IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Institute for Quality and Efficiency in Health Care

IQWiG Reports · Year: 2006 No. 04[1]

Negative Pressure Wound Therapy

Final report

[1] The translation is based on the German final report "Vakuumversiegelungstherapie von Wunden" (Commission N04-03, Version 1.0, Status: 13 March 2006). Publication date of English translation: 25.02.2008. Please note: this translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Theme: Evaluation of the benefits and harms of negative pressure wound therapy

Contracting Agency: Federal Joint Committee

Date of the Commission: 21 December 2004

Internal Commission Number: N04-03

External Experts:

Dr. Stefan Sauerland, Institut für Forschung in der Operativen Medizin, Lehrstuhl für Chirurgische Forschung der Universität Witten/Herdecke, Ostmerheimer Straße 200, 51109 Köln [Institute for Research in Operative Medicine, Chair of Surgical Research, Witten/Herdecke University]

Dr. Sven Gregor, Klinik für Viszeral-, Gefäß- und Transplantationschirurgie, Krankenhaus Merheim, Kliniken der Stadt Köln gGmbH, Lehrstuhl Chirurgie I der Universität Witten/Herdecke; Ostmerheimer Straße 200, 51109 Köln [Clinic for Visceral, Vascular and Transplantation Surgery, Merheim Hospital, Cologne City Hospitals Ltd, Chair of Surgery I, Witten/Herdecke University]

Dr. Jan F. Krahn, Institut für Forschung in der Operativen Medizin, Lehrstuhl für Chirurgische Forschung der Universität Witten/Herdecke; Ostmerheimer Straße 200, 51109 Köln [Institute for Research in Operative Medicine, Chair of Surgical Research, Witten/Herdecke University]

Dr. Marc Maegele, Klinik für Unfallchirurgie, Krankenhaus Merheim, Kliniken der Stadt Köln gGmbH, Lehrstuhl für Unfallchirurgie/Orthopädie der Universität Witten/Herdecke; Ostmerheimer Straße 200, 51109 Köln [Clinic for Accident Surgery, Merheim Hospital, Cologne City Hospitals Ltd, Chair of Accident Surgery and Orthopaedics, Witten/Herdecke University]

Prof. Edmund A. M. Neugebauer MD, Institut für Forschung in der Operativen Medizin, Lehrstuhl für Chirurgische Forschung der Universität Witten/Herdecke; Ostmerheimer Straße 200, 51109 Köln [Institute for Research in Operative Medicine, Chair of Surgical Research, Witten/Herdecke University]

External Peer Review:

Dr. Christoph M. Seiler, Studienzentrum der Deutschen Gesellschaft für Chirurgie, Abteilung für Allgemein-, Viszeral-, Unfallchirurgie und Poliklinik, Ruprecht-Karls-Universität Heidelberg; Im Neuenheimer Feld 110, 69120 Heidelberg [Study Centre of the German Society for Surgery, Department for General, Visceral and Accident Surgery and Outpatient Clinic, Heidelberg University]

Contact:

Institute for Quality and Efficiency in Health Care

Dillenburger Str. 27

51105 Cologne

Germany

Internet: http://www.iqwig.de/

Tel.: +49-221-356850; Fax: +49-221-356851

E-Mail: N04-03@iqwig.de

The date of access is always given for documents taken from the Internet and cited. If these documents can no longer be found at the Internet address given, they can be inspected at the Institute for Quality and Efficiency in Health Care (IQWiG).

TABLE OF CONTENTS

INDEX OF TABLES

INDEX OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Meaning
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
CCT	Controlled clinical trial
CE	Communautés Européennes (European Community)
CI	Confidence interval
CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DF	Degrees of freedom
EMBASE	Excerpta Medica Database
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HTA	Health technology assessment
KCI	Kinetic Concepts, Inc
ID	Identification code
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	Intention to treat
MDD	Medical devices directive
MEDLINE	Medical Literature Analysis and Retrieval System Online
M	Mean value
NPWT	Negative pressure wound therapy
OR	Odds ratio
PTB	Physikalisch Technische Bundesanstalt (Federal Institute for Physics and Technology)
RCT	Randomised controlled trial
SD	Standard deviation
SEM	Standard error of the mean
SMD	Standardised mean difference
UK	United Kingdom
USA	United States of America
V.A.C.®	Vacuum-Assisted Closure®

1 Objectives of the investigation

On the basis of the published literature on this theme, the objectives of the present investigation are to evaluate (with regard to therapy goals relevant to patients)

- the benefits and harms of negative pressure wound therapy compared with conventional forms of wound care

and

- the benefits and harms of different forms of negative pressure wound therapy compared with each other

in patients with acute or chronic skin wounds of any cause or localisation.

"Negative pressure wound therapy" (NPWT) means closed wound treatment with drainage through an externally or internally drained sponge, including a system producing the negative pressure needed for drainage.

This evaluation of benefits and harms is based on a comparison and consideration of the desired and undesired effects of NPWT.

2 Background

Commission

The Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), in a letter dated 21 December 2004, commissioned the Institute for Quality and Efficiency in Health Care to evaluate the benefits and harms and medical necessity of NPWT. The commission was specified on 21 March 2005.

Wounds and wound healing – complications and consequences

With rare exceptions, wounds and wound care are linked to intense pain [1]. This requires analgesic therapy, which can trigger adverse events. Moreover, wounds and their successful closure can cause restriction in function, which may be long-term. Wounds or ulcers which do not heal, or which heal poorly, may impair a patient's ability to work, physical mobility, and general condition to a greater or lesser extent. This can have a direct effect on the quality of life, either directly or indirectly, for example, due to the unpleasant smell of the wound. Scars, too, are a late complication which can greatly impair all aspects of quality of life. In addition, chronic wounds can spread, making amputation of the extremities necessary. Chronic wounds also provide a suitable environment for micro-organisms. These can spread locally and be transmitted through the blood stream, colonising the whole body, sometimes leading to death from sepsis. Wounds can therefore be accompanied by a considerable impairment in physical well-being, quality of life and a specific risk of secondary conditions, including amputation and death [2, 3].

These possible consequences provide the basis for the patient-relevant therapeutic goals of wound therapy – the maintenance of physical functions, physical well-being and quality of life, together with the avoidance of complications.

Conventional wound therapy

In conventional wound therapy, the wound is covered with wound dressings consisting of various materials (e.g., gauze, hydrocolloids, alginate) which can be used either dry or after moistening. Conventional wound therapy is subject to a very wide range of variations. There

is no generally valid uniform standard [4,5]. Dressings are usually changed once or several times daily [2].

Wound therapy may include not only elimination or treatment of the causes of a chronic or non-healing wound, but also the surgical removal of dead (necrotic) tissue (debridement), support of granulation, the maintenance of a moist wound bed, and the control of infection.

Negative pressure wound therapy

NPWT is delivered by a closed wound system, with drainage over a large area through an externally or internally drained sponge. The negative pressure needed for drainage is produced by a vacuum pump or a Redon suction bottle and maintained with the help of an adhesive foil with airtight cover [6].

With a closed wound dressing and with the help of the negative pressure system, NPWT is designed to lead to removal of the exudate, reduction in oedema, and improvement in perfusion. This is coupled to improved oxygen supply and provision of nutrients to the boundaries of the wound, and should contribute to shortening the time for the wound to heal [7]. It is either used as an alternative to conventional wound therapy, or after primary failure of conventional wound therapy.

A complete system for NPWT is marketed in Germany by a commercial manufacturer (V.A.C.® Therapy™, Kinetic Concepts, Inc. [KCI], San Antonio, Texas, USA). This consists of a vacuum pump, a collecting canister for wound exudate, a drainage tube as connection between dressing and pump, and a dressing consisting of a foam wound inlay and an airtight cover foil. The intensity of the negative pressure on the wound can be preset and is kept constant by the system. In addition, there is an intermittent suction setting. A pressure sensor is placed within the wound dressing, which transmits pressure changes to the pump unit. This serves to detect leaks in the wound cover. KCI is the sole licence holder for the product. The patent holder is Wake Forest University, Winston-Salem, North Carolina, USA.

Various results have been published and different data provided to address the question of the most suitable negative pressure for the treatment of wounds [8-10]. Current research is also addressing this issue [11]. Continuous negative pressure of 125 mmHg – corresponding to 16.7 kPa in the units approved in Germany [12] – is mostly used in clinical practice. This is

based on various recommendations from the manufacturer, which in turn are largely based on animal experiments.

Indications for negative pressure wound therapy

NPWT is mostly used for the treatment of non-healing (chronic) wounds requiring secondary healing. Wounds from a very wide variety of causes can be treated, including chronic pressure sores (decubitus), sores due to vascular conditions (venous or arterial) and/or neural abnormalities (diabetic foot syndrome) and infected wounds. The technique can also be used in open abdominal treatments. It can be used to support split-thickness skin transplantation [11] and in the therapy of acute and complicated injuries, for example, from burns or avulsions [2,3,13].

Adverse events in the use of negative pressure wound therapy

There are several reports in the literature on adverse events occurring during the use of NPWT and some of these events were serious. However, these reports are mostly in the form of case reports or small case series [14]. There have been explicit reports of sepsis [15,16], toxic shock syndrome [17], hypovolaemic shock from fluid loss [18], arterial erosion bleeding and amputation of an extremity [20]. However, in none of these cases of severe adverse events can the possibility be excluded that there was either an individual error in the use of NPWT or that the adverse event should not be regarded as a complication of NPWT, but rather as an inevitable consequence of the underlying disease.

Maceration of the skin can develop in the immediate vicinity of the wound, particularly in sensitive skin areas. This can be partially avoided by using dressings with good skin tolerability. Skin maceration may also develop as a consequence of the inexpert use of excessively large sponges or if loss of pressure has been overlooked [21], although an alarm is triggered in modern negative pressure pumps on loss of pressure. There is also a case report in which evidently NPWT was inexpertly performed, leading to a chronically infected wound sinus caused by an overlooked fragment of polyurethane sponge [22]. Finally, some authors who investigated the bacterial colonisation of the wound found that the count of some bacteria was increased [15,23], whereas the numbers of other bacterial species were evidently reduced [24].

There have also been reports of pain and slight bleeding during the change of dressing; these are thought to be linked to the negative pressure used, the sponge material, and the frequency of change of dressing [25]. However, pain and slight bleeding generally occur when any dressing is changed.

3 Course of the project

The project was commissioned by the Federal Joint Committee on 21 December 2004 and specified in writing on 21 March 2005. The report plan was then produced and published on the Institute's website on 13 May 2005.

External experts were involved in the subsequent processing of the project and they participated in preparing the report plan, the literature search and evaluation, and in writing the preliminary report. The preliminary report in the version of 23 November 2005 was published on 01 December 2005 and submitted to external peer review. Written statements on this preliminary report could be submitted by all interested parties (see **Appendix F**). The deadline for statements was 22 December 2005.

All parties providing statements who had disclosed potential conflicts of interest (in accordance with the methods of the Institute) were invited to a scientific hearing on 10 January 2006, during which the essential points raised in the written statements were discussed (see **Appendix E**). After this scientific hearing, the present final report was prepared.

4 Methods

The methods for preparing the report were specified in advance in the report plan of 13 May 2005. Any relevant changes made in the course of preparing the report are given in Section 4.5.

4.1 Criteria for study inclusion

The criteria are listed below for the inclusion of a study in this report (inclusion criteria), together with the criteria leading to exclusion (exclusion criteria).

4.1.1 Population

Studies in patients with acute or chronic skin wounds were included. There were no additional restrictions on the patients investigated in the studies.

4.1.2 Intervention and comparator treatment

Studies were included in which a type of NPWT was compared with conventional (traditional) wound therapy, or with another type of NPWT.

4.1.3 Outcomes

The outcomes for the investigation had to permit an evaluation of the following patient-relevant therapeutic goals:

- Shortening of the wound healing time
- Avoidance of wound recurrence and reduction in the necessity of revision operations
- Avoidance of amputations
- Reduction in mortality
- Improvement or maintenance of disease-related quality of life and avoidance of restrictions in activities of everyday life
- Reduction in pain from the wound and from wound care
- Reduction or avoidance of time spent in hospital
- Reduction in the necessity for dressing change or for debridement
- Reduction in adverse effects and therapeutic complications
- Reduction in scar formation and improvement of subjective cosmetic results

The studies included were investigated with respect to quantifiable data on all the above therapeutic goals.

4.1.4 Study types

Randomised controlled studies (RCTs) provide the most reliable results for the evaluation of the benefits and harms of a medical intervention, as the results are least uncertain, insofar as the methods used are adequate and they are appropriate to the issue examined. For this reason, RCTs were primarily used as relevant scientific literature in this evaluation.

However, as the available evidence is apparently limited [1-3,7,26,27], non-randomised intervention studies with concurrent controls were also included to avoid overlooking essential results. Inclusion of the results of non-randomised trials can provide valuable additional results, particularly for surgical questions [28,29].

Thus the following study types were included in the investigation:

- Randomised controlled studies (RCTs)
- Non-randomised trials, insofar as there was a concurrent control group:
  - Controlled clinical studies (CCTs) without randomisation; this includes studies with clearly inadequate concealment (for example, alternating allocation procedure)
  - Prospective comparative cohort studies
  - Retrospective comparative cohort studies
  - Case control studies

Both interindividual comparisons from studies in parallel group design and intra-individual comparisons and crossover studies were considered [30,31].

4.1.5 Other study characteristics

There were no restrictions in other study characteristics.

4.1.6 Inclusion and exclusion criteria

In summary, studies were included in the evaluation, which fulfilled all the following inclusion criteria and none of the following exclusion criteria.

Inclusion criteria

I1 Patients with acute or chronic skin wounds

I2 Intervention: A type of NPWT

I3 Comparator intervention: Conventional wound therapy or another type of NPWT

I4 Outcomes in accordance with Section 4.1.3

I5 Controlled clinical trials (with concurrent control groups), as defined in Section 4.1.4.

Exclusion criteria

E1 Experimental animal studies

E2 Multiple publications without relevant additional information

E3 No full-text publication available (*)

* In this context, a full-text publication also includes non-confidential transmission of a study report to the Institute or non-confidential provision of a report on the study, which fulfils the criteria of the CONSORT Statement [32] and permits an evaluation of the study.

4.2 Literature search

The aim of the literature search was to identify fully published and non-published clinical studies which provide essential information related to the benefits and harms of NPWT.

4.2.1 Literature sources

The search for relevant literature was initially performed on 04 May 2005 in the following bibliographic databases. The search was repeated with a broader strategy on 20 May 2005.

- Ovid: MEDLINE "In-Process & Other Non-Indexed Citations 1966 to Present" (current)
- Ovid: EMBASE "1980 to 2005"
- Ovid: CINAHL "1982 to 2005"

- Wiley InterScience: "The Cochrane Library: The Cochrane Central Register of Controlled Trials (CENTRAL)"

The detailed search strategies are documented in **Appendix B**. They were modified for each database to do justice to the specific differences between the literature databases, particularly with respect to the use of subject headings.

The systematic search for non-randomised trials is problematical [33]. After the initial search on 04 May 2005, in the development of the search strategy, the focus of the strategy was extended with respect to the types of publication and study to maximise the cover of non-randomised concurrent comparative studies. This means that all publications reporting comparative studies were included in the circle of potentially relevant documents. The information query ("Retrieval") was performed in a modified manner in the second search step to increase the completeness of the cover in this sense ("Recall"). The modified search was performed on 20 May 2005.

The search for relevant secondary publications (systematic reviews and HTA reports) was performed on 20 May 2005 in the following bibliographic databases from the "The Cochrane Library" from Wiley InterScience:

- "The Cochrane Database of Systematic Reviews (Cochrane Reviews)"
- "Database of Abstracts of Reviews of Effects (DARE)"
- "Health Technology Assessment Database (HTA)"

The search for relevant primary studies and secondary publications was complemented by the reference lists provided in the 29 statements from interested professional groups transmitted by the Federal Joint Committee to the Institute.

The literature search was repeated on 07 October 2005 in these literature databases, using the research strategy recorded in **Appendix B**, to search for relevant studies which might have been published for the first time between 20 May 2005 and 07 October 2005.

4.2.2 Search for additional published and non-published studies

The following steps were taken to search for additional published and non-published studies:

- Manual search in congress volumes

1) 4th European Vacuum Therapy Symposium. Advances in Wound Care: Topical Negative Pressure (TNP) Wound Therapy, 16-18 June 2005, Salisbury, United Kingdom
2) V.A.C.® Wundtherapie, 10 Jahre V.A.C., Drei-Länder-Kongress [V.A.C. Wound Therapy, 10 Years of V.A.C., Three-Country Congress] 10-11 June 2005, Graz, Austria
3) Symposium on Advanced Wound Care, 21-25 April 2005, San Diego, California, USA
4) 2nd World Union of Wound Healing Societies Meeting, 8-13 July 2004, Paris, France
5) V.A.C.® Wundtherapie, Anwendungsmöglichkeiten der V.A.C.®-Therapie im ambulanten sowie im klinischen Bereich, Drei-Länder-Kongress [V.A.C. Wound Therapy, Possible Uses of V.A.C. Therapy for Outpatients and Inpatients, Three-Country Congress] 21-22 May 2004, Mainz, Germany
6) Topical Negative Pressure (TNP) Therapy, Focus Group Meeting, December 2003, London, United Kingdom
7) Vacuum Assisted Closure (V.A.C.®), 16-17 May 2003, Salzburg, Austria
8) 11th Annual Meeting and Educational Symposium, Wound Healing Society, 16-18 May 2001, Albuquerque, New Mexico, USA

- Written enquiry to authors for indications of additional potentially relevant studies
- Written enquiries to manufacturers

– Kinetic Concepts, Inc. (KCI), San Antonio, Texas, USA
– Blue Sky Medical, La Costa, California, USA

- Internet search in publicly accessible study registers and other sources

– U.S. Department of Health & Human Services, Washington, DC, USA: ClinicalTrials.gov: http://clinicaltrials.gov/ (Accessed on 27 September 2005)
– United Kingdom's National Health Service (NHS), London, United Kingdom: The National Research Register (NRR): http://www.nrr.nhs.uk/ (Accessed on 27 September 2005)

- Search at or written enquiries to regulatory agencies or "notified bodies"

– U.S. Food and Drug Administration: http://www.fda.gov/ (Accessed on 27 September 2005)
– Federal Institute for Drugs and Medical Devices, Bonn
– TÜV Süddeutschland Holding AG, Munich [Technical Supervision Association, South Germany]

The written enquiries to the manufacturers and the authors included a standardised table, which was intended to serve as a template for the transmission of information desired by IQWiG.

4.2.3 Search for additional information on relevant studies

Additional information on the already identified published and non-published studies was searched for in the documents obtained in accordance with Section 4.2.2. In addition, letters were written to first authors and sponsors of identified published studies, to request essential additional information for a valid evaluation of these studies.

4.2.4 Selection of relevant studies

The bibliographic details of the publications and documents (according to the above sections) were imported into a database ("Reference Manager 11", Adept Scientific GmbH, Frankfurt am Main) for further processing and archiving.

In the first selection step ("first screening"), it was decided on the basis of the title and abstract (if present) which publications, according to the inclusion and exclusion criteria noted above, should be classified as "definitely not relevant (definite exclusion)" and should be excluded from further processing. This applied to publications which were independently rated as "not relevant" by 2 experts. All other publications were regarded as "potentially relevant". Specific

reasons for exclusion were not documented in this step. For the studies included in the systematic reviews on the subject and those considered in the HTA reports, a comparison was made with the results of the primary search. All these studies [1-3,7,26,27] had already been found in the primary search.

In the second selection step ("second screening"), the full texts of the potentially relevant publications were acquired. Some of these texts were in Chinese or Russian. These were translated by external Russian or Chinese native speakers with medical expertise. The full texts of all potentially relevant studies were independently inspected by 2 experts, to decide which publications could be rated as "definitely relevant (definite inclusion)", on the basis of the above exclusion and inclusion criteria. In doubtful cases, agreement was reached by consensus. The reasons for exclusion in the second screening are documented in detail in **Appendix A1.**

4.2.5 Obtainment of written statements / scientific hearing

The publication of the preliminary report was followed by a period of 4 weeks to allow statements. A form was provided for this purpose, which allowed statements on 3 main aspects:

- Original studies missing in the preliminary report
- Faulty evaluation of original studies in the preliminary report
- Comments on the project-specific methods

After the deadline for statements, a scientific hearing took place, in which the relevance of essential aspects of the statements received for the final report was discussed.

4.3 Evaluation of information

The evaluation of the included studies was performed on the basis of the available information and was therefore strongly dependent on the quality of the publication and other sources of information.

The evaluation was made in 3 steps:

- Extraction of the study data
- Evaluation of the study and publication quality

- Evaluation of the data consistency within the publication and, where applicable, between different sources of information on the same study

At the end of this 3-step process and on the basis of the study and publication quality and the consistency of the information, a final decision was made for each study as to whether it should be included in the evaluation, with a detailed description of the study in the final report.

4.3.1 Data extraction

The content and biometric details of the studies included were separately entered by each of the 2 evaluators into standardised data extraction forms. Two different extraction forms were used, one for the data from RCTs and one for the data from non-randomised trials. After this, the evaluators compared their evaluations for each study. If their results for the different evaluation criteria were different, the text was reassessed and a shared interpretation was reached as consensus.

4.3.2 Study and publication quality

As a completely blinded study design was impracticable for the research questions investigated in this report, blinded recording of the outcomes was regarded as an essential quality criterion of the studies to be evaluated. Moreover, it had to be guaranteed that in comparative studies including conventional wound therapy, the latter was performed in a qualitatively high manner. It was also considered to what extent there were differences between the groups compared in aspects related to wound care or accompanying treatment – apart from the intervention being studied. To be able to check the permanence of the wound closure and the occurrence of complications, the studies should include an adequately long follow-up period. In this context, the U.S. registration agency, the Food and Drug Administration (FDA), demands a minimum follow-up period after wound closure of 3 months [34]; other authorities demand studies of at least 5 months in duration, with an additional follow-up period of 3 months [35].

Information on the following aspects of the quality of RCTs was systematically extracted:

- Randomisation process and concealment of the group allocation
- Blinding of the recorder of the findings

- Complete description of possible dropouts or important violation of the intent-to-treat principle

In addition, an overall classification was made of the study and publication quality, on the basis of the above aspects. Four different categories of the parameter "biometric quality" were available:

- No evident deficiencies
- Minor deficiencies
- Major deficiencies
- Unclear

These classes were predefined as follows: "Minor deficiencies" are present when it is assumed that their correction will essentially have no effect on the results and thus the overall conclusion of the study. With "major deficiencies", the overall conclusion of the study would have to be called into question, even if the deficiencies were rectified. As described above, the evaluation of the study quality is directly influenced by the quality and consistency of the available information, so that the designation of "major deficiencies" is not necessarily a description of the quality of the study itself, but may also be influenced by the quality of the publication.

4.3.3 Consistency of information

Where relevant, the data extraction was followed by a comparison with information found in the extended search on published studies described in Sections 4.2.2 and 4.2.3. If discrepancies were identified (also with regard to discrepant information within the publication itself) which could have a major influence on the results or on their interpretation, this was documented in the corresponding sections in the results.

4.4 Information synthesis and analysis

Aspects of the study design, study quality and the results of the studies were presented in summary for the total study pool.

4.4.1 Meta-analysis

The data on a therapeutic goal were to be summarised quantitatively in a meta-analysis, insofar as this appeared meaningful on the basis of the content and methods of the studies.

Possible heterogeneity between the individual study results was primarily evaluated on the basis of the I^2 value; if $I^2 >= 50\%$, this is taken to be unusual, corresponding to "moderate" heterogeneity [36].

Because of the expected low number of randomised trials, meta-analyses were also considered for non-randomised concurrent comparative studies, insofar as there was at least 1 randomised trial of adequate quality for the corresponding outcome. The results of randomised and non-randomised trials were not aggregated.

To allow for the possible use of different methods of measurement for the same therapeutic goal – for example, measurement of wound volume or wound surface to assess wound healing – the weighted standardised mean difference was used as an effect measure for continuous data.

All statistical analyses were performed with software from the SAS Institute Inc., Cary, North Carolina, USA (Version 9.1.3). A statistical model with random effects was used for the primary analysis.

4.4.2 Sensitivity analysis

Specific sensitivity analysis was preplanned for

- The biometric quality assessment (see Section 4.3.2)
- Intention-to-treat evaluations described in the publications versus per-protocol evaluations (insofar as possible) and
- A (statistical) model with fixed effects versus a model with random effects.

4.4.3 Subgroup analyses

If they were reasonable and feasible, subgroup analyses were performed for the following characteristics:

- Type of wound (chronic versus acute)
- Gender
- Age

4.5 Deviations from the report plan

In the course of the report production, there were changes from the methods described in advance in the report plan. On the one hand, these were related to the necessity of specifying or clarifying an issue, without essential relevance to the content. On the other hand, there were changes in the methodological procedure itself. The essential changes are listed below.

4.5.1 Changes before the preparation of the preliminary report

Changes in content from the previously planned procedure

- The studies included contained little evaluable information on the outcome "shortening of wound healing time". The surrogate parameter "change in wound area or wound volume" was reported in several studies and was therefore included, even though the validity of this surrogate parameter is unclear.
- In a similar manner, the data were complemented by including the surrogate parameter "change in wound surface after skin transplantation", even though the validity of this surrogate parameter is also unclear. This primarily corresponds to the proportion of successfully vascularised skin of the transplanted (also bioartificial) skin ("graft take rate").
- Search for unpublished studies and additional information on published studies in congress volumes and study registers.
- Search at or enquiries to regulatory agencies or "notified bodies".

Changes without relevant consequence for the contents

- Specification of the term "full-text publication" for studies which had not yet been published in a scientific journal when the report was written.
- Explicit statement of the assessment of data consistency both within and between sources of information.

4.5.2 Changes after publication of the preliminary report

Changes in content from the previously planned procedure

There were no changes in content from the previously planned procedure.

Changes with essentially no consequence for the contents

- Designation of the levels of evidence for the studies included in the evaluation (Section 9)
- Separate section to describe how statements were obtained and how the scientific hearing was performed
- Referencing of the studies included in the evaluation on the basis of study designations in Section 9
- Inclusion of the results of the additional search in the flow chart on the result of the literature search (Section 5.1.1, **Figure 1**)

5 Results

The results of the literature search will first be described, i.e., the search for published and unpublished studies and additional information from various sources on these studies. This is followed by an aggregated description of the relevant studies and statements as to whether, and to what extent, prior planned meta-analyses and sensitivity and subgroup analyses were in fact performed and what the results were.

5.1 Literature search

5.1.1 Result of the literature search

The results of the search for published studies in bibliographic databases, in the reference lists in relevant secondary publications, and in the statements to the Federal Joint Committee are shown in **Figure 1.**

The search in 7 electronic literature databases resulted in 2512 hits. The 29 statements to the Federal Joint Committee contained 851 references. After a search in study registers, a manual search in congress reports, and enquiries to manufacturers (see following sections), 17 additional citations were found, including references to randomised trials which have not yet been fully published. Two additional citations of this type had already been identified in the primary search.

Duplicates with identical bibliographic details were removed (923), leaving 2457 citations for the selection of studies. As a result of the first screening, 2206 were excluded as definitely not relevant; 251 potentially relevant publications were left. In the second screening, 21 citations (19 studies) were initially included for the extraction of study data. The reasons for the exclusion of the 223 non-relevant articles are documented in **Appendix A1.** In addition, 7 systematic reviews and HTA reports were searched for additional relevant studies (**Appendix A2**); 6 of these systematic reviews and HTA reports published in recent years [1-3,7,26,27] did not contain any additional relevant primary studies. The seventh HTA report published in 2003 was from a commercial agency [37] and was not freely available. The year of publication (other HTA reports were more recent) and study of a sample HTA report from this agency suggested that no essential additional information was to be expected.

In 2 of these reports [3,7], the 1994 Davydov study [38] was considered relevant. After translation from Russian, it turned out that this publication described wound drainage, but not NPWT, so that this study was excluded from the evaluation.

The additional search on 07 October 2005 resulted in 156 hits, or 120 hits after removal of duplicates. This included 2 additional relevant HTA reports [39,40] (**Appendix A2**), but no additional relevant primary studies, not even in the additional HTA reports. One publication in the additional search reported on the economic evaluation of a randomised trial which had already been identified [41].

During the preparation of the preliminary report, a randomised trial was published [42]. This was naturally not found in the systematic literature search as described, but was considered in the evaluation.

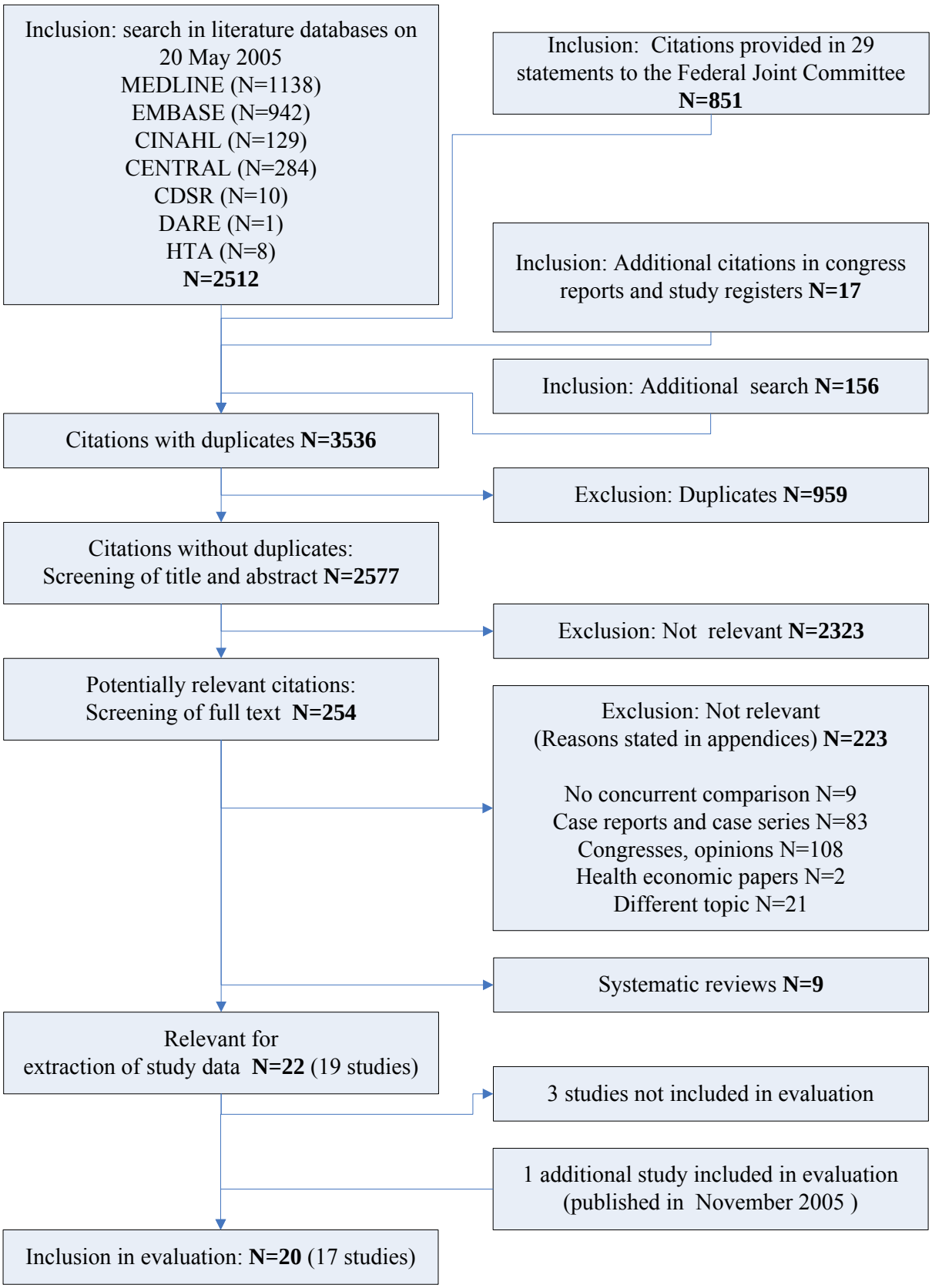


Figure 1. Results of the literature search

5.1.2 Enquiries to manufacturers

The manufacturer KCI of "V.A.C.® Therapy™" products supported or still supports 13 studies whose full-text publications had not been published before the enquiries to the manufacturer or before the publication of abstracts [43-55]. According to the manufacturer, 5 of these studies [43,45,46,50,54] have been terminated in the meantime because of slow enrolment, high attrition rates, changes in clinical practice, or design flaws. Three studies have now been completed [47,51,56] and 2 of these [47,51] have been published [42,57].

The manufacturer of the instrument "Versatile 1 Wound Vacuum System", Blue Sky Medical, only referred to case reports.

5.1.3 Manual search in congress reports

The congress report "2nd World Union of Wound Healing Societies Meeting" (July 2004, Paris, France) contained 10 [44,45,48-55] of the 13 references provided by KCI published as abstracts and not published otherwise up to this date, together with 2 other abstracts [58,59]. The congress report "11th Annual Meeting and Educational Symposium, Wound Healing Society" (May 2001, Albuquerque, New Mexico, USA) contained information on another unpublished study [60]. The other congress reports named contained no further references to unpublished studies.

5.1.4 Search in publicly accessible study registers and other sources in the Internet

Information on 6 as yet unpublished studies was found in study registers [56,61-65], of which 1 [56] had already been identified in the enquiry to KCI [55]. Of the remaining 5, 2 are still in progress [63,64], 2 have already been completed [61,65] and the status of 1 [62] is currently unknown.

5.1.5 Search/enquiries: regulatory agencies/notified bodies

No further references to unpublished randomised trials were found on the website of the U.S. Food and Drug Administration.

"V.A.C.® Therapy™" from KCI is a medical device, classified in Class IIa, on the basis of Guideline 93/42/EWG [66]. The CE marking of this product expresses the fact that it is in accordance with the relevant product guidelines of the European Union. Attachment of the CE mark and the preceding evaluations are the duty of the manufacturer. With Class II products,

a neutral test office, the so-called notified body, performs an audit of the manufacturer's quality management system. If this does not exist, a prototype test is performed. TÜV Süddeutschland Holding AG, Munich, as the notified body, was requested for information as to whether there are competing medical devices to "V.A.C.® Therapy™". We were informed by phone on 23 September 2005 that, because of the lack of a central European database, no binding statement could be made as to whether CE certification had been applied for a competing medical device at any of the many European notified bodies. It is planned to establish a corresponding database in the future.

The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) only regulates reporting of serious adverse events for medical devices. The BfArM was requested for information as to whether serious adverse events related to NPWT had been reported. It was reported by e-mail on 22 August 2005 that there had been a single user notification a considerable time ago, but that no conclusive evaluation of this had been performed. According to information in a telephone conversation of 22 August 2005, these notifications are confidential and may only be transmitted to the Federal Ministry for Health and to the federal state authorities responsible. Nevertheless, the fact that the processing of the event had been slow permitted the interpretation that it was not a "general problem". The BfArM emphasised that the frequency of notifications of this sort did not allow any conclusions about the quality of the medical devices.

5.1.6 Systematic reviews

Samson 2004 [2] mentioned 10 randomised trials supported by KCI which had not been published at that time [43-45,48-54]. These 10 studies had already been identified from the manual search in the congress volumes (see Section 5.1.3).

The preliminary results of the 2 abstract reports on the randomised trial of Greer 1999 [46] (not continued because of poor recruitment; see Section 5.1.2) and of Heath 2002 [47] (in the meantime concluded and published [57]; see Section 5.1.2) were considered by Pham 2003 [3]. In addition, Pham 2003 [3] cited 3 of the randomised trials not yet published [61,62,65] which had already been identified in the search in the study registers (see Section 5.1.4).

According to the "Regional Group Coordinator" of the "Cochrane Wounds Group" in an e-mail on 14 October 2005, this group is working on 2 systematic reviews on NPWT. The titles

are "Topical negative pressure for partial thickness burns" and "Topical negative pressure for acute and traumatic wounds". The presumed dates of publication are not yet known.

5.1.7 Enquiries to authors

The search described in Sections 5.1.2 to 5.1.6 led to a total of 21 abstract reports of studies which had initially not (yet) been identified elsewhere as full-text publications (see **Appendix C**). We wrote to the authors of these reports to ask for standardised information on the status of the study development, the publication status and (where relevant) transfer of preliminary results and submitted journal manuscripts. These enquiries led to the identification of 2 full-text publications, so that references remain to 19 unpublished studies.

In addition, the authors of 3 published studies [67-69] were requested to add results which had not been reported.

In the context of the statement procedure (see **Appendix F**), there was extensive correspondence with the authors of the Armstrong study published in November 2005 and, in particular, with the study sponsor, KCI.

5.1.8 Information from statements and the scientific hearing

The statements obtained (**Appendix F**) and the subsequent scientific hearing (**Appendix E**) provided no evidence of studies which had not yet been considered or identified and which were in accordance with the predefined inclusion and exclusion criteria for inclusion in the evaluation.

The statements on the Armstrong study (2005) [42] and the relevant correspondence afforded additional aspects for the description of this study (see Section 5.2.3, description of Armstrong 2005).

Additional aspects presented in the statements and in the scientific hearing are dealt with in Section 7 ("Discussion").

5.1.9 Resulting study pool

The various steps in the search, with the inclusion of the 2005 Armstrong study [42], resulted in 20 completed studies which were initially classified as relevant and which were reported in 23 publications (**Tables 1 and 2**); 9 of these were classified as randomised trials (**Table 1**) and 11 as non-randomised concurrent comparative studies (**Table 2**). All these studies

compared NPWT with conventional wound treatment. The non-randomised trial of Wild 2004 [69] also included a comparison between 2 different types of NPWT in the treatment of the open abdomen.

Table 1. List of identified randomised trials

Study	Assigned full-text publication	Ref.	Inclusion in evaluation
Armstrong 2005	Armstrong DG, Lavery LA. Lancet. 2005; 366: 1704-1710	[42]	Yes
Buttenschön 2001	Buttenschön K et al. Foot Ankle Surg. 2001; 7: 165-173.	[67]	No
Eginton 2003	Eginton MT et al. Ann Vasc Surg. 2003; 17: 645-649.	[21]	Yes
Ford 2002	Ford CN et al. Ann Plast Surg. 2002; 49: 55-61.	[70]	Yes
Jeschke 2004	Jeschke MG et al. Plast Reconstr Surg. 2004; 113: 525-530. Jeschke G. Plastische Chirurgie. 2003; 3: 127-131.	[71,72]	No
Joseph 2000	Joseph E et al. Wounds. 2000; 12: 60-67.	[73]	Yes
Moisidis 2004	Moisidis E et al. Plast Reconstr Surg. 2004; 114: 917-922.	[57]	Yes
Mouës 2004	Mouës CM et al. Wound Repair Regen. 2004; 12: 11-17. Mouës CM et al. J Wound Care. 2005; 14: 224-227	[24] [41]	Yes
Wanner 2003	Wanner MB et al. Scand J Plast Reconstr Surg Hand Surg. 2003; 37: 28-33.	[74]	Yes

The results of 2 randomised trials [67,71] and 1 non-randomised trial [75] were excluded from the actual evaluation because of particularly serious deficiencies. The justification for this is included in the description of the studies in Sections 5.2.3 und 5.2.4.

Table 2. List of identified non-randomised trials

Study	Assigned full-text publication	Ref.	Inclusion in evaluation
Doss 2002	Doss M et al. Eur J Cardiothorac Surg. 2002; 22: 934-938.	[76]	Yes
Etöz 2004	Etöz A et al. Wounds. 2004; 16: 264-269.	[25]	Yes
Genecov 1998	Genecov DG et al. Ann Plast Surg. 1998; 40: 219-225.	[77]	Yes
Huang 2003	Huang J et al. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2003; 17: 456-458.	[75]	No
Kamolz 2004	Kamolz LP et al. Burns. 2004; 30: 253-258. Haslik W et al. Zentralbl Chir. 2004; 129: S62-S63.	[78,79]	Yes
McCallon 2000	McCallon SK et al. Ostomy Wound Manage. 2000; 46: 28-34.	[80]	Yes
Page 2004	Page JC et al. Adv Skin Wound Care. 2004; 17: 354-364.	[81]	Yes
Scherer 2002	Scherer LA et al. Arch Surg. 2002; 137: 930-934.	[82]	Yes
Schrank 2004	Schrank C et al. Zentralbl Chir. 2004; 129: S59-S61.	[83]	Yes
Stone 2004	Stone P et al. Wounds. 2004; 16: 219-223.	[84]	Yes
Wild 2004	Wild T et al. Zentralbl Chir. 2004; 129: S20-S23.	[69]	Yes

5.1.10 Potential study pool

A search in abstract reports and enquiries to authors and manufacturers led to the identification of an additional 19 potentially relevant studies (see Sections 5.1.2 to 5.1.6 and the tabular summary of characteristics in **Appendix C**): 5 of these 19 studies had been prematurely terminated, the status of 4 is unclear, 10 potentially relevant studies therefore

remain (including 3 already completed and 7 currently being performed) of which the results have not yet been published as full-text papers.

5.2 Characteristics of the studies included in the evaluation

5.2.1 Study design and study populations

In all of the 20 studies initially classified as relevant, NPWT was compared with conventional wound therapy. In addition, 1 of these studies (Wild 2004) employed a 3-arm design, with a comparison between 2 types of NPWT (classical versus abdominal wound-specific NPWT). The originally planned comparison between different types of NPWT is therefore restricted to mentioning this study. The subsequent comparisons between NPWT and conventional wound treatment pool these 2 NPWT groups in this study, as they gave similar results.

There are 9 randomised trials (Armstrong 2005, Buttenschön 2001, Eginton 2003, Ford 2002, Jeschke 2004, Joseph 2000, Moisides 2004, Mouës 2004, Wanner 2003) reported in 11 publications, and 11 non-randomised concurrent comparative trials (Doss 2002, Etöz 2004, Genecov 1998, Kamolz 2004, Huang 2003, McCallon 2000, Page 2004, Scherer 2002, Schrank 2004, Stone 2004, Wild 2004) reported in 12 publications. General study details (general study characteristics, inclusion and exclusion criteria, description of test and control interventions, and baseline data) and the methodological aspects of both study types are presented as tables in Sections 5.2.3 (**Tables 3 to 7**) and 5.2.4 (**Tables 8 to 12**). These tables are preceded by a description of the essential and/or special aspects of the studies.

There were differences in the design of the studies with respect to the study or observation unit of "Patient" or "Wound". In most of the studies, the authors performed interindividual comparisons. On the other hand, some studies employed an intra-individual design, in which 2 wounds of the same patient were assigned to the test or control group (Joseph 2000, Genecov 1998, Kamolz 2004, Schrank 2004). In 1 study (Moisides 2004), 2 halves of the same wound were assigned to the 2 groups. Finally, there was 1 study in which a classical crossover design was selected (Eginton 2003).

The indications included in the studies include acute and chronic wounds. In 5 studies, patients were examined with plastic skin cover or split thickness grafting (both donor and

recipient) (Jeschke 2004, Mosidis 2004, Genecov 1998, Scherer 2002, Stone 2004); 4 studies examined diabetic foot ulcers (Eginton 2003, Etöz 2004, McCallon 2000, Page 2004); 3 studies examined decubitus ulcers (Ford 2002, Joseph 2000, Wanner 2003); 2 studies examined burns of the hand (Kamolz 2004, Schrank 2004); 2 studies examined fractures of the extremities (Buttenschön 2001, Huang 2003); 1 study examined postoperative sternum osteomyelitis (Doss 2002); 1 study examined open abdomen with peritonitis (Wild 2004); 1 study examined diabetic foot amputation wounds (Armstrong 2005); 1 study included patients with wounds of various origins (Mouës 2004). The form of conventional wound treatment used appeared to be adequate in all studies, even though the information given was sparse in some cases and there were great differences in the procedures applied.

A sample size calculation was only reported in the study of Armstrong 2005. It is striking that this study included a higher number of patients than the other studies. Sample size calculation was not reported in any other study. Mouës 2004 mentions a calculation of this sort. However, he gives no details or results. In all the 20 studies initially rated as relevant, 677 patients were included, made up of 371 in randomised and 306 in non-randomised trials. The corresponding figures for the 17 studies included in the evaluation are 602 (total), 324 (randomised trials) and 278 (non-randomised trials).

The maximum follow-up period in the studies was 1 year (Page 2004). However, this period was much shorter in most studies and was also shorter than the minimum follow-up of 3 months after wound closure demanded by the FDA [34] and was, with a few exceptions, inadequate for recording possible secondary complications or recurrence of the wounds.

The mean age of the patients in all studies was between 40 and 70 years. When the gender distribution was given, there was always a preponderance of male patients. In 1 study (Page 2004), exclusively male patients were examined. Gender-specific differences were not examined in any study. Additional description of the patients in the studies was moderately good. The distribution of relevant concomitant diseases and therapies (such as diabetes mellitus, peripheral disturbances in perfusion, infectious diseases, immunosuppressive systemic diseases, treatment with corticosteroids, dialysis treatment, nutritional status) between the test and control groups was often not clear, even though this is particularly important in non-randomised trials if the comparability of the groups is to be assessed.

5.2.2 Study and publication quality

Taken together, the quality of the studies and reports of all relevant studies must be described as poor. It is particularly striking that the randomisation technique is often not given in the randomised trials. In addition, there are often discrepancies between the results as given in the text and those given in the tables.

There was no clear description of the concealment of group allocation in any publication. However, on the basis of written information from the authors, there was clear allocation concealment in 2 studies (Armstrong 2005, Buttenschön 2001). Nevertheless, a detailed review of the Buttenschön 2001 study led to exclusion from the evaluation (see Section 5.2.3, description of Buttenschön 2001). Although the studies of Etöz 2004 and McCallon 2000 describe themselves as RCTs, the description of the randomisation was more in accord with so-called "pseudo"- or "quasi"-randomisation, with a clear lack of concealment of the patient allocation, so that these studies were assigned to the group of non-randomised trials.

Blinding of the responsible physicians or patients could hardly have been expected. Blinded documentation of outcomes was only conducted in 5 of the 9 RCTs and in 1 of the non-randomised trials. However, in 1 RCT (Armstrong 2005), the value of this quality parameter was limited, in that the primary result reported in the publication, complete wound closure, could also be achieved by operation. However, the indication for this was decided by the responsible physicians, who were not blinded.

In all non-randomised trials (in accordance with the inclusion criteria for this report), the therapy and control groups were treated concurrently. There was only incomplete overlap between the treatment periods in the study of Doss 2002. The data collection in the non-randomised studies was only partially prospective. In Doss 2002, Page 2004, Scherer 2002 and Stone 2004, the clinical data were retrospectively collected from the patient files. In Huang 2003 and Wild 2004, detailed data on the time course of the investigation were missing. As there was no indication that these studies had a prospective design, they were classified as retrospective studies.

A primary outcome was explicitly named in only 3 studies. In the remaining studies, adjustment for multiple testing was only performed in 1 case, although it was unclear how the adjustment was conducted (Jeschke 2004).

Because of the unclear presentation of the results, in almost none of the 20 studies was it possible to evaluate whether an ITT analysis had been performed or how dropouts had been handled. If there were unusual features in the patient flow (e.g. inconsistent information on the number of patients in the different groups) and no explicit consideration of dropouts, violation of the ITT principle was assumed. Of the RCTs, only Armstrong 2005 and Jeschke 2004 and – with reservations – Buttenschön 2001 observed the ITT principle. However, after a thorough review, the results of the last 2 studies could not be considered (see Section 5.2.3). A criticism of Armstrong 2005 is that the patient flow was not clearly described in the publication, and that the application of the ITT principle for a (patient-relevant) secondary outcome, the amputation rate, may have been performed in an anti-conservative manner (see Section 5.2.3, description of Armstrong 2005).

5.2.3 Specific aspects of the randomised trials

Armstrong 2005

This study deserves to be discussed in somewhat more detail, as with 162 enrolled patients it is by far the largest randomised trial; the patient number is greater than the sum of the patients in all the other 6 randomised trials considered in the evaluation. Moreover, it fulfils higher quality standards, even though there are considerable deficiencies in the quality of the study and report (see below).

In this multicentre study, wounds were investigated after partial foot amputation in patients with diabetes mellitus (about 90% type II). The wounds were on average 6 weeks old, although there was a great variability (standard deviation 5 months). The duration of observation given in the publication was 16 weeks.

The main quality aspects of the design and evaluation of the study will now be presented. Some of these details can be found in the statements and in the additional correspondence with the authors and the study sponsor, KCI.

Primary outcome

The definition of the primary outcome and the distinction from secondary outcomes were not unambiguously clear in the publication. It is legitimate to ask whether the definition of the primary outcome – complete wound closure with 100% re-epithelialisation – also implies the possibility of surgical wound closure, as the rates of wound healing or the facilitation of

surgical wound closure was also defined as a secondary outcome. Without anticipating the presentation of the results, a separate consideration of complete wound closure without surgical intervention as a primary outcome would have led to a negative result in the study, i.e. no statistical significance in the difference between the groups.

In the publication, the combined outcome consisting of complete wound closure with and without surgical interventíon was prominently presented in the results section. Correspondence with the authors and the sponsor of the study failed to clarify this question conclusively. However, it could be established that the primary outcome of the study was modified in an amendment to the protocol in July 2004. At this point in time, the first data from the study had already been evaluated and been published with unblinded group allocation.

This modification included the reduction of the 3 primary outcomes initially planned namely:

(1) Incidence of complete wound closure

(2) Accelerated wound healing or facilitation of surgical wound closure

(3) Change in the wound area over time

to a single primary outcome, namely parameter (1) above (without adjustment of the level of error, as explained by company representatives on enquiry during the hearing). The 2 remaining parameters were declared to be secondary parameters. The statement from KCI on the preliminary report contains the following information:

"In the interest of trying to conform to US FDA guidance, the 19 July 2004 amendment to the protocol changed the primary aim of the study to complete wound closure by 100% epithelialization without drainage. As a result, complete wound closure by surgical means was therefore relegated to a secondary endpoint instead of a primary aim as previously positioned. This change was made even though wound closure by surgical means is a primary clinical goal of V.A.C.® Therapy™. Therefore, the authors evaluated the incidence of complete wound closure both including and excluding the incidence of closure by surgical means."

However, despite this explanation, it is still doubtful whether the criterion "100% epithelialization without drainage" really should include wound closure with surgical help.

In their statement, the authors declared: "To clarify, the primary objective was to evaluate the proportion of wounds healed (with or without surgical intervention)."

The Institute repeatedly requested the study protocol, the protocol amendment, and the clinical study report. However, this was not granted, with reference to copyright (as the procedure for preparing the IQWiG report would lead to publication of this information) or it was stated that the document was not yet ready. Only extracts from the study protocol were provided without further verification. Although the statistical analysis plan was made available, the problem could not be solved on this basis.

Finally, the last letter from the sponsor suggested that the evaluation criteria for successful therapy ("complete wound closure") were defined differently in the NPWT group – as 100% filling of the wound with granulation tissue – than in the control group (100% re-epithelialisation). Should this be correct, unambiguous interpretation of the data on wound closure – as presented in the publication – would be difficult to achieve. Conclusive clarification of the problem would only be possible after inspection of the study protocol and possibly the study report – which was, as already mentioned, refused by the sponsor.

Concealed allocation

On the basis of the publication, it cannot be stated unambiguously whether there was concealed allocation. However, the authors clarified this issue during the procedure of submitting statements: ("Specifically, envelopes used for screening were opaque, sealed, and sequentially numbered. They were allocated in a permuted block and blinded manner.")

Blinding

The primary outcome (see above) was measured twice; by the responsible physicians, who were not blinded, and by planimetric measurement of digital photographs of the wounds, which were evaluated in ignorance of the group allocation. With 2 exceptions in the control group, the evaluations agreed. In both cases, a decision was made in favour of the control group, i.e. conservatively with respect to the evaluation of NPWT. The evaluation of the primary outcome must be qualified by the comment that the declared primary outcome of complete wound closure can – as mentioned above – also be achieved by surgical intervention, with the indication for surgery made by the responsible physicians, who were not blinded. It could not be established whether the surgically closed wounds in the 2 groups were similar in residual size before closure, so it is unclear whether the indication for surgical wound closure in the 2 treatment groups was similar.

ITT evaluation and patient flow

An ITT evaluation was performed for the declared primary outcome. In this, patients who withdrew from the study during the planned observation period of 16 weeks and for whom no complete wound closure was recorded before withdrawal were evaluated as therapy failures. This corresponds to a conservative approach for the therapy success rates assumed in the sample size planning and observed in the study, if it is assumed that the proportion of therapy failures in patients who withdraw from the study is greater than for the patients who remain in the study. The qualification must nevertheless be added that the patient flow was not illustrated clearly enough in the publication and that, for example, no reasons for withdrawals were given. It is also an essential question in this context whether the patients withdrew from both treatment arms at comparable points in time. The latter could be essentially confirmed by data provided by the sponsor.

On the other hand, in their written statement, the authors presented a table on premature withdrawals which was not only inherently inconclusive, but which also gave a much higher withdrawal rate than that in the publication. The sponsor explained this contradiction by stating that this table contained data on a later study phase (after 16 weeks), which was not reported in the publication. The request to extract the information for the first study phase (the only phase of interest here) was not responded to. Only the deaths were extracted (see **Appendix F**). It should also be noted that the information on the occurrence of deaths (also in the first study phase) was not provided in the publication.

There was an ITT analysis of the patient-relevant secondary outcome "re-amputation rate"; this was performed in exactly the opposite manner to the corresponding analysis of the primary outcome. This means that one can assume that patients who withdrew during the planned observation period of 16 weeks were rated as therapy successes (no re-amputation). With the assumed and observed re-amputation rates, this possibly led to an anti-conservative estimate, if it is assumed that the proportion of therapy failures in patients who withdrew from the study was higher than those who remained in the study.

In summary, the results of the Armstrong study 2005 can only be interpreted with reservations because of the problems described with main quality criteria or contradictory reporting. It would be expected that the questions raised could be largely clarified if the study protocol and possibly study report were available – which has been repeatedly refused by the sponsor, KCI.

Buttenschön 2001

This study included patients with status after closed malleolar fracture. The main focus was on changes in numerous biochemical inflammation parameters in the groups, which lay beyond the outcomes defined in the report plan of this report. In addition, a primary wound suture was used in the control group; this is not a conventional wound treatment in the sense of the report plan. The pressure of –600 mmHg (–80 kPa) used in the study substantially exceeds the clinically conventional value of –125 mmHg.

The incidence of complications during a follow-up period of 1 year was reported for this study. We wrote to the author, who provided detailed information on the complication rates (see **Appendix D**). The following points were striking here: Firstly, it was reported in the study that patients were clinically examined in a follow-up visit ("morbidity was checked 1 year after surgery by clinical examination"), whereas the author wrote that the patients were only followed up by a mailed questionnaire. Secondly, the number of complications was given in the abstract of the publication as 7 (of 18 patients in the NPWT group) vs. 5 (of 17 patients in the control group). However, in the author's written response referring to the patient responses to the questionnaire, the number of complications is given as 8 (of 16 NPWT patients) vs. 2 (of 15 control patients) (2nd of 4 questions "Did complications occur in the time after operation?") Thirdly, the time of the occurrence of pain and restriction to movement was not given, so that it is difficult or hardly possible to establish a direct connection with the initial mode of wound care. The level of the negative pressure may possibly be connected with the incidence of postoperative pain given by the author (6/14 vs. 2/15).

Because of the questionable clinical relevance of this study as reported (patient cohort and therapy form) and the contradictory presentation of the results, the results of the Buttenschön study were not included in the evaluation and are therefore not listed in the following tables.

Eginton 2003

This crossover study employed NPWT and conventional wound therapy over a period of 2 weeks each, without an intermediate "wash-out phase". Even though a therapy-free interval between the 2 phases would not have been medically acceptable, possible carry-over effects must be discussed. The inclusion of 1 patient with 2 separate foot wounds in the study produced dependent data, without adequate consideration in the evaluation. An essential point

of criticism is that only 6 of the 10 patients initially enrolled (7 of the initial 11 wounds) were included in the evaluation. The exclusion reasons were clearly reported and included failure of the NPWT in 1 case. However, it was not reported in which of the 2 phases the exclusions took place. There was no information in the publication on the significance tests performed.

Ford 2002

The authors describe the presentation of the study results as an interim analysis. It remains unclear whether the publication of an interim analysis was preplanned, what the reasons were for this interim publication and whether the study was continued. Moreover, it remains open if and when a final publication is planned and who the authors are, so does the final number of patients. Even though the randomisation in the study was clearly on the basis of the patients, it was not clearly described whether several wounds per patient were treated with the allocated therapy. This might have the consequence that several wounds of the same patient were considered as independent statistical analysis units in the analysis of the wound volumes of several wounds. Although 28 patients with 41 decubitus ulcers were included in the study, results were only presented for 22 patients with 35 wounds. The reasons for the withdrawal of the patients were explicitly documented. However, the allocation of the unreported patients to the different therapy groups could not be found in the publication. It is not clear that there was a separate crossover analysis for the 3 patients whose therapy was changed. The wound size was measured in a blinded manner.

Jeschke 2004

This study investigated the "take-rate" of a collagen matrix in the initial wound treatment of acute or chronic wounds. In the test group, the patients were treated with both NPWT and fibrin spray adhesive, whereas the fibrin spray adhesive was not used in the control group. Thus any therapeutic effect could be totally or partially due to the fibrin adhesive. The outcome "take-rate" is rather subjective and was not recorded in a blinded manner.

As the selected study design does not permit any separation between the effects of NPWT and the fibrin spray adhesive (especially with respect to the main outcome of the study), the results of Jeschke were not used for the subsequent report and are therefore not listed in the following tables.

Joseph 2000

Patients were prospectively randomised into 1 of 2 treatment groups receiving either NPWT or standard wound therapy. Study files were made, including colour coding for group allocation (silver for the NPWT, black for conventional wound treatment), and were randomly organised in a locked cabinet. This is not regarded as reliable concealment in the present report, as the possibility is not excluded that the file could have been returned if the allocation was not desired. As the randomisation was made on the basis of the wounds, in several cases 2 wounds from the same patient were allocated to the same therapy. The dependence of the data was not considered, which violates basic statistical principles.

Data on the initial wound volume were contradictory. In Table 2 of the publication, the mean initial wound volume before the start of treatment was given as 38 cm^3 for the test group and 24 cm^3 for the control group. However, the sum of the individual values in Table 4 of the publication gives mean values of 53 (SD 46) cm^3 and 25 (SD 25) cm^3, respectively. This difference between the groups is significant in the Welch t-test with $p = 0.0312$. The statistical analyses are not comprehensible, as the test used is not given and it is also unclear whether means or medians are given. Confidence intervals are given for the multivariate model given in Table 3 of the publication, but effect estimators are missing. The deficiencies in reporting extend to the figures. Several graphs contain errors. In Figure 1 of the publication the group allocations in the legend have evidently been confused. Figure 5 of the publication does not illustrate the change in wound volume over time, but is identical to Figure 4 of the publication, but with different scales. The measurement of the wound size and its evaluation were performed by a blinded microbiologist.

Moisidis 2004

The special feature of this study is the intra-individual randomisation of large wounds covered with split-thickness skin graft, where each wound was split by a barrier into 2 halves which were separately allocated to the test or to the control group. It is not discussed and is unclear what effect this separation had on the wound healing. The loss of 9% (2 of 22) in the follow-up was described without further details. These 2 cases were excluded from the evaluation. This violates the ITT principle, even if the 2 groups were equally affected. The clinical evaluation of the wound results was conducted in a blinded manner.

Mouës 2004

There was initially some imbalance between the groups with respect to some patient characteristics, although this tended not to favour the test group. There are no data of any sort on the initial wound size, although the percentage change in wound size is given. Randomisation of the wounds in this study was performed by withdrawing a sealed envelope containing the description of therapy. Allocation concealment is unclear, as it is not mentioned whether the envelopes were transparent, reliably sealed, and given a running number.

Of the 54 patients (29 vs. 25), only 28 (15 vs. 13) were evaluated in the analysis of the change in wound area. This is a gross violation of the ITT principle, particularly as no reason of any kind is given for this procedure. The "ready for surgical therapy" analysis gives an overall description of the reasons for censorship (when "ready for surgical therapy" was not reached within 30 days or follow-up was stopped for reasons of death, sepsis, or refusal of further cooperation). However, the distribution of the reasons between the groups is not given, with the exception of "ready for surgical therapy" not reached within 30 days as a reason for censorship (concerns 1 patient in the control group; 3 patients in the test group and 1 patient in the control group were censored for other reasons).

The microbiological evaluation of the wound biopsies was blinded, whereas the clinical evaluation of the wounds (as patient-relevant outcome) could, according to the authors, not be blinded, as the NPWT left a visible imprint on the wound.

Wanner 2003

It is a noticeable feature of this study that the dressings in the NPWT group were only changed every 2 to 7 days; this is less frequently than usual. Two of the 24 patients with pressure ulcers in the pelvic region were not considered in the evaluation. One of these patients was lost to follow-up. In the other patient, the dressing for NPWT could not be fixed because of severe diarrhoea. The ITT principle was thus violated.

The evident change in the hypothesis tested is a clear deficiency. Whereas it was initially assumed that the NPWT would be (clearly) superior to standard therapy with regard to more rapid wound healing, reference is made in the statistics and results section to an equivalence test, which however was not significant either, even though there was only a minimal

difference between the groups. This implies that the sample size was unsuited for any statement. This study reports how many of the potential patients could be recruited into the study (24 of 34).

Table 3. Study characteristics (randomised trials)

Study	Design	Observation period	Number of patients / wounds at start of study[a]	Country / setting	Relevant outcomes[b]
Armstrong 2005	Parallel Multicentre	16 Weeks	NPWT[c]: 77 Patients Control: 85 Patients	USA Inpatients and outpatients	o **Proportion of patients with complete wound closure at study end** o Proportion of patients with re-amputations o Therapy-related complications
Eginton 2003	Crossover 2 Centres	2 Weeks per sequence	10 Patients (11 wounds)	USA Inpatients and outpatients	o Reduction of wound volume and wound area within 2 weeks
Ford 2002	Parallel[d] Single centre	3 to 10 months	28 Patients (41 wounds) Allocation of patients to groups not given	USA Inpatients	o Complete wound healing within 6 weeks o Reduction in wound volume within 6 weeks o Complications (local and systemic)
Joseph 2000	Parallel Single centre	Up to 10 weeks	NPWT: 12 Patients/18 wounds Control: 12 Patients/18 wounds	USA Inpatients, domestic care and nursing home	o **Time till 90% reduction in wound volume** o Reduction in wound volume within 6 weeks
Moisidis 2004	Parallel, intra-individual Single centre	2 Weeks	NPWT: 22 Wound halves Control: 22 Wound halves	Australia Inpatients	o Epithelialisation of wound
Mouës 2004	Parallel Single centre	Up to 1 month	NPWT: Wound closure: 29 patients, Wound surface: 15 patients Control: Wound closure: 25 patients, Wound surface: 13 patients	Netherlands Inpatients	o **Time till operative wound closure** o Change in wound area
Wanner 2003	Parallel Single centre	Up to 8 weeks	24 Patients Allocation of patients to groups not given	Switzerland Inpatients	o Time till 50% reduction in wound volume o Reduction in wound volume

[a] Number of patients or wounds primarily recruited in the study.
[b] Patient-relevant outcomes in accordance with Section 4.1.3 and surrogates for "Shortening of wound healing time" (in bold print, if declared as primary outcome).
[c] NPWT: negative pressure wound therapy.
[d] 3 Patients were subsequently investigated by Ford 2002 per crossover.

Table 4. Inclusion and exclusion criteria (randomised trials)

Study	Wound types / patient groups considered	Main inclusion criteria	Main exclusion criteria
Armstrong 2005	Acute or chronic wounds after partial foot amputation in diabetes mellitus patients	Age at least 18 years, patients with diabetes mellitus, wounds with partial foot amputation up to the transmetatarsal level Evidence of perfusion in the foot: either $tcPO_2$[(a)] ≥ 30 mmHg or ankle-arm index 0.7-1.2	Active Charcot arthropathy of the foot, burns, venous failure, untreated cellulitis, osteomyelitis after amputation; collagen vascular disease, malignant disease of the wound, uncontrolled hyperglycaemia with HbA1c > 12%; treatment with corticosteroids, immunosuppressives or chemotherapy, NPWT[(b)] therapy within the last 30 days
Eginton 2003	Chronic wounds in diabetic foot ulcers	Wounds which could not be healed within 1 month	Treatment with growth factors, hyperbaric O_2 therapy within 30 days before or during the study period, untreated cellulitis (deep tissue infection), malignant tumour in the wound, much necrotic tissue in the wound, osteomyelitis, NPWT not covered by health insurance fund
Ford 2002	Chronic wounds in pressure sores in any localisation	Age 21-80 years[(c)] Grade 3 or 4 ulcer (present for at least 4 weeks) Serum albumin ≥ 2.0 g/dl Ulcer volume after debridement 10 to 150 ml	Fistulas, malignant tumours in the wound, sepsis, burns from exposure to electric current, radiation or chemicals, connective tissue disease, chronic renal or pulmonary disease, uncontrolled diabetes mellitus, corticosteroids or immunosuppressives, recently implanted osteosynthesis material
Joseph 2000	Chronic wounds in any localisation	Wounds which could not be healed within 4 weeks	Urinary infection, pneumonia, wound infection, serum albumin < 3.0 g/dl, chronic diseases (of the lungs, kidneys or other), uncontrolled diabetes mellitus, hypertension, corticosteroids, other immunosuppressive therapy, anticoagulation, osteomyelitis, malignant tumours within the wound borders, fistulas
Moisidis 2004	Acute or chronic wounds receiving a split-thickness skin transplantation	Adult patients with skin defects ≥ 25cm^2, who are to be given a split-thickness skin transplantation	No information
Mouës 2004	Acute or chronic wounds of any localisation	Wounds which could not be immediately closed by surgery, because of infection, contamination or chronicity	Cancer, deep fistulas, sepsis, current bleeding, poorly controlled diabetes mellitus, unstable skin surrounding the edge of the wound
Wanner 2003	Chronic wounds from pressure sores in paraplegic or tetraplegic patients	Patients with pressure sores in the pelvic region, extending at least into the subcutaneous fat tissue	No information

[a] $tcPO_2$: Transcutaneously measured oxygen pressure.
[b] NPWT: negative pressure wound therapy.
[c] Contradictory data: in Table 1 of the publication Ford 2002: 21-80 years, in publication text: 18-80 years.

Table 5. Wound treatment (randomised trials)

Study	Test group	Control group
Armstrong 2005	NPWT[(a)] dressing (V.A.C.® [(b)], KCI) with initial debridement No information on application form and the pressure level Dressing changed every 2 days	Various forms of moist wound cover with alginate, hydrocolloid, foam, hydrogel. Initial debridement. Dressing changed daily
Eginton 2003	NPWT dressing (V.A.C.®, KCI) with continuous application of -125 mmHg pressure Dressing changed 3 times weekly, or more if necessary	Moist dressing with hydrocolloid wound gel Dressing changed daily
Ford 2002	NPWT dressing (V.A.C.®, KCI) after debridement No information on application form or level of pressure Dressing changed 3 times weekly Treatment duration 6 weeks	Gel wound cover after debridement with Cadexomer iodine or an enzymatic wound ointment (papain-urea-chlorophyllin copper complex) Dressing changed once to twice daily Therapy duration 6 weeks
Joseph 2000	NPWT dressing (V.A.C.®, KCI) with negative pressure - no further details No information whether continuous or intermittent application Dressing changed every 2 days for a period of 6 weeks	Moist dressing with NaCl solution with adhesive foil cover Dressing changed 3 times per day over a period of 6 weeks
Moisidis 2004	NPWT dressing (V.A.C.®, KCI) with continuous application of -100 mmHg pressure Silicone layer between skin and sponge for 5 days, then dressing removed and standard dressing applied with dressings soaked in petroleum and physiological saline with crepe dressing changed daily No dressing change in the first 5 days	Standard dressing with acriflavine wool and "Standard Foam" with silicone layer between skin and dressing for 5 days then removal of dressing and application of a standard dressing with daily change of dressings soaked in petroleum and physiological saline with crepe dressing No dressing change in the first 5 days
Mouës 2004	NPWT dressing (V.A.C.®, KCI) with continuous application of -125 mmHg pressure Dressing changed every 2 days till surgical wound closure	Moist standard dressings with one of the following solutions: 0.9% NaCl, 0.2% nitrofuralam, 1% acetic acid or 2% Na hypochloride Dressing change twice daily
Wanner 2003	NPWT dressing (V.A.C.®, KCI) after wound debridement with -125 mmHg pressure Dressing change every 2 to 7 days, till surgical wound closure	Moist dressings, soaked in Ringer solution after wound debridement Dressing changed 3 times daily till surgical wound closure

[a] NPWT: negative pressure wound therapy; [b] VAC®: vacuum-assisted closure.

Table 6. Baseline data (randomised trials)

Study	Number of evaluated patients / wounds[a]	Age in years[b]	Gender (women / men in %)	Initial wound area or volume[b]
Armstrong 2005	162 (of 162) Patients	NPWT[c]: 57.2 (13.4) Control: 60.1 (12.2)	NPWT: 14/86 Control: 22/78	NPWT: 22.3 cm^2 Control: 19.2 cm^2
Eginton 2003	6 (of 10) Patients 7 (of 11) Wounds	No information	17/83[d]	Length 7.7 cm, Breadth 3.5 cm, Depth 3.1 cm[d]
Ford 2002	22 (of 28) Patients 35 (of 41) Wounds	NPWT: 42 Control: 54	No information	10-150 cm^3[d]
Joseph 2000	24 (of 24) Patients 36 (of 36) Wounds	NPWT: 56 Control: 49 (p = 0.17)	NPWT: 34/66 Control: 56/44 (p = 0.18)	NPWT: 38 cm^3 Control: 24 cm^3 (p = 0.08)
Moisidis 2004	20 (of 22) Patients 40 (of 44) Wound halves[e]	60 (18)[e,f]	40/60[e,f]	128 (126)[e,f] cm^2
Mouës 2004	Wound closure: 54 (of 54), Wound surface: 28 (of 54) Patients	NPWT: 48 (20) Control: 48 (17)	NPWT: 28/72 Control: 44/56	No information
Wanner 2003	22 (of 24) Patients	NPWT: 49 (25-73)[g] Control: 53 (34-77)[g]	NPWT: 36/64 Control: 27/73	NPWT: 50 (33) cm^3 Control: 42 (16) cm^3

[a] If the number of patients and wounds is the same, only the number of patients is given (in brackets, the primary number of patients/wounds included in the study).
[b] Unless otherwise stated, means with standard deviations in brackets.
[c] NPWT: negative pressure wound therapy.
[d] No allocation to therapy groups given.
[e] Intra-individual comparison.
[f] Calculated by us from the raw values given in the publication.
[g] Range (no standard deviation or raw values given).

Table 7. Quality of the studies/publications (randomised trials)

Study	Randomisation / allocation concealment	Blinding			Sample size planning	Intention-to-treat	Study discontinuations[b]	Biometric quality
		Patient	Physician	Evaluator[a]				
Armstrong 2005	Yes[c]	No	No	(Yes)[d]	Yes	(Yes)[e]	38 without details	Major deficiencies [f]
Eginton 2003	Unclear	No	No	Yes	No	No	4 with details	Major deficiencies
Ford 2002	Unclear	No	No	Yes	No	No	6 with details	Major deficiencies
Joseph 2000	Unclear	No	No	Yes	No	Unclear	No information	Major deficiencies
Moisidis 2004	Unclear	No	No	Yes	No	No	2 without details	Major deficiencies
Mouës 2004	Unclear	No	No	No	Mentioned without details	No	26 without details[g]	Major deficiencies
Wanner 2003	Unclear	No	No	No	No	No	2 with details	Major deficiencies

[a] For at least 1 outcome
[b] All cases of discontinued study participation. During therapy: "Withdrawal" after protocol violation and "Dropout" on the part of the patient. After therapy: "Loss to follow-up" if the follow-up after end of treatment was missing.
[c] According to authors' written information.
[d] However, in this case, this quality characteristic is qualified by the fact that the main result reported in the publication - complete wound closure - could also sometimes be achieved by surgical intervention and the indication for this was made by the responsible physicians, who were not blinded.
[e] The qualification must be made that the patient flow in the publication and in the correspondence with the authors and the sponsor was not transparent and that the application of the ITT principle for the (patient-relevant) secondary outcome of the rate of re-amputation may possibly have been anti-conservative.
[f] This classification is due to unresolvable lack of clarity in the definition of the primary outcome and only limited fulfilment of essential quality characteristics.
[g] The study of Mouës 2004 reports the results for the measurement of wound area for only 28 of 54 patients.

5.2.4 Specific aspects of the non-randomised trials

Doss 2002

The study period for this study on sternum osteomyelitis extended from 1998 to 2000. Until May 1999, only conventional wound treatment was used, but after this, also NPWT. Thus the test group was partially compared to a historical control. As the control group was partially concurrent, the study was rated as relevant in the sense of the report plan. The allocation to the 2 groups was to some extent dependent on the availability of NPWT and to some extent on the decision of the responsible surgeon. The 2 groups are comparable with respect to age, microbial spectrum, comorbidity and type of operation. Data were collected retrospectively.

The presentation of the results is not quite transparent, as some of the information on measures of spread of the data are missing. The duration of treatment was a parameter which was largely determined subjectively. The measurement of wound size was not defined in more detail and is not clear either.

Etöz 2004

In the text to this publication, the allocation of the patients was described as random. It must nevertheless be assumed that the randomisation was not genuine, as allocation to the groups was performed on the basis of the final number of the hospital registration number (pseudorandomisation). When the final number was odd, the patient was given NPWT and when it was even, control therapy. The 2 therapy groups were not treated with analgesics in the same way. All patients in the NPWT group were given intravenous analgesics, but those in the control group were only given oral analgesics as needed.

The data in Table 1 of the publication contain calculation errors (patient identification numbers 9 and 11) and differ from the information in the text (mean reduction in wound size 19.5 cm^2 in the table, but 20.4 cm^2 in the text).

Genecov 1998

This study contains an intra-individual comparison and reports on the results, with only 10 of the 15 patients originally included. The reasons for the exclusion from the evaluation are

reported and include 1 case of faulty application of NPWT (disconnection of the pump). The ITT principle was thus violated. The manner of allocation to the 2 treatment groups was not reported. It is unclear whether the initial wound size was similar in the 2 groups. The presentation of the results is not transparent, as no absolute values were given for the 2 groups, but only a p-value for the group comparison.

Huang 2003

This study was translated from Chinese and presents the wound treatment of patients with open fractures. The time course of the treatment was not explicitly described. It is presumably a retrospective design with a concurrent control group. The criticism must be made that the type of fracture care in the 2 groups was different. Whereas the fractures in the NPWT group were treated with primary internal osteosynthesis, in the control group a 2-step procedure was used with primary external fixation. Osteomyelitis and wound sinus formation were evidently counted as wound infection and assigned to conventional wound treatment. However, these are rather to be regarded as complications of external fixation. The negative pressure for the NPWT was set at a value of 375 mmHg to 450 mmHg (50 to 60 kPa) within the first 24 hours of the operation with a Redon bottle. The level of negative pressure during the subsequent period remains unclear.

Two of the patients included in the study were excluded from the evaluation and not described in more detail; this violates the ITT principle. Some patients with 2 fractures were included in the study.

As the selected study design allows no separation between the effects of NPWT and operative technique (1- or 2-step procedure), the results of Huang 2003 are not considered in the evaluation in this report and not listed in the tables below. Moreover, the selected negative pressure is clearly outside the usual clinical range.

Kamolz 2004

Patients with first or second degree burns on both hands were prospectively investigated. Each patient had burns on both hands, which were allocated to different treatment groups (design with intra-individual comparison); the more severely burnt hand was given NPWT and the other hand was assigned to the control group. However, information on the initial wound size and the exact severity of the burns are missing. The study primarily examined the

perfusion of both hands by laser fluorescence angiography. Even if this was blinded, this is a surrogate parameter, with uncertain validity in the context of patient-relevant outcomes. The method of recording pain is also unclear.

McCallon 2000

Group allocation for this study was performed for the first patient by tossing a coin and then in alternating sequence. This procedure corresponds to pseudorandomisation. Because of the small number of patients (5 patients per group), the authors did not conduct an inferential statistical analysis of the results. The reported measures of variability are not unambiguously designated, but can be partially calculated from the given individual values.

Page 2004

The 2 treatment groups in this study are not comparable with respect to wound size (which was statistically significantly larger in the NPWT group) or albumin serum concentration (significantly lower in the NPWT group), so that these and other characteristics (age, ethnicity, and diabetes mellitus) were taken into account as confounding factors in the multivariate analysis. In the multivariate analyses on revision operations, complications and readmissions to hospital, it is not reported how frequent these events were overall and how they were defined (amputations were evidently not rated as complications). The patient flow is unclear, as "interruption in treatment" was defined as an exclusion criterion, without any statement of how frequent this was. Finally, it is unclear how the parameter "wound volume" was measured in this retrospective study.

Scherer 2002

In a comparative retrospective study (N = 61 patients), the treatment of wounds covered with split-thickness skin was studied. The initial wound size was statistically significantly larger than in the control group. However, the authors emphasise in the discussion that none of the repeated skin transplantations took place in patients with large skin defects. The patient flow and analysis are unclear, as 2 of the drop-out patients (transplant failed to "take" after conventional wound treatment) were nevertheless partially included in the analysis.

Schrank 2004

This publication is evidently a partial evaluation of a single centre in a multicentre prospective comparative study. The report describes 11 patients with second degree burns on both hands. An intra-individual design was used in which the more severely burnt hand was assigned to NPWT, while the less severely burnt hand was assigned to the control group (evaluation by 2 experienced surgeons independently of one another). There is however no specific information on wound size and the exact degree of the burns. The publication contains no data of any sort on the results (it was stated that the exact data will be presented in additional publications in the near future). Nor are there any details on the exact conduct of the study. In general, the quality of the reporting is so rudimentary that no conclusions are possible. The publication does not contain any literature citations. We wrote to the first author in July 2005 to ask for more details about the study. No answer has so far been received. The available data are nevertheless presented in this report.

Stone 2004

This comparative retrospective cohort study examined wounds covered with split-thickness skin (N = 46 in 40 patients). Group allocation was decided by the responsible surgeon. The initial wound size was smaller in the NPWT group ($p = 0.08$). It is unclear whether the patient or the wound was the observational unit. The description of patient flow is acceptable. The heading of Table 2 in the publication wrongly gives the total of grafts in the conventional therapy group as 23 rather than 25.

Wild 2004

This 3-arm study on the treatment of the open abdomen in peritonitis compared 2 types of NPWT (each N = 8) with conventional wound therapy (N = 5). The publication contains no information of any sort on the comparability of the patient groups with respect to the type and severity of the underlying disease, comorbidity, age or gender. It is also unclear from the publication whether it was performed retrospectively or prospectively. The presentation of the results is not clear, as the measures of spread and units are often not given.

We then wrote 2 letters to the author with the request for additional information, such as on the inclusion of patients in the study and the distribution of characteristics relevant to the prognosis, to help us to evaluate the results. However, we have not yet received any

information, except by phone that the study was retrospective. It was also reported that a database for the prospective recording of clinical data from patients with similar clinical presentations is now being built up in more than 50 centres in Europe. This would also record the type of wound care (with NPWT or conventional). However, randomisation was not planned.

Table 8. Study characteristics (non-randomised trials)

Study	Design	Observation period[a]	Number of patients / wounds at start of study [b]	Country / setting	Relevant outcome criteria[c]
Doss 2002	Partially parallel Retrospective Single centre	5 Weeks[d]	NPWT[e]: 20 Patients Control: 22 Patients	Germany Inpatient	o Change in wound area o Time till operative wound closure o Period in hospital
Etöz 2004	Parallel, pseudorandomised Prospective Single centre	4 to 24 days	NPWT: 12 Patients Control: 12 Patients	Turkey Inpatient	o Time till operative wound closure o Change in wound area o Necessity of operations o Pain (method of measurement unclear) o Complications (local and systemic)
Genecov 1998	Parallel, intra-individual Prospective Single centre	1 week	15 Patients (30 wounds) NPWT: 15 wounds Control: 15 wounds	USA Inpatient	o Re-epithelialisation on day 7 o Pain on day 4 (comparison between sides) o Local complications
Kamolz 2004	Parallel, intra-individual Prospective Single centre	3 days	7 Patients (14 wounds) NPWT: 7 wounds Control: 7 wounds	Austria Inpatient	o Pain (method of measurement unclear) o Necessity of operations
McCallon 2000	Parallel, pseudorandomised Prospective Single centre	1 to 13 weeks	NPWT: 5 Patients Control: 5 Patients	USA Inpatient	o Time till wound closure o Change in wound area o Pain (method of measurement unclear) o Complications (local and systemic)
Page 2004	Parallel Retrospective Single centre	1 year	NPWT: 22 Patients Control: 25 Patients	USA Inpatient	o Time to wound filling (deepest part of wound within 2 mm of the surrounding epithelium) o Time till complete wound closure o Necessity of operations o Complications (local and systemic) o Readmission to hospital

Table 8. Study characteristics (non-randomised trials) (continued)

Study	Design	Observation period[a]	Number of patients / wounds at start of study[b]	Country / setting	Relevant outcome criteria[c]
Scherer 2002	Parallel Retrospective Single centre	1 to 13 weeks	NPWT: 34 Patients Control: 27 Patients	USA Inpatient	o Rate of take of the split-thickness skin transplant o Necessity of operations o Period in hospital o Local complications
Schrank 2004	Parallel, intra-individual Prospective Single centre	No information	11 Patients (22 wounds) NPWT: 11 wounds Control: 11 wounds	Germany Inpatient	o Time till wound closure o Necessity of operations o Frequency of change of dressing
Stone 2004	Parallel Retrospective Single centre	5 to 41 days	NPWT: 17 Patients (21 wounds) Control: 23 Patients (25 wounds)	USA Inpatient	o Necessity of operations o Duration of treatment o Period in hospital
Wild 2004	Parallel Retrospective Single centre	42 to 65 days	NPWT: 8 Patients NPWT with abdominal dressing: 8 Patients Control: 5 Patients	Austria Inpatient	o Period on intensive care unit o Survival o Necessity of operations o Frequency of dressing change

[a] Observation period: Treatment period + follow-up period (if different periods are stated, the respective range is given).

[b] Number of patients primarily enrolled in the study.

[c] Patient-relevant outcome criteria in accordance with Section 3.1.3 and surrogates for "Shortening of wound healing time".

[d] Information in the letter from the author (Doss) in response to a letter to the editor [85].

[e] NPWT: negative pressure wound therapy.

Table 9. Inclusion and exclusion criteria (non-randomised trials)

Study	Wound types / patient groups considered	Main inclusion criteria	Main exclusion criteria
Doss 2002	Acute wounds in osteomyelitis after sternotomy	Wounds requiring surgical re-exploration	No information
Etöz 2004	Chronic wounds with diabetic foot ulcers	No (additional) information	No information
Genecov 1998	Acute wounds after split-thickness skin removal	Necessity of split-thickness skin removal on at least 2 sites in the thigh	No information
Kamolz 2004	Acute wounds from burns	Burns on both hands, extending to the dermis (grade II)	Interval till admission to hospital > 6 hours, Age < 20 years
McCallon 2000	Chronic wounds with diabetic foot ulcers	Wounds which have been present for at least 1 month	Persistent infection, Age > 75 years or < 18 years, venous insufficiency, coagulation disorders
Page 2004	Foot wounds	Soft tissue defects of > 2 cm in depth after debridement or amputation	Persistent infection, Age > 75 years or < 18 years, residual necrotic tissue, interruption or change to therapy
Scherer 2002	Acute wounds with receipt of a split-thickness skin transplant	Wounds after injury or burns which require split-thickness skin transplantation	No information
Schrank 2004	Acute wounds from burns	Burns on both hands, extending to the dermis (grade IIa-b)	Interval till admission to hospital > 6 hours
Stone 2004	Acute wounds with receipt of a split-thickness skin transplant	Wounds after injury which require a split-thickness skin transplantation	High grade contamination of the wound
Wild 2004	Acute wounds with open abdomen in peritonitis	No (additional) information	No information

Table 10. Wound treatment (non-randomised trials)

Study	Test group	Control group
Doss 2002	NPWT[a] dressing (V.A.C.® [b], KCI) after debridement and re-cerclage of the sternum Continuous application of -125mmHg pressure; but pressure partially produced with a simple Redon bottle. Dressing change every 2 to 3 days	Conventional dressing after debridement and re-cerclage of the sternum In some cases, a suction and rinsing drain was attached.
Etöz 2004	NPWT dressing (aspiration pump from the firm Bicakcilar, Istanbul, Turkey) after debridement Continuous application of -125mmHg pressure Dressing changed every 2 days with administration of intravenous analgesics	Moist dressing after debridement Dressing changed twice daily, in some cases after administration of oral analgesics
Genecov 1998	NPWT dressing (V.A.C.®, KCI) with continuous application of -125mmHg pressure Dressing changed every 4 days, therapy end after 7 days	Water tight foil dressing permeable to air, with wound cushion Dressing changed after 4 days. Therapy end after 7 days.
Kamolz 2004	NPWT glove dressing (V.A.C.®, KCI). Wound covered with paraffin gauze. Continuous application of -125mmHg pressure Dressing changed daily	Silver sulfadiazine dressing Daily dressing change
McCallon 2000	NPWT dressing (V.A.C.®, KCI) after debridement Application of -125 mmHg pressure, first continuously for 2 days and then intermittently Dressing changed every 2 days	Moist dressing, soaked in saline solution after debridement Dressing change twice daily
Page 2004	NPWT dressing (V.A.C.®, KCI) with continuous or intermittent application of a pressure of -100 to -150 mmHg after debridement or amputation	Moist dressing, soaked in saline solution after debridement or amputation Dressing changed as required ("frequently enough to maintain a moist wound environment")
Scherer 2002	NPWT dressing (V.A.C.®, KCI) with continuous application of -125mmHg pressure No dressing change, as therapy end after 4 days No information on debridement	Moist dressing, soaked in 5% Mafenide solution (an antimicrobial substance) No dressing change, as therapy end after 4 days
Schrank 2004	NPWT glove dressing (V.A.C.®, KCI) with application of -125mmHg pressure. No information whether continuous or intermittent	No further information
Stone 2004	NPWT dressing (V.A.C.®, KCI) with non-adherent wound cover No dressing change, as mean therapy end after mean of 5 days	Moist dressing, soaked in saline solution Dressing fixed with nylon sutures No dressing change, as therapy end after mean of 5 days
Wild 2004	NPWT dressing (V.A.C.®. KCI) after covering the abdominal contents with either silicone net or with special foil No information on negative pressure and dressing change	Conventional dressing laying towels Wound rinsed with saline or Ringer solution

[a] NPWT: negative pressure wound therapy; [b] VAC®: Vacuum-assisted closure.

Table 11. Baseline data (non-randomised trials)

Study	Number of evaluated patients / wounds [a]	Age in years[b]	Gender (women / men in %)	Initial wound area / volume[b]
Doss 2002	42 (of 42) Patients	NPWT [c]: 66[d] (45-82)[e] Control: 66[d] (50-83)[e]	NPWT: 55/45 Control: 14/86	No information
Etöz 2004	24 (of 24) Patients	NPWT: 66.2 (7) Control: 64.7 (5)	NPWT: 17/83 Control: 8/92	NPWT: 109 (69) cm^2 Control: 94.8 (21) cm^2
Genecov 1998	10 (of 15) Patients 20 (of 30) Wounds[f]	(39–81) [e,f]	No information	No information
Kamolz 2004	7 (of 7) Patients 14 (of 14) Wounds[f]	44.2 (22) [f]	No information	No information
McCallon 2000	10 (of 10) Patients	NPWT: 55.4 (12.8) Control: 50.2 (8.7)	No information	NPWT: 22 (24) $cm^{2(g)}$ Control: 20 (21) $cm^{2(g)}$
Page 2004	47 (of 47) Patients	NPWT: 66 (12) Control: 60 (11)	NPWT: 0/100 Control: 0/100	Only qualitative information on wound size
Scherer 2002	61 (of 61) Patients	NPWT: 33 (23) Control: 41 (20)	No information	NPWT: 387[h] (573) cm^2 Control: 984 (996) cm^2
Schrank 2004	11 (of 11) Patients 22 (of 22) Wounds[f]	No information	No information	No information
Stone 2004	40 (of 40) Patients 46 (of 46) Wounds	NPWT: 35.4 (14) Control: 39.0 (17)	No information	No information
Wild 2004	21 (of 21) Patients	No information	No information	No information

[a] If the number of patients and wounds is the same, only the number of patients is given. The figure in brackets is the number of patients or wounds primarily included.
[b] Means given, with SD in brackets, if not otherwise stated.
[c] NPWT: negative pressure wound therapy.
[d] Median.
[e] Range (no standard deviation or raw values given).
[f] Intra-individual comparison.
[g] Wound area assessed by us from the bar chart in Figure 4 of the publication of McCallon 2000.
[h] In the publication Scherer 2002, the value 386 is given in the abstract and the value 387 in Table 1.

Table 12. Quality of the studies / publications (non-randomised trials)

Study[a]	Concurrent control group	Any sort of blinding	Allowance for confounding factors	Consecutive patient inclusion	Intention-to-treat	Study discontinuations	Biometrical quality
Doss 2002	No	No	No	Unclear	No	No	Major deficiencies
Etöz 2004	Yes	No	No	No	Yes	No	Major deficiencies
Genecov 1998	Yes	Yes	No	No	No	Yes	Major deficiencies
Kamolz 2004	Yes	No	No	Yes	Yes	No	Major deficiencies
McCallon 2000	Yes	No	No	No	Yes	No	Major deficiencies
Page 2004	Yes	No	Yes	Unclear	No	Unclear	Major deficiencies
Scherer 2002	Yes	No	No	Yes	No	No	Major deficiencies
Schrank 2004	Yes	No	No	Unclear	Unclear	No	Major deficiencies
Stone 2004	Yes	No	No	Yes	Unclear	Unclear	Major deficiencies
Wild 2004	Yes	No	No	Unclear	Unclear	No	Major deficiencies

[a] Pseudorandomised trials are printed in **bold.**

5.3 Results on therapeutic goals

The study results will now be discussed for the different therapeutic goals.

Sensitivity and subgroup analyses had originally been planned, but could not be conducted as the data were very limited and – in most cases – inadequately presented. Only the authors of Armstrong 2005 provided separate presentations of the results for the primary outcome for acute and chronic wounds, within the framework of submission of statements. There were no significant differences in the proportion of patients who achieved full (100%) wound closure for acute vs. chronic wounds.

5.3.1 Shortening of the time to wound healing

Information on this therapeutic goal was given in 5 randomised (Armstrong 2005, Ford 2002, Joseph 2000, Mouës 2004, Wanner 2003) and in 4 non-randomised trials (Doss 2002, Etöz 2004, McCallon 2000, Page 2004). However, the results were expressed (operationalised) in very different manners. In 3 studies (Joseph 2000, Mouës 2004, Page 2004), the wound healing period was investigated (under consideration of censoring) in a Kaplan-Meier analysis. In 4 studies (Wanner 2003, Doss 2002, Etöz 2003, McCallon 2000), no censoring was performed and means or medians were given. Two of the studies with Kaplan-Meier analyses also gave median times to healing (Mouës 2004, Page 2004). Finally, 2 studies used a dichotomous outcome as the proportion of wounds with complete wound closure (Armstrong 2005, Ford 2002); in Armstrong 2005, this was either with or without surgical intervention.

Of the 7 studies in which the wound healing period was described quantitatively, 5 gave the time until the wound had closed to such an extent that surgical intervention (operative wound cover or secondary wound suture) was possible (Mouës 2004, Doss 2002, Etöz 2004, McCallon 2000, Page 2004); 2 studies defined that either 90% (Joseph 2000) or 50% (Wanner 2003) wound closure was necessary for the indication to additional surgical intervention.

Blinded recording of this outcome was only planned in Armstrong 2005. However, this quality parameter was of restricted value in this study, as complete wound closure could also be achieved by surgical intervention, but the indication for this was made by the responsible physicians, who were not blinded.

Table 13. Time to wound closure[a] (randomised trials)

Study	Outcome	NPWT M (SD/sample size)[b]	Control M (SD/sample size)	Group difference
Armstrong 2005	Complete wound closure with or without surgical intervention	12+31 (-/77)	8+25 (-/85)	p = 0.04
Ford 2002	Successful secondary wound healing within 6 weeks (number)	2 (-/20)	2 (-/15)	No information
	Surgical closure with flap plastic surgery	6 (-/20)	6 (-/15)	No information
Joseph 2000	Time till 90% change in wound volume (in days, estimated from the Kaplan-Meier analysis)	approx. 45[c,d] (-/18)	approx. 56[c,d] (-/18)	p = 0.04
Mouës 2004	Time till operative closure was possible (in days) Kaplan-Meier analysis	6[c] (0.52[e]/29)	7[c] (0.81[e]/25)	p = 0.19
Wanner 2003	Time till 50% reduction in wound volume (in days)	27 (10/11)	28 (7/11)	Only statement "no time benefit"

[a] Or number of patients with complete wound healing.
[b] NPWT: negative pressure wound therapy; M: Mean; SD: Standard deviation.
[c] Median given.
[d] The values were derived from Figure 1 in the publication of Joseph 2000. It was assumed that the labelling of the curves had been exchanged. The values 45 for control and 56 for NPWT can be derived from this figure. This, however, contradicts the trends described in the text (the text was given precedence, as the labelling of other figures was also wrong).
[e] Standard errors (given as SEM in the publication).

Table 14. Time to wound closure (non-randomised trials)

Study	Outcome	NPWT M (SD/Sample size)[a]	Control M (SD/Sample size)	Group difference
Doss 2002	Time till operative wound closure (in days)	17.2 (5.8/20)	22.9 (10.8/22)	p = 0.009
Etöz 2004	Time till operative wound closure (in days)	11.25 (5.5/12)	15.75 (2.5/12)	p = 0.05
McCallon 2000	Time till operative wound closure or till secondary wound healing (in days)	22.8 (17.4/5)	42.8 (32.5/5)	No information
Page 2004	Time till secondary wound healing (in days) Kaplan-Meier Analysis	110[b] (79-184[c]/22)	124[b] (105-284[c]/25)	Only statement "not significant"

[a] NPWT: negative pressure wound therapy; M: Mean; SD: Standard deviation.
[b] Medians given.
[c] 95% confidence intervals given.

Overall 2 of the 5 randomised trials – Armstrong 2005 und Joseph 2000 – reported statistically significant differences in favour of NPWT, whereas the remaining studies did not

find any statistically significant differences. Two of the 4 non-randomised trials found statistically significant differences in favour of NPWT (Doss 2002, Etöz 2004).

The measurement of this outcome in all studies was either unblinded or not fully blinded. It follows that bias cannot be excluded with adequate confidence, so that no unambiguous interpretation is possible. An additional problem in Armstrong 2005 was the lack of clarity in the definition of the primary outcome (see Section 5.2.3). Because of the restricted possibility of interpreting the data and the different techniques of operationalisation used, a quantitative summary of the results did not seem meaningful. In Armstrong 2005, there were no significant differences in the proportion of patients who achieved full (100%) wound closure for acute vs. chronic wounds.

5.3.2 Change in wound area or volume

As already discussed in Section 4.5, the parameter "Change in wound area or wound volume" was also recorded, as it was measured in many studies in a comparatively uniform manner – in some cases also blinded. A total of 8 studies gave results. In the Eginton 2003 study, several dimensions (length, breadth, depth, area and volume) were given.

Although the wound areas were measured every second day in the studies of Etöz 2004 and McCallon 2000, the end in time of the wound area measurements was not laid down, but depended on the end of the wound therapy (with indication for operative wound closure or discharge from hospital). For this reason, the time intervals were different in the NPWT and control groups, so that the percentage change in the wound area was biased as a result. In McCallon 2000, the time interval was 22.8 days in the test group and 42.8 days in the control group. In Etöz 2004, NPWT took place over 11.25 days and conventional wound therapy over 15.75 days. There was however no correction for this, as the bias tended to lead to a more conservative estimate.

Table 15. Quantitative change in wound volume (randomised trials)

Study	Outcome	NPWT M (SD/Sample size)[a]	Control M (SD/Sample size)	Group difference
Eginton 2003	Relative change in volume after 2 weeks. Recorded blinded	-59.0% (9.7/7)	-0.1% (14.7/7)	p = 0.005
Ford 2002	Relative change in volume after 6 weeks. Recorded blinded	-51.8% (38[b]/20)	-42.1% (38[b]/15)	p = 0.46
Joseph 2000	Relative change in volume after 6 weeks. Recorded blinded	-78%[c] (72[b]/18)	-30%[c] (61[b]/18)	p = 0.038
Wanner 2003	Relative change in volume after 2 weeks.	-25%[d] (26/11)[d]	-14%[d] (30/11)[d]	No information

[a] NPWT: negative pressure wound therapy; M: Mean; SD: Standard deviation.
[b] We calculated the SD ourselves from the given p-value.
[c] Taken from the data in the text of the publication Joseph 2000. Derivation from Figure 5 in this publication gives the contradictory values of NPWT -47% vs. Control -39%.
[d] Derived from Figure 3 in the publication Wanner 2003. Derivation from Figure 4 gives the values NPWT -27% vs. Control -10%.

Table 16. Quantitative change in wound area (randomised trials)

Study	Parameter	NPWT M (SD/Sample size)[a]	Control M (SD/Sample size)	Group difference
Eginton 2003	Relative change in area after 2 weeks Recorded blinded	-16.4% (6.2/7)	+5.9% (17.4/7)	Only information "not significant"
Mouës 2004	Relative change in area per day	-3.8% (1.9[b]/15)	-1.7% (2.2[b]/13)	p < 0.05

[a] NPWT: negative pressure wound therapy; M: Mean; SD: Standard deviation.
[b] We calculated the SD ourselves from the value given for standard error.

Table 17. Quantitative change in wound area (non-randomised trials)

Study	Parameter	NPWT M (SD/Sample size)[a]	Control M (SD/Sample size)	Group difference
Doss 2002	Change in area per day (in cm^2)	-4.6 (No information/20)	-3.2 (No information/22)	No information
Etöz 2004	Change in area till operative wound closure (in cm^2)	-20.5[b] (11.9/12)	-9.5 (4.1/12)	p = 0.032
McCallon 2000	Relative change in area till operative wound closure or release from hospital	-28.4% (24.3/5)	+9.5% (16.9/5)	No information

[a] NPWT: negative pressure wound therapy; M: Mean; SD: Standard deviation.
[b] Calculated from the raw data in Table 1 of the publication. The values are not given there correctly.

As the studies on wound volume and wound area reported data which had been analysed in a comparatively uniform manner, a meta-analysis was performed. The separation between randomised and non-randomised trials was maintained.

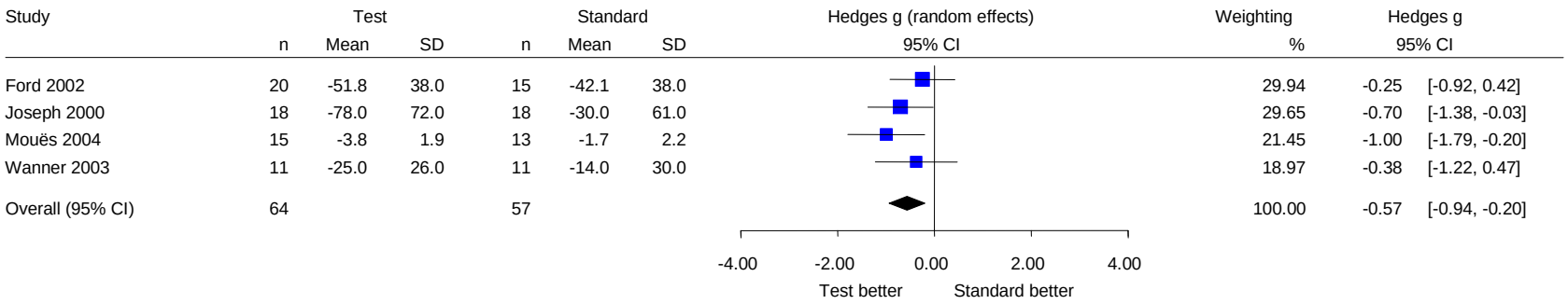
The non-randomised trial of Doss 2002 was not included, as no measures of spread were given in the text and these could not be retrospectively calculated or estimated on the basis of other data. The study of Eginton 2003 was excluded from the meta-analysis for 2 reasons. Firstly, it would have been the only study in the meta-analysis with an intra-individual design (crossover design), which leads to special methodological problems [86,87]. Secondly, adding this study would have led to a high degree of heterogeneity. On the other hand, the studies of Joseph 2000 and Ford 2002 were included in the meta-analysis, as in these cases only some of the patients (those with multiple wounds) were included more than once in the analysis. The dependence of the data must nevertheless be regarded as a biometric weakness of the meta-analysis.

In the analysis of the randomised trials (see **Figure 2**), there was an advantage of unclear relevance for the NPWT, with a standardised mean difference (SMD) of -0.57 (95% CI: -0.94 to -0.20, $p = 0.002$). The non-randomised trials showed a somewhat larger effect: SMD -1.30 (95% CI: -2.07 to -0.54, $p < 0.001$), although it should be emphasised that the outcome was not recorded in any case in a blinded manner. The following comments can be made on the interpretation of the SMD. If, for example, the difference between the NPWT and control groups in relative change in wound volume is 40%, with a standard deviation of the same order of magnitude, then an SMD of 0.5 implies that the difference between the groups can be quantified as 20% (relative change in wound volume).

The statistical evaluation of heterogeneity for both analyses gave an I^2 value of 0%, corresponding to no statistically demonstrable heterogeneity between the individual studies. Evaluation of the data with a model with fixed effects consequently gave almost identical results.

On the basis of the heterogeneity analysis, the pooling of studies with measurement of wound volume and those with measurement of wound area also appears to be justified.

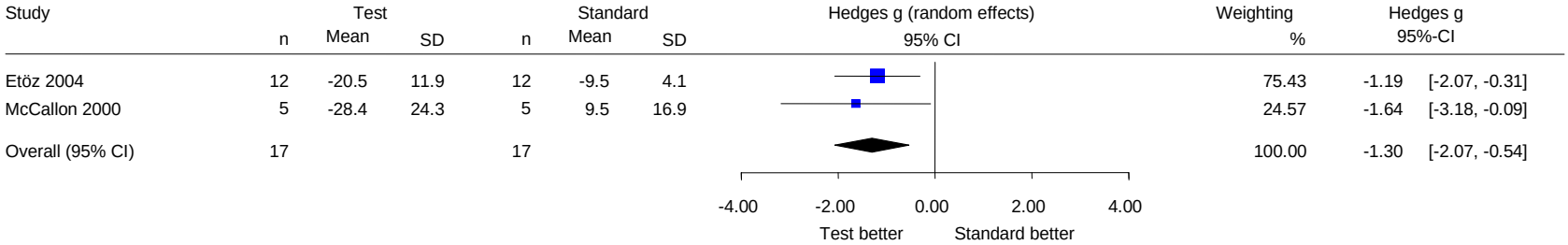
Randomised trials



Heterogeneity: Q=2.34, df=3 (p=0.506), I²=0%

Overall effect: Z Score=-3.03 (p=0.002), tau²=0.000

Non-randomised trials



Heterogeneity: Q=0.24, df=1 (p=0.626), I²=0%

Overall effect: Z Score=-3.33 (p=0.001), tau²=0.000

Figure 2. Meta-analysis of the quantitative (percentage) change in wound size

The effects are presented as Hedges g - an adjusted calculation method for standardised mean differences - for each individual study (squares) and the results of the meta-analysis (diamonds). The error bars and the breadth of the diamonds depict the 95% confidence intervals. df = degrees of freedom.

The studies of Joseph 2000 and Ford 2002 involved an analysis based on individual wounds, generating dependent data which were not allowed for in the analysis. These studies could be removed from the meta-analysis without leading to an important change in the results for the randomised trials: SMD -0.70 (95% CI: -1.31 to -0.10).

5.3.3 Change in wound surface with skin transplantation

Split-thickness skin was used in the skin transplantations, giving a transplant with a net structure. As a result, conventional measurements of wound area or volume could not be made at the removal or donor sites. This is the reason that the portion of the skin transplant (or skin substitute) is usually quantified as the portion which takes ("graft take rate") or in which new epithelium grows. The same applies to the use of artificial bioskin as temporary skin replacement. Again, it should be mentioned that this outcome is only a surrogate for the rapidity and the eventual success of the wound healing (see 4.5); 3 of the 4 studies on skin transplantation reported on results for this outcome.

Table 18. Change in the wound surface with skin transplantation (randomised trials)

Study	Parameter	NPWT M (SD/Sample size)[(a)]	Control M (SD/Sample size)	Group difference
Moisidis 2004	Relative fraction of area of the skin transplant which has successfully taken after 2 weeks	86% (12.5[(b)]/20)	86.75% (18.2[(b)]/20)	No information

[a]NPWT: negative pressure wound therapy; M: Mean; SD: Standard deviation.
[b]We calculated the SD ourselves from the information in the publication on the standard error.

Table 19. Change in the wound surface with skin transplantation (non-randomised trials)

Study	Parameter	NPWT M (SD/Sample size)[(a)]	Control M (SD/Sample size)	Group difference
Genecov 1998 [77]	Quality of the re-epithelialisation (scale 0 to 4) after 1 week. Sides compared	7[(b)] (-/10)	1[(b)] (-/10)	No information
Scherer 2002 [82]	Relative proportion of the area of successfully taken skin transplant	96% (6/34)	89% (20/27)	p = 0.06

[a] NPWT: negative pressure wound therapy; M: Mean; SD: Standard deviation.
[b] The number of patients is given for which there was an advantage on the basis of comparing sides.

Only the study of Moisidis 2004 was randomised. Percentages of graft take are only given for 2 evaluable studies. The published result of Genecov 1998 is difficult to interpret, as it remains unclear by how much the regrowth of epithelium (re-epithelialisation) was better in each treatment group. Moisidis 2004 reported that there was no difference in the quantitative extent of regrowth of epithelium. However, he considered that there was an advantage for NPWT in the quality of the graft take, as subjectively categorised by the surgeon. The direct intra-individual comparison in 20 wounds showed that the transplant take was qualitatively better in 10 wound halves (50%) with NPWT. With the control therapy, only 2 or 3 wound halves were better (the numbers given in the text and in Figure 3 of the publication do not agree).

5.3.4 Avoidance of wound recurrence and revision operations

A distinction was made between planned and unplanned revision operations, as it is usual with large wounds to continue with conservative wound therapy only until operative wound closure is possible. The type of wound closure is a possible surrogate parameter here, as some procedures (rotation flaps, free flap transposition) are more complicated and invasive than a simple suture or a split-thickness skin cover. However, the studies listed in the tables do not show any clear advantage for NPWT in avoiding complicated operations.

Information on revision operations was exclusively provided by non-randomised trials. No information on wound recurrence was provided in the studies.

Page 2004 not only reported the univariate odds ratio given in the table, but also stated that this result was hardly changed by multivariate adjustment for age, serum albumin concentration or wound size. However, the result was no longer statistically significant after adjustment for initial wound size.

Even though all 3 studies indicate that NPWT apparently reduces the necessity of revision operations, no reliable interpretation is possible because of the non-randomised study design and the lack of blinding.

Table 20. Avoidance or simplification of surgical wound closure (randomised trials)

Study	Wound closure	NPWT[a]	Control	Group difference
Ford 2002 [70]	Flap plastic surgery Secondary healing Additional conservative therapy	6 (of 20) 2 (of 20) 12 (of 20)	6 (of 15) 2 (of 15) 7 (of 15)	No information

[a]NPWT: Negative pressure wound therapy.

Table 21. Avoidance or simplification of surgical wound closure (non-randomised trials)

Study	Wound closure	NPWT[a]	Control	Group difference
Etöz 2004 [25]	Flap plastic surgery Split-thickness skin cover Secondary healing	1 (of 12) 10 (of 12) 1 (of 12)	3 (of 12) 9 (of 12) 0 (of 12)	No information
Kamolz 2004 [79]	Split-thickness skin cover Keratinocyte administration Secondary healing	2 (of 7) 2 (of 7) 3 (of 7)	4 (of 7) 0 (of 7) 3 (of 7)	No information
McCallon 2000 [80]	Flap plastic surgery Split-thickness skin cover Simple suture Secondary healing	0 (of 5) 3 (of 5) 1 (of 5) 1 (of 5)	1 (of 5) 1 (of 5) 0 (of 5) 3 (of 5)	No information

[a] NPWT: Negative pressure wound therapy.

Table 22. Avoidance of revision operations (non-randomised trials)

Study	Parameter	NPWT[a]	Control	Group difference
Etöz 2004 [25]	Revision after operative wound closure	0/12	1/12	No information
Page 2004 [81]	Necessity of additional surgical revision	No information	No information	Odds ratio 0.24 (0.068-0.84; 95%-CI), p = 0.026[b]
Scherer 2002 [82]	Necessity of repeated skin transplantation	In 1 patient (of 34)	In 5 patients (of 27)	p = 0.04

[a] NPWT: Negative pressure wound therapy.
[b] Raw data not given.

5.3.5 Avoidance of amputations

Avoidance of amputations was only evaluated as a secondary outcome in a single study (Armstrong 2005). Re-amputations during the observation period of 16 weeks were recorded for patients with diabetes mellitus who had undergone partial foot amputation. Re-amputation

was necessary in 3% of patients in the NPWT group, in comparison with 11% in the control group. The difference was not statistically significant (p = 0.06). Five of the re-amputations in the control group (6%) were above the foot; none of the re-amputations in the NPWT group were above the foot (p = 0.06). It is to be assumed that patients who discontinued the study were included in this analysis as therapy successes (no re-amputation) (Section 5.2.3). This procedure may have led to an anti-conservative bias in the estimation, making the results more difficult to interpret. It is noticeable that the re-amputation rate in the control group was much lower than that assumed during the study planning (11% rather than 26%).

Table 23. Avoidance of amputations (randomised trials)

Study	Parameter	NPWT[(a)]	Control	Group difference
Armstrong 2005	Re-amputations (all)	3% (2 of 77)	11% (9 of 85)	p = 0.060
	Re-amputations above the foot	0% (0 of 77)	6% (5 of 85)	p = 0.060

[a]NPWT: Negative pressure wound therapy.

The necessity of amputations or their avoidance is otherwise only cursorily mentioned in 2 studies. In the methods section of Page 2004, it is mentioned that foot amputations took place in the patients examined, namely 3 in the NPWT group and 2 in the control group. Ford 2002 also reported that there was 1 amputation in the NPWT group, presumably due to the complication of wound sepsis. No information was provided in the other publications in this regard.

5.3.6 Reduction in mortality

None of the studies was designed to detect a statistically significant difference between the 2 treatment groups with respect to this outcome. Deaths were explicitly mentioned in only 3 non-randomised trials (Doss 2002, Page 2004, Wild 2004). To some extent, this may be due to the short follow-up periods, the small sample sizes and the lack of severity of the underlying diseases. Information on the mortality in Armstrong 2005 was only found in the statements submitted and in the further correspondence with the authors and sponsors (Section 5.2.3).

Table 24. Reduction in mortality (randomised trials)

Study	Parameter	NPWT[(a)] (total sample size)	Control (total sample size)	Group difference
Armstrong 2005	Mortality within 16 weeks	1 (77)	2 (85)	No information

[a]NPWT: Negative pressure wound therapy.

Table 25. Reduction in mortality (non-randomised trials)

Study	Parameter	NPWT[(a)] (total sample size)	Control (total sample size)	Group difference
Doss 2002	Hospital mortality	1 (20)	1 (22)	No information
Page 2004	Mortality from any cause within 1 year	1 (22)	1 (25)	No information
Wild 2004	Hospital mortality	1 (16)	3 (5)	$p < 0.05$

[a]NPWT: Negative pressure wound therapy.

In the Wild 2004 publication, a possible reduction in the mortality rate was pointed out in patients who had been treated for open abdomen and peritonitis; however, only 5 patients were included in the control group. The relative risk was 0.10 (95% CI: 0.01 to 0.79). However, the description of the methods used is totally inadequate, particularly with respect to the allocation of the patients to the treatment groups and the consideration of possible confounding factors. As a result, unambiguous interpretation of these results is not possible, even though the difference between groups is so large. In the other 3 studies there was no clear difference in mortality. Page 2004 emphasises that there was no evident connection between the wound treatment and the 2 cases of death in the study. In Armstrong 2005, the cause of the single death in the NPWT group is given as myocardial infarction (therapy discontinued 29 days before the time of death). A patient in the control group also died of myocardial infarction (under therapy). A second patient in the control group died of seizures under high-dose anticoagulants (discontinuation of therapy 13 days before the time of death).

5.3.7 Improvement or maintenance of quality of life

No information was provided in the included studies on the improvement or maintenance of disease-related quality of life and on the avoidance of restrictions in the activities of daily living. Only Etöz 2004 makes the rudimentary comment for both groups that "No negative

impact was seen on extremity function and psychology of patients." It is known from the authors' statement that the study of Armstrong 2005 also collected data on quality of life. This information has been reserved for an additional publication.

5.3.8 Avoidance of pain

The randomised trials provide no results on this outcome. In none of the included studies was pain quantified with validated scales or questionnaires.

Table 26. Reduction in pain (non-randomised trials)

Study	NPWT[(a)]	Control
Etöz 2004	Pain described when the polyurethane sponge was changed	No pain reported
Genecov 1998	No difference in pain intensity reported	
Kamolz 2004	No pain reported	No pain reported

[a]NPWT: Negative pressure wound therapy.

Etöz 2004 reports on evidence for pain when the dressing was being changed in the NPWT group, even though all the patients in this study group were given intravenous analgesics. In the intra-individual comparative study of Genecov 1998, the patients were asked on the fourth day after removal of the split-thickness skin whether either of the 2 sites of removal was more painful, which was negated by all patients. Kamolz 2004 reported that no pain was reported, but mentioned that pain therapy was necessary.

In McCallon 2000, it is stated that pain was reported by some NPWT patients without it being possible to extract reliable information about this. There was no information on pain or administration of analgesics in the other studies.

5.3.9 Avoidance of admissions to hospital

None of the randomised trials was designed to detect a statistically significant difference between the 2 treatment groups with respect to this outcome. This criterion was defined in the studies either as total time in hospital or as time in hospital after the operation. In addition, 1 study measured the time in intensive care and 1 study measured the period of readmission to hospital, if this occurred. In Page 2004, the initial time in hospital is given as a mean (standard deviation) for both groups: 20.1 (11.7; N = 20) versus 15.5 (8.8; N = 25). However, these data refer to the preoperative time in hospital, whereas the postoperative time is not given. All of the studies with this outcome listed in Table 27 below are non-randomised.

Table 27. Time in hospital in days (non-randomised trials)

Study	Parameter (in days)	NPWT M (SD/Sample size)[a]	Control M (SD/Sample size)	Group difference
Doss 2002	Total time in hospital	27.2 (6.5/20)	33.0 (11.0/22)	p = 0.03
Page 2004	Time of readmission	(0 - 27)[b]	(0 - 52)[b]	p = 0.078
Scherer 2002	Total time in hospital	27 (16/34)	32 (25/27)	p = 0.37
	Time in hospital after operation	14 (10/34)	19 (15/27)	p = 0.10
Stone 2004	Total time in hospital	20.9 (10/17)	15.3 (7.5/23)	p = 0.06
Wild 2004	Time in intensive care ward	47.5 (No information/16)	65 (No information/5)	No information

[a] NPWT: Negative pressure wound therapy; M: Mean; SD: Standard deviation.
[b] Only ranges given.

Wild 2004 found that the time in intensive care was shorter for patients who received a type of NPWT for open abdomen. The statistical significance of this is unclear.

Although Doss 2002 and Scherer 2002 both found that the time in hospital was 5 to 8 days shorter for the NPWT group, Stone 2004 found that the period in hospital was shorter for the control group. Only the results in Doss 2002 were statistically significant.

Page 2004 performed a multivariate analysis of re-admissions to hospital. This found a significant advantage for NPWT. The odds ratio was 0.20 (95% CI: 0.05 to 0.77), with a p-value of 0.019. Apart from the lack of uniformity in the trend, the interpretation here too is made more difficult by the exclusively non-randomised and non-blinded designs of the underlying studies. No meta-analysis was performed, as there were no data from a randomised trial on this outcome. However, it is known from the statement of the authors of the Armstrong 2005 study that health economic data were also collected in this study - possibly also related to admissions to hospital or time in hospital. These data are to be reserved for a later publication.

5.3.10 Reduction in the necessity for dressing change

For the NPWT, it is recommended to change the sponge and foil every 48 hours [44,69]. Conventional dressings without a suction device must usually be changed more frequently for

practical reasons. If the wound is losing a lot of fluid, the dressings may even have to be changed many times a day. For these reasons, the frequency of dressing change was not assessed as an outcome in most studies, but was rather a predefined procedure described in the methods section. In the studies on split-thickness skin transplants, the dressings in all treatment groups were for the most part initially changed after the same period of time.

Intervals for the change of the NPWT dressing are otherwise reported as lying between 48 hours and 7 days. Dressings in the control group were reported as being changed up to 3 times daily, or imprecisely as being changed "daily" or "often enough to maintain a moist environment". In the health economic publication on the study Mouës 2004 and in Wild 2004, it is explicitly reported in the results section that the frequency of dressing change was markedly lower in the NPWT group. However, Mouës 2004 also reported that a single dressing change took more time in the NPWT group.

5.3.11 Reduction in the necessity of debridement

The frequency that renewed debridement was required (after initial debridement in all patients) was only explicitly reported in a single (randomised trial) (Armstrong 2005). This was reported for 21% (16 of 77) of patients in the NPWT group, in comparison with 26% (22 of 85) of patients in the control group. This difference was not statistically significant ($p = 0.464$).

In response to a letter to the editor [85] on his study (Doss 2002), Doss [88] reported that renewed debridement was necessary in 1 of the 22 patients in the control group and none of the patients in the NPWT group.

There was otherwise no information in the publications on this therapeutic goal. It was rather the case that the surgical standard was assumed that wound debridement would be performed at the start of treatment and if necrotic tissue subsequently developed in the wound, without data on this being collected.

5.3.12 Reduction in adverse effects and complications

Four randomised trials presented data on this, although it was unclear in 2 studies whether complications were systematically recorded at all. The complication rate in the study of Joseph 2000 (17% vs. 44%) refers to the number of wounds rather than the number of patients. The cause of the sepsis reported by Ford 2002 is not clearly described. However, as

an amputation was performed as a consequence of the sepsis, it appears that this may have been a wound complication.

Five non-randomised trials contain additional information on complications of various degrees of severity. Etöz 2004 also reported slight bleeding when the NPWT dressing was being changed, although this was not quantified and is therefore not listed in the table. It is only stated that the bleeding was not regarded as being severe enough to be clinically relevant.

Table 28. Reduction in complications (randomised trials)

Study	Parameter	NPWT[a] (total sample size)	Control (total sample size)	Group difference
Armstrong 2005	AE[b] total	40 (of 77)	46 (of 85)	p = 0.875
	Wound infections	13 (of 77)[c] 3 mild 6 moderate 4 severe	5 (of 85)[c] 2 mild 1 moderate 2 severe	No information[d]
Eginton 2003	No information	1 (of 7): Skin maceration	No information	No information
Ford 2002	No information	1 (of 20): Sepsis and amputation	0 (of 15)	No information
Joseph 2000	Total complication rate	3 (of 18)[e]	8 (of 18)[e]	p = 0.0028

[a] NPWT: Negative pressure wound therapy.
[b] AE: Adverse events.
[c] Causality: None classified as connected with therapy in the NPWT group. Two in the control group classified as connected with the therapy. One of the latter was serious (unblinded evaluation).
[d] All wound infections: p = 0.043, exact Fisher Test, our own calculation.
[e] However, data in publication inconsistent.

Table 29. Reduction in complications (non-randomised trials)

Study	Parameter	NPWT[a] (total sample size)	Control (total sample size)	Group difference
Etöz 2004	Wound infections	0 (of 12)	0 (of 12)	No information
Genecov 1998	Wound infections	0 (of 10)	0 (of 10)	No information
Page 2004	Total complication rate	No information	No information	Odds ratio 0.17 (0.046-0.61; 95% CI), p = 0.0067[b]
Scherer 2002	Total complication rate	3 (of 34): Transplant rejection (1)	5 (of 27): Transplant rejection (5)	No information
Stone 2004	Transplant rejection	0 (of 21)	1 (of 25)	p = 0.54

[a] NPWT: Negative pressure wound therapy.
[b] Raw data on rates not given.

In summary, the results are not uniform. Armstrong 2005 found a substantially higher rate of wound infections in the NPWT group (with similar overall rates of adverse events). However, none of the 13 wound infections found in the NPWT group was classified by the responsible physicians as being connected with the test therapy, although this was the case for 2 (of 5) wound infections in the control group. A classification of this sort must be regarded with a great deal of reservation, particularly if the evaluation was conducted in a non-blinded manner. In contrast, another randomised and another non-randomised trial found much higher complication rates in the control group (Joseph 2000, Page 2004). No meta-analysis was performed, because of the disparities in the complications and time windows in the studies.

5.3.13 Improvement in the cosmetic result

None of the included studies recorded the degree of scar formation or the subjective cosmetic results.

6 Summary

This report includes the results of studies in which NPWT of acute and chronic wounds of various origins was compared with conventional wound care. The systematic search in bibliographic databases identified 20 relevant published studies including 9 randomised ones; 17 studies (7 randomised), were finally included in the evaluation.

(Partial) outpatient use of NPWT, mostly in specialised centres, was only described in 3 studies. The follow-up period in most studies did not exceed the actual duration of treatment, with a maximum of 1 year. The number of patients in the studies was low (the randomised trials included a total of 371 patients).

The quality of the studies and publications investigated was inadequate. One of the randomised trials (Armstrong 2005) was superior to the others because of the greater number of patients included (N = 162) and the better methodological quality.

There was evidence in favour of NPWT for the following patient-relevant therapeutic goals:

- Shortening in the wound healing time: However, these results are difficult to interpret, as there was either no blinding of outcome evaluation, or this was not fully implemented. However, this is supported by results on a surrogate parameter, the reduction in wound volume and or area.
- Reduction in (re-)amputation rates in patients with diabetes mellitus and status after partial foot amputation: Data on this outcome were mainly obtained from a comparatively large (N = 162) randomised trial that was of better methodological quality than the other studies, but this outcome was not statistically significant ($p = 0.06$). No unambiguous interpretation of the results is possible, as the analysis of the study discontinuations is unclear.
- Reduction in the mortality of patients with open abdomen in peritonitis: Data on this outcome are essentially based on a non-randomised trial with a very small number of patients in the control group (N = 5) and a completely inadequate description of the methods; an unambiguous interpretation is accordingly not possible.

- Shortening of the time spent in hospital: This outcome was only described in non-randomised trials which were moreover unblinded. Therefore no unambiguous interpretation is possible.

The results on the occurrence or avoidance of adverse events or complications are inconsistent. In 1 randomised trial, wound infections were substantially more frequent in the NPWT group (with similar overall rates of adverse events); however, these were classified by the responsible physicians as not being related to NPWT. In any case, a classification of this sort must be regarded with a great deal of reservation, particularly if the evaluation was conducted in a non-blinded manner. In contrast, 1 other randomised and 1 non-randomised trial found much higher complication rates in the control group.

Essentially no significant differences between the treatment groups could be established for any other patient-relevant therapeutic goal – or these outcomes were not even considered in the studies. The number of dressing changes was lower for NPWT in all studies in which this information was reported. However, this was either due to the methods used or to the procedures defined in the study protocol. It was reported in 1 (randomised) trial that more time was required to change the dressing in the NPWT group than in the control group.

The search for unpublished randomised trials showed that we can expect a large number of publications on further randomised trials in the next few years. We can expect these to include more patients and to be of better methodological quality.

7 Discussion

The main result of this systematic literature search, evaluation, and synthesis is that the available evidence for the alleged benefit of NPWT for the treatment of acute and chronic wounds is, at best, sparse. This is in contrast to the wide use of this method [27,89]. As only 3 of the 17 included studies described (partial) outpatient use of NPWT, valid statements on its use in this setting are particularly doubtful. Apart from the low quantity of the available evidence, the quality is poor. Almost no study contains long-term results relevant to the patient.

The wounds included in these studies were heterogeneous and included some of the most important areas of use of NPWT. Both acute and chronic wounds were investigated. Although there are hardly any relevant reliable data, there is no evidence that the effects of NPWT are principally different in different types of wounds. It is hardly possible to make any statement on the optimal strength of suction, mode of suction (intermittent or continuous) or the materials used (sponge, cover, etc.) [90]. There are only some indications that a very low negative pressure (–600 to –900 mmHg with Redon drainage) may be locally painful. The technique of producing the negative pressure for NPWT with a simple Redon drain used to be employed in Germany [91]; this approach has now been largely abandoned. Modern negative pressure pumps with warning systems promise more comfort and greater safety for the patient (specifically to avoid loss of pressure and overfilling of the fluid canister). Because of lack of evidence from controlled clinical trials, no statement can be made on the newer types of NPWT, such as intermittent instillation of fluid, antibiotics, antiseptics, fibrinolytics or local anaesthetics into the wound sponge.

The only study which appears, at first glance, to be of higher quality (Armstrong 2005), contains striking ambiguities and discrepancies in the presentation of the results, both in the original publication and in the subsequent correspondence to the authors and manufacturer. The results of this study must therefore be regarded with considerable reservation, particularly as we were not sent the appropriate study documentation for definitive clarification, in spite of many requests.

In this context, the favourable effects of NPWT described in the available studies with regard to an additional patient-relevant benefit must be regarded as very uncertain. This uncertainty

will possibly be reduced in the coming years, when the results of a series of new RCTs are expected.

In the discussion of the requirements for studies used in evaluation of the benefits and harms of non-pharmacological interventions in particular, it is frequently asserted that RCTs are either impracticable or inappropriate [92]. This also applies to NPWT [93]. Assertions of this sort are disproved by the large number of RCTs on NPWT found during the preparation of this report.

The results from non-randomised controlled trials were not basically different from those from RCTs. Only the study of Wild 2004 described a great effect on reduction in mortality when NPWT is used in patients with open abdomen in peritonitis. However, this result is of unclear validity and cannot be interpreted, as no information of any sort was presented in the publication on the comparability of the treatment groups and the methodological procedure to control confounding factors.

The 36 scientific publications provided in the written statements do not change this result. These are:

Two abstracts; 3 publications dealing with another theme; 4 case reports; 11 case series (including 1 with another indication as comparator group) or other non-comparative studies; 1 expression of opinion; 3 articles on health economics; 1 publication on basic research; 2 guidelines; 1 letter to the editor; 1 non-systematic review; 2 randomised trials which had already been identified; a systematic review which had also been already identified; a database study; 3 studies with historical controls (therefore non-concurrent) (**Appendix A3**).

The latter 4 studies and the results of a case series were assigned special importance in the statement procedure (and to some extent also in the scientific hearing), because, although they failed to fulfil the predefined inclusion and exclusion criteria for the present evaluation, their results were regarded by those providing statements as so convincing that they thought that they had to be considered.

- The "database study" [94] is the evaluation of outpatients treated in the USA. These patients were insured with Medicare or Medicaid. The data were collected during a "quality assurance offensive" and were based on a retrospective data collection with a standardised instrument ("Outcome and Assessment Information Set", OASIS). The resulting database contained almost 2 million cases for the period 2003-2004. A portion

of this database was kept by an external service provider (Outcome Concept Systems, OCS), which also performed this study.

The study initially included about 31 000 patients with stage III or IV decubitus ulcers; 2288 of these patients were treated with conventional wound therapy, in comparison with 60 patients given NPWT. The patients with conventional wound therapy were only selected from those institutions which did **not** offer NPWT. No justification was offered for this procedure, which greatly restricts the comparability of the groups – particularly as no information was provided on the structural and other characteristics of these institutions. Although the opposite was asserted in the text of the publication ("Patient characteristics in the NPWT group were similar to those in the comparison group"), the patients in the NPWT group were in the mean more than 6 years younger than the patients in the control group (65 years versus 71.4 years, with a standard deviation of about 18 years). There is no evidence in the publication that there was adjustment for this difference or for other potential confounding factors. For these reasons, the results provided on admissions to hospital and emergency procedures due to the wounds cannot be interpreted.

The 3 studies with historical controls investigated patients with post-sternotomy mediastinitis or deep sternal wound infections [95-97]. In particular, the study of Sjögren 2005 [95] must be emphasised, as this reported a striking difference in 90-day mortality. Between 1999 and 2003, 61 patients were treated with NPWT and then compared with 40 patients who received conventional wound therapy in the period 1994 to 1998. After 90 days, 6 patients (15%) in the control group had died, but none in the NPWT group. It is unclear why this time point was selected for mortality data. The reason why this is of particular importance is that – as can be seen in Figure 1 of the publication, together with the information in the text – 5 patients in the NPWT group successively died in the period between 90 days and 1 year (at least 8% – "at least" because the data in this period were censored, see below); these patients died shortly after the 90-day period. In contrast, only 1 patient died between 90 days and 1 year in the control group. This would then greatly qualify the difference in the 90-day mortality given above. Moreover, as far as can be seen, all patients in the control group were observed for at least 3 years in follow-up, but at least 7 patients in the NPWT group were censored in the first year, followed by 5 in the second year and 17 in the third year. Thus the data on long-term survival (up to 5 years)

reported in the study cannot be interpreted. In summary, this study provides no evidence that NPWT reduces mortality in patients with poststernotomy mediastinitis, in comparison with conventional wound therapy.

The results on mortality of the other 2 studies for this indication are contradictory. While Fuchs 2005 reported 1 case of death (application-linked) in the total of 35 patients in the NPWT group and 4 deaths (in 33 patients) in the control group [96], Song 2003 reported 3 deaths (in 17 patients) in the NPWT group and 1 death (in 18 patients) in the control group [97]. It should however be noted that these data relate to the mortality before wound closure and therefore presumably cover a much shorter period of observation.

Sjögren 2005 refers to an additional study with historical controls, in which 1 of 9 patients in the NPWT group died within 6 months and none of 10 patients in the control group [98].

The above list cannot claim to be complete, as it does not come from any systematic search. It is solely intended to demonstrate that this apparently major – but doubtful – effect as described by Sjögren 2005 is qualified when additional studies are also considered.

The present evaluation included the study of Doss 2002 with patients with poststernotomy osteomyelitis, in which the 2 groups at least partially overlapped in time [76]. Here too, no differences in patient mortality during their time in hospital were reported.

– Miller 2002 [99] reported a study with (initially) 148 patients whose fasciae were not primarily closed after a laparotomy for a variety of reasons and who were therefore given a temporary abdominal wall closure (the so-called "open abdomen"). It is not quite clear what the study design was. It is most likely that it was a (retrospective) case series, as all reported patients were treated with different types of NPWT; this was sometimes with an early type (alone or in combination), in which a surgical towel was used as drainage (the so-called "vacuum pack"), rather than a polyurethane or polyvinylalcohol sponge. However, no clear classification of how many patients were treated with which method is possible on the basis of the publication. 65 patients (44%) died before secondary closure of the fasciae could be performed.

  For 24 of the remaining 83 patients, a procedure had to be chosen in which there was initially no stable or successful closure of the fasciae (due to a delay in time), resulting in

a hernia of the abdominal wall (the so-called "planned hernia"). In such cases, an additional operation for surgical reconstruction can be performed later, usually after several months. In 37 patients, the fasciae were closed early - within 9 days of the initial laparotomy (the "early" group). In the remaining 22 patients, the fasciae could be closed later ("late" group), after a mean of 21 days. A polyurethane sponge was used in all patients in the late group, i.e. NPWT was delivered with the V.A.C.® system. According to the authors, a late closure of this sort with the precursor type or with other treatment options in patients with an open abdomen was either impossible or highly unusual for this procedure.

The result for the 22 patients with late closure was projected to a "success rate" of 65% (22 of 34), as 12 patients using V.A.C.® had to be assigned to the group with planned hernia. However, this calculation did not include patients who had already died (see above), presumably corresponding to 12 more patients using V.A.C.®. No statement was made on the success rate with the other NPWT type.

In a subsequent publication from the same working group in 2004 [100] with a further series of 53 patients with open abdomen, a success rate of 88% was reported. This included the patients with early closure, but once again excluded the patients who had previously died (15%, 8 of 53). All patients had been treated with V.A.C.®. The data in this publication exhibit some discrepancies or ambiguities; e.g., a success rate of 78% was given for 45 of 53 initial survivors.

This subsequent publication was subjected to discussion in the publishing journal, which was printed immediately after it. One participant in the discussion pointed out that the indications were not made in a comparable manner. Whereas in the present study about 25% of patients with laparotomy after abdominal injury were treated with an "open abdomen" procedure, the comparable figure in his own series had only been 10% (using another method for temporary abdominal wall closure). The series and literature data on the success rates with regard to secondary closure of the fasciae were not comparable anyway. The only way to identify the best procedure would be to perform a randomised trial. In response to this comment, Miller confirmed the possibility that the indication had changed in recent years.

Studies without a control group or with only a historical control group pose the serious problem that it is not possible to adjust for the confounding factor of "time". The results of

studies of this sort can only be interpreted if really large or "dramatic" effects are found, as not only patient characteristics may change with time, but also other aspects, such as concomitant treatments, indications, or diagnostic procedures - sometimes rapidly. An additional factor is that the retrospective nature of these studies means that the quality of the data (at least in the control group) cannot be influenced in important respects.

It is legitimate to speak of a dramatic effect if a (quasi) deterministic clinical course can be influenced by an intervention [101]. In the evidence classification of the Centre of Evidence Based Medicine this is described as an "all or nothing situation" [102]. This is certainly not the case in these studies on the use of NPWT in patients with poststernotomy mediastinitis or deep sternal wound infection or open abdomen. Thus a benefit of NPWT in this regard can only be proven with adequately controlled, preferably randomised trials.

This necessity is clearly stated in the discussion on the study of Miller 2002 (and 2004) in patients with open abdomen (see above) and also implied by the authors of a study on deep sternal wound infections [96]: "From the scientific point of view our results should be confirmed by randomized, prospective studies." This is however qualified, using the argument that the incidence of sternal infections in excellent cardiac surgery clinics is low: "Data indicate that for heart centers with good surgical practice it is unrealistic to prospectively and **mono**centrically [our emphasis] evaluate the benefit of the NPWT technique compared to the conventional technique." This is an unconvincing argument, as **multicentre** surgical studies can be performed [103]. KCI planned a multicentre study for patients with open (presumably sternal) wounds, although this was terminated for unknown reasons (study Bayer 2004 in **Appendix C**). In an abstract on this study, an involved centre stated: "We still believe completing the prospective randomized trial will provide important data for health care providers and policy makers." [45].

Statements on the possible unfavourable effects of the use of NPWT are subject to the same reservations as statements on the possible favourable effects. Results from uncontrolled studies can hardly be interpreted – if at all – and generally only serve as indications for specific investigations in controlled studies, which should preferably be randomised. Complications and other adverse events were only systematically recorded in a few studies. There was no unambiguous increase or decrease in such events from the use of NPWT. However, the high incidence of wound infections in the NPWT group in the study of

Armstrong 2005 was striking; this contradicts the conventional theory that NPWT tends to control infection. To establish that this was not a random effect, further studies should investigate this issue.

During the scientific hearing, those present were requested to name indications in which the use of NPWT could lead to a "dramatic" effect, in their own opinion and proven by the literature. The following indications were named: post-sternotomy mediastinitis; open abdomen; exposed vascular prosthesis; prosthesis infection; open wound over malignant tissue; irradiated wounds; open fractures; exposed bradytrophic tissue or exposed implants; omentum plastic surgery; wounds after chronic cortisone application; wounds with disturbed perfusion; decubitus ulcers in the buttocks or hips; wounds in lymphatic oedema and lymphatic fistulas; wounds in morbid obesity; postthrombotic ulcers on the legs; pyodermia fistulans significa; vaginal reconstruction in the Rokitansky-Küster syndrome.

In addition, procedural advantages in the use of NPWT were asserted. It was said to open the possibility of the abdominal position for ARDS prevention with (large) abdominal wounds or open abdomen; for very strongly secreting wounds (also palliative); wound treatment in uncooperative patients (for example, children); cover with plastic surgery using Integra or split-thickness skin, with protection by the NPWT; bridging therapy until cover with plastic surgery.

For some of these indications, the problems of uncontrolled or historically controlled studies and the necessity of performing controlled, preferably randomised trials in the corresponding areas has already been discussed (poststernotomy mediastinitis, open abdomen, see above). For other indications, results of controlled studies are available, some of them randomised (for example, Moisidis 2004 or Scherer 2002 on split-thickness skin cover, Ford 2002 or Wanner 2003 on decubitus ulcers). For still other indications, randomised trials were or are being performed, but their results are not yet available (for example, Study VAC 2001-02 on ulcers in chronic venous failure [43]/discontinued, McCarthy 2005 on wounds from ischaemia in the lower extremities [64]/ongoing, Study VAC 2001-06 on open fractures [54]/discontinued, see too **Appendix C**). Moreover, some of the indications named are actually currently contraindications for NPWT, for example, exposed vessels or malignancy in the wound bed [104]. It may finally be argued that very large observed or assumed effects (if not "dramatic effects" as defined above) militate against the conduct of RCTs as, in such

cases the proof of superiority only requires a very small sample size, and qualitatively adequate RCTs would be able to supply the necessary reliability of the results.

This indication list nevertheless brought us to investigate the case reports and case series identified during the literature search for the current evaluation for possible "dramatic" effects after the use of NPWT. This however assumes that the clinical course without use of NPWT was precisely described in these publications. This was rarely the case:

- For example, Halama 2004 reported (modified) intra-oral NPWT in a patient who had been given a cystectomy on the lower jaw bone, followed by defect filling with an autologous spongiosa transplant, and who had then developed a wound infection with loss of the transplant [105]. The authors described that this shortened the time of treatment by many months in comparison with conventional obturator treatment.
- Nouraei 2003 applied NPWT to a 32-year-old female patient with cervicofacial necrotising fasciitis [106]. According to the authors, conventional treatment would have required radical excision of a skin flap and skin transplantation or a complicated flap reconstruction, which would have led to an "extremely poor" aesthetic result. The use of NPWT was accompanied by much lower morbidity, a shorter time in hospital and an "acceptable" cosmetic result.
- Schintler 2004 treated cervical anastomosis leaks after oesophagectomy and reconstruction by gastric elevation in 3 patients with NPWT [107]. According to the authors, this made it possible for the patients to be fed with semisolid food by the natural route, thus avoiding the use of a nasoenteral probe.

A definitive clarification of whether these really are "dramatic effects" would, methodologically speaking, require an independent literature search on conventional treatment for these conditions. As this would exceed the scope of the current report, we must trust the statements of the respective authors. The examples given are largely procedural advantages, so that these advantages do not necessarily have to be examined in a controlled study. One example of this might be the possibility of collecting large volumes of exudate from strongly secreting large wounds or for covering wounds over malignant tissue in palliative care. It is also described that NPWT permits reliable or more reliable fixation on anatomically difficult sites, such as the genital or perineal region, not only improving wound

protection, but also permitting or facilitating secondary measures, such as split-thickness skin transplantation [108].

This implies that a benefit cannot be excluded in the individual case, particularly as the last possible approach. Conversely, this alone does not justify broad application of this method beyond such individual cases. The particular problem in the discussion of these (more or less) spectacular successes is the possibility of publication bias in such situations. If the probability of publication of a clinical study with negative - usually meaning statistically non-significant - results is reduced, it is even more unlikely that an unsuccessful attempt at individual treatment will be published as a case report or case series [109].

In summary, it may be deduced from the present report that there are indications that the use of NPWT brings additional benefits which are relevant to the patient. There is nevertheless considerable uncertainty in this regard. Broad application of this method outside well-controlled settings - such as clinical studies - therefore appears to be unjustified at the moment. However, results are expected from randomised trials in the coming years and this could improve the available evidence. In any case, the results of those studies which have recently been discontinued must also be published (see Section 5.1.2 and **Appendix C**).

8 Conclusion

There are at present no results of adequate reliability which provide proof of the superiority of NPWT in comparison with conventional therapy and which would justify broad use of this method outside clinical trial settings. It would be advisable to re-examine this question in 2 to 3 years.

9 List of included studies

Study Armstrong 2005 (Ib*)

Armstrong DG, Lavery LA, for the Diabetic Foot Study Consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet. 2005; 366: 1704-1710.

Study Doss 2002 (III)

Doss M, Martens S, Wood JP, Wolff JD, Baier C, Moritz A. Vacuum-assisted suction drainage versus conventional treatment in the management of poststernotomy osteomyelitis. Eur J Cardiothorac Surg. 2002; 22: 934-938.

Study Eginton 2003 (Ib)

Eginton MT, Brown KR, Seabrook GR, Towne JB, Cambria RA. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. Ann Vasc Surg. 2003; 17: 645-649.

Study Etöz 2004 (IIb)

Etöz A, Özgenel Y, Özcan M. The use of negative pressure wound therapy on diabetic foot ulcers: a preliminary controlled trial. Wounds. 2004; 16: 264-269.

Study Ford 2002 (Ib)

Ford CN, Reinhard ER, Yeh D, Syrek D, De Las MA, Bergman SB, Williams S, Hamori CA. Interim analysis of a prospective, randomized trial of vacuum-assisted closure versus the healthpoint system in the management of pressure ulcers. Ann Plast Surg. 2002; 49: 55-61.

Study Genecov 1998 (IIb)

Genecov DG, Schneider AM, Morykwas MJ, Parker D, White WL, Argenta LC. A controlled subatmospheric pressure dressing increases the rate of skin graft donor site reepithelialization. Ann Plast Surg. 1998; 40: 219-225.

Study Joseph 2000 (Ib)

Joseph E, Hamori CA, Bergman S, Roaf E, Swann NF, Anastasi GW. A prospective randomized trial of vacuum-assisted closure versus standard therapy of chronic nonhealing wounds. Wounds. 2000; 12: 60-67.

Study Kamolz 2004 (IIb)

Kamolz LP, Andel H, Haslik W, Winter W, Meissl G, Frey M. Use of subatmospheric pressure therapy to prevent burn wound progression in human: first experiences. Burns. 2004; 30: 253-258.

Haslik W, Kamolz LP, Andel H, Meissl G, Frey M. Der Einsatz der V.A.C.-Therapie bei der Verminderung des "Nachbrennens": Erste Ergebnisse in der Verbrennungsbehandlung. [The use of subatmospheric pressure to prevent burn wound progression: First experiences in burn wound treatment]. Zentralbl Chir. 2004; 129 Suppl 1: S62-S63.

Study McCallon 2000 (IIb)

McCallon SK, Knight CA, Valiulus JP, Cunningham MW, McCulloch JM, Farinas LP. Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds. Ostomy Wound Manage. 2000; 46: 28-32, 34.

Study Moisidis 2004 (Ib)

Moisidis E, Heath T, Boorer C, Ho K, Deva AK. A prospective, blinded, randomized, controlled clinical trial of topical negative pressure use in skin grafting. Plast Reconstr Surg. 2004; 114: 917-922.

* Level of evidence in accordance with the code of procedure of the Federal Joint Committee. Code of procedure of the Federal Joint Committee, 2005 (Verfahrensordnung des Gemeinsamen Bundesausschusses). http://www.g-ba.de/cms/upload/pdf/abs2/beschluesse/2005-09-20-VO-BANZ.pdf (last access on 01 February 2006)

Study Mouës 2004 (Ib)

Mouës CM, Vos MC, van den Bemd GJ, Stijnen T, Hovius SE. Bacterial load in relation to vacuum-assisted closure wound therapy: a prospective randomized trial. Wound Repair Regen. 2004; 12: 11-17.

Mouës 2004: Mouës CM, van den Bemd GJ, Meerding WJ, Hovius SE. An economic evaluation of the use of TNP on full-thickness wounds. J Wound Care. 2005; 14: 224-227.

Study Page 2004 (III)

Page JC, Newswander B, Schwenke DC, Hansen M, Ferguson J. Retrospective analysis of negative pressure wound therapy in open foot wounds with significant soft tissue defects. Adv Skin Wound Care. 2004; 17: 354-364.

Study Scherer 2002 (III)

Scherer LA, Shiver S, Chang M, Meredith JW, Owings JT. The vacuum assisted closure device: a method of securing skin grafts and improving graft survival. Arch Surg. 2002; 137: 930-934.

Study Schrank 2004 (IIb)

Schrank C, Mayr M, Overesch M, Molnar J, Henkel von Donnersmarck G, Mühlbauer W, Ninkovic M. Ergebnisse der Vakuumtherapie (V.A.C.-Therapie) von oberflächlich und tiefdermalen Verbrennungen. [Results of vacuum therapy (V.A.C.(R)) of superficial and deep dermal burns]. Zentralbl Chir. 2004; 129 Suppl 1: S59-S61.

Study Stone 2004 (III)

Stone P, Prigozen J, Hofeldt M, Hass S, DeLuca J, Flaherty S. Bolster versus negative pressure wound therapy for securing split-thickness skin grafts in trauma patients. Wounds A Compendium of Clinical Research and Practice. 2004; 16: 219-223.

Study Wanner 2003 (Ib)

Wanner MB, Schwarzl F, Strub B, Zaech GA, Pierer G. Vacuum-assisted wound closure for cheaper and more comfortable healing of pressure sores: a prospective study. Scand J Plast Reconstr Surg Hand Surg. 2003; 37: 28-33.

Study Wild 2004 (III)

Wild T, Stremitzer S, Budzanowski A, Rinder H, Tamandl D, Zeisel C, Holzenbein T, Sautner T. "Abdominal Dressing" - Eine neue Methode in der Behandlung des offenen Abdomens bei der sekundären Peritonitis. ["Abdominal Dressing" - A new method of treatment for open abdomen following secondary peritonitis]. Zentralbl Chir. 2004; 129 Suppl 1: S20-S23.

10 Literature

[1] Evans D, Land L. The Cochrane Library, editor. Topical negative pressure for treating chronic wounds. The Cochrane Database of Systematic Reviews. Art. No.: CD001898. DOI: 10.1002/14651858. West Sussex, United Kingdom: John Wiley & Sons Ltd; 2001. http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME (Access on 27 September 2005).

[2] Samson DJ, Lefevre F, Aronson N. Wound healing technologies: low-level laser and vacuum-assisted closure. Rockville, MD, USA: Agency for Healthcare Research and Quality (AHRQ); 2004. http://www.ahrq.gov/clinic/epcsums/woundsum.htm (Access on 27 September 2005).

[3] Pham C, Middleton P, Maddern G. Vacuum-assisted closure for the management of wounds: an accelerated systematic review. Adelaide, Australia: Australian safety and efficacy register of new interventional procedures - surgical (ASERNIP-S); 2003. http://www.surgeons.org/asernip-s/publications_vacuum.htm (Access on 27 September 2005).

[4] Vermeulen H, Ubbink DT, Goossens A, de Vos R, Legemate DA. Systematic review of dressings and topical agents for surgical wounds healing by secondary intention. Br J Surg. 2005; 92: 665-672.

[5] Singh A, Halder S, Menon GR, Chumber S, Misra MC, Sharma LK, Srivastava A. Meta-analysis of randomized controlled trials on hydrocolloid occlusive dressing versus conventional gauze dressing in the healing of chronic wounds. Asian J Surg. 2004; 27: 326-332.

[6] Tautenhahn J, Bürger T, Lippert H. Der Stand der Vakuumversiegelungstherapie. Chirurg. 2004; 75: 492-497.

[7] Fisher A, Brady B. Vacuum assisted wound closure therapy. Ottawa, Canada: The Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2003. http://www.ccohta.ca/publications/pdf/221_vac_cetap_e.pdf (Access on 27 September 2005).

[8] Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg. 1997; 38: 553-562.

[9] Morykwas MJ, Faler BJ, Pearce DJ, Argenta LC. Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine. Ann Plast Surg. 2001; 47: 547-551.

[10] Miller M, Lowery C. Negative pressure wound therapy: a rose by any other name. Ostomy Wound Manage. 2005; 51: 44-49.

[11] Wetzel-Roth W, Zöch G. Konsensus der Deutschen und der Österreichischen Gesellschaften fur Wundheilung und Wundbehandlung zur Vakuumversiegelung und V.A.C.(R)-Therapieeinheit. [Consensus of the German and Austrian societies for wound healing and wound management on vacuum closure and the V.A.C.(R) treatment unit]. Zentralbl Chir. 2004; 129 Suppl 1: 7-11.

[12] PTB. Die gesetzlichen Einheiten in Deutschland. Braunschweig: Physikalisch-Technische Bundesanstalt; 2004. http://www.ptb.de/de/publikationen/download/einheiten.pdf (Access on 27 September 2005).

[13] Maegele M, Gregor S, Steinhausen E, Bouillon B, Heiss MM, Perbix W, Wappler F, Rixen D, Geisen J, Berger-Schreck B, Schwarz R. The long-distance tertiary air transfer and care of tsunami victims: injury pattern and microbiological and psychological aspects. Crit Care Med. 2005; 33: 1136-1140.

[14] Willy C. Nebenwirkungen und Risiken der Vakuumtherapie. In: Willy C, editor. Die Vakuumtherapie. Grundlagen, Indikationen, Fallbeispiele, praktische Tipps. Altusried-Krugzell: Kösel; 2005. p. 91-9.

[15] Chester DL, Waters R. Adverse alteration of wound flora with topical negative-pressure therapy: a case report. Br J Plast Surg. 2002; 55: 510-511.

[16] Karl T. Ergebnisse der V.A.C.-Therapie in der Gefäßchirurgie. [Results of V.A.C. therapy in vascular surgery]. Vasomed. 2004; 16: 172-176.

[17] Gwan-Nulla DN, Casal RS. Toxic shock syndrome associated with the use of the vacuum-assisted closure device. Ann Plast Surg. 2001; 47: 552-554.

[18] Barringer CB, Gorse SJ, Burge TS. The VAC dressing--a cautionary tale. Br J Plast Surg. 2004; 57: 482

[19] White RA, Miki RA, Kazmier P, Anglen JO. Vacuum-assisted closure complicated by erosion and hemorrhage of the anterior tibial artery. J Orthop Trauma. 2005; 19: 56-59.

[20] Wu SH, Zecha PJ, Feitz R, Hovius SER. Vacuum therapy as an intermediate phase in wound closure: a clinical experience. Eur J Plast Surg. 2000; 23: 174-177.

[21] Eginton MT, Brown KR, Seabrook GR, Towne JB, Cambria RA. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. Ann Vasc Surg. 2003; 17: 645-649.

[22] Fox A, Tadros A, Perks AG. An unusual complication of Vacuum Assisted Closure in the treatment of a pressure ulcer. J Wound Care. 2004; 13: 344-345.

[23] Weed T, Ratliff C, Drake DB. Quantifying bacterial bioburden during negative pressure wound therapy: does the wound VAC enhance bacterial clearance? Ann Plast Surg. 2004; 52: 276-280.

[24] Mouës CM, Vos MC, van den Bemd GJ, Stijnen T, Hovius SE. Bacterial load in relation to vacuum-assisted closure wound therapy: a prospective randomized trial. Wound Repair Regen. 2004; 12: 11-17.

[25] Etöz A, Özgenel Y, Özcan M. The use of negative pressure wound therapy on diabetic foot ulcers: a preliminary controlled trial. Wounds. 2004; 16: 264-269.

[26] Higgins S. The effectiveness of vacuum assisted closure (VAC) in wound healing. Clayton, Australia: Centre for Clinical Effectiveness (CCE); 2003. http://www.med.monash.edu.au/healthservices/cce/evidence/pdf/c/991fr.pdf (Access on 27 September 2005).

[27] Mayer ED, Boukamp K, Simoes E. Vakuumversiegelung in der Wundbehandlung - Verfahren nach EbM-Kriterien evaluiert? Bewertung aus sozialmedizinischer Sicht. Lahr (Schwarzwald): Medizinischer Dienst der Krankenkassen (MDK) Baden-Württemberg; 2002.

[28] McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. BMJ. 2002; 324: 1448-1451.

[29] Norris SL, Atkins D. Challenges in using nonrandomized studies in systematic reviews of treatment interventions. Ann Intern Med. 2005; 142: 1112-1119.

[30] Reed JF, III. Crossover designs in lower extremity wounds. Int J Low Extrem Wounds. 2003; 2: 158-163.

[31] Sauerland S, Lefering R, Bayer-Sandow T, Bruser P, Neugebauer EA. Fingers, hands or patients? The concept of independent observations. J Hand Surg. 2003; 28: 102-105.

[32] Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001; 285: 1987-1991.

[33] Gotzsche PC, Harden A. Searching for non-randomised studies. Kopenhagen, Dänemark: The Cochrane Non-Randomised Studies Methods Group (NRSMG) at The Nordic Cochrane Centre; 2000. http://www.cochrane.dk/nrsmg/docs/chap3.pdf

[34] FDA. Draft guidance for industry. Chronic cutaneous ulcer and burn wounds - developing products for treatment. Rockville, Maryland, USA: United States Food and Drug Administration (FDA); 2000. http://www.fda.gov/cber/gdlns/ulcburn.pdf (Access on 27 September 2005).

[35] Steed DL. Wound-healing trajectories. Surg Clin North Am. 2003; 83: 547-555.

[36] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327: 557-560.

[37] Hayes Inc. Negative pressure wound therapy for wound healing. Lansdale, Pennsylvania, USA: Hayes, Inc; 2003.

[38] Davydov I, Abramov AI, Darichev AB. Reguliatsiia ranevogo protsessa u bol'nykh pozhilogo i starcheskogo vozrasta metodom vakuum-terapii. [Regulation of wound process by the method of vacuum therapy in middle-aged and aged patients]. Khirurgiia (Mosk). 1994; 7-10.

[39] Ontario Health Technology Advisory Committee (OHTAC). Vacuum assisted closure therapy for wound care. Toronto, Ontario, Canada: Ontario Ministry of Health and Long-Term Care (MOHLTC); 2004. http://www.health.gov.on.ca/english/providers/program/mas/reviews/docs/vac_1204.pdf (Access on 27 September 2005).

[40] Costa V, Brophy J, McGregor M. Vacuum-assisted wound closure therapy (V.A.C (R)). Montreal, Quebec, Canada: Technology Assessment Unit of the McGill University Health Centre (MUHC); 2005. http://upload.mcgill.ca/tau/VAC_REPORT_FINAL.pdf (Access on 27 September 2005).

[41] Moues CM, van den Bemd GJ, Meerding WJ, Hovius SE. An economic evaluation of the use of TNP on full-thickness wounds. J Wound Care. 2005; 14: 224-227.

[42] Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet. 2005; 366: 1704-1710.

[43] Venous stasis ulcers. Study with the KCI identification number VAC 2001-02. Not an abstract report, not a publication, communication from KCI after a written enquiry; 2005.

[44] Armstrong DG, Lavery LA, Frykberg RG, Andros G, Attinger CE, Boulten AJM. VAC therapy appears to heal complex DFU. Paris, France: Second World Union of Wound Healing Societies Meeting (08-13 July); 2004.

[45] Bayer L, Orgill DP. Has the wound VAC become the standard of care for the sternal wounds? Paris, France: Second World Union of Wound Healing Societies Meeting (08-13 July); 2004.

[46] Greer SE, Longaker MT, Margiotta M. Preliminary results from a multicenter, randomized, controlled study of the use of subatmospheric pressure dressing for pressure ulcer healing. Wound Repair Regen. 1999; 7: Abstract A255.

[47] Heath T, Moisidis E, Deva A. A prospective controlled trial of vacuum assisted closure (VAC) in the treatment of acute surgical wounds requiring split skin grafting (Abstract). Fourth Australian Wound Management Association Conference. 2002; 41

[48] Molnar JA, Heimbach DM, Tredgett EE, Mozingo DW. Prospective, Randomized, Controlled, Multicenter Trial Applying Subatmospheric Pressure to Acute Hand Burns: An Interim Report. Paris, France: Second World Union of Wound Healing Societies Meeting (08-13 July); 2004.

[49] Niezgoda JA. A Comparison of Vacuum Assisted Closure Therapy to Moist Wound Care in the Treatment of Pressure Ulcers: Preliminary Results of a Multicenter Trial. Paris, France: Second World Union of Wound Healing Societies Meeting (08-13 July); 2004.

[50] Orgill DP, Bayer L. Preliminary results indicate VAC therapy facilitates faster closure of open abdominal wounds. Paris, France: Second World Union of Wound Healing Societies Meeting (08-13 July); 2004.

[51] Payne W. VAC therapy vs. moist wound therapy in the treatment of diabetic foot amputation wounds: preliminary results of a multicenter trial. Paris, France: Second World Union of Wound Healing Societies Meeting (08-13 July); 2004.

[52] Stannard JP, Volgas DA, Robinson J, Anglen JO, De Los Santos A. Topical negative pressure therapy as a treatment for draining hematomas following surgical stabilization of skeletal trauma: preliminary results. Paris, France: Second World Union of Wound Healing Societies Meeting (08-13 July); 2004.

[53] Stannard JP, Volgas DA, Robinson J, Anglen JO, De Los Santos A. Topical negative pressure therapy as an adjunct to soft tissue healing following open reduction and internal fixation of high risk fractures: preliminary results. Paris, France: Second World Union of Wound Healing Societies Meeting (08-13 July); 2004.

[54] Stannard JP, Volgas DA, Robinson J, Anglen JO, De Los Santos A. Topical negative pressure therapy for soft tissue management of open fractures: Preliminary results. Paris, France: Second World Union of Wound Healing Societies Meeting (08-13 July); 2004.

[55] Vuerstaek JDD, Wuite J, Neuman H, Steijlen P, Veraart JCJM. The management of recalcitrant leg ulcers. Paris, France: Second World Union of Wound Healing Societies Meeting (08-13 July); 2004.

[56] Vuerstaek JDD, Steijlen P. A Randomised Controlled Trial Comparing Vacuum Assisted Closure (V.A.C.®) with Modern Wound Dressings. 2005. http://www.clinicaltrials.gov/ct/show/NCT00243620?order=1 (Access on 18 November 2005).

[57] Moisidis E, Heath T, Boorer C, Ho K, Deva AK. A prospective, blinded, randomized, controlled clinical trial of topical negative pressure use in skin grafting. Plast Reconstr Surg. 2004; 114: 917-922.

[58] Foo L-SS, Chua B-SY, Chia GT, Tan SB, Howe TS. Vacuum assisted closure vs moist gauze dressing in post-operative diabetic foot wounds: Early results from a

randomised controlled trial (Abstract). Presented at the 2nd World Union of Wound Healing Societies Meeting, Paris, France, 8-13 July; 2004.

[59] Lantis JC, Gendics C. VAC therapy appears to facilitate STSG take when applied to venous leg ulcers (Abstract). Presented at the 2nd World Union of Wound Healing Societies Meeting 2004 (July 8-13), Paris, France. 2004;

[60] Gupta SC. Sterilizing chronic wounds with negative pressure therapy: the role of antibiotic irrigation. Presented at the 11th Annual Meeting and Educational Symposuim, Wound Healing Society 2001 (May 16-18). Albuquerque, New Mexico, USA. Wound Repair Regen. 2001; 9: Abstract 127.

[61] Adams TST. The effect of topical negative pressure on donor site wound healing P003. London, United Kingdom: National Research Register, Department of Health; 2005. http://www.nrr.nhs.uk/ViewDocument.asp?ID=N0245095365 (Access on 27 September 2005).

[62] Fryer J. Investigation of Subatmospheric Pressure Dressing on Pressure Ulcer Healing. Bethesda, Maryland, USA: ClinicalTrials.gov, National Institutes of Health (NIH); 2005. http://clinicaltrials.gov/ct/show/NCT00011531?order=1 (Access on 27 September 2005).

[63] McCarthy J. Study to Determine the Utility of Wound Vacuum Assisted Closure (VAC) Compared to Conventional Saline Dressing Changes. Bethesda, Maryland, USA: ClinicalTrials.gov, National Institutes of Health (NIH); 2005. http://clinicaltrials.gov/ct/show/NCT00121537?order=1 (Access on 27 September 2005).

[64] McCarthy M. Vacuum Assisted Closure for the Management of Ischaemic Wounds in the Lower Limb: A Randomised Controlled Trial and In Vitro Studies. London, United Kingdom: National Research Register, Department of Health; 2005. http://www.nrr.nhs.uk/ViewDocument.asp?ID=N0123138623 (Access on 27 September 2005).

[65] Walker P. A Randomised, Prospective Trial of Standard Wound Drainage Medinorm VS Constant Vacuum Drainage to Determine Whether There is any Effect on the Amount of Wound Exudate, Haemoglobin & Wound Bruising. London, United Kingdom: National Research Register, Department of Health; 2005. http://www.nrr.nhs.uk/ViewDocument.asp?ID=N0084029434 (Access on 27 September 2005).

[66] Richtlinie 93/42/EWG des Rates vom 14. Juni 1993 über Medizinprodukte. Luxembourg: Amt für amtliche Veröffentlichungen der Europäischen Gemeinschaften; 2005. http://europa.eu.int/eur-lex/de/consleg/pdf/1993/de_1993L0042_do_001.pdf (Access on 27 September 2005).

[67] Buttenschön K, Fleischmann W, Haupt U, Kinzl L, Buttenschön DC. The influence of vacuum-assisted closure on inflammatory tissue reactions in the postoperative course of ankle fractions. Foot Ankle Surg. 2001; 7: 165-173.

[68] Schrank C, Mayr M, Overesch M, Molnar J, Henkel von Donnersmarck G, Mühlbauer W, Ninkovic M. Ergebnisse der Vakuumtherapie (V.A.C.-Therapie) von oberflächlichen und tiefdermalen Verbrennungen. [Results of vacuum therapy (V.A.C.(R)) of superficial and deep dermal burns]. Zentralbl Chir. 2004; 129 Suppl 1: S59-S61.

[69] Wild T, Stremitzer S, Budzanowski A, Rinder H, Tamandl D, Zeisel C, Holzenbein T, Sautner T. "Abdominal Dressing" - Eine neue Methode in der Behandlung des offenen Abdomens bei der sekundären Peritonitis. ["Abdominal Dressing" - A new method of treatment for open abdomen following secondary peritonitis]. Zentralbl Chir. 2004; 129 Suppl 1: S20-S23.

[70] Ford CN, Reinhard ER, Yeh D, Syrek D, De Las MA, Bergman SB, Williams S, Hamori CA. Interim analysis of a prospective, randomized trial of vacuum-assisted closure versus the healthpoint system in the management of pressure ulcers. Ann Plast Surg. 2002; 49: 55-61.

[71] Jeschke MG, Rose C, Angele P, Fuchtmeier B, Nerlich MN, Bolder U. Development of new reconstructive techniques: use of Integra in combination with fibrin glue and negative-pressure therapy for reconstruction of acute and chronic wounds. Plast Reconstr Surg. 2004; 113: 525-530.

[72] Jeschke MG, Horch RE. Kombinierte Behandlung aus einer Kollagenmatrix, Fibrinkleber und Vakuum-Verbänden. Plastische Chirurgie. 2003; 3: 127-131.

[73] Joseph E, Hamori CA, Bergman S, Roaf E, Swann NF, Anastasi GW. A prospective randomized trial of vacuum-assisted closure versus standard therapy of chronic nonhealing wounds. Wounds A Compendium of Clinical Research and Practice. 2000; 12: 60-67.

[74] Wanner MB, Schwarzl F, Strub B, Zaech GA, Pierer G. Vacuum-assisted wound closure for cheaper and more comfortable healing of pressure sores: a prospective study. Scand J Plast Reconstr Surg Hand Surg. 2003; 37: 28-33.

[75] Huang J, Yao YZ, Huang XK. [Treatment of open fracture by vacuum sealing technique and internal fixation]. [Article in Chinese]. 2003; 17: 456-458.

[76] Doss M, Martens S, Wood JP, Wolff JD, Baier C, Moritz A. Vacuum-assisted suction drainage versus conventional treatment in the management of poststernotomy osteomyelitis. Eur J Cardiothorac Surg. 2002; 22: 934-938.

[77] Genecov DG, Schneider AM, Morykwas MJ, Parker D, White WL, Argenta LC. A controlled subatmospheric pressure dressing increases the rate of skin graft donor site reepithelialization. Ann Plast Surg. 1998; 40: 219-225.

[78] Haslik W, Kamolz LP, Andel H, Meissl G, Frey M. Der Einsatz der V.A.C.-Therapie bei der Verminderung des "Nachbrennens": Erste Ergebnisse in der Verbrennungsbehandlung. [The use of subatmospheric pressure to prevent burn

wound progression: First experiences in burn wound treatment]. Zentralbl Chir. 2004; 129 Suppl 1: S62-S63.

[79] Kamolz LP, Andel H, Haslik W, Winter W, Meissl G, Frey M. Use of subatmospheric pressure therapy to prevent burn wound progression in human: first experiences. Burns. 2004; 30: 253-258.

[80] McCallon SK, Knight CA, Valiulus JP, Cunningham MW, McCulloch JM, Farinas LP. Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds. Ostomy Wound Manage. 2000; 46: 28-34.

[81] Page JC, Newswander B, Schwenke DC, Hansen M, Ferguson J. Retrospective analysis of negative pressure wound therapy in open foot wounds with significant soft tissue defects. Adv Skin Wound Care. 2004; 17: 354-364.

[82] Scherer LA, Shiver S, Chang M, Meredith JW, Owings JT. The vacuum assisted closure device: a method of securing skin grafts and improving graft survival. Arch Surg. 2002; 137: 930-934.

[83] Schrank C, Mayr M, Overesch M, Molnar J, Henkel VD, Muhlbauer W, Ninkovic M. Ergebnisse der Vakuumtherapie (V.A.C.-Therapie) von oberflächlich und tiefdermalen Verbrennungen. Zentralbl Chir. 2004; 129: S59-S61.

[84] Stone P, Prigozen J, Hofeldt M, Hass S, DeLuca J, Flaherty S. Bolster versus negative pressure wound therapy for securing split-thickness skin grafts in trauma patients. Wounds A Compendium of Clinical Research and Practice. 2004; 16: 219-223.

[85] Tang ATM. Vacuum-assisted suction drainage of sternotomy infection: A new paradigm? Eur J Cardiothorac Surg. 2003; 23: 649-650.

[86] Curtin F, Altman DG, Elbourne D. Meta-analysis combining parallel and cross-over clinical trials. I: Continuous outcomes. Stat Med. 2002; 21: 2131-2144.

[87] Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol. 2002; 31: 140-149.

[88] Doss M. Reply to Tang. Eur J Cardiothorac Surg. 2003; 23: 650.

[89] Mayer ED. Versorgungssituation von Patients mit chronischen Wunden (Gutachten im Auftrag des AOK-Bundesverbandes) 07.11.2005. Lahr (Schwarzwald): Medizinischer Dienst der Krankenkassen (MDK) Baden-Württemberg; 2005.

[90] Timmers MS, Le CS, Banwell P, Jukema GN. The effects of varying degrees of pressure delivered by negative-pressure wound therapy on skin perfusion. Ann Plast Surg. 2005; 55: 665-671.

[91] Fleischmann W, Strecker W, Bombelli M, Kinzl L. Vakuumversiegelung zur Behandlung des Weichteilschadens bei offenen Frakturen. [Vacuum sealing as treatment of soft tissue damage in open fractures]. Unfallchirurg. 1993; 96: 488-492.

[92] Health technology assessment for medical devices in Europe. What has to be considered. Position Paper. Brussels, Belgium: The European Medical Technology Industry Association (Eucomed); 2001. http://www.eucomed.be/docs/HTA%20Position%20Paper%20-%20Final.pdf (Access on 23 February 2006).

[93] Die Vakuumtherapie. Grundlagen, Indikationen, Fallbeispiele, praktische Tipps. Willy C, editor. Die Vakuumtherapie. Grundlagen, Indikationen, Fallbeispiele, praktische Tipps. Altusried-Krugzell: Kösel; 2005.

[94] Schwien T, Gilbert J, Lang C. Pressure ulcer prevalence and the role of negative pressure wound therapy in home health quality outcomes. Ostomy Wound Manage. 2005; 51: 47-60.

[95] Sjögren J, Gustafsson R, Nilsson J, Malmsjö M, Ingemansson R. Clinical outcome after poststernotomy mediastinitis: vacuum-assisted closure versus conventional treatment. Ann Thorac Surg. 2005; 79: 2049-2055.

[96] Fuchs U, Zittermann A, Stuettgen B, Groening A, Minami K, Koerfer R. Clinical outcome of patients with deep sternal wound infection managed by vacuum-assisted closure compared to conventional therapy with open packing: a retrospective analysis. Ann Thorac Surg. 2005; 79: 526-531.

[97] Song DH, Wu LC, Lohman RF, Gottlieb LJ, Franczyk M. Vacuum assisted closure for the treatment of sternal wounds: the bridge between debridement and definitive closure. Plast Reconstr Surg. 2003; 111: 92-97.

[98] Catarino PA, Chamberlain MH, Wright NC, Black E, Campbell K, Robson D, Pillai RG. High-pressure suction drainage via a polyurethane foam in the management of poststernotomy mediastinitis. Ann Thorac Surg. 2000; 70: 1891-1895.

[99] Miller PR, Thompson JT, Faler BJ, Meredith JW, Chang MC. Late fascial closure in lieu of ventral hernia: the next step in open abdomen management. J Trauma. 2002; 53: 843-849.

[100] Miller PR, Meredith JW, Johnson JC, Chang MC. Prospective evaluation of vacuum-assisted fascial closure after open abdomen: planned ventral hernia rate is substantially reduced. Ann Surg. 2004; 239: 608-614.

[101] Lange S. Die Rolle randomisierter kontrollierter Studien bei der medizinischen Bewertung von Routineverfahren. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz. 2006; im Press.

[102] Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M. Levels of evidence and grades of recommendation. Oxford, UK: Centre for Evidence-Based Medicine (CEBM); 2001. http://www.cebm.net/levels_of_evidence.asp (Access on 23 February 2006).

[103] Knaebel H, Seiler C, Rothmund M, Neugebauer E, Büchler M. Klinische Studien im Aufwind. Erstes nationales Treffen zur Gründung des Studienzentrums der Deutschen Gesellschaft für Chirurgie (SDGC). CHAZ. 2004; 5: 121-125.

[104] Rexer M, Ditterich D, Rupprecht H. Vakuumtherapie in der Bauchchirurgie - Über Grenzerfahrungen und Indikationsstellung. [V.A.C.-therapy in abdominal surgery - experiences, limits and indications]. Zentralbl Chir. 2004; 129 Suppl 1: 27-32.

[105] Halama D, Hemprich A, Frerich B. Intraorale Vakuumtherapie zur Behandlung einer ausgedehnten Zyste des Unterkieferknochens. [Intraoral application of vacuum-assisted closure in the treatment of an extended mandibular keratocyst]. Zentralbl Chir. 2004; 129 Suppl 1: S53-S56.

[106] Nouraei SA, Hodgson EL, Malata CM. Cervicofacial necrotising fasciitis: management with neck dissection and topical negative pressure. J Wound Care. 2003; 12: 147-149.

[107] Schintler M, Maier A, Matzi V, Smolle-Juttner FM. Vacuum assisted closure system in the management of cervical anastomotic leakage after gastric pull-up. Interactive Cardiovascular & Thoracic Surgery. 2004; 3: 92-94.

[108] Weinfeld AB, Kelley P, Yuksel E, Tiwari P, Hsu P, Choo J, Hollier LH. Circumferential negative-pressure dressing (VAC) to bolster skin grafts in the reconstruction of the penile shaft and scrotum. Ann Plast Surg. 2005; 54: 178-183.

[109] Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L. Do the findings of case series studies vary significantly according to methodological characteristics? Health Technol Assess. 2005; 9: 1-146.

11 Appendices

Appendix A1 List of the studies examined in full text, but excluded (classified according to reason for exclusion)

Non-concurrent comparative cohort studies or case control studies

Catarino PA, Chamberlain MH, Wright NC, Black E, Campbell K, Robson D, Pillai RG. High-pressure suction drainage via a polyurethane foam in the management of poststernotomy mediastinitis. Ann Thorac Surg. 2000; 70: 1891-1895.

Fuchs U, Zittermann A, Stuettgen B, Groening A, Minami K, Koerfer R. Clinical outcome of patients with deep sternal wound infection managed by vacuum-assisted closure compared to conventional therapy with open packing: a retrospective analysis. Ann Thorac Surg. 2005; 79: 526-531.

Labler L, Keel M, Trentz O. Vacuum-assisted closure (V.A.C.) for temporary coverage of soft-tissue injury in type III open fracture of lower extremities. European Journal of Trauma. 2004; 30: 305-312.

Olivier LC, Assenmacher S, Schmidt G, Nast-Kolb D. Erste Ergebnisse der frühen Anwendung des V.A.C.-Systems bei einer offenen kontinuierlichen Saugung schwerer Handinfektionen. [V.A.C. for treatment of severe hand infection by open suction]. ZfW. 2000; 5: 7-8.

Philbeck TJ, Whittington KT, Millsap MH, Briones RB, Wight DG, Schroeder WJ. The clinical and cost effectiveness of externally applied negative pressure wound therapy in the treatment of wounds in home healthcare Medicare patients. Ostomy Wound Manage. 1999; 45: 41-50.

Shilt JS, Yoder JS, Manuck TA, Jacks L, Rushing J, Smith BP. Role of vacuum-assisted closure in the treatment of pediatric lawnmower injuries. J Pediatr Orthop. 2004; 24: 482-487.

Song DH, Wu LC, Lohman RF, Gottlieb LJ, Franczyk M. Vacuum assisted closure for the treatment of sternal wounds: the bridge between debridement and definitive closure. Plast Reconstr Surg. 2003; 111: 92-97.

Sun S, Yao Y, Li Y, Huang X, Ma X, Jiang Y. Mechanism and curative effect of vacuum sealing technique in treatment of wide chronic ulcer in the lower limbs in 24 cases. Zhongguo Linchuang Kangfu. 2003; 7: 577-578.

Yao YZ, Huang XK, Ma XL. [Treatment of traumatic soft tissue defect by vacuum sealing]. Chung-Kuo Hsiu Fu Chung Chien Wai Ko Tsa Chih. 2002; 16: 388-390.

Case series, case reports, and other non-comparative studies

Synergistic wound healing: utilizing today's technology to heal chronic wounds. Hyperbaric Medicine Today. 2000; 4.

Wound wonder. Middle East Medical. 2003; Seiten 61-65.

Argenta LC, Morykwas MJ. Vacuum-assisted closure: a new method for wound control and treatment: clinical experience. Ann Plast Surg. 1997; 38: 563-577.

Armstrong DG, Lavery LA, Abu-Rumman P, Espensen EH, Vazquez JR, Nixon BP, Boulton AJ. Outcomes of subatmospheric pressure dressing therapy on wounds of the diabetic foot. Ostomy Wound Manage. 2002; 48: 64-68.

Barker DE, Kaufman HJ, Smith LA, Ciraulo DL, Richart CL, Burns RP. Vacuum pack technique of temporary abdominal closure: a 7-year experience with 112 patients. J Trauma. 2000; 48: 201-206.

Bauer P, Schmidt G, Partecke BD. Möglichkeiten der Vorbehandlung von infizierten Hautweichteildefekten durch Vakuumversiegelung mit PVA-Schaumstoff. Handchir Mikrochir Plast Chir. 1998; 30: 20-23.

Baxandall T. Tissue viability. Healing cavity wounds with negative pressure. Nurs Stand. 1996; 11: 49-51.

Becker R, Balta D, Siedek M. Definitive Versorgung therapieresistenter superinfizierter chronischer Ulcera cruris durch Anwendung der Vakuumversiegelung und endoskopischer Perforansligatur mit Fasziotomie. ZfW. 2000; 5: 45-47.

Bettschart V, Vallet C, Majno P, Mentha G, Morel P, Gillet M, Mosimann F. Laparostomy with vacuum dressing after liver transplantation. Transplant Proc. 2002; 34: 777-778.

Bourree M, Kozianka J. Die Vakuumokklusionstherapie im multinodalen Therapiekonzept großer Weichteildefekte. [Occlusion therapy of V.A.C. in multimodal concepts of soft tissue defects]. Zentralbl Chir. 2004; 129: S42-S45.

Breinig J. Anwendung des KCI-V.A.C.-Therapie-Systems bei Dekubitus Patienten zur Verkürzung der präoperativen Behandlungsdauer vor plastischer Deckung. [Application of the KCI-V.A.C. therapy system in decubitus ulcer patients for reduction of preoperative treatment time before plastic closure]. ZfW. 2000; 5: 53-54.

Brentzel S. Treatment of a complex post-surgical wound using Vacuum Assisted Closure. Knoxville, Tennessee, USA: Baptist Hospital of East Tennessee; 1998.

Burton L. Nonhealing foot ulcer. Ostomy Wound Manage. 1999; 45: 20-21.

Caniano DA, Ruth B, Teich S. Wound management with vacuum-assisted closure: Experience in 51 pediatric patients. J Pediatr Surg. 2005; 40: 128-132.

Cedidi C, Berger A, Ingianni G. The two-stage concept with temporary subcutaneous implantation of vacuum sealing system: an alternative surgical approach in infected partial abdominal defects after lapratomy or abdominaloplasty. Eur J Med Res. 2002; 7: 399-493.

Chesher E. Use of vacuum assisted closure in the community. ACT Community Healthcare Program in Australia. Primary Intention. 1998; 6: 12-15.

Cozart RF, Atchison JR, Lett ED, Fabian TS, Brzezienski MA, Breazeale EE. The use of controlled subatmospheric pressure to promote wound healing in preparation for split-thickness skin grafting in a fourth degree burn. Tenn Med. 1999; 92: 382-384.

Cro C, George KJ, Donnelly J, Irwin ST, Gardiner KR. Vacuum assisted closure system in the management of enterocutaneous fistulae. Postgrad Med J. 2002; 78: 364-365.

de la Torre JI, Martin SA, Oberheu AM, Vasconez LO. Healing a wound with an exposed Herrington rod: a case study. Ostomy Wound Manage. 2002; 48: 18-19.

de Lange MY, Schasfoort RA, Obdeijn MC, van der Werff JFA, Nicolai JPA. Vacuum-assisted closure: indications and clinical experience. Eur J Plast Surg. 2000; 23: 178-182.

DeFranzo AJ, Marks MW, Argenta LC, Genecov DG. Vacuum-assisted closure for the treatment of degloving injuries. Plast Reconstr Surg. 1999; 104: 2145-2148.

Demaria R, Giovannini UM, Teot L, Chaptal PA. Using VAC to treat a vascular bypass site infection. J Wound Care. 2001; 10: 12-13.

Dill-Müller D, Nuber V, Wagner A, Tilgen W. Maligne Tumoren der Haut - Einsatz der Mini-V.A.C.-Therapie bei sekundärem Wundverschluss. [Malignant tumors of the skin - the use of Mini-V.A.C. treatment in secondary wound closure]. ZfW. 2000; 5: 25-26.

Dill-Müller D, Nuber V, Rass K, Tilgen W. Ulcus cruris venosum - Mini-V.A.C.-Therapie als aussichtsreiche Therapieoption. [Chronic venous leg ulcer - the Mini-V.A.C. treatment is a promising therapeutic option]. ZfW. 2000; 5: 51-52.

Domkowski PW, Smith ML, Gonyon DL J, Drye C, Wooten MK, Levin LS, Wolfe WG. Evaluation of vacuum-assisted closure in the treatment of poststernotomy mediastinitis. J Thorac Cardiovasc Surg. 2003; 126: 386-390.

Duxbury MS, Finlay IG, Butcher M, Lambert AW. Use of a vacuum assisted closure device in pilonidal disease. J Wound Care. 2003; 12: 355

Erdmann D, Drye C, Heller L, Wong MS, Levin SL. Abdominal wall defect and enterocutaneous fistula treatment with the Vacuum-Assisted Closure (V.A.C.) system. Plast Reconstr Surg. 2001; 108: 2066-2068.

Felmerer G, Allert S, Hierner R, Berger A. Die Vakuum-Versiegelung von Problemwunden zur Vorbereitung vor plastisch-chirurgischer Defektdeckung. [Vacuum assisted wound closure before plastic surgery procedures]. ZfW. 2000; 5: 62-63.

Ferbert T, Kuhfuss I, Ziegler UE. Behandlung ausgedehnter Weichteildefekte an Hand und Unterarm mittels Vakuum assistiertem Wundverschluss. [Treatment of soft tissue defects on hand and forearm with vacuum assisted closure]. Zentralbl Chir. 2004; 129: S57-S58.

Fette A, Rose C, Helmig FJ. Simultane Anwendung von Vakuumversiegelung (V.A.C.) und Derminersatz (Integra) in der kinderchirurgischen Behandlung einer schweren Verbrennung. [Simultaneous application of vacuum assisted closure (V.A.C.) and dermal regeneration template (Integra) for paediatric surgical burn treatment]. ZfW. 2003; 8: 180-184.

Fleck T, Moidl R, Giovanoli P, Wolner E, Grabenwoger M. Frühzeitiger Einsatz des V.A.C.-Systems bei sternalen Wundinfektionen verhindert die Ausbreitung der Infektion auf das Mediastinum und reduziert die Notwendigkeit plastisch chirurgischer Eingriffe. [Early treatment of sternal wound infections with vacuum assisted closure therapy reduces involvement of the mediastinum and further diminishes the need of plastic reconstructive surgery]. Zentralbl Chir. 2004; 129: S35-S37.

Fleischmann W, Strecker W, Bombelli M, Kinzl L. Vakuumversiegelung zur Behandlung des Weichteilschadens bei offenen Frakturen. [Vacuum sealing as treatment of soft tissue damage in open fractures]. Unfallchirurg. 1993; 96: 488-492.

Fleischmann W, Lang E, Russ M. Infektbehandlung durch Vakuumversiegelung. [Treatment of infection by vacuum sealing]. Unfallchirurg. 1997; 100: 301-304.

Fleischmann W, Becker U, Bischoff M, Hoekstra H. Vacuum sealing: indications, technique and results. Eur J Orthop Surg Trauma. 1995; 5: 37-40.

Fleischmann W. Vakuumversiegelung zur Behandlung von Problemwunden. Hartmann Wundforum. 1994; 4-6.

Fleischmann W, Becker U, Lang E. Vakuumversiegelung zur Behandlung des traumatischen Weichteilschadens am Oberschenkel. Osteo Int. 1995; 2: 84-88.

Gerber-Haughton R, Hain, Pellio, Strohm, Thiemann, Fedder. VAC-Therapie bei gasbildenden Anaerobiern. [The use of V.A.C. in gas producing anaerobic infections]. ZfW. 2000; 5: 60-61.

Halter G, Kapfer X, Liewald F, Bischoff M. Vacuum-sealed mesh graft transplantation in chronic cutaneous ulcers of the lower leg. Vasa. 2003; 32: 155-158.

Horch RE, Andree C, Walgenbach KJ, Voigt M, Stark GB. Der Einsatz der Vakuumversiegelung zur Deckung großflächiger Weichteildefekte und Fixierung von Spalthauttransplantaten. [Vacuum assisted closure for coverage of extensive soft tissue defects and skin graft fixation]. ZfW. 2000; 5: 17-19.

Hutchinson L. Vacuum-assisted closure: A method of facilitating wound healing. J World Council Enterost Ther. 1999; 19: 17-21.

Isago T, Nozaki M, Kikuchi Y, Honda T, Nakazawa H. Negative-pressure dressings in the treatment of pressure ulcers. J Dermatol. 2003; 30: 299-305.

Karl T. Ergebnisse der V.A.C.-Therapie in der Gefäßchirurgie. [Results of V.A.C. therapy in vascular surgery]. Vasomed. 2004; 16: 172-176.

Kirby JP, Fantus RJ, Ward S, Sanchez O, Walker E, Mellett MM, Maltz SB, Lerner TT. Novel uses of a negative-pressure wound care system. J Trauma. 2002; 53: 117-121.

Kleinert H, Ludwig A, Knizia C. Vakuumversiegelung bei Problemwunden der Extremitäten - Chancen und Grenzen. [Vacuum assisted wound closure in complicated limb wounds - Chances and limits]. ZfW. 2000; 5: 38-40.

Kopp J, Bach A, Loos B, Polykandriotis E, Kneser U, Seyhan H, Ohnolz J, Horch RE. Der Einsatz der Vakuumtherapie bei der Defektdeckung an der oberen Extremität mit freien mikrochirurgischen arterialisierten venösen Lappen. [Use of vacuum therapy during defect coverage of the upper extremity with microsurgically grafted arterialized venous flaps]. Zentralbl Chir. 2004; 129: S82-S84.

Krasner DL. Managing wound pain in patients with vacuum-assisted closure devices. Ostomy Wound Manage. 2002; 48: 38-43.

Labler L, Oehy K. Vakuumversiegelung bei Problemwunden. [Vacuum sealing of problem wounds]. Swiss Surg. 2002; 8: 266-272.

Lang E, Bauer G, Becker U, Losel S. Vacuum sealing technique for severe soft tissue trauma of the ankle and foot. Foot & Ankle Surgery. 1999; 5: 9-14.

Lee SS, Lin SD, Chen HM, Lin TM, Yang CC, Lai CS, Chen YF, Chiu CC. Management of intractable sternal wound infections with topical negative pressure dressing. J Card Surg. 2005; 20: 218-222.

Loree S, Dompmartin A, Penven K, Harel D, Leroy D. Is Vacuum Assisted Closure a valid technique for debriding chronic leg ulcers? J Wound Care. 2004; 13: 249-252.

Luckraz H, Murphy F, Bryant S, Charman SC, Ritchie AJ. Vacuum-assisted closure as a treatment modality for infections after cardiac surgery. J Thorac Cardiovasc Surg. 2003; 125: 301-305.

Maiwald G, Horster S, Baumeister RGH. Infektkonditionierung der chronischen Sternumosteomyelitis durch Vakuumversiegelung nach kardiochirurgischem Primäreingriff. [Wound conditioning of chronic sternal osteomyelitis by vacuum assisted closure]. ZfW. 2000; 5: 34-37.

Mehbod AA, Ogilvie JW, Pinto MR, Schwender JD, Transfeldt EE, Wood KB, Le Huec JC, Dressel T. Postoperative deep wound infections in adults after spinal fusion: Management with vacuum-assisted wound closure. J Spinal Disord Tech. 2005; 18: 14-17.

Miller PR, Thompson JT, Faler BJ, Meredith JW, Chang MC. Late fascial closure in lieu of ventral hernia: the next step in open abdomen management. J Trauma. 2002; 53: 843-849.

Miller PR, Meredith JW, Johnson JC, Chang MC. Prospective evaluation of vacuum-assisted fascial closure after open abdomen: planned ventral hernia rate is substantially reduced. Ann Surg. 2004; 239: 608-614.

Molnar JA, DeFranzo AJ, Hadaegh A, Morykwas MJ, Shen P, Argenta LC. Acceleration of integra incorporation in complex tissue defects with subatmospheric pressure. Plast Reconstr Surg. 2004; 113: 1339-1346.

Mullner T, Kutscha-Lissberg F, Kwasny O, Vecsei V. Die Vakuumversiegelung nach infizierter Osteosynthese mit begleitendem Hautweichteildefekt. [Vacuum sealing technique after infected osteosynthesis with accompanied tissue defect]. Acta Chirurgica Austriaca. 1997; 29: 111-112.

Mullner T, Mrkonjic L, Kwasny O, Vecsei V. The use of negative pressure to promote the healing of tissue defects: a clinical trial using the vacuum sealing technique. Br J Plast Surg. 1997; 50: 194-199.

Nienhuijs SW, Manupassa R, Strobbe LJ, Rosman C. Can topical negative pressure be used to control complex enterocutaneous fistulae? J Wound Care. 2003; 12: 343-345.

Nitschmann K, Chrostek J, Hupp T. Wundbehandlung im Wandel der Zeit - V.A.C.(R)-Therapie in der Gefaesschirurgie. [Wound treatment throughout time]. Zentralbl Chir. 2004; 129: S71-S73.

O'Connor J, Kells A, Henry S, Scalea T. Vacuum-assisted closure for the treatment of complex chest wounds. Ann Thorac Surg. 2005; 79: 1196-1200.

Othman T, Friese G, Gierth T, Ziegler G, Scherbaum W. Die Anwendung der Vakuumpumpentherapie (V.A.C.-System) beim Diabetischen Fußsyndrom. [The treatment of heel pressure ulcer with the vacuum therapy (V.A.C. system)]. Zentralbl Chir. 2004; 129: S116-S118.

Ottomann C, Schonborn A, Hartmann B. Komplikationsmanagement mittels V.A.C.-Therapie bei phlegmonösen Bauchdeckeninfektionen nach Abdominoplastik. [Management with v.a.C. in phlegmonous tissue defects of the abdominal wall after abdominoplasty]. Zentralbl Chir. 2004; 129: S85-S88.

Panfil EM, Borger M. Akzeptanz der V.A.C.-Therapie im Home Care Bereich (Studienbericht zur klinischen Erfahrung von Anwendern der VAC-Therapie im außerklinischen Bereich). Frankfurt am Main: Hessisches Institut für Pflegeforschung; 2003.

Riechers G. V.A.C.-Therapie beim Abdomen apertum. Pflegerische Aspekte. [The importance of the vacuum sealing in the treatment in necrotising fasciitis]. ZfW. 2000; 5: 64-66.

Rosser CJ, Morykwas MJ, Argenta LC, Bare RL. A new technique to manage perineal wounds. Infect Urol. 2000; 13: 45-55.

Scheufler O, Peek A, Kania NM, Exner K. Beschleunigter Wundverschluss mit der VAC-Therapie nach akuter Ischämie und Kompartmentsyndrom am Unterschenkel. [Vacuum assisted wound closure after acute ischemia and compartment syndrome of the lower limb]. ZfW. 2000; 5: 32-33.

Schipper J, Ridder GJ, Maier W, Kopp J, Bach AD, Horch RE. Präfabrikation dreidimensionaler Lappenkonstrukte mittels Vakuumtherapie. ZfW. 2003; 8: 93-99.

Schneider AM, Morykwas MJ, Argenta LC. A new and reliable method of securing skin grafts to the difficult recipient bed. Plast Reconstr Surg. 1998; 102: 1195-1198.

Seip GU, Berger T, Thiele H. Die Vakuumtherapie bei chronischen Ulcera cruris vor und nach Mesh Graft Plastik. [The V.A.C. therapy in wound management of chronic ulcers of the lower limb before and after mesh graft]. ZfW. 2000; 5: 23-24.

Skillman J, Kirkpatrick N, Coombes A, Coghlan B, Waterhouse N, Joshi N, Kelly M. Vacuum Assisted Closure (VAC) dressing for skin graft application following exenteration of the orbit. Orbit. 2003; 22: 63-65.

Sposato G, Molea G, Di CG, Scioli M, La R, Ziccardi P. Ambulant vacuum-assisted closure of skin-graft dressing in the lower limbs using a portable mini-VAC device. Br J Plast Surg. 2001; 54: 235-237.

Stocker HJ, Chilov B. Der Einsatz des V.A.C. Systems in der Therapie von problematischen Wunden. [Use of the V.A.C. system in the treatment of complicated wounds]. ZfW. 2000; 5: 20-22.

Stucker M, Herde M, Hoffmann K, Altmeyer P. Vacuum sealing technique in therapy of open venous ulcer. Phlebologie. 1998; 27: 206-209.

Tachi M, Hirabayashi S. Adjuvant therapy for pressure ulcer management. Japanese Journal of Plastic & Reconstructive Surgery. 2003; 46: 477-483.

Vuerstaek JDD, Veraart JC, Wuite J, van der Kley AMJ, Neumann HAM. Un nouveau concept de cicatrisation active des ulceres rebelles veineux ou mixtes: le Vacuum Assisted Closure. Trois ans d'experience clinique. Phlebologie. [A new concept in active healing of mixed or resistant venous ulcers: Vacuum assisted closure. A 3 year experience]. 2002; 55: 15-19.

Walgenbach KJ, Riabikhin AW, Bannasch H, Galla T, Bach A, Andree C, Voigt M, Stark GB, Horch RE. Die Vakuumversiegelung in der Behandlung chronischer Wunden. [Vacuum sealing in the treatment of chronic wounds]. ZfW. 2000; 5: 6-8.

Wassel P. Vakuumversiegelung. Modernes Wundmanagement zur Konditionierung und Rekonstruktion von Weichteilschäden. ZfW. 1999; 4: 5-7.

Weinberg Group Inc T. Technology Assessment of the V.A.C. for In-home Treatment of Chronic Wounds. Washington, District of Columbia, USA: The Weinberg Group Inc; 1999.

Whelan C, Stewart J, Schwartz BF. Mechanics of wound healing and importance of vacuum-assisted closure in urology. J Urol. 2005; 173: 1463-1470.

Wu SH, Zecha PJ, Feitz R, Hovius SER. Vacuum therapy as an intermediate phase in wound closure: a clinical experience. Eur J Plast Surg. 2000; 23: 174-177.

Ziegler UE, Schmidt K, Breithaupt B, Menig R, Debus ES, Thiede A. Ambulante Wundbehandlung durch Vakuumversiegelung. [Ambulant treatment of wounds by vacuum sealing]. Zentralbl Chir. 2000; 125: 87-89.

Zuckermann-Becker H, Müller JM. Vakuumversiegelung bei Problemwunden in der Abdominalchirurgie. [Vacuum assisted wound closure in complicated wounds in abdominal surgery]. ZfW. 2000; 5: 11-12.

Conference reports, Opinions, Narrative surveys, Guidelines, Letters to the editor, Basic research

Firm brochure V.A.C. Freedom. Das mobile und effektive Wundbehandlungssystem. San Antonio, Texas, USA: Kinetic Concepts Inc; 2004.

KCI says wound closure device will save money, promote healing process. Health Ind Today; 1995. http://www.findarticles.com/p/articles/mi_m3498/is_n9_v58/ai_18133684 (Access on 27 September 2005).

Mit Kombinationstherapie heilen Wunden doppelt schnell. Ärzte Zeitung; 2001. http://www.aerztezeitung.de/docs/2001/12/12/225a1901.asp?cat= (Access on 27 September 2005).

Mit Unterpress gegen chronische Wunden. Ärztliche Allgemeine. 2001; 18.

Mit Unterpress Wunden schneller heilen. Hausarzt. 2002; 74.

Mit Vakuum gegen chronische Wunden. Ärzte Zeitung; 2002.

V.A.C. Home Care Data Analysis. San Antonio, Texas, USA: Kinetic Concepts Inc; 2003.

V.A.C. Therapie jetzt von der IKK empfohlen. Med Tribune 37; 2002.

V.A.C. überzeugt Experten. Klinische Bewertung der V.A.C.-Therapie im stationären und ambulanten Bereich. Gesundheitsprofi. 2003; 6: 36-37.

Vacuum device can speed wound healing. 1997.

Vacuum tackles chronic wounds. 663 Clinica; 1995. http://www.kciresearch.com/Studies/Clinical_Studies_Articles.asp?id=10 (Access on 27 September 2005).

Vakuumverschluss lässt chronische Wunden heilen. Ärzte Zeitung; 2003.

Vakuumversiegelung kann die Haut retten. Therapie für Patients mit schweren Brandverletzungen vermindert Ödeme und verbesssert den Blutfluss. Ärzte Zeitung; 2001.

Watch out for these VAC complications. Wound Care; 1997.

Wound closure therapy cuts healing time. Amsterdam: Elsevier BV; 1995. http://www.kciresearch.com/Studies/Clinical_Studies_Articles.asp?id=10 (Access on 27 September 2005).

Agarwala S, Mulay S. Use of mini-vacuum drains in small surgical wounds. Plast Reconstr Surg. 1998; 101: 1421-1422.

Argenta LC. Editorial response. Ann Plast Surg. 2000; 45: 335-336.

Azad S, Nishikawa H. Topical negative pressure may help chronic wound healing. BMJ. 2002; 324: 1100.

Bader R. Modernes Wundmanagement ist nicht schwer. Chronische Wunde; 2002.

Baer W, Lerch K, Ziegler UE, Schaller P, Martin R. Die Vakuumversiegelung - Eine Therapieoption bei Problemwunden. [Vacuum treatment - A therapeutic option in problem wounds]. ZfW. 2003; 8: 123-133.

Banwell P, Holten I, Martin DL. Negative pressure therapy: clinical applications and experience with 200 cases. Wound Repair Regen. 1998; 6: Abstract A460.

Banwell P. Novel perspectives in wound care: Topical negative pressure therapy. European Tissue Repair Society Bulletin. 2002; 9: 49-50.

Banwell P, Withey S, Holten I. The use of negative pressure to promote healing. Br J Plast Surg. 1998; 51: 79.

Banwell PE. Skin graft fixation. Br J Oral Maxillofac Surg. 1998; 36: 480-481.

Banwell PE. Topical negative pressure therapy in wound care. J Wound Care. 1999; 8: 79-84.

Banwell PE, Teot L. Topical negative pressure (TNP): the evolution of a novel wound therapy. J Wound Care. 2003; 12: 22-28.

Banwell PE, Evison D, Whitworth IM. Vacuum therapy in degloving injuries of the foot: technical refinements. Br J Plast Surg. 2002; 55: 264-266.

Baxter H, Ballard K. Vacuum-assisted closure. Nurs Times. 2001; 97: 51-52.

Brown AS. The Vac-Pac. Plast Reconstr Surg. 1988; 81: 301-302.

Cooper SM, Young E. Topical negative pressure in the treatment of pressure ulcers. J Am Acad Dermatol. 1999; 41: 280.

Cooper SM, Young E. Topical negative pressure. Int J Dermatol. 2000; 39: 896-898.

Edwards AR. Vacuum device closes gap in wound care. BioMechanics. 2001; 8: 27-34.

Einsiedel T, Bischoff M, Kolodziej S, Vogel M, Kinzl L, Schmelz A. Revascularisation, control of infection and reconstruction - Current aspects for the treatment of wounds: An overview. Klinikarzt. 2004; 33: 239-245.

Fleischmann W, Russ MK, Moch D. Chirurgische Wundbehandlung. [Surgical wound treatment]. Chirurg. 1998; 69: W222-W232.

Fleischmann W. Die Vakuumversiegelung. Neue Technik für alte Probleme. ZfW. 1996; 6.

Fleischmann W, Russ M. Die Vakuumversiegelungstechnik bei chronischen Wunden. Klinikarzt. 1996; 25: 188-190.

Fleischmann W, Russ M, Kinzl L. Die Vakuumversiegelungstechnik bei chronischen Wunden. OP -Journal. 1996; 55-57.

Fleischmann W, Becker U, Bischoff M, Hoekstra H. Indication and operative technique in vacuum sealing. J Bone and Joint Surg. 1994; 98: 76-B Suppl 2&3.

Fleischmann W. Vakuumversiegelung. Wirkungsweise, Indikationen, Ergebnisse und Gefahren. MedReport. 2003; 27: 14.

Foo L-SS, Chua B-SY, Chia GT, Tan SB, Howe TS. Vacuum assisted closure vs moist gauze dressing in post-operative diabetic foot wounds: Early results from a randomised controlled trial (Abstract). Presented at the 2nd World Union of Wound Healing Societies Meeting, Paris, France, 8-13 July; 2004.

Food and Drug Administration. V.A.C; Letter October 10, 2003. Rockville, Maryland, USA: U.S. Food and Drug Administration; 2003.

Froiland KG. Nursing interventions in oncology. Complex wound care: Use of negative pressure therapy for wound healing in an ovarian cancer patient. 2001. http://www.kci1.com/clinicalevidence/Clinical_Studies_Articles.asp?id=3 (Access on 27 September 2005).

Gebhard F, Becker U, Lang E, Fleischmann W. Infektprophylaxe und Behandlung des traumatischen Weichteilschadens mit Vakuumversiegelung. Wehrmed Monatsschr. 1995; 39: 177-180.

Giovanni UM, Demaria RG, Otman S, Chaptal PA, Teot L. Treatment of poststernotomy wounds with negative pressure. Plast Reconstr Surg. 2002; 109: 1747.

Gray M, Peirce B. Is negative pressure wound therapy effective for the management of chronic wounds? Evidence-based report card: from the Center for Clinical Investigation. J WOCN. 2004; 31: 101-105.

Greer SE, Longaker MT, Margiotta M. Preliminary results from a multicenter, randomized, controlled study of the use of subatmospheric pressure dressing for pressure ulcer healing. Wound Repair Regen. 1999; 7: Abstract A255.

Greer SE. Whither subatmospheric pressure dressing? Ann Plast Surg. 2000; 45: 332-334.

Grimm K, Geßlein M. Offenes Bein. Neue Maßstäbe für die Wundbehandlung. Hausarzt. 2003; 50-52.

Gupta S, Cho T. A literature review of negative pressure wound therapy. Ostomy Wound Manage. 2004; 50: 2S-4S.

Gupta SC. Sterilizing chronic wounds with negative pressure therapy: the role of antibiotic irrigation. Presented at the 11th Annual Meeting and Educational Symposuim, Wound Healing Society 2001 (May 16-18). Albuquerque, New Mexico, USA. Wound Repair Regen. 2001; 9: Abstract 127.

Hardcastle MR. Vacuum assisted closure therapy: the application of negative pressure in wound healing. Primary Intention. 1998; 6: 5-10.

Harlan JW. Treatment of open sternal wounds with the vacuum-assisted closure system: a safe, reliable method. Plast Reconstr Surg. 2002; 109: 710-712.

Heinze J. Spart Kosten und Zeit: die V.A.C. Therapie. Ambulante Chirurgie. 2003; 7: 36.

Horch RE. Grundlagen und Ergebnisse der Vakuumtherapie (V.A.C.) in der rekonstruktiven Chirurgie. [Basics foundation and results of the vacuum therapy in the reconstructive surgery]. Zentralbl Chir. 2004; 129: S2-S5.

Horch RE, Bach AD, Loos B, Schipper J, Kopp J. Prefabrication of threedimensional newly generated compound flaps in plastic surgery with the use of V.A.C. Eur Surg. 2003; 35: 18-20.

Horch RE, Bach A, Loos B, Kopp J. Sicherheitsaspekte und Indikationen der V.A.C.-Therapie in der plastischen Chirurgie. Eur Surg. 2003; 35: 5-7.

Horch RE. Ulcus cruris. Chirurgische Verfahrenswahl, Debridement, Shaving, Fasziektomie, Transplantation. MedReport. 2003; 27: 8.

Huss S. Prozessorgesteuerte Wunddrainage. DERMAforum; 2003.

Husted DS, Grauer JN, Hilibrand AS. The use of wound vacuums in the management of postoperative wound infections. Seminars in Spine Surgery. 2004; 16: 182-187.

Hutchinson L, Cuttino C. Four new treatments for chronic wounds save time and money. Advance for Nurses. 1999; 1: 21-22.

Kleinert H. Vakuum verhindert Sekretstau in der Wunde. Chronische Wunde. 2002; 30.

Kochanek U. Schreiben vom 11.10.2002 an Herrn Prof. Nord. Essen: Bundesverband Ambulante Dienste; 2002.

Masters J. Reliable, inexpensive and simple suction dressings. Br J Plast Surg. 1998; 51: 267.

Medicare. Negative pressure wound therapy pumps. Local Medical Review Policy. Original Policy Effective Date 2000-10-01. Baltimore, Maryland, USA: Centers for Medicare & Medicaid Services; 2000. http://www.cms.hhs.gov/mcd/viewlmrp.asp?lmrp_id=5008&lmrp_version=8&basket=lmrp%3A5008%3A8%3ANegative+Pressure+Wound+Therapy+Pumps%3ADMERC%3APalmetto+GBA+%2800885%29%3A (Access on 27 September 2005).

Mendez-Eastman S. Determining the appropriateness of negative pressure wound therapy for pressure ulcers. Ostomy Wound Manage. 2004; 50: 13-16.

Mendez-Eastman S. New treatment for an old problem: negative-pressure wound therapy. Nursing. 2002; 32: 58-63.

Mentzel M, Fleischmann W, Kinzl L. Versorgunsgstrategie bei traumatischen Defektwunden. Klinikarzt. 1997; 27: 138-141.

Moch D, Russ M, Fleischmann W. Kausale Therapie der chronischen Wunde. Klinikarzt. 1998; 27: 126-130.

Molnar JA, Heimbach DM, Tredgett EE, Mozingo DW. Prospective, Randomized, Controlled, Multicenter Trial Applying Subatmospheric Pressure to Acute Hand Burns: An Interim Report (Abstract D008). Presented at the 2nd World Union of Wound Healing Societies Meeting, Paris, France, 8-13 July; 2004.

Nord D. Bedeutung der V.A.C.-Therapie im stationären und ambulanten Bereich - Klinische Bewertung aus der Sicht von Experten. Heidelberg, 2002. Konstanz: Dietrich Nord; 2002.

Ovington LG. 1, 2, 3, s-t-r-e-t-c-h; vacuum enhances wound closure. Adv Wound Care. 1999; 125-127.

Patel CT, Kinsey GC, Koperski-Moen KJ, Bungum LD. Vacuum-assisted wound closure. Am J Nurs. 2000; 100: 45-48.

Petrie N, Potter M, Banwell P. The management of lower extremity wounds using topical negative pressure. Int J Low Extrem Wounds. 2003; 2: 198-206.

Pfadenhauer A, Rösken F, Deiler S, Mutschler W, Stock W. Vakuumversiegelung zur Konditionerung kritischer Wunden vor plastisch-chirurgischer Deckung. [Vacuum-assisted closure to prepare critical wounds for surgical closure]. ZfW. 2000; 5: 13-14.

Pfänder J. DRG und KCI - eine ideale Synergie. ZfW. 2003; 8: 62-63.

Pignatti M, Bruti M, Rigotti G. Mobile-VAC for the treatment of lower limb ulcers. Plast Reconstr Surg. 2001; 108: 1837-1838.

Russ M, Fleischmann W, Moch D. Postoperative traumatologische Wundheilungsstörungen - Möglichkeiten der Therapie mit der Vakuumversiegelungstechnik. Jahrbuch Chir. 1999; 229-234.

Russ M, Fleischmann W, Moch D. Postoperative, traumatologische Wundheilungsstörungen - Möglichkeiten der Therapie mit der Vakuumversiegelungstechnik. Praxis Journal. 2002; 11-15.

Rutherford EJ. Management of the patient with an open abdomen: Techniques in temporary and definitive closure. Current Problems in Surgery. 2004; 41: 821-876.

Saklani AP, Delicata RJ. Vacuum assisted closure system in the management of enterocutaneous fistula. Postgrad Med J. 2002; 78: 699.

Sames CP. Sealing of wounds with vacuum drainage. Br Med J. 1977; 2: 1123.

Sauter ER. Temporary closure of open abdominal wounds by the modified sandwich-vacuum pack technique. Br J Surg. 2003; 90: 1021-1022.

Schintler MV, Spendel S, Schramayer G, Rappl T, Wittgruber G, Prandl EC, Hellbom B, Scharnagl E. Die Wertigkeit der vakuum-unterstützten Wundbehandlung beim geriatrischen und polymorbiden Patients. Vasomed. 2003; 15: 92-98.

Schmidt U, Krettek C. Die Vakuumtherapie. Wundbehandlungsmethode der Zukunft. Unfallchirurg. 2001; 104: 917-917.

Schmitt J, Bertram M. Schreiben vom 20. Juni 2000 an den Sachverständigenrat für die Konzertierte Aktion im Gesundheitswesen. Befragung durch den Sachverständigenrat für die Konzertierte Aktion im Gesundheitswesen, hier: "Unter-/Fehlversorgung im Bereich der Versorgung chronischer Wunden". BVMed Bundesfachverbands Medizinprodukte Industrie e.V.; 2000.

Schübel C, Prestel R. Klinische Bewertung vom 05.07.2001. V.A.C. (Vacuum Assisted Closure) Therapie System. München: TÜV Product Service GmbH; 2001.

Schwamborn M, Wassel P. Vakuumversiegelung (VAC). Möglichkeiten und Grenzen der ambulanten Behandlung. ZfW. 1997; 2: 10.

Shaer WD. Inexpensive vacuum-assisted closure employing a conventional disposable closed-suction drainage system. Plast Reconstr Surg. 2001; 107: 292-293.

Sibbald RG, Mahoney J, Therapy Canadian Consensus Group VAC. A consensus report on the use of vacuum-assisted closure in chronic, difficult-to-heal wounds. Ostomy Wound Manage. 2003; 49: 52-66.

Simmang CL. Intestinal fistulas. Clinics in Colon & Rectal Surgery. 2003; 16: 213-220.

Smith N. The benefits of VAC therapy in the management of pressure ulcers. Br J Nurs. 2004; 13: 1359-1365.

Soleimannian A. Bundesverband der IKK empfiehlt die Vakuumtherapie V.A.C. Der niedergelassene Chirurg. 2002; 6: 30-31.

Stannard JP. Complex orthopaedic wounds: prevention and treatment with negative pressure wound therapy. Adv Skin Wound Care. 2004; 17 Suppl: 2-10.

Stewart KJ, Wilson Y, Keating JF. Suction dressings are no substitute for flap cover in acute open fractures. Br J Plast Surg. 2001; 54: 652-653.

Stremitzer S, Zeisel C, Holzenbein T, Sautner T, Wild T. Selected commentary to: 'Prospective evaluation of vacuum-assisted fascial closure after open abdomen: Planned ventral hernia rate is substantially reduced' (Miller PR, Meredith JW, Johnson JC, Chang MC, Ann Surg 239: 608-614, 2004). European Surgery - Acta Chirurgica Austriaca Supplement. 2004; 36: 266-267.

Sunog T. Closing time: vacuum-assisted closure helps wounds heal faster, cuts down on infection rates and improves patient outcomes. Advances for Nurses. 2003; 34.

Tang ATM, Doss M. Vacuum-assisted suction drainage of sternotomy infection: A new paradigm? Eur J Cardiothorac Surg. 2003; 23: 649-650.

Thoner B, Fleischmann W, Moch D. Wundbehandlung durch Vakuumversiegelung. Krankenpfl J. 1998; 36: 78-82.

Todd J. V.A.C. Assessment. Letter of 24 November; 1997.

Valenta AL. Using the vacuum dressing alternative for difficult wounds. Am J Nurs. 1994; 94: 44-45.

Voinchet V, Magalon G. Le vacuum assisted closure. La cicatrisation par pression d'air negative. [Vacuum assisted closure. Wound healing by negative pressure]. Ann Chir Plast Esthet. 1996; 41: 583-589.

Walgenbach KJ, Riabikhin AW, Andree C, Galla TJ, Schaefer DJ, Kopp J, Bannasch H, Voigt M, Horch RE, Stark GB. Induktion von Angiogenese durch Vakuumversiegelung. Klinische und histologische Untersuchungen. [Induction of angiogenesis following vacuum sealing]. ZfW. 2000; 13: 9-10.

Wallenfang K. Konzept für eine phasenadaptierte Wundbehandlung: Von A wie Alginate bis V wie Vakuumversiegelung. Pflege Z. 2002; 55: 401-405.

Webb LX, Schmidt U. Wundbehandlung mit der Vakuumtherapie. Unfallchirurg. 2001; 104: 918-926.

Wiederkumm M. Pflegerische Aspekte in der V.A.C.-Therapie. [Care aspects in v.a.C. therapy]. Zentralbl Chir. 2004; 129: S40-S41.

Willy C, Gerngross H. Der wissenschaftliche Hintergrund der Vakuumversiegelung - Eine Übersicht. [Scientific background of the vacuum closure - an abstract]. Zentralbl Chir. 2004; 129: S6.

Zamierowski DS. All foam sponges are not equal in vacuum dressings. Br J Plast Surg. 1999; 52: 79.

Ziegler UE, Schmidt K, Breithaupt B, Menig R, Debus ES, Thiede A. Erfahrungen in der ambulanten Wundbehandlung chronischer Wunden mit der Vakuumversiegelung. [Experience in the outpatient-treatment of chronic wounds by vacuum sealing]. ZfW. 2000; 5: 45-47.

Articles on health economics

Birchall L, Street L, Clift H. Developing a trust-wide centralised approach to the use of TNP. J Wound Care. 2002; 11: 311-314.

Neubauer G, Ujlaky R. The cost-effectiveness of topical negative pressure versus other wound-healing therapies. J Wound Care. 2003; 12: 392-393.

Other themes

Firm form on wound documentation San Antonio, Texas, USA: Kinetic Concepts, Inc; 2000.

Acus RW, III, Clark JM, Gradisar IA, Jr., Kovacik MW. The use of postoperative suction drainage in total hip arthroplasty. Orthopedics. 1992; 15: 1325-1328.

Armstrong DG, Kunze K, Martin BR, Kimbriel HR, Nixon BP, Boulton AJ. Plantar pressure changes using a novel negative pressure wound therapy technique. J Am Podiatr Med Assoc. 2004; 94: 456-460.

Baskov AV. Khirurgicheskoe lechenie prolezhnei u bol'nykh so spinnomozgovoi travmoi. [The surgical treatment of decubitus ulcers in patients with spinal cord trauma]. Zh Vopr Neirokhir Im N N Burdenko. 2000; 7-10.

Calvat S, Trouillet JL, Nataf P, Vuagnat A, Chastre J, Gibert C. Closed drainage using Redon catheters for local treatment of poststernotomy mediastinitis. Ann Thorac Surg. 1996; 61: 195-201.

Dahl HD, Henrich MH. Licht- und rasterelektronenmikroskopische Untersuchungen zur Pathogenese des Sinus pilonidalis und der Analfistel. [Light and scanning electron microscopy study of the pathogenesis of pilonidal sinus and anal fistula]. Langenbecks Arch Chir. 1992; 377: 118-124.

Davydov I, Larichev AB, Abramov AI, Men'kov KG. Kontseptsii kliniko-biologicheskogo upravleniia ranevym protsessom pri lechenii gnoinykh ran s pomoshch'iu vakuum-terapii. [Concept of clinico-biological control of the wound process in the treatment of suppurative wounds using vacuum therapy]. Vestn Khir Im I I Grek. 1991; 146: 132-136.

Davydov I, Larichev AB, Kozlov AG. Patogeneticheskie mekhanizmy vliianiia vakuum-terapii na techenie ranevogo protsessa. [Pathogenetic mechanisms of the effect of vacuum therapy on the course of the wound process]. Khirurgiia (Mosk). 1990; 66: 42-47.

Davydov I, Abramov AI, Darichev AB. Reguliatsiia ranevogo protsessa u bol'nykh pozhilogo i starcheskogo vozrasta metodom vakuum-terapii. [Regulation of wound process by the method of vacuum therapy in middle-aged and aged patients]. Khirurgiia (Mosk). 1994; 7-10.

Davydov I, Abramov AI, Larichev AB. Vakuum-terapiia v preduprezhdenii posleoperatsionnoi ranevoi infektsii. [Vacuum therapy in the prevention of postoperative wound infection]. Vestn Khir Im I I Grek. 1991; 147: 91-95.

Fleischmann W, Suger G, Kinzl L. Treatment of bone and soft tissue defects in infected nonunion. Acta Orthop Belg. 1992; 58: 227-235.

Food and Drug Administration. V.A.C. Vacuum Assisted Closure. Rockville, Maryland, USA: U.S. Food and Drug Administration; 2002. http://www.fda.gov/cdrh/pdf2/k021500.pdf (Access on 27 September 2005).

Gracias VH, Braslow B, Johnson J, Pryor J, Gupta R, Reilly P, Schwab CW. Abdominal compartment syndrome in the open abdomen.[see comment]. Arch Surg. 2002; 137: 1298-1300.

Iusupov I, Epifanov MV. Aktivnoe drenirovanie rany. [Active drainage of a wound]. Vestn Khir Im I I Grek. 1987; 138: 42-46.

Kutschka I, Frauendorfer P, Harringer W. Vakuumtherapie bei sternalen Wundinfektionen - Auswirkungen auf die frühpostoperative Lungenfunktion. [Vacuum assisted closure therapy improves early postoperative lung function in patients with large sternal wounds]. Zentralbl Chir. 2004; 129: S33-S34.

McAuley WJ, Nordin AJ, Naik R, de-Barros LA, Monaghan JM. A randomised controlled trial of groin wound suction drainage after radical vulvectomy and bilateral groin node dissection. International Journal of Gynecological Cancer. 2003; 13: 5.

Miasnikov AD, Ataev AR. Primenenie vakuum-terapii pri gnoinykh zabolevaniiakh pal'tsev i kisti. [Use of vacuum therapy in suppurative diseases of fingers and hands]. Klin Khir. 1994; 13-15.

National Pressure Ulcer Advisory Panel (NPUAP). PUSH Tool 3.0. Washington, DC, USA: National Pressure Ulcer Advisory Panel (NPUAP); 2005. http://www.npuap.org/push3-0.html (Access on 27 September 2005).

Parikh RS, Upasani V, Joshi R, Mathur SK. Self-adhesive drape (Opsite) for management of leaking abdominal wounds. Indian J Gastroenterol. 2000; 19: 178-180.

Svetukhin AM, Karlov VA, Amiraslanov I, Matasov VM, Blatun LA. Obshchie printsipy lecheniia gnoinykh ran i gnoinykh khirurgicheskikhzabolevanii. [General principles of the treatment of suppurative wounds and suppurative surgical diseases]. Khirurgiia (Mosk). 1990; 79-84.

Wagner FW. The diabetic foot: a personal experience of 50 years. Foot Ankle Int. 1999; 20: 684-686.

Appendix A2 Systematic reviews, meta-analyses, HTA reports

Costa V, Brophy J, McGregor M. Vacuum-assisted wound closure therapy (V.A.C (R)). Montreal, Quebec, Canada: Technology Assessment Unit of the McGill University Health Centre (MUHC); 2005. http://upload.mcgill.ca/tau/VAC_REPORT_FINAL.pdf (Access on 27 September 2005).

Evans D, Land L. Topical negative pressure for treating chronic wounds. In: The Cochrane Library, editor. The Cochrane Database of Systematic Reviews.West Sussex, United Kingdom: John Wiley & Sons Ltd; 2001. http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME (Access on 27 September 2005).

Fisher A, Brady B. Vacuum assisted wound closure therapy. Ottawa, Canada: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2003. http://www.ccohta.ca/publications/pdf/221_vac_cetap_e.pdf (Access on 27 September 2005).

Hayes Inc. Negative pressure wound therapy for wound healing. Lansdale, Pennsylvania, USA: Hayes, Inc; 2003.

Higgins S. The effectiveness of vacuum assisted closure (VAC) in wound healing. Clayton, Australia: Centre for Clinical Effectiveness (CCE); 2003. http://www.med.monash.edu.au/healthservices/cce/evidence/pdf/c/991fr.pdf (Access on 27 September 2005).

Mayer ED, Boukamp K, Simoes E. Vakuumversiegelung in der Wundbehandlung - Verfahren nach EbM-Kriterien evaluiert? Bewertung aus sozialmedizinischer Sicht (MDK Medizinischer Dienst der Krankenkassen). Lahr (Schwarzwald): MDK Baden-Württemberg; 2002.

Ontario Health Technology Advisory Committee (OHTAC). Vacuum assisted closure therapy for wound care. Toronto, Ontario, Canada: Ontario Ministry of Health and Long-Term Care (MOHLTC); 2004. http://www.health.gov.on.ca/english/providers/program/mas/reviews/docs/vac_1204.pdf (Access on 27 September 2005).

Pham C, Middleton P, Maddern G. Vacuum-assisted closure for the management of wounds: an accelerated systematic review. Adelaide, Australia: Australian safety and efficacy register of new interventional procedures - surgical (ASERNIP-S); 2003. http://www.surgeons.org/asernip-s/publications_vacuum.htm (Access on 27 September 2005).

Samson DJ, Lefevre F, Aronson N. Wound healing technologives: low-level laser and vacuum-assisted closure. Rockville, MD, USA: Agency for Healthcare Research and Quality (AHRQ); 2004. http://www.ahrq.gov/clinic/epcsums/woundsum.htm (Access on 27 September 2005).

Appendix A3 List of the studies provided in the written statements

Publication	Classification
Armstrong DG, Lavery LA, Frykberg RG, Andros G, Attinger CE, Boulten AJM. VAC therapy appears to heal complex DFU. Presented at the 2nd World Union of Wound Healing Societies Meeting 2004 (July 8-13), Paris, France. 2004; Abstract H013.	Abstract
Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care. 1998; 21: 855-859.	Other theme
Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet. 2005; 366: 1704-1710.	RCT; considered in the evaluation
Augustin M, Zschocke I. Nutzenbewertung der ambulanten und stationären VAC-Therapie - aktuelle Studiendaten mit Patients-relevanten Endpunkten. Kongress der European Wound Management Association (EWMA), der European Tissue Repair Society (ETRS) und der Deutschen Gesellschaft für Wundheilung und Wundbehandlung e V (DGfW) vom 15 bis 17 September 2005 in Stuttgart. 2005; Abstract.	Abstract
Augustin M, Zschocke I. Nutzenbewertung der ambulanten und stationären VAC-Therapie aus Patientssicht - MultizenterStudy mit Patients-relevanten Endpunkten. Münchener Medizinische Weeksschrift. 2006; (im Press).	Case series and other non-comparative study
Barringer CB, Gorse SJ, Burge TS. The VAC dressing--a cautionary tale. Br J Plast Surg. 2004; 57: 482	Letter to the editor
Chantelau E. Becaplermin. Arzneimittel-, Therapie-Kritik & Medizin und Umwelt. 2001; 33: 347-349.	Other theme
Demaria RG, Giovannini UM, Teot L, Frapier JM, Albat B. Topical negative pressure therapy. A very useful new method to treat severe infected vascular approaches in the groin. J Cardiovasc Surg (Torino). 2003; 44: 757-761.	Case report
Domkowski PW, Smith ML, Gonyon DL J, Drye C, Wooten MK, Levin LS, et al. Evaluation of vacuum-assisted closure in the treatment of poststernotomy mediastinitis. J Thorac Cardiovasc Surg. 2003; 126: 386-390.	Case series and other non-comparative study
Dosluoglu HH, Schimpf DK, Schultz R, Cherr GS. Preservation of infected and exposed vascular grafts using vacuum assisted closure without muscle flap coverage. J Vasc Surg. 2005; 42: 989-992.	Case report
Fleck T, Moidl R, Giovanoli P, Wolner E, Grabenwoger M. Frühzeitiger Einsatz des V.A.C.-Systems bei sternalen Wundinfektionen verhindert die Ausbreitung der Infektion auf das Mediastinum und reduziert die Notwendigkeit plastisch chirurgischer Eingriffe. Zentralbl Chir. 2004; 129: S35-S37.	Case series and other non-comparative study

Publication	Classification
Fuchs U, Zittermann A, Stuettgen B, Groening A, Minami K, Koerfer R. Clinical outcome of patients with deep sternal wound infection managed by vacuum-assisted closure compared to conventional therapy with open packing: a retrospective analysis. Ann Thorac Surg. 2005; 79: 526-531.	Retrospective comparative cohort study. However, non-concurrent comparison
Gustafsson R, Johnsson P, Algotsson L, Blomquist S, Ingemansson R. Vacuum-assisted closure therapy guided by C-reactive protein level in patients with deep sternal wound infection. J Thorac Cardiovasc Surg. 2002; 123: 895-900.	Case series and other non-comparative study
Heinze J. Spart Kosten und Zeit: die V.A.C. Therapie. Ambulante Chirurgie. 2003; 7: 36.	Expression of opinion
Karl T. Ergebnisse der V.A.C.-Therapie in der Gefäßchirurgie. Vasomed. 2004; 16: 172-176.	Case series and other non-comparative study
Katz IA, Harlan A, Miranda-Palma B, Prieto-Sanchez L, Armstrong DG, Bowker JH, et al. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care. 2005; 28: 555-559.	Other theme
Lee SS, Lin SD, Chen HM, Lin TM, Yang CC, Lai CS, et al. Management of intractable sternal wound infections with topical negative pressure dressing. J Card Surg. 2005; 20: 218-222.	Case series and other non-comparative study
Luckraz H, Murphy F, Bryant S, Charman SC, Ritchie AJ. Vacuum-assisted closure as a treatment modality for infections after cardiac surgery. J Thorac Cardiovasc Surg. 2003; 125: 301-305.	Case series and other non-comparative study
Maiwald G, Horster S, Baumeister RGH. Infektkonditionierung der chronischen Sternumosteomyelitis durch Vakuumversiegelung nach kardiochirurgischem Primäreingriff. ZfW. 2000; 5: 34-37.	Case series and other non-comparative study
Miller PR, Thompson JT, Faler BJ, Meredith JW, Chang MC. Late fascial closure in lieu of ventral hernia: the next step in open abdomen management. J Trauma. 2002; 53: 843-849.	Case series and other non-comparative study
Morbach S, Müller E, Reike H, Risse A, Sprau M. Evidenzbasierte Leitlinien - Diagnostik, Therapie, VerlaufsControl und Prävention des diabetischen Fußsyndroms. Diabetes und Stoffwechsel. 2004; 13: 9-30.	Guideline
Moues CM, van den Bemd GJ, Meerding WJ, Hovius SE. An economic evaluation of the use of TNP on full-thickness wounds. J Wound Care. 2005; 14: 224-227.	RCT; considered in the evaluation
Neubauer G, Ujlaky R. The cost-effectiveness of topical negative pressure versus other wound-healing therapies. J Wound Care. 2003; 12: 392-393.	Health economic study
Neubauer G. Die V.A.C.(R)-Therapie: Eine gesundheitsoekonomische Perspektive. Zentralbl Chir. 2004; 129: S122-S124.	Health economic study

Publication	**Classification**
Nord D, Pfänder J. Die V.A.C.-Therapie unter gesundheitsökonomischen Aspekten: Ersparnis von Geld und Leid. Pflegezeitschrift. 2003; 434-437.	Health economic study
Ontario Health Technology Advisory Committee (OHTAC). Vacuum assisted closure therapy for wound care. Toronto, Ontario, Canada: Ontario Ministry of Health and Long-Term Care (MOHLTC); 2004.	Systematic review; considered in the evaluation
Pinocy J, Albes JM, Wicke C, Ruck P, Ziemer G. Treatment of periprosthetic soft tissue infection of the groin following vascular surgical procedures by means of a polyvinyl alcohol-vacuum sponge system. Wound Repair Regen. 2003; 11: 104-109.	Case series and other non-comparative study
Saxena V, Hwang CW, Huang S, Eichbaum Q, Ingber D, Orgill DP. Vacuum-assisted closure: microdeformations of wounds and cell proliferation. Plast Reconstr Surg. 2004; 114: 1086-1096.	Basic research
Schwien T, Gilbert J, Lang C. Pressure ulcer prevalence and the role of negative pressure wound therapy in home health quality outcomes. Ostomy Wound Manage. 2005; 51: 47-60.	Database study, unclear selection of comparator group
Seiberlich H. Wirtschaftlicher Einsatz und Überleitungsmanagement der V.A.C.-Therapie am Beispiel. Zentralbl Chir. 2004; 129: S125-S128.	Case report
Singer AJ, Clark RA. Cutaneous wound healing. N Engl J Med. 1999; 341: 738-746.	Non-systematic review
Sjogren J, Gustafsson R, Nilsson J, Malmsjo M, Ingemansson R. Clinical outcome after poststernotomy mediastinitis: vacuum-assisted closure versus conventional treatment. Ann Thorac Surg. 2005; 79: 2049-2055.	Retrospective comparative cohort study. However, non-concurrent comparison
Sjogren J, Nilsson J, Gustafsson R, Malmsjo M, Ingemansson R. The impact of vacuum-assisted closure on long-term survival after post-sternotomy mediastinitis. Ann Thorac Surg. 2005; 80: 1270-1275.	Case series with comparator group of another indication
Song DH, Wu LC, Lohman RF, Gottlieb LJ, Franczyk M. Vacuum assisted closure for the treatment of sternal wounds: the bridge between debridement and definitive closure. Plast Reconstr Surg. 2003; 111: 92-97.	Retrospective comparative cohort study. However, non-concurrent comparison
V.A.C.® Therapy™ Clinical Guidelines: A reference source for clinicians. San Antonio, Texas, USA: Kinetic Concepts Inc; 2005.	Guideline
White RA, Miki RA, Kazmier P, Anglen JO. Vacuum-assisted closure complicated by erosion and hemorrhage of the anterior tibial artery. J Orthop Trauma. 2005; 19: 56-59.	Case report

Appendix B Search strategy

Ovid: MEDLINE

Import of 935 data sets on 04 May 2005

Import from the database "Ovid MEDLINE(R) In-Process, Other Non-Indexed Citations, Ovid MEDLINE(R)"

Number of query	Search term	Number of hits
1	amputation$.ti,ab.	15692
2	exp AMPUTATION/	11041
3	exp AMPUTATION TRAUMATIC/	3002
4	burn$.ti,ab.	37302
5	exp BURNS/	32610
6	decubit$.ti,ab.	2770
7	deglov$.ti,ab.	407
8	diabet$.ti,ab.	194662
9	exp DIABETES MELLITUS/	173603
10	electric$ injur$.ti,ab.	717
11	frostbite$.ti,ab.	625
12	exp FROSTBITE/	1070
13	laceration$.ti,ab.	5106
14	exp LACERATIONS/	408
15	open-abdom$.ti,ab.	356
16	exp ABDOMINAL WALL/su	203
17	plastic-surg$.ti,ab.	7326
18	exp SURGERY, PLASTIC/	17669
19	reconstruct$-surg$.ti,ab.	6617
20	exp RECONSTRUCTIVE SURGICAL PROCEDURES/	22152
21	skin-graft$.ti,ab.	8604
22	skin-transplant$.ti,ab.	791
23	exp SKIN TRANSPLANTATION/	21679
24	surg$ flap.ti,ab.	100
25	exp SURGICAL FLAPS/	28273
26	thermal injur$.ti,ab.	2975
27	exp ELECTRIC INJURIES/	3436
28	ulcer$.ti,ab.	95421
29	ul#us$.ti,ab.	495
30	exp SKIN ULCER/	21221
31	exp SOFT TISSUE INFECTIONS/	806
32	exp ULCER/	5988
33	wound$.ti,ab.	67693
34	exp WOUND INFECTION/	26134
35	exp WOUND HEALING/	47539
36	wound dehiscence.ti,ab.	1001
37	exp SURGICAL WOUND DEHISCENCE/	4053
38	"mini-v.a.c.$".ti,ab.	5
39	negative-pressur$.ti,ab.	3118
40	subatmospheric-pressur$.ti,ab.	158
41	sub-atmospheric-pressur$.ti,ab.	11
42	$suction$.ti,ab.	9080
43	exp SUCTION/	7337
44	vacuum$.ti,ab.	8839
45	exp VACUUM/	1628
46	(clin$ adj25 trial$).ti,ab.	111711
47	clinical trial.pt.	401452
48	exp CLINICAL TRIALS/	163241
49	(control$ or prospectiv$ or volunteer$).ti,ab.	1556758
50	controlled clinical trial.pt.	67924
51	COMPARATIVE STUDY.sh.	1178074
52	DOUBLE BLIND METHOD.sh.	80840
53	exp EVALUATION STUDIES/	513600
54	FOLLOW-UP STUDIES.sh.	296994
55	(metaanaly$ or (meta and analy$) or ((review or search$) and (medical database$ or medline or pubmed or	37873

	embase or cochrane or systemat$))).ti,ab.	
56	placebo$.ti,ab.	89686
57	PLACEBOS.sh.	23536
58	PROSPECTIVE STUDIES.sh.	184783
59	random$.ti,ab.	316804
60	randomized controlled trial.pt.	198976
61	RANDOM ALLOCATION.sh.	52769
62	RANDOMIZED CONTROLLED TRIALS.sh.	36396
63	RESEARCH DESIGN.sh.	40093
64	SINGLE BLIND METHOD.sh.	8786
65	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	81639
66	or/1-37	571359
67	or/38-45	25588
68	or/46-65	3328964
69	and/66-68	935

Import of a further 203 data sets on 20 May 2005.

Import after modification of the search strategy and removal of the hits according to the strategy of 04 May 2005 from the database "Ovid MEDLINE(R) In-Process, Other Non-Indexed Citations, Ovid MEDLINE(R)". Total number of the imports: 935 + 203 = 1138

Number of query	Search term	Numbr of hits
1	amputation$.ti,ab.	15750
2	exp AMPUTATION/	11070
3	exp AMPUTATION TRAUMATIC/	3004
4	burn$.ti,ab.	37475
5	exp BURNS/	32698
6	decubit$.ti,ab.	2790
7	deglov$.ti,ab.	407
8	diabet$.ti,ab.	195579
9	exp DIABETES MELLITUS/	174368
10	electric$ injur$.ti,ab.	722
11	frostbite$.ti,ab.	628
12	exp FROSTBITE/	1073
13	laceration$.ti,ab.	5129
14	exp LACERATIONS/	412
15	open-abdom$.ti,ab.	362
16	exp ABDOMINAL WALL/su	207
17	plastic-surg$.ti,ab.	7343
18	exp SURGERY, PLASTIC/	17685
19	reconstruct$-surg$.ti,ab.	6650
20	exp RECONSTRUCTIVE SURGICAL PROCEDURES/	22293
21	skin-graft$.ti,ab.	8639
22	skin-transplant$.ti,ab.	795
23	exp SKIN TRANSPLANTATION/	21728
24	surg$ flap.ti,ab.	100
25	exp SURGICAL FLAPS/	28362
26	thermal injur$.ti,ab.	2981
27	exp ELECTRIC INJURIES/	3450
28	ulcer$.ti,ab.	95747
29	ul#us$.ti,ab.	496
30	exp SKIN ULCER/	21327
31	exp SOFT TISSUE INFECTIONS/	813
32	exp ULCER/	5999
33	wound$.ti,ab.	68021
34	exp WOUND INFECTION/	26188
35	exp WOUND HEALING/	47684
36	wound dehiscence.ti,ab.	1007
37	exp SURGICAL WOUND DEHISCENCE/	4063
38	"mini-v.a.c.$".ti,ab.	5
39	negative-pressur$.ti,ab.	3132
40	subatmospheric-pressur$.ti,ab.	158
41	sub-atmospheric-pressur$.ti,ab.	11
42	$suction$.ti,ab.	9107
43	exp SUCTION/	7358
44	vacuum$.ti,ab.	8877
45	exp VACUUM/	1634
46	(clin$ adj25 trial$).ti,ab.	112328
47	clinical trial.pt.	403160
48	exp CLINICAL TRIALS/	163958
49	(control$ or prospectiv$ or volunteer$).ti,ab.	1563369
50	controlled clinical trial.pt.	68096
51	COMPARATIVE STUDY.sh.	1183307
52	DOUBLE-BLIND METHOD.sh.	81093
53	exp EVALUATION STUDIES/	515789
54	FOLLOW-UP STUDIES.sh.	297997
55	(metaanaly$ or (meta and analy$) or ((review or search$) and (medical database$ or medline or pubmed or embase or cochrane or systemat$))).ti,ab.	38174
56	placebo$.ti,ab.	90017
57	PLACEBOS.sh.	23589

58	PROSPECTIVE STUDIES.sh.	185758
59	random$.ti,ab.	318430
60	randomized controlled trial.pt.	199782
61	RANDOM ALLOCATION.sh.	52877
62	RANDOMIZED CONTROLLED TRIALS.sh.	36685
63	RESEARCH DESIGN.sh.	40283
64	SINGLE BLIND METHOD.sh.	8839
65	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	81891
66	or/1-37	573546
67	or/38-45	25676
68	or/46-65	3342964
69	and/66-68	940
70	amputation$.ti,ab.	15750
71	exp AMPUTATION/	11070
72	exp AMPUTATION TRAUMATIC/	3004
73	burn$.ti,ab.	37475
74	exp BURNS/	32698
75	decubit$.ti,ab.	2790
76	deglov$.ti,ab.	407
77	diabet$.ti,ab.	195579
78	exp DIABETES MELLITUS/	174368
79	electric$ injur$.ti,ab.	722
80	frostbite$.ti,ab.	628
81	exp FROSTBITE/	1073
82	laceration$.ti,ab.	5129
83	exp LACERATIONS/	412
84	open-abdom$.ti,ab.	362
85	exp ABDOMINAL WALL/su	207
86	plastic-surg$.ti,ab.	7343
87	exp SURGERY, PLASTIC/	17685
88	reconstruct$-surg$.ti,ab.	6650
89	exp RECONSTRUCTIVE SURGICAL PROCEDURES/	22293
90	skin-graft$.ti,ab.	8639
91	skin-transplant$.ti,ab.	795
92	exp SKIN TRANSPLANTATION/	21728
93	surg$ flap.ti,ab.	100
94	exp SURGICAL FLAPS/	28362
95	thermal injur$.ti,ab.	2981
96	exp ELECTRIC INJURIES/	3450
97	ulcer$.ti,ab.	95747
98	ul#us$.ti,ab.	496
99	exp SKIN ULCER/	21327
100	exp SOFT TISSUE INFECTIONS/	813
101	exp ULCER/	5999
102	wound$.ti,ab.	68021
103	exp WOUND INFECTION/	26188
104	exp WOUND HEALING/	47684
105	wound dehiscence.ti,ab.	1007
106	exp SURGICAL WOUND DEHISCENCE/	4063
107	"mini-v.a.c.$".ti,ab.	5
108	negative-pressur$.ti,ab.	3132
109	subatmospheric-pressur$.ti,ab.	158
110	sub-atmospheric-pressur$.ti,ab.	11
111	$suction$.ti,ab.	9107
112	exp SUCTION/	7358
113	vacuum$.ti,ab.	8877
114	exp VACUUM/	1634
115	exp CASE-CONTROL STUDIES/	279512
116	(clin$ adj25 trial$).ti,ab.	112328
117	clinical trial.pt.	403160
118	exp CLINICAL TRIALS/	163958
119	exp COHORT STUDIES/	524871
120	(compare or compared or versus).ti,ab.	1324296
121	(control$ or prospectiv$ or volunteer$).ti,ab.	1563369
122	controlled clinical trial.pt.	68096
123	exp CONTROL GROUPS/	652
124	(compare or compared or versus).ti,ab.	1324296
125	exp COMPARATIVE STUDY/	1183307
126	exp DOUBLE-BLIND METHOD/	81093

127	evaluation Studies.pt.	53483
128	exp FOLLOW-UP STUDIES/	297997
129	(metaanaly$ or (meta and analy$) or ((review or search$) and (medical database$ or medline or pubmed or embase or cochrane or systemat$))).ti,ab.	38174
130	exp META-ANALYSIS/	5904
131	placebo$.ti,ab.	90017
132	exp PLACEBOS/	23589
133	exp PROSPECTIVE STUDIES/	185758
134	random$.ti,ab.	318430
135	randomized controlled trial.pt.	199782
136	exp RANDOM ALLOCATION/	52877
137	exp RANDOMIZED CONTROLLED TRIALS/	36685
138	exp RESEARCH DESIGN/	189913
139	exp SINGLE BLIND METHOD/	8839
140	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	81891
141	or/70-106	573546
142	or/107-114	25676
143	or/115-140	3839983
144	and/141-143	1120
145	144 not 69	203

Ovid: EMBASE

Import of 653 data sets on 04 May 2005

Import from database " Ovid EMBASE <1980 to 2005 Week 21>"

Number of query	Search term	Number of hits
1	amputation$.ti,ab.	11608
2	exp AMPUTATION/	10351
3	burn$.ti,ab.	27807
4	exp BURN/	18220
5	decubit$.ti,ab.	1903
6	deglov$.ti,ab.	353
7	exp DIABETES MELLITUS/	160625
8	diabet$.ti,ab.	155325
9	electric$ injur$.ti,ab.	532
10	exp ELECTRIC INJURY/	3845
11	frostbite$.ti,ab.	349
12	laceration.ti,ab.	2340
13	exp LACERATION/	1842
14	open-abdom$.ti,ab.	277
15	exp ABDOMINAL WALL CLOSURE/	307
16	plastic-surg$.ti,ab.	5525
17	exp PLASTIC SURGERY/	72266
18	reconstruct$ surg$.ti,ab.	5098
19	skin injur$.ti,ab.	464
20	exp SKIN INJURY/	19012
21	skin-graft$.ti,ab.	6951
22	skin-transplant$.ti,ab.	442
23	exp SKIN TRANSPLANTATION/	17292
24	surg$ flap$.ti,ab.	104
25	thermal$ injur$.ti,ab.	2541
26	exp THERMAL INJURY/	32593
27	ulcer$.ti,ab.	67862
28	ul#us$.ti,ab.	376
29	exp SKIN ULCER/	13404
30	exp SOFT TISSUE INFECTION/	2244
31	wound$.ti,ab.	48126
32	wound dehiscence.ti,ab.	768
33	exp WOUND/	47647
34	exp WOUND CARE/	16500
35	"mini-v.a.c.$".ti,ab.	6
36	negative-pressur$.ti,ab.	2446
37	subatmospheric-pressur$.ti,ab.	130
38	sub-atmospheric-pressur$.ti,ab.	12
39	$suction$.ti,ab.	7175
40	exp SUCTION/	1241
41	vacuum$.ti,ab.	6774
42	exp VACUUM/	1392
43	(clin$ adj25 trial$).ti,ab.	101788
44	clinical trial.pt.	0
45	exp CLINICAL TRIAL/	342223
46	COMPARATIVE STUDY.sh.	60481
47	controlled clinical trial.pt.	0
48	(control$ or prospectiv$ or volunteer$).ti,ab.	1310293
49	DOUBLE-BLIND PROCEDURE.sh.	55376
50	FOLLOW UP.sh.	155829
51	(metaanaly$ or (meta and analy$) or ((review or search$) and (medical database$ or medline or pubmed or embase or cochrane or systemat$))).ti,ab.	31279
52	placebo$.ti,ab.	84942
53	PLACEBO.sh.	76539
54	PROSPECTIVE STUDY.sh.	46117
55	random$.ti,ab.	273023
56	RANDOMIZATION.sh.	14598
57	randomized controlled trial.pt.	0
58	RANDOMIZED CONTROLLED TRIAL.sh.	94193

59	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	77298
60	SINGLE-BLIND PROCEDURE.sh.	5252
61	or/1-34	476333
62	or/35-42	16573
63	or/43-60	1861753
64	and/61-63	653

Import of a further 289 data sets on 20 May 2005.

Import after modification of the search strategy and subtraction of the hits according to the strategy of 04 May 2005 from the database "Ovid EMBASE <1980 to 2005 Week 21>". Total number of imports: 653 + 289 = 942.

Number of query	Search term	Number of hits
1	amputation$.ti,ab.	11657
2	exp AMPUTATION/	10411
3	burn$.ti,ab.	27897
4	exp BURN/	18266
5	decubit$.ti,ab.	1907
6	deglov$.ti,ab.	354
7	exp DIABETES MELLITUS/	161608
8	diabet$.ti,ab.	156097
9	electric$ injur$.ti,ab.	537
10	exp ELECTRIC INJURY/	3868
11	frostbite$.ti,ab.	349
12	laceration.ti,ab.	2349
13	exp LACERATION/	1858
14	open-abdom$.ti,ab.	282
15	exp ABDOMINAL WALL CLOSURE/	313
16	plastic-surg$.ti,ab.	5542
17	exp PLASTIC SURGERY/	72574
18	reconstruct$ surg$.ti,ab.	5116
19	skin injur$.ti,ab.	468
20	exp SKIN INJURY/	19139
21	skin-graft$.ti,ab.	6970
22	skin-transplant$.ti,ab.	444
23	exp SKIN TRANSPLANTATION/	17351
24	surg$ flap$.ti,ab.	104
25	thermal$ injur$.ti,ab.	2547
26	exp THERMAL INJURY/	32715
27	ulcer$.ti,ab.	68066
28	ul#us$.ti,ab.	380
29	exp SKIN ULCER/	13474
30	exp SOFT TISSUE INFECTION/	2260
31	wound$.ti,ab.	48314
32	wound dehiscence.ti,ab.	773
33	exp WOUND/	47889
34	exp WOUND CARE/	16606
35	"mini-v.a.c.$".ti,ab.	6
36	negative-pressur$.ti,ab.	2458
37	subatmospheric-pressur$.ti,ab.	131
38	sub-atmospheric-pressur$.ti,ab.	12
39	$suction$.ti,ab.	7200
40	exp SUCTION/	1249
41	vacuum$.ti,ab.	6803
42	exp VACUUM/	1408
43	(clin$ adj25 trial$).ti,ab.	102453
44	clinical trial.pt.	0
45	exp CLINICAL TRIAL/	344667
46	COMPARATIVE STUDY.sh.	61331
47	controlled clinical trial.pt.	0
48	(control$ or prospectiv$ or volunteer$).ti,ab.	1315980
49	DOUBLE-BLIND PROCEDURE.sh.	55639
50	FOLLOW UP.sh.	157442
51	(metaanaly$ or (meta and analy$) or ((review or search$) and (medical database$ or medline or pubmed or embase or cochrane or systemat$))).ti,ab.	31636
52	placebo$.ti,ab.	85320
53	PLACEBO.sh.	77126
54	PROSPECTIVE STUDY.sh.	46687
55	random$.ti,ab.	274633
56	RANDOMIZATION.sh.	14832
57	randomized controlled trial.pt.	0
58	RANDOMIZED CONTROLLED TRIAL.sh.	94853
59	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	77603

60	SINGLE-BLIND PROCEDURE.sh.	5292
61	or/1-34	478565
62	or/35-42	16641
63	or/43-60	1871378
64	and/61-63	660
65	amputation$.ti,ab.	11657
66	exp AMPUTATION/	10411
67	burn$.ti,ab.	27897
68	exp BURN/	18266
69	decubit$.ti,ab.	1907
70	deglov$.ti,ab.	354
71	exp DIABETES MELLITUS/	161608
72	diabet$.ti,ab.	156097
73	electric$ injur$.ti,ab.	537
74	exp ELECTRIC INJURY/	3868
75	frostbite$.ti,ab.	349
76	laceration.ti,ab.	2349
77	exp LACERATION/	1858
78	open-abdom$.ti,ab.	282
79	exp ABDOMINAL WALL CLOSURE/	313
80	plastic-surg$.ti,ab.	5542
81	exp PLASTIC SURGERY/	72574
82	reconstruct$ surg$.ti,ab.	5116
83	skin injur$.ti,ab.	468
84	exp SKIN INJURY/	19139
85	skin-graft$.ti,ab.	6970
86	skin-transplant$.ti,ab.	444
87	exp SKIN TRANSPLANTATION/	17351
88	surg$ flap$.ti,ab.	104
89	thermal$ injur$.ti,ab.	2547
90	exp THERMAL INJURY/	32715
91	ulcer$.ti,ab.	68066
92	ul#us$.ti,ab.	380
93	exp SKIN ULCER/	13474
94	exp SOFT TISSUE INFECTION/	2260
95	wound$.ti,ab.	48314
96	wound dehiscence.ti,ab.	773
97	exp WOUND/	47889
98	exp WOUND CARE/	16606
99	"mini-v.a.c.$".ti,ab.	6
100	negative-pressur$.ti,ab.	2458
101	subatmospheric-pressur$.ti,ab.	131
102	sub-atmospheric-pressur$.ti,ab.	12
103	$suction$.ti,ab.	7200
104	exp SUCTION/	1249
105	vacuum$.ti,ab.	6803
106	exp VACUUM/	1408
107	exp CASE CONTROL STUDY/	11578
108	(clin$ adj25 trial$).ti,ab.	102453
109	clinical trial.ti,ab.	29395
110	exp CLINICAL TRIAL/	344667
111	exp COHORT ANALYSIS/	26183
112	(compare or compared or versus).ti,ab.	1144596
113	exp COMPARATIVE STUDY/	214053
114	controlled clinical trial.ti,ab.	3637
115	(control$ or prospectiv$ or volunteer$).ti,ab.	1315980
116	exp CONTROLLED STUDY/	1959306
117	exp CONTROL GROUP/	217
118	exp DOUBLE BLIND PROCEDURE/	55639
119	evaluation stud$.ti,ab.	2038
120	exp FOLLOW UP/	157442
121	exp INTERMETHOD COMPARISON/	69379
122	(metaanaly$ or (meta and analy$) or ((review or search$) and (medical database$ or medline or pubmed or embase or cochrane or systemat$))).ti,ab.	31636
123	exp META ANALYSIS/	21463
124	placebo$.ti,ab.	85320
125	PLACEBO.sh.	77126
126	exp PROSPECTIVE STUDY/	46687
127	random$.ti,ab.	274633

128	exp RANDOMIZATION/	14832
129	randomi?ed controlled trial.ti,ab.	10742
130	exp RANDOMIZED CONTROLLED TRIAL/	94853
131	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	77603
132	exp SINGLE BLIND PROCEDURE/	5292
133	exp "SYSTEMATIC REVIEW"/	4484
134	or/65-98	478565
135	or/99-106	16641
136	or/107-133	3542604
137	and/134-136	949
138	137 not 64	289

Ovid: CINAHL

Import of 101 data sets on 04 May 2005

Import from the database "Ovid CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to May Week 2 2005>"

Number of query	Search term	Number of hits
1	amputation$.ti,ab.	1521
2	exp AMPUTATION/	1460
3	exp AMPUTATION TRAUMATIC/	165
4	burn$.ti,ab.	6025
5	exp BURNS/	4741
6	decubit$.ti,ab.	248
7	deglov$.ti,ab.	17
8	diabet$.ti,ab.	17259
9	exp DIABETES MELLITUS/	17609
10	electric$ injur$.ti,ab.	82
11	frostbite$.ti,ab.	57
12	exp FROSTBITE/	115
13	laceration$.ti,ab.	467
14	exp "TEARS AND LACERATIONS"/	579
15	open-abdom$.ti,ab.	30
16	abdominal wall.ti,ab.	121
17	plastic-surg$.ti,ab.	331
18	exp SURGERY, PLASTIC/	1492
19	reconstruct$-surg$.ti,ab.	261
20	exp SURGERY RECONSTRUCTIVE/	1200
21	skin-graft$.ti,ab.	301
22	skin-transplant$.ti,ab.	10
23	exp SKIN TRANSPLANTATION/	695
24	surg$ flap.ti,ab.	6
25	exp SURGICAL FLAPS/	586
26	thermal injur$.ti,ab.	187
27	exp ELECTRIC INJURIES/	375
28	ulcer$.ti,ab.	5674
29	ul#us$.ti,ab.	4
30	exp SKIN ULCER/	7408
31	exp SOFT TISSUE INFECTIONS/	80
32	exp ULCER/	288
33	wound$.ti,ab.	8004
34	exp WOUND INFECTION/	2257
35	exp WOUND HEALING/	4137
36	wound dehiscence.ti,ab.	37
37	exp SURGICAL WOUND DEHISCENCE/	126
38	exp "WOUNDS AND INJURIES"/	50994
39	"mini-v.a.c.$".ti,ab.	2
40	negative-pressur$.ti,ab.	241
41	subatmospheric-pressur$.ti,ab.	10
42	sub-atmospheric-pressur$.ti,ab.	1
43	$suction$.ti,ab.	715
44	exp SUCTION/	909
45	vacuum$.ti,ab.	409
46	exp VACUUM/	24
47	(clin$ adj25 trial$).ti,ab.	9451
48	clinical trial.pt.	13420
49	exp CLINICAL TRIALS/	29986
50	(control$ or prospectiv$ or volunteer$).ti,ab.	75787
51	controlled clinical trial.pt.	0
52	COMPARATIVE STUDIES.sh.	27812
53	DOUBLE-BLIND STUDIES.sh.	6079
54	exp EVALUATION RESEARCH/	7995
55	(metaanaly$ or (meta and analy$) or ((review or search$) and (medical database$ or medline or pubmed or embase or cochrane or systemat$))).ti,ab.	8347
56	placebo$.ti,ab.	5872

57	PLACEBOS.sh.	2678
58	PROSPECTIVE STUDIES.sh.	37359
59	random$.ti,ab.	29206
60	randomized controlled trial.pt.	0
61	RANDOM ASSIGNMENT.sh.	9587
62	RANDOMIZED CONTROLLED TRIALS.sh.	0
63	STUDY DESIGN.sh.	1573
64	SINGLE-BLIND STUDIES.sh.	1513
65	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	4338
66	or/1-38	89833
67	or/39-46	1719
68	or/47-65	151480
69	and/66-68	101

Import of a further 289 data sets on 20 May 2005.

Import after modification of the search strategy and subtraction of the hits according to the strategy of 04 May 2005 from the database "Ovid CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to May Week 2 2005>". Total number of imports: 101 + 28 = 129.

Number of query	Search term	Number of hits
1	amputation$.ti,ab.	1533
2	exp AMPUTATION/	1470
3	exp AMPUTATION TRAUMATIC/	166
4	burn$.ti,ab.	6072
5	exp BURNS/	4767
6	decubit$.ti,ab.	249
7	deglov$.ti,ab.	17
8	diabet$.ti,ab.	17514
9	exp DIABETES MELLITUS/	17841
10	electric$ injur$.ti,ab.	82
11	frostbite$.ti,ab.	58
12	exp FROSTBITE/	117
13	laceration$.ti,ab.	473
14	exp "TEARS AND LACERATIONS"/	591
15	open-abdom$.ti,ab.	30
16	abdominal wall.ti,ab.	122
17	plastic-surg$.ti,ab.	335
18	exp SURGERY, PLASTIC/	1498
19	reconstruct$-surg$.ti,ab.	261
20	exp SURGERY RECONSTRUCTIVE/	1204
21	skin-graft$.ti,ab.	303
22	skin-transplant$.ti,ab.	10
23	exp SKIN TRANSPLANTATION/	697
24	surg$ flap.ti,ab.	6
25	exp SURGICAL FLAPS/	589
26	thermal injur$.ti,ab.	188
27	exp ELECTRIC INJURIES/	375
28	ulcer$.ti,ab.	5716
29	ul#us$.ti,ab.	4
30	exp SKIN ULCER/	7463
31	exp SOFT TISSUE INFECTIONS/	83
32	exp ULCER/	290
33	wound$.ti,ab.	8053
34	exp WOUND INFECTION/	2275
35	exp WOUND HEALING/	4164
36	wound dehiscence.ti,ab.	37
37	exp SURGICAL WOUND DEHISCENCE/	126
38	exp "WOUNDS AND INJURIES"/	51468
39	"mini-v.a.c.$".ti,ab.	2
40	negative-pressur$.ti,ab.	241
41	subatmospheric-pressur$.ti,ab.	10
42	sub-atmospheric-pressur$.ti,ab.	1
43	$suction$.ti,ab.	723
44	exp SUCTION/	917
45	vacuum$.ti,ab.	413
46	exp VACUUM/	25
47	(clin$ adj25 trial$).ti,ab.	9644
48	clinical trial.pt.	13707
49	exp CLINICAL TRIALS/	30458
50	(control$ or prospectiv$ or volunteer$).ti,ab.	76913
51	controlled clinical trial.pt.	0
52	COMPARATIVE STUDIES.sh.	28268
53	DOUBLE-BLIND STUDIES.sh.	6180
54	exp EVALUATION RESEARCH/	8072
55	(metaanaly$ or (meta and analy$) or ((review or search$) and (medical database$ or medline or pubmed or embase or cochrane or systemat$))).ti,ab.	8488
56	placebo$.ti,ab.	5987
57	PLACEBOS.sh.	2706

58	PROSPECTIVE STUDIES.sh.	38036
59	random$.ti,ab.	29711
60	randomized controlled trial.pt.	0
61	RANDOM ASSIGNMENT.sh.	9823
62	RANDOMIZED CONTROLLED TRIALS.sh.	0
63	STUDY DESIGN.sh.	1601
64	SINGLE-BLIND STUDIES.sh.	1546
65	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	4438
66	or/1-38	90736
67	or/39-46	1735
68	or/47-65	153682
69	and/66-68	102
70	amputation$.ti,ab.	1533
71	exp AMPUTATION/	1470
72	exp AMPUTATION TRAUMATIC/	166
73	burn$.ti,ab.	6072
74	exp BURNS/	4767
75	decubit$.ti,ab.	249
76	deglov$.ti,ab.	17
77	diabet$.ti,ab.	17514
78	exp DIABETES MELLITUS/	17841
79	electric$ injur$.ti,ab.	82
80	frostbite$.ti,ab.	58
81	exp FROSTBITE/	117
82	laceration$.ti,ab.	473
83	exp "TEARS AND LACERATIONS"/	591
84	open-abdom$.ti,ab.	30
85	abdominal wall.ti,ab.	122
86	plastic-surg$.ti,ab.	335
87	exp SURGERY, PLASTIC/	1498
88	reconstruct$-surg$.ti,ab.	261
89	exp SURGERY RECONSTRUCTIVE/	1204
90	skin-graft$.ti,ab.	303
91	skin-transplant$.ti,ab.	10
92	exp SKIN TRANSPLANTATION/	697
93	surg$ flap.ti,ab.	6
94	exp SURGICAL FLAPS/	589
95	thermal injur$.ti,ab.	188
96	exp ELECTRIC INJURIES/	375
97	ulcer$.ti,ab.	5716
98	ul#us$.ti,ab.	4
99	exp SKIN ULCER/	7463
100	exp SOFT TISSUE INFECTIONS/	83
101	exp ULCER/	290
102	wound$.ti,ab.	8053
103	exp WOUND INFECTION/	2275
104	exp WOUND HEALING/	4164
105	wound dehiscence.ti,ab.	37
106	exp SURGICAL WOUND DEHISCENCE/	126
107	exp "WOUNDS AND INJURIES"/	51468
108	"mini-v.a.c.$".ti,ab.	2
109	negative-pressur$.ti,ab.	241
110	subatmospheric-pressur$.ti,ab.	10
111	sub-atmospheric-pressur$.ti,ab.	1
112	$suction$.ti,ab.	723
113	exp SUCTION/	917
114	vacuum$.ti,ab.	413
115	exp VACUUM/	25
116	(clin$ adj25 trial$).ti,ab.	9644
117	clinical trial.pt.	13707
118	exp CLINICAL TRIALS/	30458
119	(compare or compared or versus).ti,ab.	53645
120	exp COMPARATIVE STUDIES/	28268
121	(control$ or prospectiv$ or volunteer$).ti,ab.	76913
122	controlled clinical trial.ti,ab.	383
123	exp DOUBLE-BLIND STUDIES/	6180
124	exp EVALUATION RESEARCH/	8072
125	(metaanaly$ or (meta and analy$) or ((review or search$) and (medical database$ or medline or pubmed or embase or cochrane or systemat$))).ti,ab.	8488

126	placebo$.ti,ab.	5987
127	exp PLACEBOS/	2706
128	exp PROSPECTIVE STUDIES/	38154
129	random$.ti,ab.	29711
130	randomized controlled trial.ti,ab.	2215
131	exp RANDOM ASSIGNMENT/	9823
132	exp RANDOMIZED CONTROLLED TRIALS/	30458
133	exp STUDY DESIGN/	137887
134	exp SINGLE-BLIND STUDIES/	1546
135	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	4438
136	or/70-107	90736
137	or/108-115	1735
138	or/116-135	215081
139	and/136-138	130
140	139 not 69	28

Wiley Interscience: The Cochrane Library

Overview of the imports of 303 data sets from the individual data bases on 20 May 2005

Databases of the "The Cochrane Library"	Number of hits
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	[10]
Database of Abstracts of Reviews of Effects (DARE)	[1]
The Cochrane Central Register of Controlled Trials (CENTRAL)	[284]
Health Technology Assessment Database (HTA)	[8]

Import of 303 data sets (of a total of 311 hits) on 20 May 2005

Number of query	Search term	Number of hits
#1	amputation* in Abstract or amputation* in Record Title	456
#2	MeSH descriptor Amputation explode all trees in MeSH products	205
#3	MeSH descriptor Amputation, Traumatic explode all trees in MeSH products	12
#4	burn* in Abstract or burn* in Record Title	1827
#5	MeSH descriptor Burns explode all trees in MeSH products	680
#6	decubit* in Abstract or decubit* in Record Title	209
#7	deglov* in Abstract or deglov* in Record Title	0
#8	diabet* in Abstract or diabet* in Record Title	10779
#9	MeSH descriptor Diabetes Mellitus explode all trees in MeSH products	6956
#10	electric* injur* in Abstract or electric* injur* in Record Title	109
#11	frostbite* in Abstract or frostbite* in Record Title	5
#12	MeSH descriptor Frostbite explode all trees in MeSH products	4
#13	laceration* in Abstract or laceration* in Record Title	246
#14	MeSH descriptor Lacerations explode all trees in MeSH products	28
#15	open* abdom* in Abstract or open* abdom* in Record Title	449
#16	MeSH descriptor Abdominal Wall explode all trees with qualifier: SU in MeSH products	4
#17	plastic* surg* in All Fields or plastic* surg* in Record Title	1033
#18	MeSH descriptor Surgery, Plastic explode all trees in MeSH products	81
#19	reconstruct* surg* in Abstract or reconstruct* surg* in Record Title	613
#20	MeSH descriptor Reconstructive Surgical Procedures explode all trees in MeSH products	623
#21	skin* graft* in Abstract or skin* graft* in Record Title	332
#22	skin* transplant* in Abstract or skin* transplant* in Record Title	100
#23	MeSH descriptor Skin Transplantation explode all trees in MeSH products	224
#24	surg* flap in Abstract or surg* flap in Record Title	519
#25	MeSH descriptor Surgical Flaps explode all trees in MeSH products	437
#26	thermal injur* in Abstract or thermal injur* in Record Title	140
#27	MeSH descriptor Electric Injuries explode all trees in MeSH products	10
#28	ulcer* in Abstract or ulcer* in Record Title	8609
#29	ul*us* in Abstract or ul*us* in Record Title	134
#30	MeSH descriptor Skin Ulcer explode all trees in MeSH products	1030
#31	MeSH descriptor Soft Tissue Infections explode all trees in MeSH products	28
#32	MeSH descriptor Ulcer explode all trees in MeSH products	84
#33	wound* in Abstract or wound* in Record Title	4804
#34	MeSH descriptor Wound Infection explode all trees in MeSH products	2139
#35	MeSH descriptor Wound Healing explode all trees in MeSH products	2054
#36	wound dehiscence in Abstract	156
#37	MeSH descriptor Surgical Wound Dehiscence explode all trees in MeSH products	192
#38	mini-v.a.c.* in Abstract or mini-v.a.c.* in Record Title	0
#39	negative pressur* in Abstract or negative pressur* in Record Title	1031
#40	negative*pressur* in Abstract or negative*pressur* in Record Title	13
#41	subatmospheric pressur* in Abstract or subatmospheric pressur* in Record Title	13
#42	sub-atmospheric pressur* in Abstract or sub-atmospheric pressur* in Record Title	2
#43	*suction* in Abstract or *suction* in Record Title	894
#44	MeSH descriptor Suction explode all trees in MeSH products	460
#45	vacuum* in Abstract or vacuum* in Record Title	426
#46	MeSH descriptor Vacuum explode all trees in MeSH products	45
#47	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR	30489

	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37)	
#48	(#38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46)	2486
#49	(#47 AND #48)	311

Information on the search technique of the supplier "Ovid"

Sign	Meaning
$	Wild card for 0, 1 or more than 1 sign ("unlimited truncation")
#	Wild card for 1 sign ("limited truncation")
?	Wild card for 0 or 1 sign ("optional wild card")
.ti,ab.	Limitation to the fields "Title" and "Abstract"
exp	Explosion to all other specified Subject Headings in the hierarchy of the subject heading index
/	Involvement of all subsidiary terms intended for restrictions to content
adj25	The two terms flanking this expression are adjacent with a maximal interval of 25 words
/su	Restriction to the content of a subject heading to the subsidiary term "surgery"
.pt.	Restriction to the field "publication type"
.sh.	Restriction to the field "subject heading"
Small letters "trial"	Free text in the sense of sign sequence
Capital letters "TRIAL"	Subject heading in the sense of a defined content

Appendix C References to unpublished randomised trials

Study KCI identification where applicable	Patients	Expected number of patients	Outcomes	According to abstract	Question to	Response from	Status November 2005
-[No authors listed] 2005* [43] KCI-ID: VAC 2001-02	Leg ulcers in venous insufficiency – Duration ≥ 30 days – Area < 100cm^2	214	Complete wound closure	Multi-centre	KCI	KCI: Study was not continued	Discontinued. Publication not known
Adams 2005* [61]	Wound after split-thickness skin removal	No information	Wound healing for donor site	Single centre UK	Adams	No	Completion Publication not known
Armstrong 2004 [44] KCI-ID: VAC 2001-08	Diabetic foot wounds – Wagner Stage ≥ 2 – Area ≥ 2cm^2	206	Complete wound closure within period of observation	Multicentre USA	Armstrong	Armstrong: Independent study, not yet complete	Running
Bayer 2004 [45] KCI-ID: VAC 2002-09	Poststernotomy wounds	116	Support of surgical wound closure	Multicentre USA	Orgill KCI	No KCI: Study was not continued	Discontinued. Publication not known
Foo 2004 [58]	Diabetic foot wounds	No information	Wound area (Surrogate)	Singapore	Foo	No	Unclear Publication not known
Fryer 2005* [62]	Pressure sores	120	Quantitative wound dimensions (Surrogate)	Single centre UK	Fryer	No	Unclear Publication not known

Appendix C References to unpublished randomised trials (continued)

Study KCI identification where applicable	Patients	Expected number of patients	Outcomes	According to abstract	Question to	Response from	Status November 2005
Greer 1999 [46] KCI, no ID	Pressure sores – Stage 3 or 4 – Area ≥ 2cm^2 and < 100cm^2	80	Quantitative wound dimensions (surrogate)	Multi-centre USA	Greer KCI	No KCI: Study not continued	Discontinued Publication not known
Gupta 2001 [60]	Chronic wounds	No information	Quantitative wound dimensions (surrogate)	USA	Gupta	No	Unclear Publication not known
Lantis 2004 [59]	Wounds covered with split-thickness skin	No information	Qualitative acceptance of split-thickness skin by recipient	Multi-centre USA	Lantis	No	Unclear Publication not known
McCarthy J 2005* [63]	Compartment syndrome with fasciotomy of the lower extremities	30	Wound healing	USA	McCarthy J	No	Running
McCarthy M 2005* [64]	Ischaemic wounds of the lower extremities	No information	Time till full growth of epithelium in wound	UK	McCarthy M	McCarthy M: Currently being performed. Interim results not available	Running
Molnar 2004 [48] KCI-ID VAC 2001-00	Burns on both hands Grade 2 to 3	50	Quantitative wound dimensions (surrogate)	Multi-centre USA	Molnar KCI	No KCI: Publication planned for 2005.	Running
Niezgoda 2004 [49] KCI-ID VAC 2001-01	Pressure sores – Torso and trochanter Regions – Stages 3 and 4	214	Complete wound closure	Multi-centre USA	Niezgoda KCI	No KCI: Publication planned for 2008	Running

Appendix C References to unpublished randomised trials (continued)

Study KCI identification where applicable	Patients	Expected number of patients	Outcomes	According to abstract	Question to	Response from	Status November 2005
Orgill 2004 [50] KCI-ID VAC 2002-10	Surgical or traumatic abdominal wounds	116	Support of closure of open abdominal wounds	Multi-centre USA	Orgill KCI	No KCI: Study not continued	Discontinued Publication not known
Stannard 2004 [52] KCI-ID VAC 2001-04	Haematoma formation after osteosynthetic operation	100	Number of haematoma needing surgical treatment	Single centre, USA	Stannard KCI	Stannard: Independent study, not completed. KCI: Publication planned for 2008	Running
Stannard 2004 [53] KCI-ID VAC 2001-05	Operation wounds after internal osteosynthesis of calcaneus, pilon, or tibia head fractures	300	Time needed for drainage	Single centre USA	Stannard KCI	Stannard: Independent study, not completed. KCI: Publication planned for 2008	Running
Stannard 2004 [54] KCI-ID VAC 2001-06	Severe open fractures with wounds of large area – Severity grade ≥ 2	300	Postoperative adverse events	Single centre USA	Stannard KCI	Stannard: Independent study, not completed KCI: Study not continued	Discontinued Publication not known
Vuerstaek 2004 [55] KCI-ID VAC VLU	Chronic leg ulcers	60	Time till complete wound healing	Single centre Netherlands	Vuerstaek KCI	No KCI: Publication planned for 2006	Completed Publication not known
Walker 2005* [65]	No information	48	Quantity of wound exudate	Single centre UK	Walker	No	Completed Publication not known

* When the year 2005 is given, this does not mean the year of publication as with other authors. This year means the year in which the information was accessed on the appropriate Internet page or - in 1 case - the year in which the information was communicated.
ID: Identification number. KCI: Kinetic Concepts, Inc.

Appendix C References to unpublished randomised trials (continued)

The publication of Ford 2002 [70] referred to a study which was being performed by another investigator (Orgill) in another hospital in the same city. This is the study Bayer 2004 in the table. This investigator did not respond to our enquiry. However, KCI informed us that the two studies managed by this investigator (Bayer 2004, Orgill 2004) had been discontinued.

Wu 2000 [20] presented a case series in his publication and mentioned a planned randomised trial. It has now been reported that this randomised trial has been completed and published as Mouës 2004 [24].

Appendix D Responses from authors

Buttenschön 2001 [67]

After treatment with or without NPWT, the 35 patients were sent a questionnaire. 29 completed forms were returned within a period of 6 to 14 months after the start of treatment. (Response letter 01 August 2005).

Question "Did complications occur in the time after operation?" Answer:

Group	Yes	No	Type of complication (multiple answers can be given)
NPWT	8	8	Inflammation of wound (1), Metal loosened (1), Pain (6), Restriction to movement (6), Swelling (1), Giddiness (1)
Control	2	13	Inflammation of wound (1), Metal loosened (1), Pain (2), Restriction to movement (1)

The results differences between groups. Complications were found in 8 (of 16) patients in the NPWT group and in 2 (of 15) patients in the control group. As regards the type of complication, the frequency of pain with 6 vs. 2 and of restriction to movement with 6 vs. 1 is noticeable.

Armstrong

We were informed by e-mail on 01 October 2005 that the manuscript with the study results of the completed study had been accepted for publication in the November 2005 edition of the Lancet: "Armstrong DG, Lavery LA. Negative Pressure Wound Therapy Heals Wounds Faster than Standard Wound Care Following Partial Diabetic Foot Amputation: Results from a Randomised Multicentre Clinical Trial. Lancet. 2005."

Deva

We were informed by e-mail on 18 August 2005 that the abstract of Heath 2002 [47] presented preliminary results from a study which was finally published by Moisidis 2004 [57]. We were also informed that a second study had been completed which would presumably be published in 2006 in the journal "Plastic and Reconstructive Surgery". Data on this study were not provided.

Stannard

We were informed by e-mail on 15 August 2005 that two independent studies were being performed and that publication was planned for 2008.

Appendix E Protocol of the scientific hearing

The (German-language) minutes of the scientific hearing can be found in the German final report under: http://www.iqwig.de/index.download.ccffd630f13aa9271cb98c283975b3db.pdf

Appendix F Statements

The statements submitted on the preliminary report can be found in the German final report under: http://www.iqwig.de/index.download.ccffd630f13aa9271cb98c283975b3db.pdf