-£7793, £3494]	-£1821 [-£8659, £3749]
Vs. AWC	Gabriel 2008†	-£7669 [-£12,527, -£4317]	-£9751 [-£15,497, -£5226]	-£9670 [-£15,501, -£5102]
	Timmers 2009†	-£12,845 [-£23,309, -£6370]	-£10,939 [-£28,000, £1070]	-£10,844 [-£26,046, £176]
	Deleyto 2018	-£8112 [-£17,678, £1838]	-£2918 [-£18,536, £11,407]	-£2731 [-£18,761, £9,431]
	Chowdry 2019	£1103 [-£2178, -£195]	-£1066 [-£2327, -£202]	-£1083 [-£2291, -£310]

Abbreviations: AWC, advanced wound care; CrI, credibility interval; NPWT, negative pressure wound therapy; NPWTi, negative pressure wound therapy with instillation.
Key: Green means costs do not cross zero, NPWTi is cost-saving. Amber means costs cross zero, there is increased uncertainty on whether NPWTi is cost-saving.
* EAC removed PSA in parameters it considered were fixed (dressing and V.A.C. VERAFLO daily rental costs).
† Studies excluded in the EAC clinical assessment.

9.4 *The EAC's interpretation of the economic evidence*

Four published economic studies were identified that were considered to be in scope. However, these were based on data from small retrospective studies of limited methodological quality, and were not considered to be generalisable to the UK NHS.

The company submitted a *de novo* model set in the NHS of England and Wales. This was a costing model that was conceptually simple, comparing NPWTi with NPWT alone or AWC. There were three outcomes in the model that determined overall costs; these were LoS, which reported costs incurred through bed usage; LoT, which reported direct costs associated with each technology; and debridement costs, which was a cost associated with the requirement for assumed repeat surgical debridement. The model was informed from mainly retrospective studies of low methodological quality identified through the clinical literature search, including studies that had been excluded by the EAC, and not including two studies that the EAC considered were relevant. Input from clinical experts was minimal. The company performed extensive sensitivity analysis, which included scenario (or subgroup) analysis, DSA, and PSA. The base case was reported by aggregating data from the informing scenarios ("lower limb", "mixed wound", "prosthetic implant" and "surgical infection").

The company reported that in the base case NPWTi was cost saving by £3,251 compared with NPWT, and by £8,312 compared with AWC. The principal driver of the cost savings was the reduction in LoS, as shown by DSA. The company reported that NPWTi was cost-saving in all scenarios and in most of these PSA indicated the probability of NPWTi being cost saving was ≥ 94%.

The EAC had significant reservations concerning the *de novo* model. Firstly, the company's study selection was unsatisfactory. The selected studies did not match the scenarios described, and two studies that reported equivocal outcomes were not included. Secondly, the EAC considered the quality of the studies was insufficient to establish causality between the intervention and the reported outcomes. This was exacerbated by the company transforming data from one study using data from another unrelated study. Thirdly, the informing studies were based on heterogeneous case mixes of patients that could not be generalised to an NHS population; furthermore the applicability of patient pathways, in particular use of repeated surgical debridement, was unclear. And fourthly, the method of reporting the base case results was unsatisfactory, as it was not directly based on appropriate empirical data and was not accordingly weighted to reflect this. The EAC also considered that the scale of the structural and parameter uncertainty in the model meant that sensitivity analyses were uninformative.

The EAC replicated the company's *de novo* model and made some modifications, in an attempt to improve accuracy and consistency. The main alteration was to use data from the RCT by Kim *et al.* (2020), which the EAC considered was the most robust evidence available. The main limitation to this analysis was that the RCT did not report LoS, so this was assumed to be the same as LoT. Using these assumptions, NPWTi was found to be cost-incurring by £480 using deterministic analysis. However, there was considerable uncertainty in this result, with PSA from the EAC indicating an average cost expenditure of £471 (95% CrI -£1085 to £2015). Thus the cost saving potential of NPWTi was considered to be uncertain.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The company performed a literature search which identified 32 studies they considered were in scope, including one conference abstract and an unpublished study that was academic in confidence and now fully published (Kim *et al.*, 2020). The EAC repeated the search and identified 19 studies that were considered to be in scope. The principal reason the EAC excluded the company's studies was due to the intervention not being in scope (either the predecessor technology or NPWTi from a different company).

Nine studies were comparative, and of these, 3 were RCTs (combined n = 303), and 6 were observational (combined n = 302). Ten were single-armed (combined n = 373). The EAC considered the RCT by Kim *et al.* (2020) was the most relevant and robust of the identified studies. This study randomised patients with acute or chronic wounds of various aetiologies (n = 181) to receive either NPWTi or NPWT. The authors reported that NPWTi was associated with significant reductions in bacterial bioburden. This is a surrogate outcome not directly related to clinical endpoints. The study did not report significant differences in the primary outcome, the frequency of surgical debridement, or any of the other secondary outcomes. Length of hospital stay for the whole cohort was not reported [redacted].

The other comparative studies were generally retrospective observational studies. Issues common to many of these studies included poorly reported patient selection; small sample sizes; use of historical control groups without adequate description of how these were selected; lack of sufficient matching of cohorts, including a lack of statistical matching techniques; and a lack of confidence in how endpoints were measured, recorded and reported. Taking these issues together, the EAC concluded that a unequivocal association between the intervention and outcomes had not been satisfactorily demonstrated. Uncertainty in the patient pathways and the heterogeneous case mix of patients included in the studies meant it was not possible to generalise data to the NHS (none of the studies were conducted in the UK). None of the studies reported PROMS or HRQoL data necessary to understand the impact of the technology from a patient perspective. Additionally, there is a lack of evidence in general regarding the benefits of NPWT compared with other treatment modalities (Section 3.3). The single-armed studies reported on patient characteristics and some procedural measurements, but otherwise did not inform the decision problem.

Thus the EAC concluded that there was insufficient evidence from the published evidence base on which to inform clinical recommendations on the benefits of NPWTi. However, the caveat to this is that a lack of evidence is not the same as evidence of no effect. The EAC noted the technology had plausible system benefits over precursor technologies. Additionally, it was noted that NICE clinical experts were supportive of the technology, and unanimously believed it had clinical benefits in appropriately selected patients (EAC External correspondence log, 2020). Further research is therefore required to establish the place of VAC VERAFLO in the NHS.

10.2 *Conclusions from the economic evidence*

Current economic evidence in the published literature base was not directly relevant to the decision problem. The company constructed a *de novo* economic model which focussed on the potential for NPWTi to reduce healthcare costs, by reducing LoS, LoT, and reducing the requirement for repeat surgical debridement. It estimated cost savings of around £3,300 (compared NPWT) to £8,300 (compared with AWC) could be made if NPWTi was used in the average, indicated patient.

The EAC did not consider the economic analysis was representative of NHS practice. This was for two fundamental reasons. Firstly, because there was a lack of confidence in the informing clinical data. In the opinion of the EAC the studies selected for use in the model did not demonstrate a causal relationship between the use of NPWTi and improved clinical outcomes. It was noted that the one informative RCT (Kim *et al.*, 2020) did not replicate the benefits reported in the observational studies selected. Secondly, the heterogeneous case mix of the populations used to inform the model, in combination with doubts about the appropriateness of the clinical pathways described, meant that the economic results could not be clearly generalised to the NHS of the UK.

The EAC reran the model using finessed assumptions and parameters, most notably the use of the Kim *et al*. (2020) RCT as the base case scenario. Using PSA, it was found that NPWTi was potentially cost-incurring by £471 (95% CrI -£1085 to £2015); thus there was material uncertainty in the direction of results. However, this analysis was subject to much of the same limitations as the company's analysis. In conclusion, the EAC did not consider there was adequate clinical evidence to inform meaningful economic analysis and the cost-saving potential of NPTWi remains unknown.

11 Summary of the combined clinical and economic sections

The clinical evidence to inform the effectiveness of NPWTi using the VAC VERAFLO system is limited in terms of quality. Nineteen studies were identified by the EAC, nine of which were comparative observational studies or RCTs. Whilst most of these published studies reported positive outcomes, firm conclusions could not be made because they were of low methodological quality. Limitations included the retrospective nature of the research, poor reporting, and lack of generalisability to the NHS. One recently published RCT did not report significant clinical benefits of NPWTi compared with NPWT.

The company developed a *de novo* economic model that reported large cost savings associated with NPWTi, principally through the reduction in hospital LoS, allowing earlier discharge into the community. However, in the opinion of the EAC, the informing clinical evidence was not sufficiently robust to give confidence in these findings. In the future, improved economic analysis will be dependent on data generated from better-quality clinical research.

12 Implications for research

Further clinical research into the safety and effectiveness of NPWTi using VAC VERAFLO would be beneficial in establishing its place in therapy. Ideally, experimental research in the form of an RCT would be most informative. The study population should consist of a definable cohort (for example pressure ulcers or diabetic foot ulcers). Inclusion and exclusion criteria should be clearly stated. It should be adequately powered using a primary outcome which is clinically important, and preferably it should also report PROMs or HRQoL outcomes.

It is recognised that RCTs are difficult, time-consuming and expensive to design and implement. If for these reasons observational research was preferred, this should be undertaken to a high standard of quality. If possible, such research should be publically registered, prospective, have a large sample size, and include statistical matching techniques to minimise the effects of confounding and bias. Once a clinical effect has been established through high-quality research, it may be possible to reasonably extrapolate this to other patient groups, and to validate this with additional observational research.

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14 Appendices

Appendix A - Literature searching methodology

Appendix B – Critical appraisal of clinical studies

Appendix C – Economic assumptions and additional results

Appendix D – Economic literature search

Appendix A: Literature searching methodology

Search strategy

The search strategy was designed to identify evidence related to the V.A.C. Veraflo™ therapy system. A search strategy developed by the company was submitted as below:

The following strategy was used to perform a literature search in PubMed, EMBASE and QUOSA.

("Lavage" OR "instil" OR "instillation" OR "irrigated" OR "irrigation" OR "topical solution" OR "topical wound solution" OR "topic solution" OR "VERAFLO" OR "VERAFLOW" OR "Veraflo dressing" OR "Veraflo cleanse dressing" OR "Veraflo cleanse choice dressing" OR "Ulta") AND ("Negative Pressure Wound Therapy" OR "NPWT" OR "vacuum assisted closure" OR "vacuum sealing" OR "NPWTi" OR "NPWTi-d")

This strategy was critiqued using the PRESS (Peer Review of Electronic Search Strategies) tool as shown below:

Question	Y/N	Notes
Translation of the research question		
Does the search strategy match the research question/PICO?	Query	The strategy focusses on the intervention only, but this may be appropriate as this may retrieve only a small number of results, as it is very specific.
Are the search concepts clear?	Query	The 2 concepts appear to be: Topical interventions AND negative pressure wound therapy
Are there too many or too few PICO elements included?	Query	See above
Are the search concepts too narrow or too broad?	Okay	

Does the search retrieve too many or too few records? (Please show number of hits per line.)	Okay	
Are unconventional or complex strategies explained?	N/A	
Boolean and proximity operators (these vary based on search service)		
Are Boolean or proximity operators used correctly?	Yes	
Is the use of nesting with brackets appropriate and effective for the search?	N/A	
If NOT is used, is this likely to result in any unintended exclusions?	N/A	
Could precision be improved by using proximity operators (e.g., adjacent, near, within) or phrase searching instead of AND?	Query	Possibly, I will test this when I develop the search strategy further
Is the width of proximity operators suitable (e.g., might adj5 pick up more variants than adj2)?	N/A	
Subject headings (database specific)		
Are the subject headings relevant?	Query	It appears that no MeSH headings have been used
Are any relevant subject headings missing; for example, previous index terms?	Query	I will investigate if there are any appropriate MeSH headings
Are any subject headings too broad or too narrow?	N/A	
Are subject headings exploded where necessary and vice versa?	N/A	

Are major headings (“starring” or restrict to focus) used? If so, is there adequate justification?	N/A	
Are subheadings missing?	N/A	
Are subheadings attached to subject headings? (Floating subheadings may be preferred.)	N/A	
Are floating subheadings relevant and used appropriately?	N/A	
Are both subject headings and terms in free text (see the following) used for each concept?	N/A	
Text word searching (free text)		
Does the search include all spelling variants in free text (e.g., UK vs. US spelling)?	N/A	I can’t see any terms that would have an alternative spelling.
Does the search include all synonyms or antonyms (e.g., opposites)?	Query	I will check this when I develop the search strategy
Does the search capture relevant truncation (i.e., is truncation at the correct place)?	Query	No truncation has been used, though this may be appropriate e.g. instil*
Is the truncation too broad or too narrow?	N/A	
Are acronyms or abbreviations used appropriately? Do they capture irrelevant material? Are the full terms also included?	Query	Most acronyms appear appropriate, I’m not sure if “Ulta” is an acronym or a spelling mistake (I think this may be a type of veraflo technology)
Are the keywords specific enough or too broad? Are too many or too few keywords used? Are stop words used?	Query	I will review this using some of the known papers provided

Have the appropriate fields been searched; for example, is the choice of the text word fields (.tw.) or all fields (.af.) appropriate? Are there any other fields to be included or excluded (database specific)?	Query	It is not clear which fields have been searched
Should any long strings be broken into several shorter search statements?	No	
Spelling, syntax, and line numbers		
Are there any spelling errors?	Query	See comment above re “ulta”
Are there any errors in system syntax; for example, the use of a truncation symbol from a different search interface?	No	No syntax has been used
Are there incorrect line combinations or orphan lines (i.e., lines that are not referred to in the final summation that could indicate an error in an AND or OR statement)?	No	
Limits and filters		
Are all limits and filters used appropriately and are they relevant given the research question?	Query	A date restriction of January 2005 has been applied, but no justification is given for this
Are all limits and filters used appropriately and are they relevant for the database?	Query	It is not obvious how the date restriction was applied in each database
Are any potentially helpful limits or filters missing? Are the limits or filters too broad or too narrow? Can any limits or filters be added or taken away?	Query	An animal/human limit could be applied, though preclinical trials are included. Certain publication types could be excluded according to the exclusion criteria.

Are sources cited for the filters used?	N/A	
Further comments:		
Limited databases used – PubMed, Embase and QUOSA (I think this may be an internal database of articles within the company). I would certainly add in CINAHL as this is a wound management device, which is likely to match relevant literature in a nursing database. The inclusion/exclusion criteria are contradictory – conference abstracts are included in both lists A number of the included papers refer to other companies' products, not the VAC Veraflo		

The concepts of the search were identified as:

(Instillation/irrigation AND Negative Pressure Wound therapy) OR (veraflo OR ulta)

Terms relating to the population were not necessary, as the intervention is specific to those with wounds.

The search strategy was developed in MEDLINE and tested using papers that had been previously identified by the company.

The company strategy did not include subject headings so these were identified and added as appropriate. The final strategy comprised a combination of subject headings and free text searching using the title, abstract and keyword fields.

Non-English language publications were excluded from the results, and the search was restricted to publications from 2011 onwards to coincide with the introduction of the V.A.C. Veraflo™ therapy system.

The MEDLINE strategy was translated as appropriate into other relevant databases:

- Embase (OVID) 1996 – 2020 March 19

- CINAHL (EBSCO) 1981 – March 2020
- Cochrane Database of Systematic Reviews (Cochrane Library, Wiley)
- Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley)

The search dates, search strategies and retrieved record numbers for each of the database searches are presented below (A1 to A4).

In total 983 records were retrieved across all databases, following deduplication 606 unique records remained.

A.1: Source: MEDLINE Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to February 17, 2020.

Interface/URL: OvidSP
Database coverage dates: 1946 to present
Search date: 20/03/20
Retrieved records: 305
Search strategy:

1 Therapeutic Irrigation/

2 lavage.ti,ab,kw,kf.

3 Instillation, Drug/

4 instillation.ti,ab,kw,kf.

5 irrigation.ti,ab,kw,kf.

6 Administration, Topical/

7 (topic* adj2 solution*).ti,ab,kw,kf.

8 or/1-7

9 veraflo*.ti,ab,kw,kf.

10 ulta*2.ti,ab,kw,kf.

11 9 or 10

12 Negative-Pressure Wound Therapy/

13 "negative pressure wound therapy".ti,ab,kw,kf.

14 NPWT*.ti,ab,kw,kf.

15 "vacuum assisted closure".ti,ab,kw,kf.

16 "vacuum sealing".ti,ab,kw,kf.

17 or/12-16

18 8 and 17

19 11 or 18

20 limit 19 to (english language and yr="2011 -Current")

A.2: Source: Ovid Embase 1974 to 2020 March 19.

Interface/URL: OvidSP
Database coverage dates: 1996 to present
Search date: 20/03/20
Retrieved records: 397
Search strategy:

1 lavage/

2 lavage.ti,ab,kw.

3 drug instillation/

4 instillation.ti,ab,kw.

5 irrigation.ti,ab,kw.

6 topical drug administration/

7 (topic* adj2 solution*).ti,ab,kw.

8 or/1-7

9 veraflo*.ti,ab,kw.

10 ulta*2.ti,ab,kw.

11 9 or 10

12 vacuum assisted closure/

13 "negative pressure wound therapy".ti,ab,kw.

14 NPWT*.ti,ab,kw.

15 "vacuum assisted closure".ti,ab,kw.

16 "vacuum sealing".ti,ab,kw.

17 or/12-16

18 8 and 17

19 11 or 18

20 limit 19 to (english language and yr="2011 -Current")

A.3: Source: CINAHL®

Interface/URL: EBSCOhost Web
Database coverage dates: 1981 to present
Search date: 20/03/20
Retrieved records: 221
Search strategy:

S20 S16 OR S18 Limiters - Published Date: 20110101-20201231; Narrow by Language: - english

S19 S16 OR S18

S18 S8 AND S17

S17 S11 OR S12 OR S13 OR S14 OR S15

S16 S9 OR S10

S15 TI "vacuum sealing" or AB "vacuum sealing"

S14 TI "vacuum assisted closure" or AB "vacuum assisted closure"

S13 TI NPWT* or AB NPWT*

S12 TI "Negative Pressure Wound Therapy" or AB "Negative Pressure Wound Therapy"

S11 (MH "Negative Pressure Wound Therapy")

S10 TI ulta* or AB ulta*

S9 TI veraflo* or AB veraflo*

S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7

S7 TI (topic* N2 solution*) or AB (topic* N2 solution*)

S6 (MH "Administration, Topical")

S5 TI irrigation or AB irrigation

S4 TI instillation or AB instillation

S3 (MH "Instillation, Drug")

S2 TI lavage or AB lavage

S1 (MH "Therapeutic Irrigation")

A.4: Source: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)

Interface/URL: Cochrane Library, Wiley
Database coverage dates: 1996 to present
Search date: 20/03/20
Retrieved records:
CDSR: 0
CENTRAL: 60
Search strategy:

#1 MeSH descriptor: [Therapeutic Irrigation] this term only

#2 (lavage):ti,ab,kw

#3 MeSH descriptor: [Instillation, Drug] this term only

#4 (instillation):ti,ab,kw

#5 (irrigation):ti,ab,kw

#6 MeSH descriptor: [Administration, Topical] this term only

#7 ((topic* near/2 solution*)):ti,ab,kw

#8 (Mahmoudiasl *et al.*-#7)

#9 (veraflo*):ti,ab,kw

#10 (ulta*):ti,ab,kw

#11 MeSH descriptor: [Negative-Pressure Wound Therapy] this term only

#12 ("negative pressure wound therapy"):ti,ab,kw

#13 (NPWT*):ti,ab,kw

#14 ("vacuum assisted closure"):ti,ab,kw

#15 ("vacuum sealing"):ti,ab,kw

#16 (Mahmoudiasl *et al.*-#15)

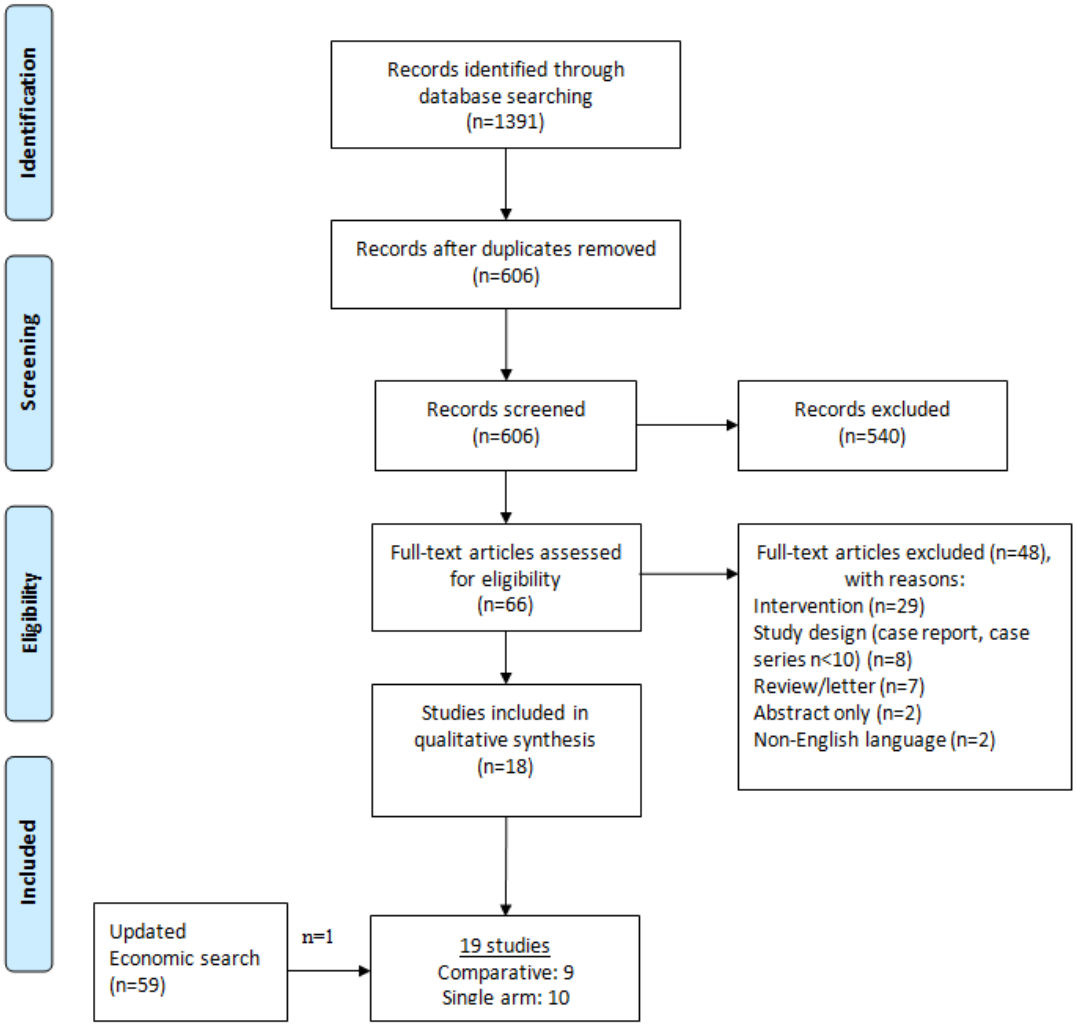
#17 #8 and #16

#18 #17 or #9 or #10

References:

McGowan, J., Sampson, M., Salzwedel, D.M., Cogo, E., Foerster, V. and Lefebvre, C., 2016. PRESS peer review of electronic search strategies: 2015 guideline statement. Journal of clinical epidemiology, 75, pp.40-46.

Figure A1. *PRISMA diagram illustrating literature search.*



Appendix B: Critical appraisal of clinical studies

Table *B1 Critical appraisal of (Kim et al., 2020)*

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	Permuted block randomisation. . "Stratified randomization by investigative site was used. For each investigative site (stratum), permuted blocks were used to achieve equal numbers of Subjects assigned to NPWTi-d and NPWT to generate a randomization schedule".	Low risk of bias
	Allocation concealment	Allocation through sealed envelopes: "Envelopes were prepared corresponding to each row in the randomization schedule. Opening of the randomization envelope occurred intraoperatively at the conclusion of the initial surgical debridement of the wound and after confirmation that patient met inclusion and no exclusion criteria"	Low risk of bias
Performance bias	Blinding of participants and personnel*	No blinding of participants or treating personnel attempted.	High risk of bias
Detection bias	Blinding of outcome assessment*	No blinding of assessors or analysts used. Some subjectivity possible in measurement of the outcomes.	High risk of bias
Attrition bias	Incomplete outcome data*	CONSORT statement provided, with reasons for loss to follow up described. Substantial attrition reported (70% in NPWTi arm, 73% in NPWT arm at follow up). Inconsistent reporting of ITT and PP analysis.	High risk of bias
Reporting bias	Selective reporting	Study protocol published (NCT01867580), 1 primary and 1 secondary outcome reported (compared with 5 secondary in draft manuscript). Secondary outcome and subgroup analysis reported without adjustment for multiple analyses.	High risk of bias
Other bias	Anything else, ideally pre-specified.	This paper is an AiC draft and has not been peer-reviewed. No disclosures reported.	Unclear risk of bias

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; ITT, intention to treat; pp, per protocol.

*Assessments should be made for each main outcome or class of outcomes.

Table B2. *Critical appraisal of (Yang et al., 2017a).*

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	No randomisation described. "Patients were sequentially enrolled into either the NPWT group or the NPWTi group in an unblinded fashion".	High risk of bias
	Allocation concealment	No description of allocation concealment.	High risk of bias
Performance bias	Blinding of participants and personnel*	No blinding of participants or treating personnel attempted.	High risk of bias
Detection bias	Blinding of outcome assessment*	No blinding of assessors or analysts used.	High risk of bias
Attrition bias	Incomplete outcome data*	No patient flow chart reported. Sample size was very small (total n = 19) but unclear if there was any withdrawal or ITT or PP were applied.	High risk of bias (ITT)
Reporting bias	Selective reporting	Only one outcome reported (bacterial concentration). No trial protocol published.	High risk of bias
Other bias	Anything else, ideally pre-specified.	Some authors had financial connections to the company: "Dr. Schultz is a paid consultant for Acelity and Smith & Nephew. Dr. Lantis is a paid consultant for Acelity, Smith & Nephew, Kerecis, and Intregra".	Unclear risk of bias

Abbreviations: ITT, intention to treat; pp, per protocol.

*Assessments should be made for each main outcome or class of outcomes.

Table B3. *Critical appraisal of (Kim et al., 2015).*

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	A priori randomisation with "1:1 allocation using a random number generator producing a list of 100 discrete spreadsheet cells [Excel], with 1 representing normal saline and 2 representing 0.1% polyhexanide plus 0.1% betaine"	Low risk of bias
	Allocation concealment	No description of allocation concealment.	High risk of bias
Performance bias	Blinding of participants and personnel*	No blinding of participants or treating personnel attempted.	High risk of bias
Detection bias	Blinding of outcome assessment*	No blinding of assessors or analysts used.	High risk of bias
Attrition bias	Incomplete outcome data*	Patient flow chart reported. All patients in ITT included in analysis. Reasons for exclusion reported for PP analysis.	Low risk of bias (ITT)
Reporting bias	Selective reporting	Outcomes were reported in trial protocol (NCT01939145). Only limited outcomes reported, but no evidence of omission (except qualitative bacterial culture).	Low risk of bias
Other bias	Anything else, ideally pre-specified.	Patients may have been inappropriately selected prior to randomisation (see Discussion)	Generalisability issues

Abbreviations: ITT, intention to treat; pp, per protocol.

*Assessments should be made for each main outcome or class of outcomes.

Table B4. *CASP checklist (cohort study) (Chowdhry and Wilhelmi, 2019).*

Question	Yes, No, Can't tell	Comment
1. Did the study address a clearly focused issue?	☑	"In this study, NPWTi-d was retrospectively compared with standard wet-to-moist dressing changes as an adjunctive modality for managing sternal wounds resulting from sternal incision complications."
2. Was the cohort recruited in an acceptable way?	☑	Appears to be consecutive recruitment: "30 most recent patients (15 patients who received NPWTi-d and 15 patients who received wet-tomoist dressings)"
3. Was the exposure accurately measured to minimise bias?	☑	The intervention and comparator are described in some detail.
4. Was the outcome accurately measured to minimise bias?	☒	Probably not possible as the study was retrospective.
5a. Have the authors identified all important confounding factors?	☒	No effort made to identify confounding variables.
5b. Have they taken account of the confounding factors in the design and/or analysis?	☒	No propensity matching or statistical adjustment employed.
6a. Was the follow up of subjects complete enough?	?	Follow up was not defined.
6b. Was the follow up of subjects long enough?	?	
7. What are the results of this study?	☑ (positive results)	"There was a significantly shorter time to closure (P < 0.0001) for group 1 when compared with group 2. In addition, there were fewer therapy days (p = 0.0041), fewer debridements/dressing changes (P = 0.0011), and shorter drain duration (P = 0.0001) for group 1 when compared with group 2".
8. How precise are the results?	☑	Graphs with confidence levels reported, hypothesis testing employed.
9. Do you believe the results?	☒	The methodology of the study is not sufficiently high enough to have confidence in the results.

10. Can the results be applied to the local population?	☒	The indication for NPWTi in this study was very specific. Therefore results cannot be generalised to other populations.
11. Do the results of this study fit with other available evidence?	?	No other studies identified for this indication.
12. What are the implications of this study for practice?	☒	No recommendations are possible on the basis of this study.

Table B5. *CASP check list (Cohort study) (Deleyto et al., 2018)*

Question	Yes, No, Can't tell	Comment
1. Did the study address a clearly focused issue?	☑	"[We] have therefore, conducted a study of costs and global efficiency, comparing the use of NPWTi with conventional wound treatment (CWT) options."
2. Was the cohort recruited in an acceptable way?	☑	Retrospective recruitment of consecutive patients with the diagnosis of abdominal wall wound dehiscence with mesh exposure during the period January 2010 to December 2013.
3. Was the exposure accurately measured to minimise bias?	☑	The NPWTi and conventional dressing processes were described in appropriate detail.
4. Was the outcome accurately measured to minimise bias?	☒	Outcome data was retrospective and may not have been accurate. No description on how outcomes were measured.
5a. Have the authors identified all important confounding factors?	☒	No effort made to identify confounding variables.
5b. Have they taken account of the confounding factors in the design and/or analysis?	☒	No propensity matching or other statistical adjustment undertaken.
6a. Was the follow up of subjects complete enough?	?	Follow up was not defined.
6b. Was the follow up of subjects long enough?	?	
7. What are the results of this study?	☑ (positive results)	Reduction in costs associated with NPWTi.
8. How precise are the results?	☑	Mean costs with 95% confidence intervals presented.
9. Do you believe the results?	☒	The reporting of the study was not sufficient to establish the veracity of the results with confidence.
10. Can the results be applied to the local population?	☒	This was primarily a Spanish economic study. The results were not generalisable to the UK.
11. Do the results of this study fit with other available evidence?	☒	Not known.
12. What are the implications of this study for practice?	☒	No recommendations are possible on the basis of this study.

Table B6. *CASP check list (Cohort study) (Omar et al., 2016)*

Question	Yes, No, Can't tell	Comment
1. Did the study address a clearly focused issue?	☑	"The purpose of this study was to compare the outcomes for patients who received negative-pressure wound therapy with instillation versus a historical control cohort of patients who received traditional negative- pressure wound therapy without instillation."
2. Was the cohort recruited in an acceptable way?	☒	NPWTi and NPWT patients were recruited retrospectively from an electtonic medical records system at a hospital. Recruitement dates and methods not reported. There is scope for selection bias.
3. Was the exposure accurately measured to minimise bias?	☑	The NPWTi and NPWT processes were described in appropriate detail.
4. Was the outcome accurately measured to minimise bias?	☒	Outcome data was retrospective and may not have been accurate.
5a. Have the authors identified all important confounding factors?	☒	No effort made to identify confounding variables.
5b. Have they taken account of the confounding factors in the design and/or analysis?	☒	No propensity matching or other statistical adjustment undertaken.
6a. Was the follow up of subjects complete enough?	?	Follow up was not defined.
6b. Was the follow up of subjects long enough?	?	
7. What are the results of this study?	☑ (positive results)	Improvements in debridements, hospital stay, wound closure.
8. How precise are the results?	☒	Standard deviation may have been reported for some outcomes. However, overall precision of results does not appear robust.
9. Do you believe the results?	☒	The study was not methodologically robust enough to interpret the results with confidence. Conclusions appear to be stronger than justified by the results given the limitations.
10. Can the results be applied to the local population?	☒	The results cannot be generalised to other populations (very broad inclusion criteria with low patient numbers in each category).

11. Do the results of this study fit with other available evidence?	☒	The evidence base in general is equivocal. However, these are not consistent with the only RCT (Kim *et al.* 2020, AiC).
12. What are the implications of this study for practice?	☒	No recommendations are possible on the basis of this study.

Table B7. *CASP check list (Cohort study) (Gabriel et al., 2014)*

Question	Yes, No, Can't tell	Comment
1. Did the study address a clearly focused issue?	☑	"To compare the outcomes of patients with extremity and trunk wounds treated with standard NPWT versus NPWTi-d with volumetric fluid instillation and to estimate differences in costs for the 2 treatment arms based on the outcomes"
2. Was the cohort recruited in an acceptable way?	☒	"All patients were treated with a similar protocol by one investigator" No information on cohort selection.
3. Was the exposure accurately measured to minimise bias?	☒	Details of interventions and co-interventions are lacking.
4. Was the outcome accurately measured to minimise bias?	☒	Probably not possible as the study was retrospective.
5a. Have the authors identified all important confounding factors?	☒	No effort made to identify confounding variables.
5b. Have they taken account of the confounding factors in the design and/or analysis?	☒	No propensity matching or statistical adjustment employed.
6a. Was the follow up of subjects complete enough?	?	Follow up was not defined.
6b. Was the follow up of subjects long enough?	?	
7. What are the results of this study?	☑ (positive results)	NPWTi reduced debridements, mean hospital stay, and time to wound closure.
8. How precise are the results?	☒	No confidence levels reported.
9. Do you believe the results?	☒	There is too much uncertainty, in particular regarding patient selection and outcome measurement, to be confident about the results.
10. Can the results be applied to the local population?	☒	The results cannot be generalised to other populations.
11. Do the results of this study fit with other available evidence?	?	The results are not consistent with the only RCT reporting these outcomes (Kim *et al.*; 2020).
12. What are the implications of this study for practice?	☒	No recommendations are possible on the basis of this study.

Table B8. *CASP check list (Cohort study) (Kim et al., 2014).*

Question	Yes, No, Can't tell	Comment
1. Did the study address a clearly focused issue?	☑	"The purpose of this study was to compare the outcomes for patients who received negative-pressure wound therapy with instillation versus a historical control cohort of patients who received traditional negative- pressure wound therapy without instillation."
2. Was the cohort recruited in an acceptable way?	☒	NPWTi and NPWT patients were recruited retrospectively from an electronic medical records system at a hospital. Recruitment dates and methods not reported. There is scope for selection bias.
3. Was the exposure accurately measured to minimise bias?	☑	The NPWTi and NPWT processes were described in appropriate detail.
4. Was the outcome accurately measured to minimise bias?	☒	Outcome data was retrospective and may not have been accurate.
5a. Have the authors identified all important confounding factors?	☒	No effort made to identify confounding variables.
5b. Have they taken account of the confounding factors in the design and/or analysis?	☒	No propensity matching or other statistical adjustment undertaken.
6a. Was the follow up of subjects complete enough?	?	Follow up was not defined.
6b. Was the follow up of subjects long enough?	?	
7. What are the results of this study?	☑ (positive results)	Improvements in debridements, hospital stay, wound closure.
8. How precise are the results?	☒	Standard deviation may have been reported for some outcomes. However, overall precision of results does not appear robust.
9. Do you believe the results?	☒	The study was not methodologically robust enough to interpret the results with confidence. Conclusions appear to be stronger than justified by the results given the limitations.
10. Can the results be applied to the local population?	☒	The results cannot be generalised to other populations (very broad inclusion criteria with low patient numbers in each category).

11. Do the results of this study fit with other available evidence?	☒	The evidence base in general is equivocal. However, these are not consistent with the only RCT (Kim *et al.* 2020, AiC).
12. What are the implications of this study for practice?	☒	No recommendations are possible on the basis of this study.

Table B9. *CASP check list (Cohort study) (Goss et al., 2012).*

Question	Yes, No, Can't tell	Comment
1. Did the study address a clearly focused issue?	☑	"The primary objective of this study was to assess the difference in chronic wound planktonic bioburden after operative debridement and 1 week of treatment with either standard NPWT or NPWT with instillation using a mild concentration of Dakin's solution."
2. Was the cohort recruited in an acceptable way?	☒	The study used prospective recruitment, but the methods of patient selection are not adequately reported. Highly likely to be susceptible to selection bias.
3. Was the exposure accurately measured to minimise bias?	☑	The NPWTi and NPWT processes were described.
4. Was the outcome accurately measured to minimise bias?	?	It is not possible to tell if the outcomes were subject to particular levels of bias.
5a. Have the authors identified all important confounding factors?	☒	No effort made to identify confounding variables.
5b. Have they taken account of the confounding factors in the design and/or analysis?	☒	No propensity matching or other statistical adjustment undertaken.
6a. Was the follow up of subjects complete enough?	?	Follow up was not defined.
6b. Was the follow up of subjects long enough?	?	
7. What are the results of this study?	☑ (positive results)	"there was a statistically significant reduction in the absolute bioburden in those wounds treated with NPWTi (p 5 0.016)".
8. How precise are the results?	☒	Distributional data not reported..
9. Do you believe the results?	☒	The study was not methodologically robust enough to interpret the results with confidence.
10. Can the results be applied to the local population?	☒	The results cannot be generalised to other populations. Sample was heterogeneous and small.
11. Do the results of this study fit with other available evidence?	☒	Not consistent with another "RCT" (Yang *et al.* 2017)
12. What are the implications of this study for practice?	☒	No recommendations are possible on the basis of this study.

Appendix C: Economic assumptions and additional results

Table C1. *EAC's critique of the assumptions made in the model (Table 2 of the Economic Submission).*

Company assumption	Company justification	Evidence source	EAC comment
The model assumes canisters, cassettes and dressing kits needs changing three times per week	In line with instructions for use	NPWTi IFU	The EAC has checked the IFU and accepts this is likely to be accurate. However, it is noted that the size of canister required will depend on patient and wound characteristics.
Number of OR visits / operations were assumed for the purpose of a debridement	KOL opinion indicates it is likely debridements would be performed for such patients even if it is not reported explicitly.	KOL opinion	The EAC considered there may be multiple reasons for OR attendances other than surgical debridement. Furthermore, NICE clinical experts verified UK guidelines (Wounds UK, 2013) that surgical debridement is often not the first-line method of debridement in many patients considered in scope (EAC External correspondence log, 2020). The EAC notes that the company's contact with KoLs was restricted to two individuals who provided confirmation of company assumptions rather than being directly involved in making them (see Section 9.2.2).
Length of therapy in Kim 2014 was assumed to be 8.01 and 13.88 days respectively for NPWTi and NPWT respectively	A ratio was worked between length of therapy and length of stay in Gabriel 2008 and was then multiplied by length of stay reported at Kim 2014	Reference Gabriel 2008 and Kim 2014	The EAC does not accept this is an appropriate method to calculate this parameter. See Section 9.2.3.
Number of debridements in Gabriel 2008 was assumed to be 2.96 and 7.88 days for NPWTi and standard wound care respectively	A ratio was worked between number of OR visits and length of stay in Kim 2014 and was then multiplied by length of stay reported at Gabriel 2008	Reference Gabriel 2008 and Kim 2014	The EAC does not accept this is an appropriate method to calculate this parameter. See Section 9.2.3.
Length of therapy in Timmers 2009 was assumed to be 18.22 and 55.68 days for NPWTi and	A ratio was worked between length of therapy and length of stay in Gabriel 2014 and was	Reference Timmers 2009 and Gabriel 2014	The EAC does not accept this is an appropriate method to calculate this parameter. See Section 9.2.3.

Company assumption	Company justification	Evidence source	EAC comment
standard wound care respectively	then multiplied by length of stay reported at Timmers 2009		
Deleyto 2018 was assumed more appropriate for extracting endpoints for prosthetic implants subgroup compared to Garcia 2016	Both studies were conducted one the same group of patients and reported the same results. Deleyto 2018 was preferred because it reported mean values for all outcomes and to the second decimal place	Reference Deleyto 2018 & Garcia 2016	The EAC accepts that selection of this study rather than the study by Garcia-Ruano *et al.* (2016) was appropriate. However, the EAC did not consider the way the studies were selected in general were acceptable. Section 9.2.3.
Length of therapy in Deleyto 2018 was assumed to be 25.19 days for standard wound care	A ratio was worked between length of therapy and length of stay in Deleyto 2018 for NPWTi and was then multiplied by length of stay for standard wound care reported at Deleyto 2018	Reference Deleyto 2018	The EAC considered this assumption was not justified. Extrapolation of data from one cohort to another does not replace direct empirical evidence. See Section 9.2.3.
Length of stay in the surgical site infections subgroup was assumed equal to length of therapy	None of the relevant studies reported the outcome of interest. Therefore, this conservative assumption was made to complete the model inputs	Reference Jurkovic 2019 and Chowdhry 2019	The EAC considered this assumption was not justified. The methodological and reporting quality of the informing studies was not adequate to estimate this parameter.
Nurse training time on NPWTi was assumed to be negligible	The assumption was made based on 1.5 hours of training needed per nurse with expected high estimations of the workload or capacity in terms of number of treated patients per nurse after training	N/A	The rationale for this assumption is not clear. However, the EAC accepts that opportunity costs forgone through training would be unlikely to have significant cost impacts in the longer term.

Abbreviations: KoL, key opinion leader; IFU, instructions for use; NPWT, negative pressure wound therapy; NPWTi, negative pressure wound therapy with instillation.

Table C2. *Studies included by company to inform economic parameters.*

<table>
<tr><th>Company scenario</th><th>Study reference, type, and setting</th><th>Population</th><th>Intervention and comparator</th><th>Outcome(s) used in economic model</th><th>Critique of statistical analysis</th><th>EAC comments</th></tr>
<tr><td>Lower limb</td><td>(Kim et al., 2014)
Retrospective observational study.
United States</td><td>“All patients with infected wounds requiring admission with at least two operative debridements and that received either negative-pressure wound therapy or negative-pressure wound therapy with instillation application at the time of the initial operation”
(n = 142)

<table><tr><th>Anatomical location</th><th>Aetiological cause</th></tr><tr><td>Forefoot</td><td>Ischaemic</td></tr><tr><td>Midfoot</td><td>Neuropathic</td></tr><tr><td>Hindfoot/heel</td><td>Decubitus wound</td></tr><tr><td>Ankle</td><td>Surgical</td></tr><tr><td>Leg</td><td>Venous</td></tr><tr><td>Thigh</td><td>Traumatic</td></tr><tr><td>Amputation site (metatarsal/below knee)</td><td></td></tr><tr><td>Back/buttock</td><td>Other</td></tr><tr><td>Abdomen</td><td></td></tr><tr><td>Arm</td><td></td></tr></table>
☑☒</td><td>I: NPWTi with VAC VeraFlo
Dwell time with Prontosan:
6 minutes (n = 34)
20 minutes (n = 34)
☑
C: NPWT (InfoVAC therapy system)
☑</td><td>LoS (NPWTi and NPWT)
☑

LoT: derived variable by multiplying LoS by scaling factor calculated from data from (Gabriel et al., 2008).
☒

Number of OR visits (surgical debridements) (NPWTi and NPWT)
☑</td><td>• Correction for multiple testing not applied.
• Test for normality for continuous variables not reported.
• Incorrect test for comparing LoS, time to final surgical procedure and number of operative visits*</td><td>The population enrolled in this study included people with wounds not of the lower leg (11.2% of population). This study was regarded as relatively high quality compared with other informing studies.
Data for NPWTi has been taken from the 6 minutes dwell time arm.
Inappropriate statistical analysis.
Note in the original study there was no evidence of dose response in dwell time.</td></tr>
<tr><td></td><td>(Gabriel et al., 2008)
Small retrospective case series
United States</td><td>Patients with a “diagnosis of complex, open, infected wounds”.
NPWTi group patient data reported only:
<table><tr><th>Type of wound</th></tr><tr><td>Abdominal necrotising fasciitis</td></tr></table></td><td>I: NPWTi with VAC Instill treatment
☒</td><td>Used to calculate ratio between LoS and LoT, and this scaling factor then applied to study</td><td>• Correction for multiple testing not applied.
• Test for normality for continuous variables not</td><td>The population was not specific to lower limb wounds.

The intervention was the</td></tr>
</table>

		Necrotising fasciitis of chest and upper extremity Stage IV sacral pressure ulcer Open knee joint with exposed hardware (n = 2) Surgical wound dehiscence Lower extremity wound Soft tissue loss of lower extremity Open ankle joint with exposed hardware Lower extremity wound with exposed bone Soft tissue loss of the lower extremity Lower extremity wound with exposed bone Abdominal surgical wound dehiscence Stage IV pressure ulcer Necrotising fascitis of the upper extremity n = 15 ☒	C: "Standard moist wound-care therapy" ☑☒	data in (Kim *et al.*, 2014). ☑ LoS (NPWTi and AWC) ☑ LoT (NPWTi and AWC) ☑	explicitly reported (but they do use t-tests and Wilcoxon rank sum meaning that they did treat parametric and non-parametric variables differently).	predecessor device (out of scope). The comparator was not NPWT. The EAC does not agree data from this study can be used to extrapolate data in the study by (Kim *et al.*, 2014).
Mixed wounds	(Gabriel *et al.*, 2014) Retrospective observational study. United States	Patients with "an infected or critically colonized wound". Anatomical position / Proportion: Upper extremity: 25/82 (30%) Lower extremity: 18/82 (22%) Trunk: 40/82 (49%) n = 82 ?	I: NPWTi with VAC VeraFlo system. (n = 48) ☑ C: NPWT with VAC Granufoam dressings. (n = 34) ☑	LoS (NPWTi and NPWT) ☑ Number of OR visits (surgical debridements) (NPWTi and NPWT) ☑ Used to calculate ratio between LoS and LoT in "mixed wound" population . This was used as scaling factor to estimate LoT	• Correction for multiple testing not applied – but given the huge differences shown this wouldn't have changed anything. • Test for normality for continuous variables not reported. The authors assumed non-normal distribution (of	The population having "mixed infection" was not clearly defined by the company. This study did not clearly define its population. The EAC does not agree data from this study can be used to extrapolate data in the study by (Timmers *et al.*, 2009).

<table>
<tr><td></td><td></td><td></td><td></td><td>in study by (Timmers et al., 2009).
☒</td><td>LoS, LoT, nOR, time to closure) and applied Wilcoxon rank sum test to compare continuous variables (valid approach).</td><td></td></tr>
<tr><td></td><td>(Timmers et al., 2009)

Retrospective observational study.

Netherlands</td><td>Patients with osteomyelitis [or other tissue infection] of the pelvis or lower leg.

<table><tr><th>Diagnosis</th><th>Proportion</th></tr><tr><td>Osteomyelitis</td><td>33/62 (53%)</td></tr><tr><td>Soft tissue infection</td><td>13/62 (21%)</td></tr><tr><td>Trauma wound</td><td>12/62 (19%)</td></tr><tr><td>Necrotising fasciitis</td><td>3/62 (5%)</td></tr><tr><td>Pilonoidal sinus</td><td>1/62 (2%)</td></tr></table>
n = 156

☒</td><td>I: NPWTi with VAC Insillation therapy. Antispetic instillation fluid (“Lavasept”). Initial debridement.
(n = 59)
☒

C: Standard care, consisting of “surgical debridement, repeated as often as felt necessary by attending physicians, systemic administration of antibiotics with confirmed activity against the aetiologic microbial agent and implantation of gentamicin beads at the site of osteomyelitis”</td><td>LoS multiplied by scaling factor derived from (Gabriel et al., 2014).
☑

LoS (NPWTi and AWC)
☑

Surgical deridements (NPWTi and AWC)
☑</td><td>Correction for multiple testing not applied.
Test for normality for continuous variables not reported.
Incorrect test for comparing number of hospital admissions, LoS *</td><td>This study was excluded by the EAC in the clinical report on the basis the intervention were not in scope.

The population of this study was in patients with osteomyelitis or related soft tissue infections. The EAC considered this was a specific population and did not represent the description of “mixed wounds”.</td></tr>
</table>

			☒ (n = 94)			
Prosthetic implants	(Deleyto *et al.*, 2018) Retrospective observational study Spain	Patients with abdominal wall wound dehiscence with mesh exposure. No patient characteristics data reported. n = 45 ?	I: NPWTi with VAC VeraFlo (n = 11) ☑ C: Conventional dressings (n = 34) ☑	LoS (NPWTi and AWC)) ☑ Surgical debridements (NPWTi and AWC) ☑ Additional mesh surgeries (NPWTi and AWC) ☒	• Correction for multiple testing not applied. • Test for normality for continuous variables not reported – the authors just assumed non-normal distribution and tested using Mann-Whitney to compare these continuous variables (valid approach).	This was a small study (11 patients in NPWTi group) specific to patients with surgical dehiscence following abdominal mesh failure. Patient characteristics were not reported. NPWT was not included in this scenario. Additional parameters are challenged by the EAC.
Surgical site infections	(Jurkovic *et al.*, 2019) Retrospective observational study Slovenia	People with infected laparotomies exhibiting fasciitis. Detailed patient characteristics unknown. n = 41 ?	I: NPWTi with VAC Instill (n = 19) ☒ C: NPWT (technology unknown) (n = 22) ☑	LoS (NPWTi and NPWT) ☒ LoT (NPWTi and NPWT) ☑ Number of surgical debridements (NPWTi and NPWT) ☑	• Published in a foreign language and difficult to interpret. • Results appear to have non-significant p value.	This study was excluded from the clinical assessment because it was published in a foreign language, and the intervention was deemed out of scope. Data from this study has not been verified as it was published in a foreign language.

	(Chowdhry and Wilhelmi, 2019) Retrospective observational study United States	People with infected sternal wounds following reconstructive surgery Wound characteristics not reported n = 30 ☑	I: NPWTi with VAC VeraFlo (n = 15) ☑ C: wet-to-moist wrappings (n = 15) ☑	LoS (NPWTi and AWC) ☑ LoT (NPWTi and AWC) ☑ Number of surgical debridements (NPWTi and AWC) ☑	• Correction for multiple testing not applied. • Test for normality for continuous variables not explicitly reported (but used Wilcoxon rank sum meaning that they did treat parametric and non-parametric variables differently).	The population enrolled in this study was highly specific and unlikely to be generalisable to other forms of surgical infection. Insufficient information was provided on wound characteristics, patient selection, and outcome measurement.

Abbreviations: ANOVA, analysis of variance; AWC, advanced wound care (not specified further, understood to mainly include use of dressings); C, comparator; I, intervention; LoS, length of [hospital] stay; Lot, length of therapy; NPWTi, negative pressure wound therapy; NPWTi, negative pressure wound therapy with instillation.

Key: ☑ aspect of study in scope; ☑☒ aspect of study partially in scope, or elements of this are not in scope; ☒ aspect of study not in scope; ? unknown.

* The authors appear to have used parametric tests, such as ANOVA and Student's t-test) on variables which are highly unlikely to follow normal distribution (e.g.LoS).

Table C3a: *Point estimates of cost differences between NPWTi and NPWT using data from different studies.*

Study	Population	NPWTi			NPWT		
		nOR	LoT	LoS	nOR	LoT	LoS
(Kim *et al.*, 2020)	Patients with Open wound > 4 cm in any plane of measurement excluding tunnels after initial surgical debridement. Acute and chronic wounds. Wound appropriate for NPWT use. (n = 181)	1.1	6.8	6.8*	1.0	6.3	6.3*
(Kim *et al.*, 2014)	Patients with infected wounds requiring admission with for operative debridement. Suitable for NPWT or NPWTi. (n = 142)	2.4	11.9*	11.9	3.0	14.92*	14.92
(Gabriel *et al.*, 2014)	Patients with "an infected or critically colonized wound".	2	4.1	8.1	4.4	20.9	27.4
(Jurkovic *et al.*, 2019)	People with infected laparotomies exhibiting fasciitis. (n = 82)	2	21*	21	3.0	23*	23
(Omar *et al.*, 2016)	Patients with acute wounds of the lower limb. (n = 20)	3.0 [median]	9.0 [median]	21.5 [median]	3.0 [median]	12.5 [median]	26.5 [median]

Abbreviations: LoS, length of stay; LoT, length of treatment; nOR, number of debridements; NPWT, negative pressure wound therapy; NPWTi, negative pressure wound therapy with instillation.

* No data was available. LoS assumed to be the same as LoT *or vice versa*.

Table C3b: Point estimates of cost differences between NPWTi and AWC using data from different studies.

Study	Population	NPWTi			NPWT		
		nOR	LoT	LoS	nOR	LoT	LoS
(Gabriel *et al.*, 2008)*	Patients with complex, open, infected wounds. (n = 15)	Not reported	9.87	14.67	Not reported	34.47	39.2
(Timmers *et al.*, 2009)*	Patients with osteomyelitis [or other tissue infection] of the pelvis or lower leg. (n = 156)	2.3	36*	36	2.4	73*	73
(Deleyto *et al.*, 2018)	Patients with abdominal wall wound dehiscence with mesh exposure. (n = 45)	0.45	69.09**	69.09	2.15	88.21**	88.21
(Chowdhry and Wilhelmi, 2019)	Patients with infected sternal wounds following reconstructive surgery. (n = 30)	1.8	5.4**	5.4	3.1	8.4**	8.4

Abbreviations: AWC, advanced wound care; LoS, length of stay; LoT, length of treatment; nOR, number of debridements; NPWTi, negative pressure wound therapy with instillation.
* Study not included in EAC clinical assessment.
** LoS assumed to be the same as LoT. Note that in Deleyto *et al.* (2018) LoT was reported in the NPWTi cohort only.

Table C4. *Summary of EAC's modifications to the model (see also Table C3a and C3b).*

Issue	Change	Justification
Aggregation of different subgroups to create a whole population	Removed	Results will be reported for each indication separately.
V.A.C. VERAFLO dressing cost (£77.76)*	Average dressing cost increased to £84.61	Using latest costs on NHS Supply Chain (April 2020): [redacted]
VAC VERALINK Cassette cost (£21.52)*	Decreased to £19.37	Using latest costs on NHS Supply Chain (April 2020): [redacted]
VAC VERALINK Canister cost (£47.23)*	Decreased to 34.06	Using latest costs on NHS Supply Chain (April 2020): average cost of [redacted] and (500ml and 1000ml canisters advised by company)
Additional procedural costs included for Prosthetic Implant subgroup only (Simple wound closure, Debridement and closure, Mesh removal, Mesh replacement)	Removed	Costs are derived from HRG codes (which are broad and will include a range of other procedures which are irrelevant to the scope). Additional procedure costs not considered for other arms. Minimal impact on debridement costs.
Rounding number of dressings to nearest whole number (modelled as "wastage")	Removed	Rounding to nearest whole number not applied consistently in model by company (was applied to dressings but not length of stay). Mean number of dressings and mean length of stay (not rounded) applied.
Median no. of OR visits/debridement (2.0) in Mixed wound population – NPWTi arm (Timmers 2009)	Changed to mean value, 2.3	Mean value used for other subgroups, changed for consistency.
Median no. of OR visits/debridement (5.0) in Mixed wound population – AWC arm (Timmers 2009)	Changed to mean value, 2.4	Mean value used for other subgroups, changed for consistency.
Mean no. of surgeries (0.8, SD 0.7) in Prosthetic implants – NPWTi arm (Deleyto 2018)	Changed to 0.82 (SD 0.75)	Using significant figures reported in the study.
Standard deviation for no. of operations, and length of stay in Mixed wound –	Calculation of standard deviation removed and	Standard deviation calculated incorrectly.

NPWTi and AWC arms (Timmers 2009)	assumed standard error to be 20% of the mean.	
Standard deviation for length of stay (33.56) in Prosthetic implants - AWC arm (Deleyto 2018)	Changed to 77.05	In line with value reported in study (will only impact PSA).
Calculated values of length of therapy inferred from other studies/other arm	Any study which did not explicitly report length of therapy in both arms, will assume length of therapy matches length of stay.	Broad assumption but applied equally to all scenario/subgroups.
Calculated values of number of surgeries/debridement inferred from other studies/other arm	Any study which did not explicitly report number of surgeries/debridement in both arms, did not incur any debridement costs.	Debridement costs are minimal, low impact on total costs.
RCT Kim 2020 not included in economic submission	Mixed population described in Kim 2020 RCT used as the base-case.	This study represents the only randomised comparative data. Due to missing length of stay data, the author has been contacted, but until that time length of stay will be assumed to match reported length of therapy in each arm.

Abbreviations: AWC, advanced wound care dressings; NPWT, negative pressure wound therapy; NPWTi, negative pressure wound therapy with instillation.

* Daily cost 3/7th of these totals (consumables changed 3 times per week).

NOTE: this table has been updated as an erratum, with changes made to the costs of VERAFLO technologies to reflect those actually used in the model.

Table C5a: *Comparison of point-estimates of cost saving when compared to the company base-case (NPWTi vs. NPWT).*

	Company base-case			EAC base-case			
Subgroup	NPWTi	NPWT	Difference	NPWTi	NPWT	Difference	Δ (EAC-Company), £
Kim 2020*	N/A	N/A	N/A	£3342	£2862	£479	N/A
Kim 2014 (lower limb)	£6427	£7657	-£1230	£6717	£7722	-£1005	**£225**
Gabriel 2014 (mixed wound)	£3890	£12,113	-£8223	£3873	£12113	-£8240	**-£17**
Jurkovic 2019 (surgical site infection)	£11,179	£11,479	-£300	£11,103	£11,479	-£376	**-£76**
Omar 2016	N/A	N/A	N/A	£10,673	£12,632	-£1960	N/A
Abbreviations: N/A, not applicable; NPWTi, negative pressure wound therapy with instillation; NPWT, negative pressure wound therapy.							

Table C5b: *Comparison of point-estimates of cost saving when compared to the company base-case (NPWTi vs. AWC).*

	Company base-case			EAC base-case			
Subgroup	NPWTi	AWC	Difference	NPWTi	AWC	Difference	Δ (EAC-Company), £
Gabriel 2008 (lower limb)	£7915	£18,934	-£11,018	£7173	£17,068	-£9895	**£1,123**
Timmers 2009 (mixed wound)	£15,478	£28,880	-£13,403	£16,857	£28,347	-£11,490	**£1,913**
Deleyto 2018 (prosthetic implants)	£29,234	£36,957	-£7723	£32,424	£35,474	-£3050	**£4,673**
Chowdry 2019 (surgical site infection)	£3289	£4394	-£1105	£3263	£4394	-£1130	**-£25**
Abbreviations: AWC, advanced wound care; NPWTi, negative pressure wound therapy with instillation.							

Appendix D – Economic literature search

The company's economics submission search strategy is as follows:

("Lavage" OR "instil" OR "instillation" OR "irrigated" OR "irrigation" OR "topical solution" OR "topical

wound solution" OR "topic solution" OR "VERAFLO" OR "VERAFLOW" OR "Veraflo dressing" OR

"Veraflo cleanse dressing" OR "Veraflo cleanse choice dressing" OR "Ulta")

AND

("Negative Pressure Wound Therapy" OR "NPWT" OR "vacuum assisted closure" OR "vacuum sealing" OR "NPWTi" OR "NPWTi-d" or "economic")

This is the same as the search conducted for the initial submission, with the addition of "economic" Or-ed into the second search concept.

This will retrieve articles that include any of the first concept terms e.g. lavage or instillation AND economic, but not necessarily any of the other terms from the second search concept. This will retrieve many unnecessary results.

As the same databases (PubMed, EMBASE AND QUOSA) were used in the company's strategy, it would be appropriate to identify any relevant articles during screening of the searches run for the initial submission. To ensure all relevant articles have been retrieved during this process, the searches were re-run with the addition of a validated filter such as those found at https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#eco, https://www.crd.york.ac.uk/CRDWeb/ or https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/filters-to-find-i to specifically identify relevant papers.

As the previous searches were run from 2011 onwards it would be appropriate to use specialised databases including NHSEED, DARE and HTA which were updated up to and including 2014 and are available via the CRD website https://www.crd.york.ac.uk/CRDWeb/ The IDEAS database https://ideas.repec.org/ indexes RePEc (**Re**search **P**apers in **Ec**onomics) and includes publications up to the present date.

Unpublished data from ClinicalTrials.gov should be identified in the initial search so no additional search would be necessary. Additional resources could include the ISRCTN registry (https://www.isrctn.com/), the WHO ICTRP

(https://www.who.int/ictrp/en/) or the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search). The WHO ICTRP is currently unavailable due to high demand related to the COVID-19 pandemic, so this will not be searched at this stage.

Additional economics searches:

Additional searches were conducted in the databases identified above, the strategies used and results obtained are shown below. The results were exported to an EndNote database, and following checking for duplicate entries, was sent to the EAC staff.

NHS EED/DARE/HTA via the CRD website (searched 23 April 2020)

1	MeSH DESCRIPTOR Therapeutic Irrigation EXPLODE ALL TREES
2	(lavage)
3	MeSH DESCRIPTOR Instillation, Drug EXPLODE ALL TREES
4	(instillation)
5	(irrigation)
6	MeSH DESCRIPTOR Administration, Topical EXPLODE ALL TREES
7	(topic* ADJ2 solution*)
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(veraflo*)
10	(ulta*)
11	#9 OR #10
12	MeSH DESCRIPTOR Negative-Pressure Wound Therapy EXPLODE ALL TREES
13	(negative pressure wound therapy)
14	(NPWT*)
15	(vacuum assisted closure)
16	(vacuum sealing)
17	#12 OR #13 OR #14 OR #15 OR #16
18	#8 AND #17
19	#11 OR #18

When results were restricted to publications from 2011 onwards 2 records remained.

IDEAS/RePEc (searched 23 April 2020)

The search conducted was:

"negative pressure wound therapy" | NPWT | veraflo | VAC | ulta | "vacuum assisted closure" | "vacuum sealing" in the title only

Where | = OR

Restricting to title only removed many irrelevant hits, one article about Ulta beauty company was excluded before sending to the EAC.

Databases

The initial database searches were re-run on 28 April 2020 with the **"broad economics filter"** from CADTH applied, which is available at https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#eco

The number of articles retrieved from these searches are shown below:

Database	**Number of results**
NHS EED/DARE/HTA (CRD website)	2
IDEAS/RePEc	2
MEDLINE Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 27, 2020.	15
Embase: OvidSP 1996 to present	28
CINAHL: EBSCOhost Web 1981 to present	22
Cochrane Library, Wiley 1996 to present	8 (trials only, no reviews)
Total number retrieved	**77**
Total following deduplication	**59**

The same date (2011 onwards) and language restrictions (English language only) were applied as the original search.

A.1: Source: MEDLINE Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 27, 2020.

Interface/URL: OvidSP
Database coverage dates: 1946 to present
Search date: 28/04/20
Retrieved records: 15
Search strategy:

1 Therapeutic Irrigation/

2 lavage.ti,ab,kw,kf.

3 Instillation, Drug/

4 instillation.ti,ab,kw,kf.

5 irrigation.ti,ab,kw,kf.

6 Administration, Topical/

7 (topic* adj2 solution*).ti,ab,kw,kf.

8 or/1-7

9 veraflo*.ti,ab,kw,kf.

10 ulta*2.ti,ab,kw,kf.

11 9 or 10

12 Negative-Pressure Wound Therapy/

13 "negative pressure wound therapy".ti,ab,kw,kf.

14 NPWT*.ti,ab,kw,kf.

15 "vacuum assisted closure".ti,ab,kw,kf.

16 "vacuum sealing".ti,ab,kw,kf.

17 or/12-16

18 8 and 17

19 11 or 18

20 limit 19 to (english language and yr="2011 -Current")

21 Economics/

22 exp "Costs and Cost Analysis"/

23 Economics, Nursing/

24 Economics, Medical/

25 Economics, Pharmaceutical/

26 exp Economics, Hospital/

27 Economics, Dental/

28 exp "Fees and Charges"/

29 exp Budgets/

30 budget*.ti,ab,kf.

31 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.

32 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2

33 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.

34 (value adj2 (money or monetary)).ti,ab,kf.

35 exp models, economic/

36 economic model*.ab,kf.

37 markov chains/

38 markov.ti,ab,kf.

39 monte carlo method/

40 monte carlo.ti,ab,kf.

41 exp Decision Theory/

42 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf.

43 or/21-42

44 20 and 43

A.2: Source: Ovid Embase 1974 to 2020 April 27.

Interface/URL: OvidSP
Database coverage dates: 1974 to present
Search date: 28/04/20
Retrieved records: 28
Search strategy:

1 lavage/

2 lavage.ti,ab,kw.

3 drug instillation/

4 instillation.ti,ab,kw.

5 irrigation.ti,ab,kw.

6 topical drug administration/

7 (topic* adj2 solution*).ti,ab,kw.

8 or/1-7

9 veraflo*.ti,ab,kw.

10 ulta*2.ti,ab,kw.

11 9 or 10

12 vacuum assisted closure/

13 "negative pressure wound therapy".ti,ab,kw.

14 NPWT*.ti,ab,kw.

15 "vacuum assisted closure".ti,ab,kw.

16 "vacuum sealing".ti,ab,kw.

17 or/12-16

18 8 and 17

19 11 or 18

20 limit 19 to (english language and yr="2011 -Current")

21 Economics/

22 Cost/

23 exp Health Economics/

24 Budget/

25 budget*.ti,ab,kw.

26 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw.

27 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2

28 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw.

29 (value adj2 (money or monetary)).ti,ab,kw.

30 Statistical Model/

31 economic model*.ab,kw.

32 Probability/

33 markov.ti,ab,kw.

34 monte carlo method/

35 monte carlo.ti,ab,kw.

36 Decision Theory/

37 Decision Tree/

38 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw.

39 or/21-38

40 20 and 39

A.3: Source: CINAHL®

Interface/URL: EBSCOhost Web
Database coverage dates: 1981 to present
Search date: 28/04/20

Retrieved records: 22
Search strategy:

S43 S20 AND S42

S42 S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41

S41 TX (decision* N2 (tree* or analy* or model*))

S40 MH "decision theory+"

S39 TX monte carlo

S38 MH "monte carlo method"

S37 TX markov

S36 MH "markov chains"

S35 AB economic model*

S34 MH "models, economic+"

S33 TX (value N2 (money or monetary))

S32 AB (cost* N2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes))

S31 AB (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)

S30 TX (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)

S29 TX budget*

S28 (MH "Budgets")

S27 (MH "Fees and Charges+")

S26 MH "economics, medical"

S25 MH "economics, hospital+"

S24 MH "economics, nursing"

S23 (MH "Economics, Dental") OR (MH "Economics, Pharmaceutical")

S22 (MH "Costs and Cost Analysis+")

S21 (MH "Economics")

S20 S16 OR S18 Limiters - Published Date: 20110101-20201231

Narrow by Language: - english

S19 S16 OR S18

S18 S8 AND S17

S17 S11 OR S12 OR S13 OR S14 OR S15

S16 S9 OR S10

S15 TI "vacuum sealing" or AB "vacuum sealing"

S14 TI "vacuum assisted closure" or AB "vacuum assisted closure"

S13 TI NPWT* or AB NPWT*

S12 TI "Negative Pressure Wound Therapy" or AB "Negative Pressure Wound Therapy"

S11 (MH "Negative Pressure Wound Therapy")

S10 TI ulta* or AB ulta*

S9 TI veraflo* or AB veraflo*

S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7

S7 TI (topic* N2 solution*) or AB (topic* N2 solution*)

S6 (MH "Administration, Topical")

S5 TI irrigation or AB irrigation

S4 TI instillation or AB instillation

S3 (MH "Instillation, Drug")

S2 TI lavage or AB lavage

S1 (MH "Therapeutic Irrigation")

A.4: Source: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)

Interface/URL: Cochrane Library, Wiley
Database coverage dates: 1996 to present
Search date: 28/04/20
Retrieved records:
CDSR: 0
CENTRAL: 8
Search strategy:

#1 MeSH descriptor: [Therapeutic Irrigation] this term only

#2 (lavage):ti,ab,kw

#3 MeSH descriptor: [Instillation, Drug] this term only

#4 (instillation):ti,ab,kw

#5 (irrigation):ti,ab,kw

#6 MeSH descriptor: [Administration, Topical] this term only

#7 ((topic* near/2 solution*)):ti,ab,kw

#8 (Mahmoudiasl *et al.*-#7)

#9 (veraflo*):ti,ab,kw

#10 (ulta*):ti,ab,kw

#11 MeSH descriptor: [Negative-Pressure Wound Therapy] this term only

#12 ("negative pressure wound therapy"):ti,ab,kw

#13 (NPWT*):ti,ab,kw

#14 ("vacuum assisted closure"):ti,ab,kw

#15 ("vacuum sealing"):ti,ab,kw

#16 (Mahmoudiasl *et al.*-#15)

#17 #8 and #16

#18 #17 or #9 or #10

#19 MeSH descriptor: [Economics] this term only

#20 MeSH descriptor: [Costs and Cost Analysis] explode all trees

#21 MeSH descriptor: [Economics, Nursing] this term only

#22 MeSH descriptor: [Economics, Medical] this term only

#23 MeSH descriptor: [Economics, Pharmaceutical] this term only

#24 MeSH descriptor: [Economics, Hospital] explode all trees

#25 MeSH descriptor: [Economics, Dental] this term only

#26 MeSH descriptor: [Fees and Charges] explode all trees

#27 MeSH descriptor: [Budgets] explode all trees

#28 (budget*):ti,ab,kw

#29 ((economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)):ti,ab,kw

#30 ((cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes))):ab

#31 (value NEAR/2 (money or monetary))

#32 MeSH descriptor: [Models, Economic] explode all trees

#33 (economic model*):ab

#34 MeSH descriptor: [Markov Chains] this term only

#35 ("Markov"):ti,ab,kw

#36 MeSH descriptor: [Monte Carlo Method] this term only

#37 ("monte carlo"):ti,ab,kw

#38 MeSH descriptor: [Decision Theory] explode all trees

#39 ((decision* NEAR/2 (tree* or analy* or model*))):ti,ab,kw

#40 {OR #19-#39}

#41 #18 and #40

National Institute for Health and Care Excellence

Medical technologies evaluation programme

MT471 The VAC Veraflo Therapy system for acute infected or chronic wounds that are failing to heal

Consultation comments table

Final guidance MTAC date: 13 November 2020

There were 57 consultation comments from 6 consultees / groups:

- 9 comments from an NHS healthcare professional
- 5 comments from a US healthcare professional
- 27 comments from the company
- 7 comments from a healthcare analytics company
- 5 comments from a professional organisation
- 4 comments from the external assessment centre (EAC)

The comments are reproduced in full, arranged in the following themes:

- Recommendations (comments 1 to 5)
- Technology costs (comment 6)
- Wording and factual inaccuracies (comments 7 to 12)
- Clinical evidence (comments 13 to 25): pilot RCT (comments 13 to 19), heterogeneity (comments 20 to 23), bacterial bioburden (comments 24 and 25)
- Recent and ongoing studies (comments 26 to 28)
- Economic modelling (comments 29 to 45): inaccuracies in the EAC model (comments 39 to 34), base case and results (comments 35 to 41), length of therapy versus length of stay (comments 42 to 51)
- Committee discussion (comments 52 and 53)
- Equality (comment 54)
- MTEP process (comments 55 to 57)

#	Consultee ID	Role	Section	Comments	NICE response
Recommendations (n = 5)					
1	2	Company	1	Section 1 of the draft guidance states “The best available evidence does not show any clinical benefit over standard negative pressure wound therapy”. Notwithstanding the pilot status of this publication (Kim 2020), whilst the primary endpoints were not statistically significant, there were two clinical benefits listed in the abstract of the study that are relevant to the decision problem: • Results showed a significantly greater mean decrease in total bacterial counts • NPWT subjects had 3.1 times the risk of re-hospitalisation compared with NPWT plus instillation subjects	Thank you for your comment. The external assessment centre noted that although Kim et al. (2020) reported a significant reduction in total bacterial counts with VAC Veraflo compared with negative pressure wound therapy (NPWT), the clinical significance of this was unknown. This has been described in section 3.6 of the guidance. The external assessment centre advised the committee that the evidence for a reduced the risk of re-hospitalisation (risk ratio of re-hospitalisation with NPWT to VAC Veraflo 3.129; 95% CI 0.883 to 11.083) was based on small numbers (3 people in the VAC Veraflo arm compared with 9 in the NPWT arm). They also noted that the p value (0.074) did not reach the level of significance used elsewhere in the study (0.05) and that the data was from post hoc analysis with no correction for multiple testing. The external assessment centre advised the committee that because of this, it was difficult to conclude with confidence that VAC Veraflo reduced the risk of hospitalisation. The committee did not make any changes to the guidance.

2	2	Company	1	The EAC have made a statement under Section 1.2 which states the following “The clinical evidence for VAC Veraflo is mostly low quality. The best available evidence does not show any clinical benefit over standard negative pressure wound therapy. Also, that evidence is from the US, and does not reflect the way VAC Veraflo is used in the NHS.” This is clearly the view of the EAC and so should be stated that is based on their best evidence and not a general opinion.	Thank you for your comment. This section of the guidance provides the rationale behind the recommendations made by the committee. It describes the committee’s conclusions only, based on committee discussion at the draft guidance meeting. The committee did not make any changes to the guidance.
3	5	Professional organisation	1	Having reviewed the evidence and discussion, agree with these recommendations.	Thank you for your comment.
4	3	US healthcare professional	1	Of course, there is a need for more data, which is the case for every device, biologic, or drug. However, reliance on RCTs to make a determination as to the effectiveness/efficacy of any therapy is not prudent. RCTs are also inherently flawed with selection bias of populations and wound types through the use of rigid eligibility criteria with poor external validity. It is important to assess the whole body of knowledge which I believe currently exists. It is unfortunate that NICE has come to their conclusions. My hope is that NICE will reconsider its conclusions. I have observed significant impact on wounds and utilize this therapy as the standard of care. Thank you	Thank you for your comment. The committee heard from clinical experts and the company about the plausibility in designing and conducting randomised controlled trials (RCTs) for VAC Veraflo in the NHS. The committee heard that, although there are several challenges in delivering RCTs for wound care therapies, there is an opportunity for a well-funded, large-scale national trial assessing the clinical impact of VAC Veraflo therapy in various sub-populations. The difficulties in running high-quality trials in wound care have been described in section 4.13 of the guidance. The committee did not make any changes to the guidance.
5	5	Professional organisation	1	This implies that there is robust evidence for standard negative pressure therapy compared to other types of dressing for promoting healing. My understanding is that this is not the case. The evidence cited in this document suggests that there is no evidence to suggest that VAC Veraflo is more effective than other types of dressings for managing wounds?	Thank you for your comment. This section of the guidance is intended to provide a rationale behind the recommendations made by the committee. To improve clarity, the committee have

					made changes to the wording of this section to refer to the comparator as 'negative pressure wound therapy without instillation'.
Technology cost (n = 1)					
6	1	External assessment centre (EAC)	2.5	This is the correct cost of the Veralink 1000ml canister. However, the EAC used the average cost of 500ml and 1000ml canisters in the model (£34.06). See EAC erratum.	Thank you for your comment. Section 2.5 of the guidance document has been amended to describe the average cost of 500 ml and 1000 ml cannisters (£34.06) used by the external assessment centre in their economic modelling.
Wording and factual inaccuracies (n = 6)					
7	5	Professional organisation	1	This wording implies that 'dressings' are the key therapeutic intervention to promote healing (which is probably not what is intended'. It would be better to add some wording... "Chronic non-healing wounds usually need more advanced dressings to manage wound symptoms and potentially improve healing"	Thank you for your comment. This section is intended to provide a summary of the technology and the rationale for the recommendations. The committee considered the current wording provided sufficient information and did not believe further clarification was necessary. The committee did not make any changes to the guidance.
8	2	Company	1	14.The draft guidance makes reference to the technology pump sucking the excess fluid from the wound. This is not a true reflection on how the technology works and should be reviewed inline with the manufacturer to clarify this position.	Thank you for your comment. This section of the guidance is intended to provide a rationale behind the recommendations made by the committee. The committee made changes to the wording to better reflect how VAC Veraflo and negative pressure wound therapy without instillation work.

9	1	External assessment centre (EAC)	3.3	For clarity, the main issue the EAC had with these studies wasn't methodological quality, it was relevance. Kim (2015) did not make a relevant comparison, whilst Yang (2017) only reported on one surrogate outcome which had unclear clinical interpretation.	Thank you for your comment. Section 3.3 of the guidance has been amended to state that the EAC considered the other randomised controlled trials by Yang et al. (2017) and Kim et al. (2015) to be of limited relevance.
10	2	Company	3.2	Under Section 3.2 it states that "19 clinical studies included". This should state that there were included by EAC, as it is a know fact that they were not included by the company.	Thank you for your comment. Section 3.2 of the guidance has been amended to make it clear that the 19 studies were included by the external assessment centre.
11	2	Company	4.10	In paragraph 4.10 the draft guidance states "One of the randomised controlled trials reported no statistically significant difference in outcomes for normal saline compared with Prontosan (Kim et al. 2015)". This statement is factually incorrect. There was a statistically significant difference in time to final surgical procedure (5.7 vs 7.7 days, p=0.038).	Thank you for your comment. Section 4.10 has since been removed from the draft guidance because it did not substantially influence the committee recommendations for the technology. The comparison of normal saline and Prontosan was not relevant to the decision problem. Section 2.1 has been amended to state that saline is the most commonly used instillation solution.
12	2	Company	3.14	In paragraph 3.14 it is factually incorrect to state that the company omitted to include Kim 2020 in the model. At the point when the company made its submission to NICE, Kim 2020 was unpublished, it was however fully referenced in the evidence submission. This statement should be amended in the final guidance as it is 3M's belief that it infers the company was attempting to mislead the committee.	Thank you for your comment. The wording of section 3.14 of the guidance has been amended to remove the term 'omitted'.
Clinical evidence – pilot RCT (n = 7)					
13	2	Company	3.3	We remain uncertain as to why it has not been made clear in the draft guidance that Kim 2020 was a feasibility pilot study designed to identify the numbers of patients that would be needed to power a future RCT. We note that there is	Thank you for your comment. The external assessment centre advised the committee that Kim et al. (2020) was a

				precedence for highlighting the pilot nature of such a study. A clear example of this can be seen in MT496 (Totty et al. & Stanirowski et al.). At present Kim 2020 is referred to 32 times as a Level 1 RCT. This is a misrepresentation and is actually incorrect. We feel the EAC has failed to take into account, and appropriately apply, the fact that within a pilot study statistical significance holds less power than within a full RCT.	prospective randomised study relevant to the decision problem and therefore the most robust evidence in terms of methodological quality. It was consistently described by the external assessment centre as an "RCT", not a "Level 1 RCT". The EAC also noted that the term pilot study infers the study was exploratory in nature (hypothesis generating) and that a larger study would be planned on the basis of its results. The EAC highlighted that Kim et al. (2020) had a clearly defined primary outcome with power calculations, meaning it was hypothesis testing. The EAC could find no further planned follow-up studies. The EAC also noted that until November 2016, the word "pilot" did not feature in its trial registry title (NCT01867580). The term appeared in the next iteration of the study in October 2017, which coincides with the publication of results. The study was fully described by the external assessment centre in their assessment report, and all strengths and limitations were appraised using appropriate methods. Kim et al. (2020) has also been described in section 3.3, 3.6, 4.1 and 4.4 of the guidance. The committee did not make any changes to the guidance.
14	2	Company	3.3	It is shown by several publications that a pilot RCT should be treated with caution. As recently published in the BMJ, they stated when reviewing NIHR HTA studies that "Pilot and feasibility studies serve an important role when determining the most appropriate trial design. However, how they are reported and in what context requires caution when interpreting the findings and delivering a definitive trial." We feel that this has not been applied in the case of VAC Veraflo. Link https://bmjopen.bmj.com/content/8/9/e022233	Thank you for your comment. Kim et al. (2020) was a prospective randomised study relevant to the decision problem and the most robust evidence in terms of methodological quality. The study was fully described by the external assessment centre in their assessment report, and all strengths and limitations

					were appraised using appropriate methods. Kim et al. (2020) has also been described in section 3.3, 3.6, 4.1 and 4.4 of the guidance The committee did not make any changes to the guidance. Please see NICE response to comment 13.
15	4	Healthcare analytics company	3.3	KIM 2020 appears to be a Pilot RCT which has been designed to look at the solution used and not a primary endpoint of LOS or LOT. But to report on the number of debridements performed on the lower limb patients. Could you help us understand why the pilot was not referenced to the committee members.	Thank you for your comment. Kim et al. (2020) was a prospective randomised study relevant to the decision problem and the most robust evidence in terms of methodological quality. The EAC also highlighted that Kim et al. (2020) had a clearly defined primary outcome with power calculations, meaning it was hypothesis testing. The study was fully described by the external assessment centre in their assessment report, and all strengths and limitations were appraised using appropriate methods. Kim et al. (2020) has also been described in section 3.3, 3.6, 4.1 and 4.4 of the guidance. The committee did not make any changes to the guidance. Please see NICE response to comment 13.
16	6	NHS healthcare professional	3	It would appear that the Study by KIM 2020 is a pilot study and potentially is under powered for the use in which the NICE has used it for. This is further supported by the following article which shows the limitations of a pilot study https://www.jospt.org/doi/10.2519/jospt.2014.0110	Thank you for your comment. Kim et al. (2020) was a prospective randomised study relevant to the decision problem and the most robust evidence in terms of methodological quality. The EAC also highlighted that Kim et al. (2020) had a clearly defined primary outcome with power calculations, meaning it was hypothesis testing. The study was fully described by

					the external assessment centre in their assessment report, and all strengths and limitations were appraised using appropriate methods. Kim et al. (2020) has also been described in section 3.3, 3.6, 4.1 and 4.4 of the guidance. The committee did not make any changes to the guidance. Please see NICE response to comment 13.
17	2	Company	3.3	3M has significant concerns that Kim 2020 was not designed to collect the outcomes the EAC have drawn upon and used as the most significant driver in their economic model. As such the company believes this is an unreasonable interpretation of the evidence.	Thank you for your comment. Kim et al. (2020) was a prospective randomised study relevant to the decision problem and the most robust evidence in terms of methodological quality. The EAC also highlighted that Kim et al. (2020) had a clearly defined primary outcome with power calculations, meaning it was hypothesis testing. The study was fully described by the external assessment centre in their assessment report, and all strengths and limitations were appraised using appropriate methods. Kim et al. (2020) has also been described in section 3.3, 3.6, 4.1 and 4.4 of the guidance. The committee did not make any changes to the guidance. Please see NICE response to comment 13.
18	2	Company	3.3	We believe that the EAC's reliance upon Kim 2020, when Prontosan was used as the instillation fluid for all patients included in the 2020 pilot, has potentially distorted the outcomes in relation to the NHS. This is because it is not reflective of standard care in the UK.	Thank you for your comment. Kim et al. (2020) was a prospective randomised study relevant to the decision problem and was deemed the most robust evidence in terms of methodological quality. The intervention in the scope was VAC Veraflo therapy using an approved

					instillation fluid, which included both Prontosan and saline. Advice from clinical experts was that Prontosan had initially been used as a VAC Veraflo instillation fluid but that normal saline is now regarded as the preferred instillation fluid. The committee did not make any changes to the guidance.
19	6	NHS healthcare professional	3	It is a surprise to see that a study which uses Prontosan has been replied upon by the EAC. As it is my experience that it is not used as standard of care in the NHS.	Thank you for your comment. Please see NICE response to comment 19.
Clinical evidence – heterogeneity (n = 4)					
20	2	Company	3	It was clear the EAC and NICE referenced a very important point that we would like to highlight. That “the heterogeneous nature of the study populations, combined with the relatively small patient numbers for each wound type made interpretation of results in specific patient groups difficult.” This fact won`t change in future, due to the impossibility to include sufficient numbers of totally comparable wounds in terms of aetiology, duration, history, comorbidities. This was further reinforced by the clinical experts. As a result for the EAC to try and find such a study is limited in its value due to this issue.	Thank you for your comment. The committee heard from clinical experts and the company about the plausibility in designing and conducting randomised controlled trials (RCTs) for VAC Veraflo in the NHS. The committee heard that, although there are several challenges in delivering RCTs for wound care therapies, there is an opportunity for a well-funded, large-scale national trial assessing the clinical impact of VAC Veraflo therapy in various sub-populations. The difficulties in running high-quality trials in wound care have been described in section 4.13 of the guidance. Section 4.3 of the guidance describes the committee’s considerations around heterogeneity in the evidence base. The committee considered this comment carefully but decided not to change the guidance.

21	4	Healthcare analytics company	3	From reviewing the NICE and EAC documents it is very clear that the comment of the fact the heterogeneous nature is an issue. However no study would be possible	Thank you for your comment. The committee considered this comment carefully but decided not to change the guidance. Please see NICE's response to comment 20.
22	3	US healthcare professional		As far the heterogeneity of the populations in the studies cited to be problematic; statistically speaking differing demographic does pose an issue. However, there is higher external validity in these mixed cohorts and more accurately reflect the ""real world"". Hospitals see mixed populations in daily practice. I think these studies are more important and relevant due to the heterogeneity of populations/wound represented. As far as the different settings, this is not surprising since ""dosing"" should be dependent on the physician experience and patient needs. This does not decrease the validity for the use of this device. Multiple multi-specialty consensus guidelines have provided ranges and recommendations that provide for safe guidelines for use.	Thank you for your comment. The RCT by Kim et al. (2020) was considered the most robust evidence but did not show any statistically significant clinical benefit for VAC Veraflo compared with negative pressure wound therapy. This study enrolled a mixed cohort of people with acute or chronic wounds of varying causes. Clinical experts advised the committee about the variation in practice because of the heterogeneity in wound types and differences in the goals of treatment, and the challenges this can have on conducting high quality trials. The committee heard from clinical experts and the company about the plausibility in designing and conducting randomised controlled trials (RCTs) for VAC Veraflo in the NHS. The committee agreed that there is an opportunity for a well-funded, large-scale national trial assessing the clinical impact of VAC Veraflo therapy in various sub-populations. The committee considered this comment carefully but decided not to change the guidance.
23	2	Company	3	It appears to be the opinion of the EAC that the studies for VAC Verflo are of a small size in population. However this further supports the nature of the types of wounds VAC Veraflo treat.	Thank you for your comment.
Clinical evidence – bacterial bioburden (n = 2)					

24	1	External assessment centre (EAC)	3.6	The EAC notes that the intervention arm of Kim (2020) used Prontosan, an antiseptic. It would be very much expected for this to reduce bacterial burden.	Thank you for your comment.
25	3	US healthcare professional	3.6	The goal of this device is to convert the wound for the next stage of healing. Unlike other wound care modalities where healing through secondary intention is the goal. Thus the traditional endpoints of complete healing is not applicable. There is broad consensus that bacteria (planktonic and biofilm) is a major factor in wound healing and inhibits the conversion of a wound to a prohealing state. There are no wound experts that would contend that lower bacterial counts is preferred over higher bacterial counts. This device essentially expedites wound bed preparation which no other drug, device, biologic is capable of achieving. There is sufficient evidence to support this devices impact on bacteria.	Thank you for your comment. Clinical experts advised the committee that, although there is a consensus that the presence of bacteria in the wound may impact healing, the published evidence to linked bacterial concentrations in the wound to wound healing to other clinical outcomes is limited in quantity and quality. The clinical experts also advised the committee that bacterial number is not routinely assessed in practice. In addition, the committee heard that the types of bacteria present in the wound may be more clinically important than bacterial number, but that current swabbing and testing methods are not optimal. The committee considered this comment carefully but decided not to change the guidance.
Recent and ongoing studies (n = 4)					
26	2	Company	3	A more recent peer reviewed publication by Kim et al. shows improved outcomes for patients receiving V.A.C Veraflo with saline, in comparison to NPWT alone. We believe this is more reflective of the standard of care in the NHS. It also showed strong statistical significance across a number of key outcomes. https://www.cureus.com/articles/35306-comparison-of-negative-pressure-wound-therapy-with-and-without-instillation-of-saline-in-the-management-of-infected-wounds. 3M feel that in order to be consistent, given that as per Kim 2020 this paper was published during the long delay in the preparation of this draft guidance, it should be shared with the committee as a means of ensuring that all relevant evidence has been taken into account.	Thank you for your comment. The external assessment centre advised the committee that the study did not contain new primary evidence. It was a re-analysis of synthesised data from two studies: a retrospective observational study (Kim et al. 2014) and an RCT comparing Prontosan with saline (Kim et al. 2015). Both studies have been appraised by the external assessment centre in their assessment report; including this new study would mean double counting study participants which is not recommended. The EAC also advised

					the committee that the paper has not published in a recognised journal and has not undergone peer review in the usual way (C*ureus Journal of Medical Scienc*e uses "crowd-sourcing" for peer review). The committee did not make any changes to the guidance.
27	2	Company	3	We would like to bring to NICE's attention, that there are currently a number of RCTs in process in the UK, which may have an impact on the outcome of this Guidance.	Thank you for your comment. Further clinical evidence for the technology published after consultation will be considered by NICE when the guidance is next reviewed. The committee did not make any changes to the guidance.
28	3	US healthcare professional	3	My name is [redacted]. I am a professor in the Departments of Plastic Surgery and Orthopedic Surgery at the University of [redacted] [in the US]. I am also the Medical Director of the Wound Program which encompasses over 900 beds at an academic medical center. I am the author of some of the publications mentioned in this document. I have over 10 years of experience on this device. Although this device may be relatively novel, it is gaining wider acceptance in the acute care setting in the United States. Evidence is slowly growing to support its use including a comprehensive supplement scheduled to be published in the Spring of 2021. This includes a meta-analysis that favors this this therapy over conventional therapies including standard NPWT.	Thank you for your comment. Further clinical evidence for the technology published after consultation will be considered by NICE when the guidance is next reviewed. The committee did not make any changes to the guidance.
Economic modelling – inaccuracies in the EAC model (n = 6)					
29	1	External assessment centre (EAC)	3.14	Regarding technology costs: Due to a translation error by the EAC, not all changes to costs were applied to the revised economic model. These omissions did not significantly affect results or change the direction of results in any instance. The EAC has provided an erratum to	Thank you for your comment. Errors in the assessment report have been corrected by the EAC with an erratum. The EAC erratum is published as part of the supporting material for this guidance.

				highlight where the mistakes occurred (all of which were in Table C4 of the appendix).	Section 2.5 of the guidance document has been amended to describe the average cost of 500 ml and 1000 ml cannisters (£34.06) used by the external assessment centre in their economic modelling. Please also see NICE response to consultation comment 6.
30	2	Company	3.14	It would appear in the EAC modelling that the number of debridements in Timmers 2009 was wrong.	Thank you for your comment. The external assessment centre (EAC) advised the committee that this parameter corresponds to what was published in Timmers et al (2009) (table 3 of the study publication). The values used by the EAC were “mean no. of operations” which were 2.3 (range 1 to 4) in the VAC Veraflo group compared with 2.4 (range 1 to 7) in the negative pressure wound therapy (NPWT) group (p = 0.577). The numbers used in the company submission model were 2 for VAC Veraflo and 5 for NPWT, which were the median values taken from the study. However, the ranges reported in the study for the median were stated as 1 to 4 and 2 to 42 for VAC Veraflo and NPWT, respectively. This was inconsistent to those of the mean, which should not have been possible. Therefore, to minimise the uncertainties identified, the EAC chose to use the mean values for the point estimates used in the model. This was also consistent with the approach taken with the other subgroups. The committee did not make any changes to the guidance.

31	2	Company	3.14	It would appear in the EAC modelling that the wrong LOT in Deleyto 2018 was used. This may be due to the limited time to review the model.	Thank you for your comment. The external assessment centre (EAC) noted that, in the absence of data for length of therapy for advanced wound care dressings, the company had extrapolated data using the following method: “a ratio was worked between length of therapy and length of stay in Deleyto 2018 for NPWTi and was then multiplied by length of stay for standard wound care reported at Deleyto 2018” (Company submission). The EAC did not accept this approach, for reasons stated in Section 9.2.3 and Table C1 in the assessment report. In the EAC’s model, a crude assumption was made that length of therapy was equivalent to length of stay. A value of 69.09 days was used for VAC Veraflo and 88.21 days used for advanced wound care dressings (taken from Table 2 of the Deleyto et al. paper). The committee did not make any changes to the guidance.
32	2	Company	3.14	It was not referenced by the EAC that the thearpy cost was changed.This differs in the model to our submission.	Thank you for your comment. The external assessment centre advised the committee that all changes to therapy costs were documented in Section 9.2.4 of the assessment report and table C4 in appendix C. This is now subject to an erratum and all data are now correct. The erratum is published as part of the supporting material for this guidance. The committee did not make any changes to the guidance.

33	2	Company	3.14	The EAC calculation of debridement cost for Deleyto 2018 is lacking the other procedures we have included such as mesh removal.	Thank you for your comment. The external assessment centre (EAC) noted that they did not accept these additional in the Deleyto et al (2018) scenario because the evidence to support their use was not considered to be sufficiently robust. This is explained fully in Section 9.2.7 of the Assessment Report and Table C4. The committee accepted this and did not make any changes to the guidance. The committee did not make any changes to the guidance.
34	2	Company	3.14	Due to the inaccuracies flagged in the EAC model, we would suggest that this is recalculated	Thank you for your comment. The committee did not consider that the factual inaccuracies reported in consultation comments 30 to 33 had been introduced into the EAC economic model. The committee, therefore, saw no justification to rerun the model. The committee did not make any changes to the guidance.
Economic modelling – base case and results (n = 7)					
35	6	NHS healthcare professional	3.14	It would appear that the KIM 2020 paper shows that in the main 75% of the patients were lower limb, however the guidance is not just lower limb and therefore should this be considered the base case for all wounds. As the wound types vary not only in speciality but also across other specialities.	Thank you for your comment. The external assessment centre advised the committee that it did not consider the Kim et al. (2020) scenario was a base case representative of all scenarios, but that it was considered it to be the scenario based on the most robust data. This is stated in section 9.2.7 of the EAC assessment report. The EAC did not exclude any scenario that was included by the company.

					Results for all scenarios are presented in Table 9.5 and 9.6 of the Assessment Report. The EAC noted that incidentally, the larger studies in the literature were in general characterised by people with lower limb wounds. This included the studies by Kim et al. (2014) (n=142), Kim et al. (2015) (n=100), and also the smaller studies by Omar et al. (2016) (n=20), and Goss et al (2012) (n=16). The committee did not fully endorse either the company model or the external assessment centre (EAC) model. The committee were aware of the limitations to both the EAC and company models and noted that the available evidence base used to inform the model was mainly made up of retrospective observational studies from outside the UK. The committee were not confident in the robustness of the cost case for the technology and therefore provided research recommendations. The committee did not make any changes to the guidance.
36	2	Company	4.2	3M note that paragraph 4.2 states “the committee concluded that the complexity of the population together with the heterogeneity of the available evidence makes generalisation of the study results difficult”. 3M agrees with this conclusion and as a result believe it is factually incorrect for the EAC to apply the outcomes reported in Kim 2020 heterogeneously across all the sub-groups contained in the scope published by NICE. This view is further reinforced by the fact that 75.7% of patients report as lower extremity in Kim 2020. The subsequent use by the EAC of these heterogeneous conclusions as the base case for the economic model, introduces misrepresentation and	Thank you for your comment. The committee understand from the external assessment centre (EAC) that the scenario based on data by Kim et al. 2020 was based on the most robust data, but was not considered to be an overarching “base case” representative of all scenarios. Limitations of this approach have been described by the EAC in Section 10.2 of their assessment report. The committee were aware of the limitations in the

				bias. For example the EAC approach takes no account of the variation in healing rates for different wound types. The EAC further tries to suggest that Kim 2020 is a mixture of wounds, however with over 50% as lower limb this is clearly not the case.	modelling and did not endorse either the company or EAC models. The committee provided research recommendations because they were not confident in the robustness of the cost case for the technology. The committee did not make any changes to the guidance. Please also see NICE response to comment 35.
37	4	Healthcare analytics company	3.14	It would appear that even though the KIM 2020 study has been performed in the main on lower limb patients. This has been considered as an acceptable base case for the total population of wounds for Veraflo. Is this acceptable and if so, would there not be clinical differences in other wound areas.	Thank you for your comment. The committee did not make any changes to the guidance. Please also see NICE response to comments 35 and 36.
38	2	Company	3.11	It would appear that from the cost saving tables shown in the EAC report Table 9.5, the overall cost saving for every study included by the EAC shows it to be cost saving, apart from Kim 2020. This does not reflect a possible issue with the use of Kim 2020 in its use by the EAC. It therefore impacts on the technology usage within the NHS, as it was unanimously declared by the clinicians, that it would be cost saving.	Thank you for your comment. The external assessment centre (EAC) noted that VAC Veraflo showed cost saving in most studies when considering the results from the deterministic analysis. However, when considering the results from the probabilistic sensitivity analysis (see Table 9.6 of the EAC assessment report) in 6 out of 9 scenarios the 95% credibility intervals cross zero, indicating uncertainty in the direction of results (including the Kim et al. 2020 scenario). The EAC also noted that the clinical experts were of the unanimous opinion that the technology had the *potential* to be cost saving, and not that the technology was cost saving. The committee were aware of the limitations in the modelling and did not endorse either the company or EAC models. The committee provided research recommendations because they were not

					confident in the robustness of the cost case for the technology. The committee did not make any changes to the guidance.
39	2	Company	3.12	It would appear that the EAC have made reference in their own findings and to quote “In the opinion of the EAC, data from Kim et al. (2020) was most robust, although the EAC has been careful to emphasise the limitations of this approach too. In the opinion of the EAC, the economic analysis is insufficient to draw firm conclusions from.” Therefore, it is clear that neither approach is robust. However when considering the innovation, all other studies show VAC Veraflo as cost saving, which demonstrates a clear point at which the EAC and the company have been able to agree on.	Thank you for your comment. The external assessment centre noted that results from the probabilistic sensitivity analysis demonstrates the uncertainty in the cost savings of the technology in most scenarios. The committee were aware of the limitations in the modelling and did not endorse either the company or EAC models. The committee provided research recommendations because they were not confident in the robustness of the cost case for the technology. The committee did not make any changes to the guidance. Please also see NICE response to comment 38.
40	4	Healthcare analytics company	3.14	After reviewing table 9.5 of the EAC report and submission from the company. It would appear the outcome of the cost consequence analysis is the same as the companies. However it would appear the EAC have said the companies modeling is wrong with the assumptions used. However if that is the case, then how is that the EAC modelling is correct, if the outcomes are closely matched. Also the only study which shows cost incurring is the KIM 2020, which again has no valid endpoints which could be used. However the EAC felt the need to assume LOT and LOS is the same.	Thank you for your comment. The external assessment centre (EAC) noted that their economic analysis was based on the company’s model, with relatively minor adjustments to parameter inputs (other than the addition of two new scenarios based on data by Kim et al. 2020 and Omar et al. 2016). It would be expected that the deterministic point estimates are similar. The EAC did however use additional probabilistic sensitivity analysis which demonstrated the uncertainty in the cost savings of the technology in most scenarios (see Table 9.6 of the EAC assessment report).

					The committee were aware of the limitations in the modelling and did not endorse either the company or EAC models. The committee provided research recommendations because they were not confident in the robustness of the cost case for the technology. The committee did not make any changes to the guidance.
41	6	NHS healthcare professional	General	It would appear that the economic approach has both from NICE and the company some challenges based on the evidence available. Therefore in support of innovation, should it not be considered to review this technology more closely as the support from the clinician opinion on the committee was that they were unanimous in their support for the technology and that it would be cost saving. Therefore, to ensure in these current times we are supporting getting patients out of hospital quicker and reducing those chances of infection during Covid-19 we are in fear of damaging the uptake.	Thank you for your comment. The committee were aware of the limitations in the modelling and did not endorse either the company or EAC models. It noted that the available evidence base used to inform the models was mainly made up of retrospective observational studies from outside the UK. The committee provided research recommendations because they were not confident in the robustness of the cost case for the technology. The committee did not make any changes to the guidance.
Economic modelling – length of therapy versus length of stay (n = 10)					
42	4	Healthcare analytics company	3.12	It would appear that the modelling approach from the EAC has also had limitations. Also there appears to be no evidence to back up the assumptions made when applying LOS to LOT. There are several studies in place which demonstrate that this would not be the case. Also clinical opinion states that it would also not be the case. Could NICE please evidence where this has been agreed and considered in its processes.	Thank you for your comment. The external assessment centre (EAC) noted that in some cases, length of stay or length of treatment was not directly reported in the studies, leading the company to undertake data transformation from unrelated studies. The EAC did not consider this was an acceptable approach. Instead, the EAC only reported data directly reported in individual studies, and where

					one parameter was not reported, it was assumed the values were equivalent. The EAC are aware of the limitations of this approach and this is stated in the EAC assessment report. The committee heard that, although length of stay was a key driver of the modelling, this outcome is subject to uncertainty due to a range of confounding factors. The EAC also noted that this is a particular concern when length of stay data is derived from retrospective observational studies in specialised healthcare environments. The committee were aware of the limitations in the modelling and did not endorse either the company or EAC models. It noted that the available evidence base used to inform the models was mainly made up of retrospective observational studies from outside the UK. The committee provided research recommendations because they were not confident in the robustness of the cost case for the technology. Section 4.12 of the guidance has been updated to clarify that there are limitations in the economic modelling because of uncertainties in the relationship between length of therapy and length of hospital stay with VAC Veraflo therapy. Section 4.13 of the guidance has also been updated to highlight the need for future studies to include length of therapy and length of stay as secondary outcome measures to better understand the relationship between these 2 parameters.
43	6	NHS healthcare professional	3.12	It would appear that NICE have used the Kim 2020 paper and applied an assumption that LOS is equal to LOT. This is not my experience in a UK NHS setting and to be knowledge I	Thank you for your comment.

				have never seen a study to demonstrate this. Therefore this assumption is inaccurate in relation to wound care in the UK.	The external assessment centre noted that none of the studies were done in the UK and issues with generalisability (of patients and care pathways) are a major source of uncertainty in all the analyses. Section 4.12 of the guidance has been updated to clarify that there are limitations in the economic modelling because of uncertainties in the relationship between length of therapy and length of hospital stay with VAC Veraflo therapy. Section 4.13 of the guidance has also been updated to highlight the need for future studies to include length of therapy and length of stay as secondary outcome measures to better understand the relationship between these 2 parameters. Please also see NICE response to comment 42.
44	6	NHS healthcare professional	3.12	It would appear also that the level of evidence in the KIM 2020 study is limited in its collection and a more recent study by Lavery et al. shows (https://www.sciencedirect.com/science/article/abs/pii/S0002961020301227 150 patients with diabetic foot ulcers comparing NPWT. Which clearly shows LOT for NPWT being 6.17 days vs. NPTWi being 4.77 days. Length of stay was reported at 13.8 days and 14.5 days for NPWT and NPWTI respectively, This supports the evidenced that LOS and Lot can not be considered as the same. It is also my professional opinion that in the NHS this is more reflective of the practice here and should be considered as a base case for the economic modelling inputs.	Thank you for your comment. The external assessment centre was asked to review the evidence identified by the consultee. The EAC noted that the intervention reported in this study was the Cardinal Pro with addition of irrigation, not VAC Veraflo. The committee agreed that this study was out of scope for this evaluation and was not considered further.
45	2	Company	3.14	3M believe that the assumption by the EAC in paragraph 3.14 that despite the data points collected in Kim 2020 being mean days to readiness for wound closure or coverage, then length of stay (LOS) and length of therapy (LOT) should be used as an appropriate substitute and set as being of equal value, is an incorrect and unreasonable interpretation of the evidence. No	Thank you for your comment. The external assessment centre (EAC) noted that in some cases, length of stay or length of treatment was not directly reported in the studies. The EAC's approach was to only use data directly

				NPWT related study that has collected these two data points and has found them to be of equal length. Examination of the EAC model clearly shows that a difference as small as 1.75 days between LOS in both arms of the study would move the economic mode from a cost incurring position to a cost saving one. Expert clinical advice given to the company has clearly stated that use of LOS as a substitute for LOT is an incorrect assumption. Given the impact that the inappropriate assumption of LOT being equal to LOS has upon the economic model developed by the EAC, 3M believe the committee should be notified of this inaccuracy and the model revisited.	reported in individual studies, and where one parameter was not reported, it was assumed the values were equivalent. The EAC are aware of the limitations of this approach and this is stated in their assessment report. Results from the EAC's probabilistic sensitivity analysis however showed there was considerable uncertainty with cost estimates, meaning no conclusion could be confidently drawn on the cost saving potential of VAC Veraflo. The committee were aware of the limitations in the modelling and did not endorse either the company or EAC models. It noted that the available evidence base used to inform the models was mainly made up of retrospective observational studies from outside the UK. The committee provided research recommendations because they were not confident in the robustness of the cost case for the technology. Section 4.12 of the guidance has been updated to clarify that there are limitations in the economic modelling because of uncertainties in the relationship between length of therapy and length of hospital stay with VAC Veraflo therapy. Section 4.13 of the guidance has also been updated to highlight the need for future studies to include length of therapy and length of stay as secondary outcome measures to better understand the relationship between these 2 parameters. Please also see NICE response to comments 42 and 43.
46	2	Company	3.14	Additionally, the EAC has not referenced any evidence to support their assumption of using LOS to equate to LOT. It is	Thank you for your comment.

				our experience from a wide variety of studies that the assumption by the EAC has not been demonstrated to support its conclusion. We would like to bring to NICE's attention, a study comparable to Kim 2020, Lavery et al 2020. This is an RCT, NPWT study, which was published in March 2020, which demonstrates a difference in LOS and LOT. (https://www.sciencedirect.com/science/article/abs/pii/S0002961020301227). Although this is not a VERAFLO study, it is an RCT with 150 patients with diabetic foot ulcers comparing KCI traditional Vac Therapy with Cardinal Health VAC with irrigation. This study shows LOT for NPWT being 148.1 hours (6.17 days) and NPTWi being 114.5 hours (4.77 days). LOS was reported as 13.8 days for NPTW vs 14.5 days NPWTi, implying that LOT represented between 33-45% of the time the patient spend in hospital as an inpatient.	The EAC noted that the intervention reported in Lavery et al. (2020) was the Cardinal Pro with addition of irrigation. The study did not include VAC Veraflo.as an intervention. The committee concluded that the study by Lavery et al. (2020) was out of scope for this evaluation and was therefore not considered further. Please also see NICE response to comment 44. Section 4.12 of the guidance has been updated to highlight that there were limitations in the economic modelling because of uncertainties in the relationship between length of therapy and length of hospital stay with VAC Veraflo therapy. Section 4.13 of the guidance has also been updated to highlight the need for future studies to include length of therapy and length of stay as secondary outcome measures to better understand the relationship between these 2 parameters.
47	2	Company	3.14	In relation to 3.14 it is also clear that the Kim 2020 study did look at the LOS for dehisced wounds and found that LOS ranged from 9.3 to 21.8 for NPWT. This is clearly significant but was not considered when modelling the cohort of patients by the EAC. Therefore, this is another marker which demonstrates the issue around using LOT as a marker for LOS.	Thank you for your comment. The external assessment centre (EAC) noted that this was a *post hoc* subgroup analysis. It was not possible to incorporate this into the model because other relevant data for this subgroup were not reported. The committee did not make any changes to the guidance.
48	6	NHS healthcare professional	3.11	The economic modelling in table 9.5 seems to show that all papers for the technology apart from KIM 2020 are cost saving. I appreciate these are not all RCTs, however they do show a difference and saving in LOT and LOS. Along with the recent Lavery study published this year, then as a clear endpoint	Thank you for your comment. The committee heard from the EAC and clinical experts and agreed that length of therapy and length of stay are unlikely to be the same. The EAC noted that in the

				which supports the model, would demonstrate that LOT and LOS should not be the same	absence of such data being reported in the Kim et al. (2020) study, there was no option but to draw this assumption. Section 4.12 and 4.13 have been updated to report this as a fundamental limitation of the economic model and the need for future studies to include length of therapy and length of stay as secondary outcome measures to better understand the relationship between these 2 parameters. Please also see NICE response to comment 42.
49	6	NHS healthcare professional	3	From reading the evidence submitted by the company and also those found by NICE, and appreciating that some are not RCTs, it would be clear that LOS and LOT have never been reported the same.	Thank you for your comment. The committee heard from the EAC and clinical experts and agreed that length of therapy and length of stay are unlikely to be the same. The EAC noted that in the absence of such data being reported in the Kim et al. (2020) study, there was no option but to draw this assumption. The EAC also noted that a causal relationship between length of stay and the intervention is unlikely to be established because of the presence of confounding factors, which have been documented in the assessment report and by clinical experts. Sections 4.12 and 4.13 of the guidance have been updated to highlight the limitations of the economic model and the need for future studies to include length of therapy and length of stay as secondary outcome measures to better understand the relationship between these 2 parameters. Please also see NICE response to comments 44 to 48.

50	3	US healthcare professional	3	The surrogate outcome endpoints of time to final surgical procedure, time to wound bed preparation (closure, or coverage with a graft) are important in determining the effectiveness/efficacy of this device. My research as well as Timmers et al. and Gabriel et al. have demonstrated this to be the case. It is important to remember that length/hospitalization is not as important due to factors including delay in discharge, other comorbidities that require management. Some erroneously assume that length of hospital stay is equivalent to treatment days of the device. In fact, there is often a delay in initial application (1-3 days) and removal of the device and discharge (1-3 days). Economic modeling based on length of hospitalization alone is faulty. Thus, I believe that time to surgical closure and wound deemed ready/coverted are better indicators of device efficacy/effectiveness.	Thank you for your comment. The committee were aware of the limitations in the modelling and did not endorse either the company or EAC models. It agreed that length of stay may not be an appropriate primary clinical outcome and that this outcome measure may be confounded by other factors, such as delays in discharge. The committee provided research recommendations because they were not confident in the robustness of the cost case for the technology. The limitations of length of stay as a primary outcome measure and the need for further research have been described in sections 4.5 and 4.13 of the guidance, respectively. Please also see NICE responses to comments 42 to 49.
51	4	Healthcare analytics company	3.4	The non-RCT studies are lower in volume, however, they do show a consistent approach to the difference in LOS and LOT, which is common in these types of wounds. However this does seem to be ignored when making an assumption by the EAC that these can be the same endpoint and value.	Thank you for your comment. The external assessment centre (EAC) noted that in some cases, length of stay or length of treatment was not directly reported in the studies. In the absence of such data being reported, there was no option but to draw the assumption that length of therapy and length of stay were equivalent. The limitations of this approach were clearly described by the EAC in their assessment report. The EAC also noted that none of the company's scenarios were excluded by the EAC; all results for different scenarios are reported in Table 9.5 and 9.6 of their assessment report. Section 4.12 and 4.13 of the guidance have been updated to report this assumption as a fundamental limitation of the economic

					model and the need for future studies to include length of therapy and length of stay as secondary outcome measures to better understand the relationship between these 2 parameters.
Committee discussion (n = 2)					
52	5	Professional organisation	4.1	Agree with this conclusion	Thank you for your comment
53	5	Professional organisation	4.1	While this is important (along with the other positive outcomes noted) this alone would not be sufficient for widespread adoption of this therapy.	Thank you for your comment
Equality (n = 1)					
54	2	Company	4.7	It was reported by the EAC that there were no protected characteristics for the patient population considered. However it was reported under MTG43 that a number of protected characteristics were relevant to the wound dressing system of NPWT. These were referenced in detail, under the Equality Act 2010. It appears that this is not being considered and could be misleading to those clinicians and HCPs who would be looking at using this technology.	Thank you for your comment. Equality considerations and the committee's discussion of these are described in section 4.8 of the guidance. The committee did not make any changes to the guidance.
MTEP process (n = 3)					
55	2	Company	Process overview	It is clear that the EAC had over 50% more time to undertake their review and modelling during the pause with Covid-19. Again to speak with KOLs, as the period of preparation for KCI was reduced by this issue. It should also be noted that NICE decided to pull the Veraflo MIB through to guidance, knowing the evidence levels. Knowing the poor quality and lack of evidence, at no point did NICE give us the option to delay the Guidance process, whilst additional evidence in a UK setting was generated.	Thank you for your comment. This comment concerns NICE MTEP processes and does not relate to the contents of the draft guidance itself. Guidance development for VAC Veraflo was paused due to COVID-19 and a lack of available clinical expert input. Whilst the guidance was paused, the external assessment centre did not continue work on the assessment report. The EAC did not

					receive additional time to undertake their review.
56	4	Healthcare analytics company	Process overview	It is important to note that during the submission process of these comments, that NICE system has crashed several times and a log was raised with the team. This is a possible issue for other clinicians to respond and may have put others off from sending their comments. Therefore during these uncertain times, should this be considered as to a possible pause of the guidance.	Thank you for your comment. This comment concerns NICE MTEP processes and does not relate to the contents of the draft guidance itself. NICE deemed this technical issue with the online comments submission system to be an isolated incident, and comments were otherwise received as normal. NICE offered an alternative method to submit comments and provided advice on how to resolve the technical issue. NICE has raised this incident with the digital service team to investigate further. NICE do not believe that this would have affected the development timeline of the guidance.
57	6	NHS healthcare professional	Process overview	Could I ask why NICE felt it was appropriate to take this technology from being a MIB within NICE and enter it in to the MTG program?	Thank you for your comment. This comment concerns NICE MTEP processes and does not relate to the contents of the draft guidance itself. The decision for routing the technology to the Medical Technology Evaluation Programme (MTEP) was made by decision-making members of NICE's Medical Technology Oversight Group (MTTOG). The decision-making process was in line with that set out by the published MTEP methods and process guide, and considered the criterion stated in Appendix C and Appendix D of the guide.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."