IQWiG Reports – Commission No. N17-01A

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

Extract

[1] Translation of Chapters 1 to 6 of the final report *Vakuumversiegelungstherapie von Wunden mit intendierter sekundärer Wundheilung* (Version 1.1; Status: 25 June 2019 [German original] / 20 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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This report was prepared in collaboration with external experts.

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 in comparison with standard wound therapy

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

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

Conclusion

For a relevant percentage of studies on negative pressure wound therapy of wounds healing by secondary intention, no data are available. Since at 24%, the calculated data gap can cause relevant bias (publication bias), the certainties of conclusion determined in the benefit assessment were downgraded.

For the outcomes “wound closure” and “length of hospital stay and (re-)hospitalization”, there was an indication of greater benefit of negative pressure wound therapy in comparison with standard wound therapy in wounds healing by secondary intention.

For the outcomes “mortality”, “adverse events”, “amputation”, “pain”, “health-related quality of life” and “functioning”, there was no hint of benefit or harm of negative pressure wound therapy of wounds healing by secondary intention. For the outcome “need of third-party help” or “need of long-term care”, no conclusion could be derived since no usable data were available.

The process of generating this benefit assessment has revealed that legal regulations are needed to improve the transparency of clinical research on non-drug interventions so that benefit assessments can be meaningfully conducted.

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
CI	Confidence interval
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICU	Intensive care unit
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
MD	Mean difference
NPWT	Negative pressure wound therapy
OR	Odds ratio
RCT	Randomized controlled trial
SAE	Serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SWT	Standard wound therapy

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 on which Final Report N04-03 and Rapid Report N06-02 were based was to assess the benefit

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

in patients with acute or chronic skin wounds of any aetiology or 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 in RCTs and 486 in non-randomized trials.

The results of the benefit assessments N04-03 and N06-02 failed to show a superiority of negative pressure wound therapy to conventional wound treatment which would justify widespread use of the method outside of studies.

However, many ongoing and/or unpublished RCTs were found during this investigation, so that conducting another investigation of negative pressure wound therapy seemed to be warranted. Further, an RCT on negative pressure wound therapy in Germany was initiated and conducted in the course of the previous assessments [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 secondary intention with regard to patient-relevant outcomes.

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

3 Methods

The target population of the benefit assessment was patients with wounds healing by secondary 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 wound volume” as well as “change in wound surface after skin graft” were surveyed to provide supplementary information. Additionally, intervention-related and sickness-related cost and patient satisfaction with treatment were to be considered and the related effects presented as supplementary information. Patient satisfaction would be included in the analysis only if it reflected health-related aspects.

Subjective outcomes (e.g., health-related quality of life) were considered only if they were surveyed with 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 retrieval of the 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 definition of the respective study pool, data were further processed in two 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

reviews was conducted in the databases MEDLINE, Embase, Cochrane Database of Systematic Reviews and 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, documents made available from hearing procedures and author queries.

Relevant studies were selected by two 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 risk of bias on the study and outcome levels was assessed and rated as high or low. The results of the individual studies were described in order according to outcomes.

If relevant completed studies without published results were identified in the systematic search, there was a risk of publication bias. To determine potential publication bias, the percentage of missing data was calculated on a study level. As a result, potential outcome reporting bias was 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 with the 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 bias was assumed to have little effect on results if the percentage of 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, was below 10%. In this case, a regular benefit assessment was conducted since the missing data were not expected to relevantly influence the results. If the percentage was between 10% and 30%, the potential publication bias was assumed to have a major effect on results. Since the missing data were expected to relevantly influence 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, no planned subgroup analyses, for instance by wound type, or surrogate validation were carried out.

If the percentage was above 30%, it was assumed that due to the potential publication bias, no conclusion could be drawn regarding benefit or harm, and no evidence map was generated.

To categorize the completeness of data submission 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 the involved manufacturers before data were submitted. This agreement applied to all projects, that is, regardless of wound type distribution. In cases where a company was

inordinately responsible for a relevant percentage of missing data, the selectively supplied data on patient-relevant outcomes were excluded.

For the sake of robustness testing, a second scenario was considered when calculating the percentage of missing data. For studies without reported results which, according to the trial registry entry, were prematurely terminated or were of unclear status, only half of the planned sample size was used, unless information to the contrary was available.

Mean differences can be influenced to a different extent due to the different wound types included in the studies; therefore, the latter were standardised, if necessary, in the meta-analytical summaries using Hedges' g.

4 Results

4.1 Results of the comprehensive information retrieval

The information retrieval identified 110 randomized controlled trials (236 documents) as relevant for N17-01A and/or N17-01B.

For N17-01A and N17-01B together, a total of 127 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 24 July 2018.

Studies to be considered for N17-01A

The information retrieval identified 62 randomized controlled trials (119 documents) as relevant for the research question of this benefit assessment on NPWT in patients with wounds healing by secondary intention.

Nine studies were only formally included because they fulfilled all inclusion criteria but failed to supply usable data on any outcome. Five additional studies reported usable data only on outcomes presented for supplementary information. For transparency purposes, these 14 studies were included in the study pool since they met the documented inclusion criteria.

Hence, the study pool included a total of 48 studies which reported usable data on patient-relevant outcomes.

For NPWT in patients with wounds healing by secondary intention, 5 planned and 7 ongoing studies were identified. Furthermore, 10 studies of unclear status, 14 prematurely terminated studies and 9 completed studies without reported results were identified.

Table 1: Study pool of the benefit assessment – wounds healing by primary intention (n =48) (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[b]	No	Yes [6] / yes [7]	--	--
14-1920	No	Yes [8] / yes [9]s	--	Yes [10][a]
AHS.2011.Prevena. Heine.03	Yes [11]	Yes [12] / yes [13]	Yes [14]	Yes [15]
AHS.2012. Customizable.01	No	Yes [16] / no	Yes [17]	Yes [18]
AHS.2012.Prevena. Cooper.01	No	Yes [19] / yes [20]	Yes [21]	Yes [22]
CCF 14-273	No	Yes [23] / yes [24]	--	Yes [23][a]
CE/US/11/01/PIC	Yes [25]	Yes [26] / no	Yes [27]	Yes [28]
Chio 2010[c]	Yes [29]	No	--	--
Crist 2017[b]	Yes [30]	Yes [31] / yes [32]	--	Yes [33]
DEPRES	Yes [34]	Yes [35] / no	--	--
Engelhardt 2018	Yes [36]	No	--	--
Gillespie 2015	Yes [37]	Yes [38] / no	--	--
H-20292	No	Yes [39] / yes [40]	--	--
HIC# 1010007535	Yes [41]	Yes [42] / yes [43]	--	--
Howell 2011[b]	Yes [44]	No	--	--
IMS-Studie	Yes [45]	Yes [46] / no	--	Yes [47]
INVIPS-Trial	Yes [48.49]	Yes [50] / no	--	--
Karlakki 2016	Yes [51.52]	Yes [53] / no	--	--
KCI VAC Study	Yes [54]	Yes [55] / no	--	Yes [56]
KCI.2013.Prevena.01	No	Yes [57] / no	Yes [58]	Yes [59]
Li 2016	Yes [60]	Yes [61] / no	--	--
Manoharan 2016	Yes [62]	Yes [63] / no	--	--
Mendame Ehya 2017	Yes [64]	No	--	--
Nordmeyer 2015[c]	Yes [65.66]	No	--	--
NPWTCS	No	Yes [67] / yes [68]s	--	Yes [69]
Pachowsky 2011[b]	Yes [70]	No	--	--
Pauser 2016[c]	Yes [71]	No	--	--

Table 1: Study pool of the benefit assessment – wounds healing by primary intention (n =48) (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)**
Peter Suh 2016	Yes [72-74]	No	--	--
PICO Trial	Yes [75]	Yes [76] / no	--	--
Pleger 2017	Yes [77]	No	--	--
PROVAC	Yes [78]	Yes [79] / yes [80]	--	Yes [81]
Pro00040054	No	Yes [82] / yes [83]	--	--
R000016785[b]	Yes [84.85]	Yes [86] / no	--	--
RRG-104871	Yes [87.88]	Yes [89] / no	--	Yes [90]
S-20130010	Yes [91]	Yes [92] / no	--	--
SAVIOR Trial[b]	No	Yes [93] / yes [94]	--	Yes [95]
Shen 2017	Yes [96]	Yes [97] / no	--	--
Shim 2018	Yes [98]	No	--	--
Tanaydin 2018	Yes [99.100]	No	--	--
The DRESSING Trial	Yes [101-103]	Yes [104] / no	--	--
Uchino 2016	Yes [105]	Yes [106.107] / no	--	--
VAC 2001-04	Yes [108.109]	Yes [110] / no	--	--
VAC 2001-05	Yes [111]	Yes [112] / no	--	--
VAC NPWT KCI Dressing Study	Yes [113]	Yes [114] / no	--	--
VACCS	Yes [115]	Yes [116] / no	--	--
Witt-Majchrzak 2014	Yes [117]	No	--	--
Yu 2017	Yes [118]	Yes [119] / yes [120]	--	--

Italicized study name: unpublished study

a: Publicly accessible

b: Only formally included due to lack of usable data: This may be due to an unclear number of patients being randomized to the respective groups or to the trials including fewer than 10 patients.

c: 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.

Table 2: Study pool of the benefit assessment – wounds healing by secondary intention (n = 62) (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 [121-123]	No	--	--
ActiVac[a]	No	Yes [124] / yes [125]	--	--
Arti 2016	Yes [126]	Yes [127] / no	--	--
Ashby 2012	Yes [128]	Yes [129] / no	--	--
Banasiewicz 2013	Yes [130]	No	--	--
Bee 2008	Yes [131]	No	--	--
Biter 2014	Yes [132.133]	No	--	--
Braakenburg 2006	Yes [134]	No	--	--
CE/044/PIC	No	Yes [135] / no	Yes [136-139]	Yes [140]
Chiang 2017	Yes [141]	No	--	--
Correa 2016	Yes [142]	Yes [143] / no	--	--
Dalla Paola 2010 S-I[b]	Yes [144]	No	--	--
Dalla Paola 2010 S-II	Yes [144]	No	--	--
De Laat 2011	Yes [145]	Yes [146] / no	--	--
DiaFu	Yes (publications of study design [3,147])	Yes [148]; [149] / no	Yes [150]; [151][c]	Yes [152][c]
Dwivedi 2016[b]	Yes [153.154]	Yes [155] / no	--	--
Eginton 2003[a]	Yes [156]	No	--	--
Ford 2002[a]	Yes [157]	No	--	--
Gupta 2013	Yes [158]	No	--	--
Hu 2009	Yes [159]	No	--	--
Huang 2006	Yes [160]	No	--	--
ISAW[a]	No	Yes [161-163] / no	Yes [164][c]	Yes [165][c]
Jayakumar 2013	Yes [166]	No	--	--
Joseph 2000[a]	Yes [167]	No	--	--
Kakagia 2014	Yes [168]	No	--	--
Karatepe 2011	Yes [169]	No	--	--
Keskin 2008[a]	Yes [170]	No	--	--
Leclercq 2016	Yes [171]	No	--	--
Liao 2012	Yes [172]	No	--	--
Llanos 2006	Yes [173]	No	--	--
Mody 2008	Yes [174]	No	--	--

Table 2: Study pool of the benefit assessment – wounds healing by secondary intention (n = 62) (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 [175]	No	--	--
Moisidis 2004	Yes [176]	No	--	--
Mouës 2004	Yes [177-179]	No	--	--
Nain 2011	Yes [180]	No	--	--
Novinščak 2010	Yes [181]	No	--	--
Perez 2010	Yes [182]	No	--	--
Rencüzoğulları 2015	Yes [183]	No	--	--
Riaz 2010[a]	Yes [184]	No	--	--
Saaiq 2010	Yes [185]	No	--	--
Sajid 2015[b]	Yes [186]	No	--	--
Shen 2013	Yes [187]	No	--	--
Sibin 2017	Yes [188]	No	--	--
Sinha 2013	Yes [189]	No	--	--
Sun 2007[b]	Yes [190]	No	--	--
SWHSI	Yes [191.192]	Yes [193] / no	--	--
TOPSKIN	Yes [194.195]	Yes [196] / no	--	--
VAC 2001-01	No	No	Yes [197, 198]	Yes [199]
VAC 2001-02	No	No	Yes [198, 200]	Yes [201]
VAC 2001-03	No	No	No[d]	No
VAC 2001-06	Yes [202]	Yes [203] / yes [204]	--	--
VAC 2001-07	Yes [205-208]	Yes [209] / no	Yes [210]	Yes [211]
VAC 2001-08	Yes [212-215]	Yes [216] / yes [217]	Yes [218]	Yes [219]
VAC 2002-09	No	No	Yes [198, 220]	Yes [221]
VAC 2002-10	No	No	Yes [198, 222]	Yes [223]
Vaidhya 2015[a]	Yes [224]	No	--	--
Vather 2018[a]	Yes [225]	No	--	--
Virani 2016	Yes [226]	No	--	--
Vuerstaek 2006	Yes [227.228]	Yes [229] / no	--	--
Wanner 2003[b]	Yes [230]	No	--	--
WOLLF	Yes [231-233]	Yes [234] / no	--	--
Xu 2015	Yes [235]	No	--	--

Table 2: Study pool of the benefit assessment – wounds healing by secondary intention (n = 62) (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)**
Italicized study name: unpublished study a: Only formally included due to lack of usable data: This may be due to an unclear 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 [236]. A presentation referencing this study is also available [237].				

4.2 Characteristics of the studies included in the evaluation

The 48 studies reporting usable results on patient-relevant outcomes for the benefit assessment provided data on a total of 4315 patients. The individual studies included between 12 and 460 patients and were conducted worldwide in the years 1998 to 2016. Most studies had two arms (n = 46). One study had 3 arms (Novinščak 2010 [181]) and one 4 arms (TOPSKIN [194]). Thirty-five studies were monocentric and 13 multicentric. Most studies (n = 38) were conducted in the inpatient sector. Forty-seven studies randomized and analysed patients, while 1 study (Moisidis 2004 [176]) randomized and analysed wound halves. In 45 studies, 1 wound per patient was analysed, while in 2 studies (Kakagia 2014 [168] and VAC 2001-06 [202]), at least 1 wound per patient was analysed.

The included studies comprised a wide range of different wounds of varying aetiologies, specifically:

- Amputation wounds (n = 1 study) (Liao 2012 [172]),
- Decubitus wounds (n = 2) (Ashby 2012 [128], VAC 2001-01 [197]),
- Diabetic foot wounds (n = 6) (Dalla Paola 2010 S-II [144], DiaFu [150], Karatepe 2011 [169], Nain 2011 [180], VAC 2001-07 [210], VAC 2001-08 [218]),
- Diabetic ulcer wounds (n = 1) (Novinščak 2010),
- Foot wounds (n = 1) (Chiang 2017 [141]),
- Fasciotomy wounds due to compartment syndrome (n = 1) (Kakagia 2014),
- Necrotising fasciitis wounds (n = 2) (Huang 2006 [160], Xu 2015 [235]),
- Open fractures (n = 7) (Arti 2016 [126], Gupta 2013 [158], Jayakumar 2013 [166], Sibin 2017 [188], VAC 2001-06, Virani 2016 [226], WOLLF [233]),

- Open abdomen (n = 4) (Bee 2008 [131], Correa 2016 [142], Rencüzoğulları 2015 [183], VAC 2002-10 [222]),
- Pilonidal sinus wounds (n = 2) (Banasiewicz 2013 [130], Biter 2014 [132]),
- Open thorax (n = 1) (VAC 2002-09 [220]),
- Traumatic wounds of different causes (n = 3) (Llanos 2006 [173], Saaiq 2010 [185], Sinha 2013 [189]),
- Leg ulcer wounds (n = 4) (Leclercq 2016 [171], VAC 2001-02 [200], VAC 2001-03 [236], Vuerstaek 2006 [227]),
- Burns (n = 2, of which 1 study in small children) (TOPSKIN, Shen 2013 [187]),
- Groin wounds due to infections (n = 1) (Acosta 2013 [121])
- And various wounds resulting from an underlying disease and/or of traumatic/iatrogenic aetiology (n = 10) (Braakenburg 2006 [134], CE/044/PIC [136], De Laat 2011 [145], Hu 2009 [159], Mody 2008 [174], Moisidis 2004, Mouës 2004 [177], Mohsin 2017 [175], Perez 2010 [182], SWHSI [192]).

4.3 Studies without reported results / calculation of data gap

Using the procedure described in Section 3 for determining potential publication bias for the assessment of NPWT for wounds healing by secondary intention, a total of 30 studies are to be considered (8 completed, 12 prematurely terminated, and 10 of unclear status). Unlike the preliminary report, they also include KCI-sponsored studies. The additional information and documents on NPWT-related studies made available by the manufacturer during the commenting procedure now sufficiently reduced the data gap. Four prematurely terminated studies sponsored by the manufacturer KCI remain, and even a generous assessment must conclude that the data provided are insufficient (Greer 1999, VAC 2001-00, VAC 2006-19 as well as VAC TRIAL). Table 3 lists the studies with the respective sample size used for calculating the data gap.

Table 3: Studies considered when 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, clinical study report, raw data (each not publicly accessible)	
Completed studies n = 8 with missing data on at least N = 522 patients					
ACTRN12614000056695	40	ACTRN12614000056695 [238] / no	--	--	Completed (12/2013)
Adams 2005 [1]	1[c]	--	--	--	Completed (03/2005)[d]
ATEC	112	ISRCTN60292377 [239] / no	--	--	Completed (09/2016)
B2108R [1]	120	NCT00011531 [240] / no	--	--	Completed (12/2001)
CTRI/2018/01/011503	54	CTRI/2018/01/011503 [241] / no	--	--	Completed (04/2017)
foryou	48	ChiCTR-TRC-12002700 [242] / no	--	--	Completed (12/2015)[e]
VACOTOL-012	28	NCT02102685 [243] / no	--	--	Completed (09/2013)
VSD	119[f]	ChiCTR-IOR-16008087 [244] / no	--	--	Completed (03/2016)[e]
Prematurely terminated studies n = 12 with missing data on at least N = 430 patients					
045-1502-226 [1]	30	NCT00121537 [245] / no	--	--	Prematurely terminated (10/2015)[e]
2008/2023-31	30[g]	NCT01191567 [246] / no	--	--	Prematurely terminated[g] (07/2012)
ANSM	36	NCT02509533 [247] / no	--	--	Prematurely terminated (07/2015)[h]
Greer 1999 [1]	16[i]	--	--	Study protocol [248], raw data [249][j]	Prematurely terminated (11/1999)[k]
HTA012-0801-01	184	NCT00691821 [250] / no	--	--	Prematurely terminated (07/2011)[e]
STOMAVAC	14[l]	ISRCTN37399763 [251] / no	--	--	Prematurely terminated (12/2014)
U1111-1132-0768	30	ACTRN12612000702819 [252] / no	--	--	Prematurely terminated[m] (not specified)[n]

Table 3: Studies considered when 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, clinical study report, raw data (each not publicly accessible)	
U1111-1133-5694	0[o]	ACTRN12612000885897 [253] / no	--	--	Prematurely terminated[o] (not specified)
U1111-1162-0654	16[p]	ACTRN12614001068651 [254]	--	--	Prematurely terminated (not specified)[p,q]
VAC 2001-00 [1]	46[r]	--	--	Study protocol [255], clinical study report [256][s]	Prematurely terminated (not specified)[k,t]
VAC 2006-19	19[u]	NCT00837096 [257] / no	--	Study protocol [258][v]	Prematurely terminated (10/2013)[e]
VAC TRIAL	9[w]	ACTRN12606000384550 [259] / no	--	Study protocol [260]	Prematurely terminated (09/2005)
Studies of "unclear" status n = 10 with missing data on at least N = 434 patients					
2015046	80	NCT02374528 [261] / no	--	--	Unclear (04/2016)
382094-2	30	NCT01857128 [262] / no	--	--	Unclear (12/2014)
ACTRN12609000149268	60	ACTRN12609000149268 [263] / no	--	--	Unclear[x] (not specified)
ACTRN12609000995279	100	ACTRN12609000995279 [264] / no	--	--	Unclear[x] (not specified)
CTRI/2014/02/004390	40	CTRI/2014/02/004390 [265] / no	--	--	Unclear[x] (not specified)
Foo 2004 [1]	--[y]	--	--	--	Unclear[d] (not specified)
Gupta 2001 [1]	1[c]	--	--	--	Unclear[d] (not specified)
ITIQ002A	90	NCT01734109 [266] / no	--	--	Unclear (03/2014)
McCarthy M 2005 [1]	1[c]	--	--	--	Unclear[z] (not specified)
NPWTvsGPA	32	NCT02314468 [267] / no	--	--	Unclear (10/2016)

a: Sample size used per study for calculating the data gap; based on trial registry unless noted otherwise
b: Based on trial registry unless noted otherwise
c: Planned sample size unknown N = 1 used as placeholder
d: Study status classified in accordance with the status in the underlying Final Report N04-03. No further information available.
e: Date of last update of the trial registry entry. Study may have been completed / prematurely terminated for longer.
f: Trial registry contains a stored Excel file that includes non-interpretable individual patient data on 50 patients. Regardless of the interpretability of data, the unanswered author query made it impossible to determine whether this is the number of actually recruited patients and the study was hence prematurely terminated, contrary to the documentation in the trial registry, or whether, for instance, they are data on patients with complete datasets, but a total of N = 119 patients were randomized, as documented in the trial registry entry.
g: According to the response to an author query, the study was prematurely terminated. The planned sample size was N = 200 according to the trial registry.
h: Registration date equals date of documentation of premature termination. Study may have been prematurely terminated earlier.
i: Planned sample size of 160 according to protocol, 80 according to [1]. According to the manufacturer KCI, only 16 patients included in the study.
j: Manufacturer KCI stated that most likely, no clinical study report exists. The raw data supplied later as part of the commenting procedure cover less than 70% of the included patients and provide no information on the planned patient-relevant outcomes. The study is therefore still considered missing.
k: According to the manufacturer KCI
l: According to the information provided by the manufacturer KCI, the study was prematurely terminated. The planned sample size was N = 100 according to the trial registry.
m: According to the response to the author query.
n: Since there was no update in the trial registry entry in a long time (07/2012) and the planned sample size was small, the study is assumed to have been prematurely terminated more than 12 months ago.
o: According to the response to an author query, the study was never started (hence sample size N = 0) and is therefore considered prematurely terminated. The planned sample size was N = 10 according to the trial registry.
p: According to the response to an author query, the study was prematurely terminated. The planned sample size was N = 30 according to the trial registry.
q: Since the trial registry entry has not been updated in a long time (10/2014), the sample size was small, and the last recruitment was originally planned for 09/2015, it was assumed that the study was prematurely terminated more than 12 months ago.
r: The study protocol stated a planned figure of 50 patients with bilateral wounds. The document provided later as part of the commenting procedure on the preliminary report refers to 23 patients with bilateral wounds.
s: The manufacturer states that most likely, no clinical study report exists. The document provided later as part of the commenting procedure on the preliminary report cannot be reliably allocated to the study. In addition, several pages were deleted. The study is therefore still considered missing.
t: According to the available information, the study should have been completed for at least 1 year.
u: According to the study protocol from the manufacturer documents, a sample size of N = 300 was planned. According to the trial registry entry, the study was prematurely terminated with 17 included patients. According to the comment of the manufacturer KCI on the preliminary report, 19 patients were included in the study.
v: The manufacturer KCI states that no clinical study report exists. The study is still considered missing.
w: According to information provided by the manufacturer KCI and a trial registry entry updated in 08/2018, the study was prematurely terminated with N = 9 included persons. According to the trial registry entry, a sample size of N = 40 was planned.
x: No update of the trial registry entry for more than 2 years; therefore status classified as unclear. According to the available information, the study should have been completed for at least 1 year.

Table 3: Studies considered when 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, clinical study report, raw data (each not publicly accessible)	
y: In N04-03, the patient-relevant outcome for this study was identified as the change in wound area; therefore, no data on patient-relevant outcomes are likely to be expected from this study. Hence, this study will not be further considered here. z: Classification based on the last available information (Final Report N04-03: 03/2006) being supplied long ago. No further information available.					

In total, data on at least 1386 patients remain unpublished. For some identified studies, the planned sample size is unknown. These studies were included in the calculations with only N = 1 missing data; hence, the amount of missing data from the studies identified for this benefit assessment alone may be even larger. In contrast, data of 4315 patients are available in analysable form (see Section 4.2). Consequently, data of at least 24% (1386/5701) of patients included in the studies on NPWT with wounds healing by secondary intention are not accessible.

Furthermore, the remaining 15 studies without reported results which did not fall under the 12-month rule as yet at the time the search was conducted (1 completed, 2 prematurely terminated, 5 planned, and 7 ongoing studies) are expected to provide data on a total of 2471 patients on the basis of planned sample size or contradictory information which is already available.

4.4 Overview of assessment-relevant outcomes

Usable data on patient-relevant outcomes could be extracted from 48 studies. Table 4 presents an overview of the available usable data on patient-relevant outcomes from the included studies. No studies reported usable data on the outcomes “need of third-party help” or “need of 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
Acosta 2013	●	●	●	●	-	●	-	-	-
Arti 2016	-	●	●	-	-	-	-	-	-
Ashby 2012	●	●	●	-	●	-	-	-	-
Banasiewicz 2013	-	-	-	-	●	-	-	●	-
Bee 2008	●	-	●	-	-	-	-	-	-
Biter 2014	-	●	●	-	●	-	-	●	-
Braakenburg 2006	●	●	●	●	-	-	-	-	-
CE/044/PIC	-	●	●	-	●	●	-	-	-
Chiang 2017	-	-	●	-	-	-	-	-	-
Correa 2016	●	-	-	-	-	-	-	-	-
Dalla Paola 2010 S-II	-	●	●	●	-	-	-	-	-

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
De Laat 2011	-	-	●	-	-	●	-	-	-
DiaFu	●	●	●	●	●	-	-	-	-
Gupta 2013	-	●	●	-	-	●	-	-	-
Hu 2009	-	●	●	●	-	-	-	-	-
Huang 2006	●	-	-	●	-	●	-	-	-
Jayakumar 2013	-	●	●	-	-	●	-	-	-
Kakagia 2014	-	●	●	-	-	-	-	-	-
Karatepe 2011	-	●	-	-	-	-	-	-	-
Leclercq 2016	-	●	-	-	-	-	-	-	-
Liao 2012	-	-	●	-	-	●	-	-	-
Llanos 2006	-	●	●	-	-	●	-	-	-
Mody 2008	-	-	●	●	●	-	-	-	-
Mohsin 2017	-	-	●	-	-	-	-	-	-
Moisidis 2004	-	●	●	-	-	-	-	-	-
Mouës 2004	●	●	●	-	-	-	-	-	-
Nain 2011	-	●	●	-	-	-	-	-	-
Novinščak 2010	-	●	-	-	-	-	-	-	-
Perez 2010	-	●	●	-	-	-	-	-	-
Rencüzoğulları 2015	●	-	●	-	-	●	-	-	-
Saaiq 2010	●	●	●	-	-	●	-	-	-
Shen 2013	-	●	-	-	-	-	-	-	-
Sibin 2017	-	●	●	-	-	●	-	-	-
Sinha 2013	-	-	●	-	-	-	-	-	-
SWHSI	-	●	●	●	●	●	●	-	-
TOPSKIN	-	-	●	-	●	●	-	-	-
VAC 2001-01	●	-	●	-	-	-	-	-	-
VAC 2001-02	-	-	●	-	-	-	-	-	-
VAC 2001-03	-	●	●	-	-	-	-	-	-
VAC 2001-06	-	●	●	●	-	●	-	-	-
VAC 2001-07	●	●	●	-	-	●	-	-	-

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**
VAC 2001-08	●	●	●	-	-	-	-	-	-
VAC 2002-09	●	●	●	-	-	-	-	-	-
VAC 2002-10	●	●	●	-	-	-	-	-	-
Virani 2016	-	●	●	-	-	-	-	-	-
Vuerstaek 2006	●	●	●	-	●	●	-	-	-
WOLLF	●	●	●	●	●	-	●	●	-
Xu 2015	●	●	●	-	-	●	-	-	-

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

4.5 Risk of bias at study and outcome levels

The risk of bias at study level was rated as low for 7 studies (Ashby 2012, DiaFu, Llanos 2006, SWHSI, VAC 2001-07, Vuerstaek 2006 and WOLLF). For the other 41 studies, the risk of bias at study level was rated as high. On the basis of the "allocation concealment" criterion alone, 37 studies have a high risk of bias at study level. For the TOPSKIN study, high risk of bias at study level resulted from the unclear generation of the randomization sequence and lack of blinding of patients and treatment providers in conjunction with selective reporting. For the studies VAC 2001-01, VAC 2001-02 and VAC 2001-08, high risk of bias at study level resulted, among other things, from a lack of blinding of patients and treatment providers in conjunction with potential selective reporting.

In the 7 studies with low risk of bias at study level, the risk of bias at outcome level was rated. In the remaining 41 studies, the high risk of bias at study level directly transferred to the risk of bias at outcome level.

For the study Ashby 2012, the risk of bias was rated as low for the outcomes "mortality" and "wound closure" and as high for the outcome "pain" since this subjective outcome was surveyed without blinding. Regarding the outcome "adverse events", the risk of bias was high for some manifestations and low for others.

For the DiaFu study, a high risk of bias was found for all outcomes. For the outcomes "mortality", "wound closure", "adverse events" and "amputation", it remained unclear whether the ITT principle had been adequately implemented. The subjective outcome "pain" was surveyed without blinding.

For the Llanos 2006 study, the risk of bias for the outcomes "wound closure", "adverse events" and "length of hospital stay" was rated as low.

For the SWHSI study, the risk of bias for the outcomes "wound closure" and "amputation" was rated as low. The risk of bias for the outcomes "adverse events", "pain", "length of hospital stay" and "health-related quality of life" was rated as high due to the lack of blinding of outcome data collection and a potential violation of the ITT principle.

For the VAC 2001-07 study, the risk of bias was rated as high for the outcomes "mortality", "wound closure", "adverse events" and "length of hospital stay" due to lack of blinding of outcome data collection and unclear implementation of the ITT principle and/or due to other (outcome-specific) aspects.

For the Vuerstaek 2006 study, a high risk of bias was found for the outcomes "mortality", "wound closure", "adverse events", "pain" and "length of hospital stay" since the outcome data collection was non-blinded or without identifiable system. In addition, it remained unclear whether the ITT principle had been adequately implemented.

For the WOLLF study, the risk of bias was rated as high for the outcomes "mortality", "wound closure", "adverse events", "amputation", "pain", "health-related quality of life" and "functioning" due to lack of blinding of outcome data collection and violation of the ITT principle and/or due to other (outcome-specific) aspects.

4.6 Results of patient-relevant outcomes

As mentioned in Section 4.3, a data gap of 10% to 30% was calculated. Since an overall data gap of 24% can be expected to relevantly affect results, the certainty of conclusions of the benefit assessment were downgraded (proof to indication, indication to hint, hint to no hint). Due to the potential publication bias, the planned subgroup analyses were omitted.

4.6.1 Results on mortality

For the outcome "mortality", usable results from 18 studies were available.

From the outcome of the study with high qualitative certainty of conclusions (Ashby 2012), no hint of an effect can be derived. The collective analysis of studies with moderate and high qualitative certainty of conclusions also failed to show a statistically significant difference between the two treatment groups.

For the outcome "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 34 studies were available. Since these studies used different operationalizations, the data were first analysed by operationalization and then aggregated for a comprehensive conclusion on the benefit for the outcome "wound closure". In the absence of information to the contrary (e.g., 95% of the wound area being covered by granulation tissue), the data identified as wound healing were documented under the outcome "wound healing". If the reported data indicated that a study included, perhaps even exclusively, surgical wound closure in the outcome "wound healing", the results were documented under the outcome "wound healing and/or surgical wound closure".

4.6.2.1 Wound healing / time to wound healing

Wound healing

Usable results on wound healing were reported in 14 studies. If data were reported at multiple time points, those from the latest time point were chosen.

From the results of the studies with high qualitative certainty of conclusions (Ashby 2012 and Llanos 2006), no hint of an effect can be derived. The collective analysis of studies with moderate and high qualitative certainty of conclusions showed a statistically significant difference between the two treatment groups in favour of NPWT (OR: 1.56; 95% CI: [1.15; 2.13]).

A sensitivity analysis was conducted to determine whether the definition of wound healing influenced study results. For this purpose, the studies in which the outcome was defined as 100% epithelialization were compared with the studies without explicit outcome definition. For the latter, there was, on the other hand, no reason to assume that the reported data should have been categorized under the operationalization "wound healing and/or surgical wound closure". No statistically significant difference was found; hence, the results can be considered robust in this regard.

Consequently, there is an indication of an effect on wound healing in favour of NPWT.

Time to wound healing

Usable results on the time to wound healing were reported in 6 studies.

In the meta-analysis using Hedges' g, a statistically significant difference was found in favour of NPWT, both in the study with high qualitative certainty of conclusions (Llanos 2006) and in the consideration of the entirety of the studies. The results were rated clinically relevant (Hedges' g: −0.77; 95% CI: [−1.19; -0.35]).

The meta-analytical summary of all studies confirms the results of the single study with high qualitative certainty of conclusions. Therefore, proof of an effect in favour of NPWT on the time to wound healing in days was initially derived.

A sensitivity analysis showed that the definition of the outcome did not influence results.

In summary, the proof of an effect in favour of NPWT on the time to wound healing in days remained in place.

4.6.2.2 Wound healing and/or surgical wound closure / time to the respective event

Wound healing and/or surgical wound closure

Usable results on wound healing and/or surgical wound closure were reported by 21 studies. If data were reported at multiple time points, those from the latest time point were used.

No hint of an effect can be derived from the result of the study with high qualitative certainty of conclusions (SWHSI). Due to heterogeneity, no combined effect was presented for the combined analysis of studies with moderate and high qualitative certainty of conclusions. 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 results exhibit different effect directions. Hence, the effect direction differs. In 8 of the 21 studies, wound closure was achieved in 100% of patients in both study arms. In order to include these studies in the calculation of the odds ratio, the odds ratio was estimated by means of the beta binomial model. This model's effect was not statistically significant.

In view of data heterogeneity, there was no hint of an effect on wound healing and/or surgical wound closure.

Time to wound healing and/or to surgical wound closure or time to wound healing after intervention and surgical wound closure

Usable results on time to wound healing and/or surgical wound closure were reported in 9 studies. Two studies reported usable results on time to wound healing after intervention and surgical wound closure in the form of continuous data. Additionally, 3 studies reported usable results on time to wound healing after intervention and surgical wound closure in the form of dichotomous data.

Time to wound healing and/or surgical wound closure

In the meta-analysis using Hedges' g, there was substantial heterogeneity ($p < 0.001$), and no combined effect was presented. The prediction interval overlaps the null, and the weight of the statistically significant studies is below 50%. The effect direction differs. Consequently, no statistically significant treatment effect can be derived.

In view of data heterogeneity, there was no hint of an effect on the time to wound healing and/or surgical wound closure in days.

Time to wound healing after intervention and surgical wound closure

For the time to wound healing after intervention and surgical wound closure in days, results were available from 2 studies with moderate qualitative certainty of conclusions, which each reported a statistically significant difference in favour of NPWT. A meta-analytical summary of the results of both studies using a model with fixed effect shows a statistically significant difference between the two treatment groups in favour of NPWT (Hedges' g: −1.14; 95% CI: [−1.45; −0.84]).

This leads to an indication of an effect on the time to wound healing after intervention and surgical wound closure in days in favour of NPWT.

The analysis of the 3 studies (each of moderate qualitative certainty of conclusions) with usable results on the time to wound healing after intervention and surgical wound closure with dichotomous data also revealed a statistically significant difference between the two treatment groups in favour of NPWT (OR: 16.07; 95% CI: [3.19; 80.97]).

This leads to an indication of an effect on the time to wound healing after intervention and surgical wound closure in days in favour of NPWT.

4.6.2.3 Conclusion on benefit regarding wound closure

Overall, for the outcome wound closure, there is initially proof of benefit of NPWT. In view of the potential publication bias due to the calculated total data gap of 24%, this proof of greater benefit must be downgraded to an indication.

In summary, for the outcome wound closure, there is an indication of greater benefit of NPWT in comparison with SWT.

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

For the outcome "AEs", usable results from 41 studies were available. Since these studies used different operationalizations, the data were first analysed by operationalization and then aggregated for a conclusion on benefit regarding AEs. "Total rate of SAEs" was the leading operationalization.

4.6.3.1 AEs: Additional measure required for direct wound closure

Twenty-three studies reported usable results on "additional measure required for direct wound closure".

From the outcome of the study with high qualitative certainty of conclusions (Ashby 2012), no hint of an effect can be derived (no events in any treatment group). The collective analysis of

studies with moderate and high qualitative reliability failed to show a statistically significant difference between the two treatment groups as well.

Consequently, there is no hint of an effect on “additional measure required for direct wound closure”.

4.6.3.2 AEs: Reintervention

Usable results on the reintervention rate were reported in 10 studies. Furthermore, one study reported the number of required surgeries until final wound closure in the form of mean differences.

From the result of the study with high qualitative certainty of conclusions (Llanos 2006), no hint of an effect can be derived. The collective analysis of studies with moderate and high qualitative certainty of conclusions showed a statistically significant difference in favour of NPWT (OR: 0.46; 95% CI: [0.24; 0.86]). Consequently, there was initially an indication of an effect on reinterventions in favour of NPWT.

On the other hand, the Perez 2010 study resulted in a hint of an effect on the number of surgeries until final wound closure to the disadvantage of NPWT. This single study with a total of 40 included patients is too small in comparison with the 10 studies in the pooled analysis, with a total of 1377 included patients, to call into question the indication of an effect in favour of NPWT, which was derived from the latter.

Consequently, there is an indication of an effect on AE: reintervention in favour of NPWT.

4.6.3.3 AEs: Bleeding

Usable results on bleeding were reported in 5 studies / 6 comparisons.

Despite homogeneous results, no combined effect was presented since no events were reported in half of the comparisons. For each of the remaining three comparisons, no statistically significant effect was found.

Consequently, there is no hint of an effect on the AE “bleeding”.

4.6.3.4 AEs: Infection

Usable results on infection were reported by 20 studies.

The meta-analytical summary of results revealed substantial heterogeneity; therefore, no combined effect was presented. All 20 studies had moderate certainty of conclusions. The heterogeneity cannot be explained by the studies being based on wounds with differing aetiologies.

The prediction interval overlaps the null, and the studies with statistically significant effects in favour of NPWT made up less than 50% of the total weight of all studies combined. The effect direction differs.

Due to the heterogeneous data, there was no hint of an effect on the AE "infection".

4.6.3.5 Total rate of SAEs

Usable results on the total rate of SAEs were reported in 12 studies.

The meta-analytical summary of the results showed no statistically significant difference between the two treatment groups.

Consequently, there is no hint of an effect on the total rate of SAEs.

4.6.3.6 Separately identified SAEs

Usable results on separately identified SAEs were reported in 16 studies. They included discontinuation due to AE, abscess, other health-related symptoms, dehiscence, fistula, life-threatening risk (direct danger to life), neurovascular complications, recurrence, sepsis, thromboses and embolisms, complete graft loss as well as soft tissue complications. The number of studies with usable results ranged between 1 and 7 for the respective SAEs. Overall, the data on the outcome "separately identified SAEs" are heterogeneous, and no hint of an effect could be derived.

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

The indication of an effect on the AE "reintervention" in favour of NPWT must be downgraded to a hint due to the potential publication bias resulting from the total calculated data gap of 24%.

Overall, for the outcome adverse events "wound complications and therapeutic complications (AEs)", led by the central operationalization "total rate of SAEs", no hint of benefit or harm of NPWT versus SWT can be derived.

4.6.4 Results on amputation

For the outcome "amputation", usable results from 10 studies were available.

From the result of the study with high qualitative certainty of conclusions (SWHSI), no statement on benefit or harm can be derived. The pooled analysis of studies with moderate and high qualitative certainty of conclusions failed to show a statistically significant difference between the two treatment groups (OR: 0.89; 95% CI: [0.55; 1.43]).

For the outcome "amputation", there is consequently no hint of benefit or harm of NPWT in comparison with SWT.

4.6.5 Results on pain

For the outcome “pain”, usable results from 10 studies were available. Since the studies used different operationalizations, the data were first analysed by operationalization and later aggregated for a conclusion on the benefit for the outcome “pain”.

4.6.5.1 Pain – continuous

Usable results on pain in the form of continuous data were reported by 6 studies.

In the meta-analytical summary using Hedges’ g, no statistically significant difference was found between the two treatment groups (Hedges’ g: −0.16; 95% CI: [−0.53; 0.21]).

Consequently, there is no hint of an effect on pain – continuous.

4.6.5.2 Pain – dichotomous

Usable results on pain in the form of dichotomous data were reported by 3 studies.

Regardless of the meta-analytical methods used to summarize the results of the 3 studies (each of moderate qualitative certainty of conclusions), no statistically significant difference between treatment groups was found.

For the operationalization “pain – dichotomous”, there is consequently no hint of an effect.

4.6.5.3 Pain – dressing change

Usable results on pain during dressing change were reported in 2 studies. One study reported continuous data and the other dichotomous data – with neither finding any statistically significant differences.

Consequently, there is no hint of an effect on “pain – dressing change”.

4.6.5.4 Conclusion on benefit regarding pain

In summary, for the outcome “pain”, 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

For the outcome “length of hospital stay and (re-)hospitalization”, usable results from 17 studies were available. Since these studies used different operationalizations, the data were first analysed by operationalization and later aggregated for a conclusion on benefit regarding the outcome “length of hospital stay and (re-)hospitalization”.

4.6.6.1 Length of hospital stay – continuous

Usable results on length of stay in the form of continuous data were reported by 10 studies.

In the meta-analysis, a statistically significant difference was found in favour of NPWT, both in the study with high qualitative certainty of conclusions (Llanos 2006) and in the consideration of the totality of all studies (MD: −4.78; 95% CI: [−7.79; −1.76]).

Since the meta-analytical summary of all studies confirms the results of the single study with high qualitative certainty of conclusions, there is proof of an effect on the length of hospital stay – continuous in favour of NPWT.

4.6.6.2 Length of hospital stay – dichotomous

Usable results on "length of hospital stay – dichotomous", that is, in the form of the percentage of patients with a length of stay below or within a certain period (in this case: 1 month) were reported in 4 studies.

The meta-analytical summary of the results of the 4 studies, each of moderate certainty of conclusions, revealed homogeneous data and a statistically significant difference between the two treatment groups in favour of NPWT (OR: 0.07; 95% CI: [0,02; 0,17]).

Consequently, there was initially an indication of an effect on "length of hospital stay – dichotomous" in favour of NPWT.

4.6.6.3 Length of stay in the intensive care unit (ICU)

Usable results on "ICU length of stay" were reported in 2 studies / 3 comparisons.

No statistically significant difference between treatment groups was found.

Consequently, there is no hint of an effect on "ICU length of stay".

4.6.6.4 Rehospitalization

Usable results on rehospitalization were reported in 4 studies.

The meta-analytical summary of the results of the 4 studies (each of moderate qualitative certainty of conclusions) revealed no statistically significant difference between the two treatment groups.

Consequently, there is no hint of an effect on rehospitalization.

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

Overall, there was initially proof of greater benefit of NPWT for the outcome "length of hospital stay and (re-)hospitalization". In view of the potential publication bias due to the calculated total data gap of 24%, this proof of greater benefit must be downgraded to an indication.

Consequently, for the outcome "length of hospital stay and (re-)hospitalization", there is an indication of greater benefit 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, each of moderate qualitative certainty of conclusions. Both studies reported data on the Physical Composite Scale and the Mental Health Composite Scale of the Short Form 12 questionnaire.

In the meta-analysis using Hedges' g on the Physical Composite Scale, no combined effect was presented due to heterogeneity. The heterogeneity cannot be explained by the studies being based on wounds of different aetiologies. The effect direction differs.

Overall, the analysis of the Mental Health Composite Scale revealed homogeneous data without a statistically significant difference between the two treatment groups (Hedges' g: 0.01; 95% CI: [−0.20; 0.22]).

Consequently, for the outcome "health-related quality of life", the data are heterogeneous and there is no hint of benefit or harm of NPWT in comparison with SWT.

4.6.8 Results on functioning

For the outcome "functioning", usable results from 3 studies, each of moderate qualitative certainty of conclusions, were available.

The reported data from 2 studies on "time until return to work or school" or "time from excision to restoration of normal activities" in days were combined in a meta-analysis. This analysis using Hedges' g showed substantial heterogeneity, and no combined effect was presented. The heterogeneity cannot be explained by the studies being based on wounds of different aetiologies. The effect direction differs.

The results on functioning surveyed using the Disability Rating Index in the third study revealed no statistically significant differences between treatment groups at any analysis point either.

For the outcome "functioning", there is therefore no hint of benefit or harm of NPWT in comparison with SWT.

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**
⇔	⇑	⇔	⇔	⇔	⇑	⇑⇓	⇔	-
⇑: 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								
SWT: Standard wound therapy; NPWT: Negative pressure wound therapy								

5 Classification of the assessment result

In this project, a broad search in many sources for the purposes of retrieving relevant data revealed large quantities of as yet unpublished data.

The studies sponsored by the manufacturer KCI, which were found with the aid of the various search steps, could not be analysed for the preliminary report (Version 1 dated 20 August 2018). Although an agreement on the submission and publication of study information was in place, KCI failed to respond to repeated requests to provide a complete overview or complete documents on all published and unpublished RCTs on NPWT. At the time the preliminary report was written, no usable data were available for at least 50% (842/1681) of patients included in KCI-sponsored studies. The possibility that even more data may not have been submitted could not be ruled out.

Consideration of the selectively provided data could have led to a potentially highly biased data basis and jeopardized the validity of the assessment results. The data which were selectively submitted by KCI were therefore not analysed in the preliminary benefit assessment (preliminary report).

The additional information and documents on NPWT-related studies made available by the manufacturer during the commenting procedure now sufficiently reduced the data gap. There are 4 prematurely terminated studies sponsored by the manufacturer KCI for which even a generous assessment must conclude that the data provided are insufficient (Greer 1999, VAC 2001-00, VAC 2006-19 as well as VAC TRIAL). According to the information provided by the manufacturer, these studies included a total of N = 90 patients. Usable data, in turn, are now available for 11 studies sponsored by the manufacturer including 1735 patients – among them 7 studies including 1168 patients with wounds healing by secondary intention. For the final report, this data situation allowed a combined assessment of all identified studies with usable data on NPWT in wounds healing by secondary intention. Since the KCI-sponsored studies could now be included, the data gap decreased from at least 40% before (see Section 4.4 of the preliminary report Version 1.0 dated 20 August 2018) to less than 30% in the remaining study pool, consisting largely of studies not sponsored by manufacturers (see Section 4.3 of this final report). While the preliminary report did not include any benefit assessment of NPWT for wounds healing by secondary intention due to the considerable data gap, after the commenting procedure on the preliminary report, an analysis was possible on the basis of the now sufficiently complete data situation.

But even the current study pool contained relevant gaps. In total, data on at least 1386 patients remain unpublished. On the other hand, data of 4315 patients are available in analysable form. Consequently, data of at least 24% (1386/5701) of patients included in the studies on NPWT with wounds healing by secondary intention are inaccessible. Even the alternative calculation method using (in the absence of information to the contrary) only half instead of the full planned sample size for prematurely terminated studies and those of unclear status would result in a data

gap of 20% (1063/5378) of patients included in such studies. Regarding the calculation of the data gap, it must be noted that potential outcome reporting bias remained unconsidered in this assessment on the study level. Therefore, the usable data found may conceivably reflect an even smaller percentage of the evidence actually generated.

Conclusions on patient-relevant outcomes could be drawn despite the fact that on the study level, no significant results were often available and the majority of the studies exhibited considerable methodological deficits. On the basis of the "allocation concealment" criterion alone, 37 studies have a high risk of bias at the study level. This is associated with an elevated risk of a systematic bias in treatment effects. Yet even 6 out of the 7 studies with a low risk of bias on the study level exhibited deficiencies on an outcome level which largely led to a high risk of bias on the outcome level. In addition to lack of blinding of outcome data collection, either in subjective outcomes or due to missing data on the system used to survey the respective outcome, there were also uncertainties or even violations regarding the adequate implementation of the ITT principle. In both cases, this is not a matter of excessive requirements being imposed on studies of non-drug interventions, but of avoidable quality deficiencies found in both the conduct and the reporting of studies.

Although 34 out of 48 studies reported usable results on the outcome "wound closure" and an indication of greater benefit of NPWT in comparison with SWT was derived, this indication is largely based on the results of 1094 patients from 14 studies, in which this outcome was operationalized as "wound healing". On the basis of the available results, no statement can be made on the stability of wound closures due to the operationalizations selected in the study, analysis times and the in many cases missing information on the analysis time. The meta-analytical summary of the 5 studies with usable results on the separately identified SAE "recurrence", which was based on the results of 408 patients, resulted in no hint of greater or lesser stability of wound closures by means of NPWT.

The need to once again include unpublished data in the assessment raises the question of how IQWiG can reliably gain access to these data. The Institute has established a procedure which allows the submission and use of unpublished data from manufacturers for the assessment of non-drug interventions with medical devices. In this regard, the Institute currently depends on the responsible manufacturers' willingness to cooperate. The relevant data gap of 24% in this benefit assessment is largely due to studies not sponsored by manufacturers. The non-publication of clinical study results, whether the studies are manufacturer-sponsored or academically initiated, can prevent or considerably delay benefit assessments. Therefore, it seems urgently necessary to bring about a positive change in scientific culture. Study registration, updates of trial registry entries and publication of all study results are important elements for this change. The process of generating this benefit assessment has demonstrated that the implementation of these changes cannot be achieved on a voluntary basis, but legal regulations are necessary as well. In case of violations, sanctions may be a useful recourse.

6 Conclusion

For a relevant percentage of studies on negative pressure wound therapy of wounds healing by secondary intention, no data are available. Since at 24%, the calculated data gap can cause relevant bias (publication bias), the certainties of conclusion determined in the benefit assessment were downgraded.

For the outcomes “wound closure” and “length of hospital stay and (re-)hospitalization”, there was an indication of greater benefit of negative pressure wound therapy in comparison with standard wound therapy in wounds healing by secondary intention.

For the outcomes “mortality”, “adverse events”, “amputation”, “pain”, “health-related quality of life” and “functioning”, there was no hint of benefit or harm of negative pressure wound therapy of wounds healing by secondary intention. For the outcome “need of third-party help” or “need of long-term care”, no conclusion could be derived since no usable data were available.

The process of generating this benefit assessment has revealed that legal regulations are needed to improve the transparency of clinical research on non-drug interventions so that benefit assessments can be meaningfully conducted.

7 References for English extract

Please see full final report for full reference list.

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Appendix A – Search strategies

A.1 – Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to July Week 2 2018
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 20, 2018
- Ovid MEDLINE(R) Daily Update July 20, 2018
- Ovid MEDLINE(R) Epub Ahead of Print July 20, 2018

The following filters were adopted:

- Systematic Review: Wong [268] – High specificity strategy
- RCT: Lefebvre [269] – 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

#	Searches
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 2006:2018[DP]

3. Embase

Search interface: Ovid

- Embase 1974 to 2018 July 20

The following filters were adopted:

- Systematic Review: Wong [268] – High specificity strategy
- RCT: Wong [268] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	vacuum assisted closure/
2	negative pressure wound therapy/

#	Searches
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.
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 7 of 12, July 2018
- Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018

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 2018, 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
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 2018

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

Search strategy
OR negative AND pressure AND dressing OR negative AND pressure AND wound OR negative AND pressure AND closure