IQWiG Reports – Commission No. N17-01B

Negative pressure wound therapy for wounds healing by primary intention[1]

Extract

[1]Translation of Chapters 1 to 6 of the final report N17-01B *Vakuumversiegelungstherapie von Wunden mit intendierter primärer Wundheilung* (Version 1.0; Status: 12 June 2019 [German original]; 25 September 2019 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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The responsibility for the contents of the report lies solely with IQWiG.

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Key statement

Research question

The objective of this investigation is to

- assess the benefit of negative pressure wound therapy (NPWT) in comparison with standard wound therapy

in patients with wounds healing by primary intention with regard to patient-relevant outcomes.

The benefit assessment of NPWT in patients with wounds healing by secondary intention was conducted as part of project N17-01A.

Conclusion

A total of 45 studies supplied usable results on patient-relevant outcomes. Most studies were on postoperative wounds in endoprosthetics, obstetrics (Caesarean section), abdominal and cardiovascular surgery. The majority of studies were done on wounds with an elevated risk of impaired wound healing. No results whatsoever were available on a relevant number of further studies (23% data gap); hence, the certainty of conclusions was downgraded to account for potential publication bias.

With regard to the outcome for wound closure, there was a hint of greater benefit of NPWT in comparison with standard wound therapy in wounds healing by primary intention. The analyses additionally revealed an indication of greater benefit of NPWT in terms of avoiding wound infection in wounds healing by primary intention. For the remaining outcomes (particularly mortality, total rate of complications, pain, length of hospital stay, and health-related quality of life), there were no hints of benefit or harm of NPWT.

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Abbreviation	Meaning
ACT	Appropriate comparator therapy
AE	Adverse event
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
EQ VAS	EuroQoL Visual Analogue Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	Intention to treat
KCI	KCI Medizinprodukte GmbH / Acelity
NPWT	Negative pressure wound therapy
OR	Odds ratio
RCT	Randomized controlled trial
S&N	Smith & Nephew GmbH
SAE	Serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SWT	Standard wound therapy
THEP	Total hip endoprosthesis

1 Background

The Institute for Quality and Efficiency in Health Care (IQWiG) has already conducted a benefit assessment with subsequent update search on negative pressure wound therapy [1, 2]. This benefit assessment already discussed the consequences of wounds for patients, treatment options, and the fundamentals of negative pressure wound therapy (NPWT).

The objective of the investigation underlying Final Report N04-03 and Rapid Report N06-02 was to assess the benefit of

- negative pressure wound therapy in comparison with conventional forms of wound care and
- different forms of negative pressure wound therapy compared with each other

in patients with acute or chronic skin wounds of any aetiology and localization with regard to patient-relevant outcomes.

A total of 12 randomized controlled trials (RCTs) and 16 non-randomized trials up to December 2006 were found to be relevant for the benefit assessment. Each of these studies compared negative pressure wound therapy in patients with acute and chronic wounds of different aetiologies with a conventional form of wound care. These studies included a total of 1082 patients, of which 596 were included in RCTs and 486 in non-randomized trials.

The results of benefit assessments N04-03 and N06-02 failed to show superiority of negative pressure wound therapy over conventional wound treatment, thus not justifying widespread use of the method outside of study conditions.

However, given that these investigations revealed many ongoing and/or unpublished RCTs, conducting another investigation of negative pressure wound therapy seemed warranted. Further, in light of the previous assessments, an RCT on negative pressure wound therapy was initiated and conducted in Germany [3].

2 Research question

The objective of this investigation is to

- assess the benefit of negative pressure wound therapy in comparison with standard wound therapy

in patients with wounds healing by primary intention with regard to patient-relevant outcomes.

The benefit assessment of negative pressure wound therapy in patients with wounds healing by secondary intention was conducted as part of project N17-01A.

3 Methods

The target population of the benefit assessment was patients with wounds healing by primary intention. The experimental intervention was treatment with negative pressure wound therapy (NPWT). The comparator intervention was standard wound therapy (SWT).

The investigation considered the following patient-relevant outcomes:

- Mortality
- Wound closure
- Adverse events: wound complications and treatment complications (AEs)
- Amputation
- Pain
- Length of hospital stay and (re-)hospitalization
- Health-related quality of life
- Functioning
- Need of third-party help or need of long-term care

The outcomes "change in wound area or volume" as well as "change in wound surface after skin transplantation" were surveyed to provide supplementary information. Additionally, intervention-related and illness-related cost and patient satisfaction with treatment were to be considered, and related effects presented as supplementary information. Patient satisfaction was to be included in the analysis only to the extent it reflected health-related aspects.

Subjective outcomes (e.g., health-related quality of life) were considered only if they were surveyed using valid measuring instruments (e.g., validated scales).

Only randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding the study duration.

This benefit assessment is based on the results of the information retrieved by previous projects N04-03 and N06-02. The information retrieval was further updated for this report to include the period not covered by the searches for commissions N04-03 and N06-02 (2006 and later). The information was retrieved jointly for the benefit assessment of NPWT in patients with wounds healing by primary intention (N17-01B) and by secondary intention (N17-01A). After the respective study pools were defined, data were further processed in 2 separate benefit assessments.

A systematic search for primary literature was conducted in the databases MEDLINE, Embase and Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic overviews was conducted in the databases MEDLINE, Embase, Cochrane Database of

Systematic Reviews, and the HTA Database. Relevant systematic reviews had to be published in 2013 or later.

The following sources of information and search techniques were additionally used: trial registries, manufacturer documents, documents sent by the G-BA, reviews of reference lists, and documents made available from hearing procedures and author queries.

Relevant studies were selected by 2 reviewers independently from one another. Any discrepancies were resolved by discussion between the two reviewers. Data were extracted into standardized tables. To assess the qualitative certainty of conclusions, the risks of bias on both the study level and the outcome level was assessed and rated as high or low. The results of the individual studies were described broken down by outcomes.

Potential publication bias was suspected if the systematic search identified relevant completed studies without published results. To determine potential publication bias, the percentage of missing data (data gap) was calculated at study level. Potential outcome reporting bias was therefore disregarded. Studies with planned outcomes to be used exclusively for supplementary information were not taken into account since they were irrelevant for the conclusion. Studies without reported results which, according to the trial registry entry, were completed, prematurely terminated, or of unclear status were included in the calculations using their planned sample size, unless information to the contrary was available. This was done only if, at the time of the search, they should have been completed for more than 12 months and no usable data were supplied upon an author query.

The potential publication bias was assumed to have little effect on results if the patients from studies which had been completed for more than 12 months at the time of the search and for which no usable data were made available, even upon an author query, made up less than 10% of the total number of patients in the study pool. In this case, a regular benefit assessment was conducted since the missing data were not expected to have a relevant influence on results. If these patients represented between 10% and 30% of all patients, the potential publication bias was assumed to have a major effect on results. Since the missing data were expected to have a relevant influence on results, the certainty of conclusions from the benefit assessment was downgraded (proof to indication, indication to hint, hint to no hint). Due to the potential publication bias, the planned subgroup analyses were omitted. The surrogate validation of the outcomes “change in wound area or volume” and “change in wound surface” was not applicable for wounds healing by primary intention.

If the data gap involved more than 30% of patients, it was assumed that, due to potential publication bias, no conclusion could be drawn regarding benefit or harm, and no conclusion on benefit was inferred.

To categorize the completeness of data submissions by manufacturers, the percentage of missing data was calculated analogously to the procedure developed for potential publication

bias. This was based on an agreement on the transfer and publication of study data entered into by the Institute and each involved manufacturer before data were submitted. This agreement applies to all projects, i.e. regardless of wound type distribution. In cases where a company was responsible for a relevant percentage of missing data at any tier, the selectively supplied data on patient-relevant outcomes were excluded.

For the sake of robustness testing, a second scenario was considered in each calculation of the percentage of missing data. For studies which reported no results and, according to the trial registry entry, were prematurely terminated or whose status is unclear, only half of the planned sample size was used in this scenario, unless information to the contrary was available.

Since mean differences can be influenced to varying degrees by wounds of different aetiologies being included in the studies, the latter were standardised in the meta-analyses using Hedges' g whenever necessary.

4 Results

4.1 Results of the comprehensive information retrieval

The information retrieval identified 121 randomized controlled trials (266 documents) as being relevant for N17-01A and/or N17-01B.

For N17-01A and N17-01B together, a total of 139 studies without reported results were found.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 8 February 2019.

Studies to be considered for N17-01B

The information retrieval identified 54 randomized controlled trials (135 documents) as being relevant for the research question of this benefit assessment on NPWT in patients with wounds healing by primary intention.

Six studies were included only formally because they fulfilled all inclusion criteria, but failed to supply usable data on any outcome. Three additional studies reported usable data only on outcomes presented for supplementary information. For transparency purposes, these 9 studies were included in the study pool since they met the documented inclusion criteria.

Hence, the study pool included a total of 45 studies which reported usable data on patient-relevant outcomes.

For NPWT in patients with wounds healing by primary intention, 14 planned and 50 ongoing studies were found. Furthermore, 10 studies of unclear status, 4 prematurely terminated studies, and 11 completed studies without reported results were found.

Table 1: Study pool of the benefit assessment – wounds healing by primary intention (n = 54) (multi-page table)

Study	**Available documents**			
	Full publication (e.g. in professional journals)	**Trial registry entry / results in the trial registry**	**Clinical study report from manufacturer documents (not publicly accessible)**	**Study protocol from manufacturer documents (not publicly accessible)**
1208434	No	Yes [4] / yes [5]	--	--
13-485[a]	No	Yes [6] / yes [7]	--	--
14-1920	No	Yes [8] / [9]	--	Yes [10][b]
7179	Yes [11]	Yes [12] / no	--	--
AHS.2011.Prevena. Heine.03	Yes [13]	Yes [14] / yes [15]	Yes [16]	Yes [17]
AHS.2012. Customizable.01	No	Yes [18] / yes [19]	Yes [20]	Yes [21]
AHS.2012.Prevena. Cooper.01	No	Yes [22] / yes [23]	Yes [24]	Yes [25]
Cantero 2014	No	No	Yes [26]	Yes [27]
CCF 14-273	Yes [28]	Yes [29] / yes [30]	--	Yes [31][b]
CE/US/11/01/PIC	Yes [32]	Yes [33] / no	Yes [34]	Yes [35]
Chio 2010[c]	Yes [36]	No	--	--
Crist 2017[a]	Yes [37]	Yes [38] / yes [39]	--	Yes [40]
DEPRES	Yes [41]	Yes [42] / no	--	--
Engelhardt 2018	Yes [43]	No	--	--
Giannini 2018	Yes [44]	No	--	--
Gillespie 2015	Yes [45]	Yes [46] / no	--	--
H-20292	No	Yes [47] / yes [48]	--	--
HIC# 1010007535	Yes [49]	Yes [50] / yes [51]	--	--
Howell 2011[a]	Yes [52]	No	--	--
IMS Study	Yes [53]	Yes [54] / no	--	Yes [55]
INVIPS Trial	Yes [56, 57]	Yes [58] / no	--	--
IRB00109564	Yes [59]	Yes [60] / no	--	--
Karlakki 2016	Yes [61, 62]	Yes [63] / no	--	--
KCI VAC Study	Yes [64]	Yes [65] / no	--	Yes [66]
KCI.2013.Prevena.01	No	Yes [67] / no	Yes [68]	Yes [69]
Keeney 2018	Yes [70]	No	--	--
Li 2016	Yes [71]	Yes [72] / no	--	--
Manoharan 2016	Yes [73]	Yes [74] / no	--	--
Mendame Ehya 2017	Yes [75]	No	--	--
NEPTUNE	Yes [76, 77]	Yes [78] / no	--	Yes [79]
Nordmeyer 2015[c]	Yes [80, 81]	No	--	--
NPWTCS	No	Yes [82] / yes [83]	--	Yes [84]

Table 1: Study pool of the benefit assessment – wounds healing by primary intention (n = 54) (multi-page table)

Study	**Available documents**			
	Full publication (e.g. in professional journals)	**Trial registry entry / results in the trial registry**	**Clinical study report from manufacturer documents (not publicly accessible)**	**Study protocol from manufacturer documents (not publicly accessible)**
Pachowsky 2011[a]	Yes [85]	No	--	--
Pauser 2016[c]	Yes [86]	No	--	--
Peter Suh 2016	Yes [87–89]	No	--	--
PICO Trial	Yes [90]	Yes [91] / no	--	--
Pleger 2017	Yes [92]	No	--	--
PROVAC	Yes [93]	Yes [94] / yes [95]	--	Yes [96]
Pro00040054	No	Yes [97] / yes [98]	--	--
R000016785[a]	Yes [99, 100]	Yes [101] / no	--	--
RRG-104871	Yes [102, 103]	Yes [104] / no	--	Yes [105]
S-20130010	Yes [106, 107]	Yes [108] / no	--	--
SAVIOR Trial[a]	No	Yes [109] / yes [110]	--	Yes [111]
Shen 2017	Yes [112]	Yes [113] / no	--	--
Shim 2018	Yes [114]	No	--	--
Tanaydin 2018	Yes [115, 116]	No	--	--
The DRESSING Trial	Yes [117–119]	Yes [120] / no	--	--
Uchino 2016	Yes [121]	Yes [122, 123] / no	--	--
VAC 2001-04	Yes [124, 125]	Yes [126] / no	--	--
VAC 2001-05	Yes [127]	Yes [128] / no	--	--
VAC NPWT KCI Dressing Study	Yes [129]	Yes [130] / no	--	--
VACCS	Yes [131]	Yes [132] / no	--	--
Witt-Majchrzak 2014	Yes [133]	No	--	--
Yu 2017	Yes [134]	Yes [135] / yes [136]	--	--

Italicized study name: unpublished study

a: Included only formally due to lack of usable data: This may be due to an unknown number of patients being randomized to the respective groups or to the trials including fewer than 10 patients.

b: Publicly accessible

c: The study reported usable data only on outcomes included for supplementary information, such as change in wound area or wound volume or intervention-related and disease-related cost.

Table 2: Study pool of the benefit assessment – wounds healing by secondary intention (n = 67) (multi-page table)

Study	**Available documents**			
	Full publication (e.g. in professional journals)	**Trial registry entry / results in the trial registry**	**Clinical study report from manufacturer documents (not publicly accessible)**	**Study protocol from manufacturer documents (not publicly accessible)**
Acosta 2013	Yes [137–139]	No	--	--
ActiVac[a]	No	Yes [140] / yes [141]	--	--
Arti 2016	Yes [142]	Yes [143] / no	--	--
Ashby 2012	Yes [144]	Yes [145] / no	--	--
Banasiewicz 2013	Yes [146]	No	--	--
Bee 2008	Yes [147]	No	--	--
Biter 2014	Yes [148, 149]	No	--	--
Braakenburg 2006	Yes [150]	No	--	--
CE/044/PIC	No	Yes [151] / no	Yes [152–155]	Yes [156]
Chiang 2017	Yes [157]	No	--	--
Correa 2016	Yes [158]	Yes [159] / no	--	--
Dalla Paola 2010 S-I[b]	Yes [160]	No	--	--
Dalla Paola 2010 S-II	Yes [160]	No	--	--
De Laat 2011	Yes [161]	Yes [162] / no	--	--
DiaFu	Yes (publications of study design [3,163])	Yes [164]; [165] / no	Yes [166]; [167][c]	Yes [168][c]
Dwivedi 2016[b]	Yes [169, 170]	Yes [171] / no	--	--
Eginton 2003[a]	Yes [172]	No	--	--
Ford 2002[a]	Yes [173]	No	--	--
Gupta 2013	Yes [174]	No	--	--
Hu 2009	Yes [175]	No	--	--
Huang 2006	Yes [176]	No	--	--
ISAW[a]	No	Yes [177–179] / no	Yes [180][c]	Yes [181][c]
Jayakumar 2013	Yes [182]	No	--	--
Johnson 2018[a]	Yes [183]	No	--	--
Joseph 2000[a]	Yes [184]	No	--	--
Kakagia 2014	Yes [185]	No	--	--
Karatepe 2011	Yes [186]	No	--	--
Keskin 2008[a]	Yes [187]	No	--	--
Leclercq 2016	Yes [188]	No	--	--
Liao 2012	Yes [189]	No	--	--
Llanos 2006	Yes [190]	No	--	--
Mody 2008	Yes [191]	No	--	--

Table 2: Study pool of the benefit assessment – wounds healing by secondary intention (n = 67) (multi-page table)

Study	**Available documents**			
	Full publication (e.g. in professional journals)	**Trial registry entry / results in the trial registry**	**Clinical study report from manufacturer documents (not publicly accessible)**	**Study protocol from manufacturer documents (not publicly accessible)**
Mohsin 2017	Yes [192]	No	--	--
Moisidis 2004	Yes [193]	No	--	--
Mouës 2004	Yes [194–196]	No	--	--
Nain 2011	Yes [197]	No	--	--
Novinščak 2010	Yes [198]	No	--	--
Perez 2010	Yes [199]	No	--	--
Rencüzoğulları 2015	Yes [200]	No	--	--
Riaz 2010[a]	Yes [201]	No	--	--
Saaiq 2010	Yes [202]	No	--	--
Sadiq 2018[a]	Yes [203]	No	--	--
Sajid 2015[b]	Yes [204]	No	--	--
Shen 2013	Yes [205]	No	--	--
Sibin 2017	Yes [206]	No	--	--
Sinha 2013	Yes [207]	No	--	--
Sun 2007[b]	Yes [208]	No	--	--
SWHSI	Yes [209, 210]	Yes [211] / no	--	--
TOPSKIN	Yes [212, 213]	Yes [214] / no	--	--
VAC 2001-01	No	No	Yes [215, 216]	Yes [217]
VAC 2001-02	No	No	Yes [216, 218]	Yes [219]
VAC 2001-03	No	No	No[d]	--
VAC 2001-06	Yes [220]	Yes [221] / yes [222]	--	--
VAC 2001-07	Yes [223–226]	Yes [227] / no	Yes [228]	Yes [229]
VAC 2001-08	Yes [230–233]	Yes [234] / yes [235]	Yes [236]	Yes [237]
VAC 2002-09	No	No	Yes [216, 238]	Yes [239]
VAC 2002-10	No	No	Yes [216, 240]	Yes [241]
VAC 2006-19	No	Yes [242] / yes [243]	--	Yes [244]
Vaidhya 2015[a]	Yes [245]	No	--	--
Vather 2018[a]	Yes [246–248]	No	--	--
Virani 2016	Yes [249]	No	--	--
Vuerstaek 2006	Yes [250, 251]	Yes [252] / no	--	--
Wanner 2003[b]	Yes [253]	No	--	--
WOLLF	Yes [254–257]	Yes [258] / no	--	--
Xu 2015	Yes [259]	No	--	--
Zhang 2017	Yes [260]	No	--	--

Table 2: Study pool of the benefit assessment – wounds healing by secondary intention (n = 67) (multi-page table)

Study	Available documents			
	Full publication (e.g. in professional journals)	**Trial registry entry / results in the trial registry**	**Clinical study report from manufacturer documents (not publicly accessible)**	**Study protocol from manufacturer documents (not publicly accessible)**
Zhu 2014	Yes [261]	No	--	--

Italicized study name: unpublished study
a: Included only formally due to lack of usable data: This may be due to an unknown number of patients being randomized to the respective groups or to the trials including fewer than 10 patients.
b: The study reports usable data only on outcomes included for supplementary information, such as change in wound area or wound volume or intervention-related and disease-related cost.
c: Clinical study report or study protocol from author queries (not publicly accessible)
d: As part of the commenting procedure, the manufacturer provided raw data [262]. Further available documents comprise a presentation [263] and an abstract [264] related to this study.

4.2 Characteristics of the studies included in the evaluation

The 45 studies reporting usable results on patient-relevant outcomes for the benefit assessment provided data on a total of 7376 evaluation units (wounds) from 6981 patients. The individual studies included between 16 and 876 patients and were conducted worldwide in the years 2001 to 2018. All studies had a 2-arm design. Thirty-five studies were monocentric and 10 multicentric. All studies were conducted in inpatient settings, and 1 study also included the home care setting (HIC#1010007535). In 38 studies, randomization and analysis were performed at the patient level. In 5 studies, randomization and analysis were done at the wound level (7179, CE/US/11/01/PIC, INVIPS-Trial, Manoharan 2016, Tanaydin 2018). In the remaining 2 studies, patients were randomized, and patients or at least 1 wound per patient were analysed, depending on the specific outcome (Pleger 2017, VAC 2001-05).

The included studies comprised a wide range of different wounds of varying aetiologies, localization and risk factors for impaired wound healing, which were distributed as follows:

- Abdominal surgery wounds (n = 10)
  - Open abdominal surgeries (n = 3) (Li 2016, PICO Trial, Shen 2017)
  - Panniculectomy (n = 2) (AHS.2012.Customizable.01, HIC# 1010007535)
  - Open kidney transplantation (n = 1) (AHS.2012.Prevena.Cooper.01)
  - Ileostomy closure (n = 1) (Uchino 2016)
  - Colorectal surgery (n = 2) (Cantero 2014, NEPTUNE)
  - Open duodenopancreatectomy (n = 1) (IRB00109564)

- Caesarean section wounds (n = 7) (AHS.2011.Prevena.Heine) 03, H-20292, NPWTCS, PROVAC, S-20130010, The DRESSING Trial, VACCS)
- Vascular surgery wounds (n = 8)
  - Exposure of the femoral artery (n = 5) (Engelhardt 2018, IMS Study, INVIPS-Trial, Pleger 2017, RRG-104871)
  - Procedure at the lower extremity (n = 3) (7179, KCI VAC Study, Yu 2017)
- Wounds after hip/knee endoprosthesis (n = 8)
  - Total hip endoprosthesis or knee endoprosthesis (n = 5) (1208434, CCF 14-273, Giannini 2018, Karlakki 2016, Keeney 2018)
  - Total hip endoprosthesis (n = 2) (14-1920, Gillespie 2015)
  - Knee endoprosthesis (n = 1) (Manoharan 2016)
- Traumatic and plastic surgery wounds (n = 5) (Mendame Ehya 2017, Peter Suh 2016, Shim 2018, VAC 2001-04, VAC 2001-05)
- Breast surgery wounds (n = 3)
  - Breast reduction (n = 2) (CE/US/11/01/PIC, Tanaydin 2018)
  - Breast reconstruction (n = 1) (DEPRES)
- Cardiac/thoracic surgery wounds (n = 2)
  - Sternotomy wounds due to heart surgery (n = 2) (KCI.2013.Prevena.01, Witt-Majchrzak 2014)
- Other wounds (n = 2) (Pro00040054, VAC NPWT KCI Dressing Study)

Forty-two studies included predominantly or exclusively patients with risk factors for impaired wound healing; of these studies, 20 included people with at least 1 wound-specific or patient-specific risk factor for impaired wound healing. This included all 7 studies on wound therapy after Caesarean section with the inclusion criterion of obesity. In contrast, only 3 studies reported no risk factors in the study population (1208434, 14-1920 and Tanaydin 2018).

4.3 Studies without reported results / calculation of data gap

On the basis of the procedure described in Section 3 for determining potential publication bias for the assessment of NPWT for wounds healing by primary intention, a total of 17 studies must be considered (7 completed, 4 prematurely terminated, and 6 of unclear status). Table 3 lists the studies with the respective sample size used for calculating the data gap.

Table 3: Studies considered for calculating the data gap (multi-page table)

Study	Sample size[a]	Available documents			Status (planned end date of the study, if applicable)[b]
		Trial registry entry / results in the trial registry	Publication of study design	Study protocol from manufacturer documents (not publicly accessible)	
Wounds healing by primary intention – completed studies					
012/2015	120	NCT02892435 [265]	--	--	Completed[c] (not specified)[d]
APIPICS	26	NCT01891006 [266]	--	--	Completed (07/2015)
NPWT Ireland	150	NCT02331485 [267]	--	--	Completed (09/2015)[c]
PICO-C	120	NCT02578745 [268]	--	--	Completed (03/2016)
PREVENA1	316	NCT02118558 [269]	--	Yes [270][e]	Completed (not specified)[f]
VAC 2001-04 [1]	50[g]	NCT00582179 [126]	--	--	Completed (03/2007)
Walker 2005 [1]	--[h]	--	--	--	Completed (03/2005)[i]
Wounds healing by primary intention – prematurely terminated studies					
1511016790	0[j]	NCT02534116 [271]	--	--	Prematurely terminated (04/2017)
HJ23-C.1-N-12	0[j]	ISRCTN31224450 [272]	--	--	Prematurely terminated (02/2014)
HP-00057511	0[j]	NCT02006511 [273]	--	--	Prematurely terminated (12/2014)
PräVAC	30[k]	DRKS00005257 [274]	Yes [275]	Yes [276][l]	Prematurely terminated[c] (not specified)[f]
Wounds healing by primary intention – studies of unclear status					
001	60	NCT02558764 [277]	--	--	Unclear (12/2016)
ACTRN12615000175572	160	ACTRN12615000175572 [278]	--	--	Unclear[m] (2016)
EUROPA trial	652	ACTRN12612001275853 [279]	Yes [280]	--[n]	Unclear[m] (not specified)[o]
KBogenhausen_04	30	NCT02526342 [281]	--	--	Unclear (09/2016)
NEPTUNE	294	DRKS00011033 [282]	--	--	Unclear[m] (not specified)[p]

Table 3: Studies considered for calculating the data gap (multi-page table)

Study	Sample size[a]	Available documents			Status (planned end date of the study, if applicable)[b]
		Trial registry entry / results in the trial registry	Publication of study design	Study protocol from manufacturer documents (not publicly accessible)	
PSF-2012	50	NCT01731769 [283]	--	--	Unclear (03/2013)

a: Sample size used for each study to calculate the data gap; based on trial registry entry unless noted otherwise
b: Based on trial registry entry unless noted otherwise
c: According to the response to the author query
d: On the basis of the response to the author query, but at least since 10/2017
e: KCI listed this study and provided the study protocol upon a query regarding the clinical study report. The manufacturer stated that the data analysis has not yet been completed and the study report was therefore not available. At a later time, the manufacturer also stated that it sponsored the study.
f: On the basis of the answer to the author query, but at least since 01/2018
g: In the publication cited in the context of the author query, data on the first 44 patients out of a total of 94 patients have already been published. Therefore, data for only 50 patients must be documented as missing.
h: N04-03 identified the patient-relevant outcome for this study as the volume of wound exudate; therefore, no data on patient-relevant outcomes are likely to be expected from this study. Hence, this study will not be further considered here.
i: Study status classified in accordance with the status in the underlying Final Report N04-03. No further information available.
j: The study was prematurely terminated before any patient recruitment; therefore, 0 patients.
k: According to the response to the author query, the study was prematurely terminated. A total of 30 patients with 60 wounds were included in the study.
l: KCI listed this study and provided the study protocol upon a query regarding the clinical study report. The manufacturer stated that the study was still ongoing and therefore no clinical study report was available. At a later time, the manufacturer also stated that it sponsored the study.
m: No update of the trial registry entry for more than 2 years; therefore, the status was classified as unclear.
n: S&N listed this study and responded to the query regarding the clinical study report by stating that it had no study protocol or clinical study report since this was an independent study.
o: The publication of the study design indicated planned recruitment until late 2017 and a follow-up of 30 days, which would result in a planned study completion in 01/2018.
p: According to the available information, the study was supposed to have been completed for at least 1 year (start in 09/2016 and 6-week follow-up).

KCI: KCI Medizinprodukte GmbH / Acelity; S&N: Smith & Nephew GmbH

In total, data on at least 2058 patients remain unpublished. Usable data are available on 6981 patients (see Section 4.2). In total, the data of at least 23% [2058 / (2058 + 6981)] of patients included in the studies on NPWT with wounds healing by primary intention are therefore inaccessible.

Furthermore, the remaining 72 studies which neither reported results nor fell under the 12-month rule yet at the time the search was conducted (4 completed, 4 of unclear status, 14 planned, and 50 ongoing studies) are expected to supply data on a total of 29 748 patients with wounds healing by primary intention on the basis of their planned sample size or any alternative information which is already available.

4.4 Overview of assessment-relevant outcomes

Data on patient-relevant outcomes were extracted from 45 studies. Table 4 presents an overview of the available data on patient-relevant outcomes from the included studies. No studies reported usable data regarding the outcomes for either amputation or the need of third-party help or need long-term care.

Table 4: Matrix of patient-relevant outcomes (multi-page table)

Study	Outcomes								
	Mortality	**Wound closure**	**Adverse events: Wound complications and treatment complications**	**Amputation**	**Pain**	**Length of hospital stay and (re-)hospitalization**	**Health-related quality of life**	**Functioning**	**Need of third-party help or need of long-term care**
1208434	●	-	●	-	-	-	-	-	-
14-1920	●	-	●	-	-	-	-	-	-
7179	-	-	●	-	-	●	-	-	-
AHS.2011. Prevena. Heine.03	●	-	●	-	●	-	-	-	-
AHS.2012. Customizable. 01	●	-	●	-	●	-	-	-	-
AHS.2012. Prevena. Cooper.01	●	-	●	-	●	-	-	-	-
Cantero 2014	-	-	●	-	-	-	-	-	-
CCF 14-273	●	●	●	-	-	●	-	-	-

Table 4: Matrix of patient-relevant outcomes (multi-page table)

Study	Outcomes								
	Mortality	**Wound closure**	**Adverse events: Wound complications and treatment complications**	**Amputation**	**Pain**	**Length of hospital stay and (re-)hospitalization**	**Health-related quality of life**	**Functioning**	**Need of third-party help or need of long-term care**
CE/US/11/01/ PIC	-	●	●	-	-	●	-	-	-
DEPRES	-	-	●	-	●	●	-	-	-
Engelhardt 2018	●	-	●	-	-	-	-	-	-
Giannini 2018	-	-	-	-	●	-	-	-	-
Gillespie 2015	-	-	●	-	-	●	-	-	-
H-20292	-	-	●	-	-	-	-	-	-
HIC# 1010007535	-	-	●	-	-	-	-	-	-
IMS Study	-	-	●	-	-	●	-	-	-
INVIPS Trial	●	-	●	-	-	-	-	-	-
IRB00109564	-	-	●	-	-	●	-	-	-
Karlakki 2016	-	●	●	-	-	●	-	-	-
KCI VAC Study	●	-	-	-	●	●	●	●	-
KCI.2013. Prevena.01	●	-	●	-	●	-	-	-	-
Keeney 2018	-	-	●	-	-	-	-	-	-
Li 2016	-	-	●	-	-	-	-	-	-
Manoharan 2016	-	-	-	-	●	●	-	-	-
Mendame Ehya 2017	-	●	●	-	●	-	-	-	-
NEPTUNE	●	-	●	-	-	●	-	-	-
NPWTCS	●	-	●	-	-	●	-	-	-
Peter Suh 2016	-	-	●	-	●	-	-	-	-
PICO Trial	-	-	●	-	-	●	-	-	-
Pleger 2017	●	-	●	-	-	●	-	-	-

Table 4: Matrix of patient-relevant outcomes (multi-page table)

Study	Outcomes								
	Mortality	Wound closure	Adverse events: Wound complications and treatment complications	Amputation	Pain	Length of hospital stay and (re-)hospitalization	Health-related quality of life	Functioning	Need of third-party help or need of long-term care
Pro00040054	●	-	●	-	●	-	-	-	-
PROVAC	●	-	●	-	-	●	-	-	-
RRG-104871	●	-	●	-	-	●	-	-	-
S-20130010	-	-	●	-	-	●	●	-	-
Shen 2017	-	-	●	-	-	-	-	-	-
Shim 2018	-	-	●	-	-	-	-	-	-
Tanaydin 2018	-	-	●	-	-	-	-	-	-
The DRESSING Trial	-	-	●	-	-	●	-	-	-
Uchino 2016	-	●	●	-	-	-	-	-	-
VAC 2001-04	-	-	●	-	-	-	-	-	-
VAC 2001-05	-	-	●	-	-	●	-	-	-
VAC NPWT KCI Dressing Study	-	-	●	-	-	-	-	-	-
VACCS	-	-	●	-	-	●	-	-	-
Witt-Majchrzak 2014	-	●	●	-	-	-	-	-	-
Yu 2017	●	-	●	-	-	-	-	-	-

Italicized study name: unpublished study
● Data available and usable
- Data not available or unusable

4.5 Assessment of the risk of bias at study level and at outcome level

The risk of bias at study level was rated as low for 8 studies (14-1920, AHS.2011.Prevena. Heine.03, CE/US/11/01/PIC, Gillespie 2015, IMS Study, NEPTUNE, S-20130010, The DRESSING Trial). For the remaining 37 studies, the risk of bias at study level was rated as

high. The criterion of allocation concealment alone already put 33 studies at a high risk of bias at study level. For the CCF 14-273 study, the risk of bias at study level was rated as high due to missing information on the generation of the randomization sequence and lack of blinding. For the Giannini 2018 study, the risk of bias at study level was rated as high particularly due to the disproportionate exclusion of patients from groups after randomization. For the RRG-104871 and Tanaydin 2018 studies, the risk of bias at study level was rated as high primarily due to reporting bias.

The risk of bias at outcome level was assessed for the 8 studies with low risk of bias at study level. In the remaining 37 studies, the high risk of bias at study level translated directly into the risk of bias at outcome level.

For 14-1920 and the IMS Study, a low risk of bias was found for all outcomes.

For AHS.2011.Prevena.Heine.03, the risk of bias was rated as high for all surveyed outcomes (mortality, adverse events, and pain), particularly since the application of the intention-to-treat (ITT) principle was inadequate or unclear.

For the CE/US/11/01/PIC study, the risk of bias for the outcome wound closure was high due to a violation of the ITT principle. The risk of bias was low with respect to the remaining outcomes (re-intervention, infection, total rate of SAEs, dehiscence, and rehospitalization).

For the studies Gillespie 2015, NEPTUNE and The DRESSING Trial, there was a high risk of bias regarding the outcome for bleeding due to a lack of blinding and absence of a recognizable system. The risk of bias was low for the remaining outcomes (mortality, reintervention, infection, dehiscence, length of hospital stay and rehospitalization).

For the S-20130010 study, a low risk of bias was found with respect to the outcomes for infection and rehospitalization. Due to subjective data collection and lack of blinding, the risk of bias regarding the outcomes for reintervention, dehiscence, and quality of life was rated as high.

4.6 Results on patient-relevant outcomes

4.6.1 Results on mortality

For the outcome “mortality”, usable results were available from 17 studies. No hint of an effect can be inferred from the results of the studies which showed high qualitative certainty of conclusions (14-1920, NEPTUNE). Similarly, the collective analysis of studies with moderate and high qualitative certainty of conclusions failed to show a statistically significant difference between the two treatment groups (OR 0.99; 95% CI [0.46; 2.11]). This analysis is not contradicted by the result of the beta-binomial model, which was used to better account for studies containing at least 1 treatment arm without events (OR 1.09; 95% CI [0.38; 3.14]). Regarding the outcome for mortality, there is consequently no hint of benefit or harm of NPWT in comparison with SWT.

4.6.2 Results on wound closure

For the outcome “wound closure”, usable results from 6 studies were available.

4.6.2.1 Wound healing and time to wound healing

Wound healing

Usable results on wound healing were reported in 4 studies with moderate certainty of conclusions. If data were reported for multiple time points, those from the 6-week point (42 days) were used. A statistically significant difference between treatment groups was found in favour of NPWT (OR 2.54; 95% CI [1.35; 4.79]). Consequently, there is an indication of an effect on wound healing in favour of NPWT.

Time to wound healing

Usable results on time to wound healing were reported in 2 studies with moderate qualitative certainty of conclusions. The meta-analysis using Hedges’ g showed a statistically significant difference in favour of NPWT. However, since the range of the 95% CI was not fully below the irrelevance threshold of −0.2, the effect was rated clinically irrelevant (Hedges’ g −0.53; 95% CI [−0.94; −0.13]). Consequently, there is no hint of an effect regarding time to wound healing.

4.6.2.2 Conclusion on benefit regarding wound closure

Overall, an indication of benefit of NPWT in comparison with SWT was initially found with respect to the outcome for wound closure. In view of the potential publication bias due to the calculated total data gap of 23%, this indication of greater benefit must be downgraded. In terms of the outcome for wound closure, this results in a hint of greater benefit of NPWT in comparison with SWT.

4.6.3 Results on adverse events: Wound complications and treatment complications (AEs)

Regarding the outcome for AEs, usable results from 42 studies were available. Since these studies used different operationalizations, the data were first analysed according to operationalization and then aggregated for a conclusion on any benefit regarding AEs.

4.6.3.1 AEs: Re-intervention

Usable results on the reintervention rate were reported in 23 studies. No hint of an effect can be inferred from the results of the studies which showed high qualitative certainty of conclusions (CE/US/11/01/PIC, IMS Study and NEPTUNE). The collective analysis of studies with moderate and high qualitative certainty of conclusions showed a statistically significant difference in favour of NPWT. The odds ratio is 0.71 (95% CI [0.51; 0.99]). This analysis is contradicted by the result of the beta-binomial model, which was used to better account for the studies with at least 1 treatment arm without an event (OR 0.70; 95% CI [0.42; 1.18]); the identified effect is therefore downgraded. Consequently, there is a hint of an effect in favour of NPWT for the AE regarding re-intervention.

4.6.3.2 AEs: Bleeding

Usable results on bleeding were reported in 7 studies which showed moderate qualitative certainty of conclusions. No statistically significant difference between treatment groups was found (OR 1.73; 95% CI [0.83; 3.64]). Consequently, there is no hint of an effect for the AE regarding bleeding.

4.6.3.3 AEs: Infection

Usable results on infection were reported in 36 studies. The meta-analysis revealed a statistically significant difference in favour of NPWT both for the studies with high qualitative certainty of conclusions (CE/US/11/01/PIC, Gillespie 2015, IMS Study, NEPTUNE, S-20130010 and The DRESSING Trial; OR 0.59; 95% CI [0.37; 0.93]) and for the totality of the studies (OR 0.62; 95% CI [0.52; 0.74]). Consequently, there is proof of an effect on infections in favour of NPWT.

4.6.3.4 Total rate of SAEs

Usable results on the total rate of SAEs were reported in 14 studies. From the results of the studies with high qualitative certainty of conclusions (14-1920 and CE/US/11/01/PIC), no hint of an effect can be inferred. Similarly, the collective analysis of studies with moderate and high qualitative certainty of conclusions failed to show a statistically significant difference between the two treatment groups (OR 0.86; 95% CI [0.54; 1.37]). This analysis is not contradicted by the result of the beta-binomial model, which was used to better account for studies containing at least 1 treatment arm without events (OR 1.21; 95% CI [0.46; 3.14]). Consequently, there is no hint of an effect on the total rate of SAEs.

4.6.3.5 Separately identified SAEs

Usable results on separately identified SAEs were reported in 23 studies. All 23 studies reported usable data regarding the outcome for dehiscence, and 4 studies did so with respect to the outcome for discontinuation due to AEs.

For the separately reported SAE of dehiscence, no hint of an effect can be inferred from the results of the studies which showed high qualitative certainty of conclusions (CE/US/11/01/ PIC, Gillespie 2015, The DRESSING Trial). The collective analysis of studies with moderate and high qualitative certainty of conclusions showed a statistically significant difference in favour of NPWT. The odds ratio is 0.76 (95% CI [0.59; 0.98]). This analysis is contradicted by the result of the beta-binomial model, which was used to better account for the studies with at least 1 treatment arm without an event (OR 0.77; 95% CI [0.44; 1.35]); the identified effect is therefore downgraded. Consequently, there is a hint of an effect on the separately reported SAE of dehiscence.

There is no hint of an effect on the separately reported SAE of discontinuation due to AEs.

4.6.3.6 Conclusion on benefit regarding adverse events: Wound complications and treatment complications (AEs)

The hint of an effect on the AE due to re-intervention in favour of NPWT must be downgraded due to the potential publication bias resulting from the total calculated data gap of 23%. Consequently, there is no hint of an effect on the AE due to re-intervention.

The proof of an effect on the AE due to infection in favour of NPWT must be downgraded to an indication due to the potential publication bias resulting from the total calculated data gap of 23%.

The hint of an effect on the separately reported SAE due to dehiscence in favour of NPWT must be downgraded due to the potential publication bias resulting from the total calculated data gap of 23%. Consequently, there is no hint of an effect regarding the separately reported SAE due to dehiscence.

Overall, for the outcome adverse events: wound complications and treatment complications (AEs), there is no hint of benefit or harm of NPWT in comparison with SWT. This result is primarily based on the total rate of SAEs, which revealed no difference between NPWT and SWT. With respect to the outcome for infection, there is consequently an indication of an effect in favour of NPWT.

4.6.4 Results on amputation

No usable results were available on this outcome.

4.6.5 Results on pain

Regarding the outcome for pain, usable results from 11 studies were available. Since the studies used different operationalizations, the data were first analysed according to operationalization and later aggregated for a conclusion on the benefit regarding the outcome for pain.

4.6.5.1 Pain – continuous

Usable results on pain in the form of continuous data were reported by 5 studies which showed moderate qualitative certainty of conclusions.

The meta-analytical summary revealed heterogeneous results; therefore, no combined effect was presented. The heterogeneity cannot be explained by the studies being based on wounds of different aetiologies.

The prediction interval overlaps the null, and the studies with statistically significant effects made up less than 50% of the total weight of all studies. The effect direction differs. Consequently, there is no hint of an effect on pain as operationalized in the form of continuous data.

4.6.5.2 Pain – dichotomous

Usable results on pain in the form of dichotomous data were reported by 6 studies which showed moderate qualitative certainty of conclusions.

The meta-analytical summary revealed heterogeneous results; therefore, no combined effect was presented. The heterogeneity cannot be explained by the studies being based on wounds of different aetiologies.

The prediction interval overlaps the null, and the studies with statistically significant effects made up less than 50% of the total weight of all studies. The effect direction differs. Consequently, there is no hint of an effect on pain as operationalized in the form of dichotomous data.

4.6.5.3 Conclusion on benefit regarding pain

In summary, regarding the outcome for pain, the data are heterogeneous and there is no hint of benefit or harm of NPWT in comparison with SWT.

4.6.6 Results on length of hospital stay and (re-)hospitalization

Regarding the outcome for length of hospital stay and (re-)hospitalization, usable results from 20 studies were available.

4.6.6.1 Length of hospital stay

Usable results on length of hospital stay were reported by 17 studies.

No hint of an effect can be inferred from the results of the studies which showed high qualitative certainty of conclusions (Gillespie 2015, IMS Study, NEPTUNE and The DRESSING Trial). The combined analysis of studies with moderate and high qualitative certainty of conclusions revealed heterogeneity; therefore, no combined effect was presented. The heterogeneity cannot be explained by the studies being based on wounds of different aetiologies.

The prediction interval overlaps the null, and the studies with statistically significant effects made up less than 50% of the total weight of all studies. The effect direction differs. Consequently, there is no hint of an effect on the length of hospital stay.

4.6.6.2 Length of stay in intensive care unit (ICU)

Usable results on ICU length of stay were reported in 2 studies. The IRB00109564 study with moderate qualitative certainty of conclusions reported the results in a continuous format. The NEPTUNE study with high qualitative certainty of conclusions used a dichotomous format. No study showed a statistically significant difference between treatment groups. Consequently, there is no hint of an effect on ICU length of stay.

4.6.6.3 Re-hospitalization

Usable results on re-hospitalization were reported in 11 studies. No hint of an effect can be inferred from the results of the studies which showed high qualitative certainty of conclusions (CE/US/11/01/PIC, Gillespie 2015, S-20130010 and The DRESSING Trial). Similarly, the collective analysis of studies with moderate and high qualitative certainty of conclusions failed to show a statistically significant difference between the two treatment groups (OR 0.87; 95% CI [0.62; 1.22]). Consequently, there is no hint of an effect on re-hospitalization.

4.6.6.4 Conclusion on benefit regarding length of hospital stay and (re-)hospitalization

Summarizing the sub-outcomes for both length of hospital stay and (re-)hospitalization, the data are heterogeneous, and there is no hint of benefit or harm of NPWT in comparison with SWT.

4.6.7 Results on health-related quality of life

Usable data on health-related quality of life were reported in 2 studies which each showed moderate qualitative certainty of conclusions. Both studies reported data on the EuroQol Visual Analogue Scale (EQ VAS). No statistically significant difference between the two treatment groups was found in the meta-analysis (Hedges' g 0.09; 95% CI [−0.04; 0.22]). Regarding the outcome for health-related quality of life, there is consequently no hint of benefit.

4.6.8 Results on functioning

Regarding the outcome for functioning, usable results from 1 study of moderate qualitative certainty of conclusions were available. The study showed no statistically significant difference between the two treatment groups. In terms of the outcome for functioning, there is consequently no hint of benefit.

4.6.9 Results on need of third-party help or need of long-term care

No usable results were available on this outcome.

4.7 Evidence map

Table 5 below shows the evidence map for patient-relevant outcomes.

Table 5: Evidence map for patient-relevant outcomes

	Morbidity					**Health-related quality of life and psychosocial aspects**		
Mortality	**Wound closure**	**Adverse events: Wound complications and treatment complications**	**Amputation**	**Pain**	**Length of hospital stay and (re-)hospitalization**	**Health-related quality of life**	**Functioning**	**Need of third-party help or need of long-term care**
⇔	⇗	⇔ / ⇑[a]	-	⇑⇓	⇑⇓	⇔	⇔	-
⇑: Indication of greater benefit of NPWT in comparison with SWT ⇗: Hint of greater benefit of NPWT in comparison with SWT ⇔: No hint, indication or proof, homogeneous result ⇑⇓: No hint, indication or proof, heterogeneous result -: No data reported								
a: Regarding the aggregate analysis for total rate of SAEs, there is consequently no hint of an effect. Regarding the outcome for infection, there is an indication of an effect in favour of NPWT.								
SAE: Serious adverse event; SWT: Standard wound therapy; NPWT: Negative pressure wound therapy								

5 Classification of the assessment result

As already discussed in detail in the preliminary report N17-01A, it was not possible to include a relevant number of studies on negative pressure wound therapy in the report; the reason behind this was that data were made available selectively or not at all. This problem was encountered with both manufacturer-sponsored and investigator-initiated studies. In total, data on at least 2058 patients with wounds healing by primary intention remained unpublished. Usable data, in contrast, were available for 6981 patients. For NPWT of wounds healing by primary intention, the data of at least 23% of patients [2058 / (2058+6981)] are therefore unavailable. Even the alternative calculation method, i.e., (in the absence of information to the contrary) using only half instead of the planned sample size for prematurely terminated studies and those of unclear status, would still result in a data gap of 17% [1420 / (1420 + 6981)].

Regarding the calculation of the data gap, it must be noted that potential outcome reporting bias was disregarded in this study-level assessment. Therefore, the usable data found for a specific outcome may conceivably reflect an even smaller percentage of the evidence actually generated.

Since it can be safely assumed that a data gap of 23% can have a relevant effect on results, the certainties of conclusion determined in the benefit assessment were downgraded.

Under consideration of the potential publication bias, an indication of greater benefit in favour of NPWT was found with respect to the outcome for infection and a hint of the same regarding the outcome for wound closure. This conclusion could be safely drawn despite the fact that, at study level, significant results were often non-existent, and the majority of the studies exhibited considerable methodological shortcomings. On the basis of the criterion of allocation concealment alone, 33 out of the 45 studies included in the assessment have a high risk of bias at study level. This is associated with an elevated risk of a systematic bias of treatment effects. Yet even the 8 studies with a low risk of bias at study level exhibited study-level deficiencies which largely led to a high risk of bias at outcome level. In addition to lack of blinding of outcome data collection for subjective outcomes or lack of information on the system used to survey the respective outcome, there were also uncertainties or even violations in terms of the adequate implementation of the ITT principle. In both instances, these are avoidable quality defects concerning study conduct as well as study reporting. Only 2 studies with a low risk of bias at study level also had a low risk of bias at outcome level for all outcomes.

The results on wound infection rates, which were available from 36 out of 45 studies, are relevant for the conclusion on benefit. To allow a clinical assessment of the reduction of wound infections, it is essential to classify infections by severity since it is important to determine if an infection may potentially have a severe course requiring further treatment or whether it represents only a mild inflammation in the course of healing. However, 16 studies exclusively reported the overall infection rate, including minor infections such as superficial skin infections. The remaining 20 studies reported the total rate as well as the severity of infection in accordance

with CDC or Szilagyi criteria. In these studies, severe infections tended to be rare, however. Serious infections were reported in the low single-digit percentage range, whereas the total rate of all infections was above 30% in some studies. This suggests that serious infections tended to be rare in the studies, and it was largely mild infections which contributed to the identified effect.

Ultimately, the positive effects of NPWT on infections are not reflected by the effects found on the total rate of SAEs or length of hospital stay. This is particularly notable since a higher rate of clinically relevant infections would presumably extend the hospital stay.

The effect found on dehiscence is worthy of discussion. The performed analyses (with and without studies having at least 1 treatment arm without event) had diverging results. The meta-analysis which excluded the studies without an event revealed a significant effect (OR 0.76 (95% CI [0.59; 0.98]), although at 0.98, the upper confidence limit is very close to the null. The analysis which included the studies without event (beta-binomial model), however, failed to show a significant effect (OR 0.77; 95% CI [0.44; 1.35]); therefore, this resulted in a hint of benefit in favour of NPWT, which was downgraded to no hint in consideration of potential publication bias. A critical evaluation of these results must also take into account, however, that the studies failed to clearly classify dehiscences. In 13 out of 23 studies included in the analysis, no information was provided on the severity of dehiscence; therefore, the recorded dehiscences cannot be conclusively defined as SAEs. Only the studies AHS.2012.Prevena.Cooper.01, CE/US/11/01/PIC and Pleger 2017 classified dehiscences by severity and analysed the data accordingly. All other studies merely analysed the total dehiscence rate, even in cases where severity data were available. This is a highly relevant issue since superficial dehiscence, where the wound margins separate only superficially but surgical structures are not exposed, typically does not require any further measures beyond normal wound care for superficial wounds. Deep dehiscence, in contrast, where the wound opens down to the structure receiving surgery, typically requires surgical revision, which should usually be reflected by other effects such as length of hospital stay.

In addition to potential publication bias and the methodological shortcomings of the majority of studies, the results found are largely based on studies which included mostly or exclusively patients with risk factors for impaired wound healing (overweight/obesity, diabetes mellitus, cardiovascular diseases, wound contamination, local tissue damage, reduced perfusion, etc.). Only 3 out of 45 studies reported no risk factors in the study population. Across groups, the mean wound infection rates in the studies analysed here were above 10% and likely represent a result of the higher overall risk of impaired wound healing in the entire study population; they are far above the absolute rates reported in Germany for postoperative wound infections following standard procedures in the inpatient sector (e.g. Caesarean section 0.1%, primary THEP 0.5% (THEP: total hip endoprosthesis), breast surgery 0.7% [284]).

In consideration of the various limitations (potential publication bias, high risk of bias at study level, risk factors for impaired wound healing included in the majority of considered studies), the effects found should be interpreted with caution.

Due to the calculated total data gap of 23%, the planned subgroup analyses were foregone. It is very unclear what influence the factors determined in these analyses would have if the data were complete. The analyses generated here therefore do not permit a conclusion on benefit to be drawn by subgroups, for instance by indication.

6 Conclusion

A total of 45 studies supplied usable results on patient-relevant outcomes. Most studies were on postoperative wounds in endoprosthetics, obstetrics (Caesarean section), abdominal and cardiovascular surgery. The majority of studies were done on wounds with an elevated risk of impaired wound healing. No results whatsoever were available on a relevant number of further studies (23% data gap); hence, the certainty of conclusions was downgraded to account for potential publication bias.

With regard to the outcome for wound closure, there was a hint of greater benefit of NPWT in comparison with SWT in wounds healing by primary intention. The analyses additionally revealed an indication of greater benefit of NPWT in terms of avoiding wound infection in wounds healing by primary intention. For the remaining outcomes (particularly mortality, total rate of complications, pain, length of hospital stay, and health-related quality of life), there were no hints of benefit or harm of NPWT.

7 References for English extract

Please see full final report for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/non-drug-interventions/n-projekte/n17-01b-negative-pressure-wound-therapy-for-wounds-healing-by-primary-intention.9666.html

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to February 07, 2019

The following filters were adopted:

- Systematic review: Wong [285] – High specificity strategy
- RCT: Lefebvre [286] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	**Searches**
1	Negative-Pressure Wound Therapy/
2	(Vacuum/ or Suction/ or Pressure/) and Wound Healing/
3	((vacuum or negative) adj3 (assisted or pressure) adj3 (therap* or dressing* or wound* or closure*)).ti,ab.
4	or/1-3
5	Randomized controlled Trial.pt.
6	controlled clinical trial.pt.
7	randomized.ab.
8	placebo.ab.
9	drug therapy.fs.
10	randomly.ab.
11	trial.ab.
12	groups.ab.
13	or/5-12
14	exp animals/ not humans.sh.
15	13 not 14
16	cochrane database of systematic reviews.jn.
17	(search or MEDLINE or systematic review).tw.
18	meta analysis.pt.
19	or/16-18
20	or/15,19
21	and/4,20
22	21 not (comment or editorial).pt.
23	limit 22 to yr="2006-Current"

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search (vacuum[TIAB] OR negative[TIAB]) AND (assisted[TIAB] OR pressure[TIAB]) AND (therap*[TIAB] OR dressing*[TIAB] OR wound*[TIAB] OR closure*[TIAB])
#2	Search clinical trial*[TIAB] OR random*[TIAB] OR placebo[TIAB] OR trial[TI]
#3	Search search[TIAB] OR meta analysis[TIAB] OR MEDLINE[TIAB] OR systematic review[TIAB]
#4	Search #2 OR #3
#5	Search #1 AND #4
#6	Search #5 NOT Medline[SB]
#7	Search #6 AND 2006:2019 [DP]

3. Embase

Search interface: Ovid

- Embase 1974 to 2019 February 07

The following filters were adopted:

- Systematic review: Wong [285] – High specificity strategy
- RCT: Wong [285] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	vacuum assisted closure/
2	negative pressure wound therapy/
3	vacuum assisted closure device/
4	(vacuum/ or suction/ or pressure/) and wound healing/
5	((vacuum or negative) adj3 (assisted or pressure) adj3 (therap* or dressing* or wound* or closure*)).ti,ab.
6	or/1-5
7	(random* or double-blind*).tw.
8	placebo*.mp.

#	Searches
9	or/7-8
10	(meta analysis or systematic review or MEDLINE).tw.
11	or/9-10
12	and/6,11
13	12 not medline.cr.
14	13 not (exp animal/ not exp humans/)
15	14 not (Conference Abstract or Conference Review or Editorial).pt.
16	..l/ 15 yr=2006-Current

4. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 2 of 12, February 2019
- Cochrane Central Register of Controlled Trials: Issue 2 of 12, February 2019

ID	Search
#1	MeSH descriptor: [Negative-Pressure Wound Therapy] this term only
#2	MeSH descriptor: [Vacuum] this term only
#3	MeSH descriptor: [Suction] this term only
#4	MeSH descriptor: [Pressure] this term only
#5	MeSH descriptor: [Wound Healing] this term only
#6	(#2 or #3 or #4) and #5
#7	((vacuum or negative) near/3 (assisted or pressure) near/3 (therap* or dressing* or wound* or closure*)):ti,ab
#8	#1 or #6 or #7
#9	#8 in Cochrane Reviews (Reviews and Protocols)
#10	#8 Publication Year from 2006 to present, in Trials

5. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR Negative-Pressure Wound Therapy
2	MeSH DESCRIPTOR Vacuum
3	MeSH DESCRIPTOR Suction
4	MeSH DESCRIPTOR Pressure

Line	Search
5	#2 OR #3 OR #4
6	MeSH DESCRIPTOR Wound Healing
7	#5 AND #6
8	((vacuum or negative) AND (assisted or pressure) AND (therap* or dressing* or wound* or closure*))
9	#1 OR #7 OR #8
10	(#9) IN HTA FROM 2006 TO 2019

A.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov/
- Type of search: Advanced Search

Search strategy
((vacuum OR negative) AND (assisted OR pressure) AND (therapy OR dressing OR wound OR closure)) [TREATMENT]

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Search strategy
vacuum AND assisted AND therapy OR vacuum AND assisted AND dressing OR vacuum AND assisted AND wound OR vacuum AND assisted AND closure OR vacuum AND pressure AND therapy OR vacuum AND pressure AND dressing OR vacuum AND pressure AND wound OR vacuum AND pressure AND closure OR negative AND assisted AND therapy OR negative AND assisted AND dressing OR negative AND assisted AND wound OR negative AND assisted AND closure OR negative AND pressure AND therapy OR negative AND pressure AND dressing OR negative AND pressure AND wound OR negative AND pressure AND closure