PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Negative Pressure Wound Therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT
AUTHORS	Seidel, Dörthe; Storck, Martin; Lawall, Holger; Wozniak, Gernold; Mauckner, Peter; Hochlenert, Dirk; Wetzel-Roth, Walter; Sondern, Klemens; Hahn, Matthias; Rothenaicher, Gerhard; Krönert, Thomas; Zink, Karl; Neugebauer, Edmund

VERSION 1 – REVIEW

REVIEWER	Jo Dumville University of Manchester
REVIEW RETURNED	15-Sep-2018

GENERAL COMMENTS	**This is a very important trial in an area with high quality evidence is lacking. I have the following comment for the paper's authors** Overall: The written English would benefit from editing in terms of readability and also ensure that the correct terms are used in some places and that the report is presented in as succinct and clear way as is possible. Suggest looking at papers from EVRA study, VenUS IV study and other large published wound trials to see the volume of information presented and the detail given. The flow of the paper is hard to follow in places and there is some detail that is not required and then soprocme important information that is not given. There are points in the papers where results are presented for elements for which there are no or limited methods I think. The interpretation of findings needs to be improved in places. There is a really important trial paper here: the important detail just needs to be extracted, presented in a linked and logical way with appropriate analyses also with suitable interpretation of data. **Background:** Epidemiological statements such as *Acute and chronic wounds affect at least 1% of the population worldwide* [1] needs better clarification: for example is this a point prevalence or a period prevalence? The fact that lots of people in the world at any one time might have a surgical wound healing by primary intention which require little additional care seems somewhat extraneous to the focus of this paper. Consider use of the term foot ulcer(s) in people with diabetes rather

	than diabetic foot ulcer as it is the person who has diabetes not the wounds. Although – reading on in the paper – if people could have an amputation – is this not foot wounds rather than ulcers. If the ulcer has been amputation – surely it is the post-surgical wound that is being treated? *Only a few of the available modern moist wound dressings and topical agents have been convincingly shown to achieve higher wound closure rates compared with traditional wet gauze dressings [6, 7]"* The references for this seem a little old and also not focused specifically on foot ulcers in people with diabetes. There is a Cochrane overview of reviews for dressings for foot ulcers in people with diabetes, also reviews on various topical agents. There are also NMAs on dressings and topical agents for pressure ulcers and VLUs – these body of work seems more recently and relevant to the points being made. *Negative pressure wound therapy (NPWT) is one of the most commonly used and well-established advanced therapies to facilitate wound healing [8].* I think that the choice of words used through-out needs to be checked carefully. I think we can only say that NPWT is used with the aim of promoting healing, not suggest that we know it facilitates healing. Whether NWPT does actually improve healing is still an uncertainty – see the several Cochrane Reviews in this area. *Positive effects of NPWT on wound healing have been SUGGESTED ~~demonstrated~~ in various basic studies* The detail on the German-specific evaluation and approval process and how it lead to the reported trial could be edited so it is shorter with just the key details as the motivation for the trial is of relevance but I don't think the reader need as much information as is presented. In general the structure of the background could probably be honed to introduce the clinical issue: the background to NPWT; the motivation for the trial from the German perspective; a summary of the current evidence base and finally the aims of the trial that is going to be reported. **Methods:** I am not sure what a *cross-sectoral* trial is? Could be me – is this the same as a multi-centre trial? Rather than describing as blinded analysis of wound photographs – if correct this could more informatively be described as blinded assessment of wound healing – I think it is the outcome being assess that is of relevance rather than the process used. *"In order to answer the overall question if NPWT is eligible to be reimbursed in clinical practice without any limitation"* I am not sure this is the question per se. It might be more logical to present the research question that relate to the trial which is used earlier re the conduct of a pragmatic trial to evaluate the relative clinical effectiveness and safety of NPWT compared with standard moist wound care (SMWC) in those with foot wounds and diabetes. The structure of the participant section could be edited to enhance its flow. I suggest listing all inclusion/exclusion elements and then listing addition statements such as *written informed consent was obtained from every participant after being informed about all aspects of the trial and before randomization and any trial-related*

	procedure after or before the eligibility criteria 'list'. Again I think less words can be used to describe the exclusion criteria more succinctly. It would be useful to clarify re the inclusion of those with ulcers – who then underwent an amputation. So to be included the patient had an ulcer – but it was removed via limb amputation and it was the post-surgical wound that was treated. *Within this healthcare research study, clinical diagnoses rather than surrogate parameters were recorded to describe the patient population* Not clear what this means. *Respective available evidence-based guidelines were referred to in the study protocol* again the relevance of this sentence to the study is not clear. In the randomisation and masking section it would be really useful to make it completely clear whether allocation concealment was facilitated. It sounds like the use of the web based system meant the investigators would be unable to subvert the allocation in anyway but it would be useful to confirm this – since understanding sequence generation and allocation concealment are so important when assessing the risk of bias of any trial. *Confirmation of wound closure was performed by independent, blinded assessment of wound photographs.* Check consistent use of wound healing or wound closure in the paper. **Suggested rewording:** All patients underwent one or more of the following no longer than six hours before randomistion: amputation, debridement or thorough wound cleansing. There are elements of *Procedures* section that are quite hard to follow. I think it is talking about measuring baseline and other 'co-intervention' details to ensure balance for key possible prognostic factors but it is quite hard to follow. Again, I am not sure that the amount of detail supplied is needed – rather the key points need to be pulled out and summarised clearly. *Before study start, the participating study sites were allocated to the manufacturers* .It is not clear if this was randomisation or some other process – it is mentioned but not with enough clarification to understand the process. *Direct comparison of the used products was explicitly not planned, since the therapy method and not the medical products are to be evaluated. NPWT as interim therapy needed to be discontinued once the condition of a wound was suitable for closing, either spontaneously by epithelialization or surgically.* As above – it is not totally clear what is being talked about here. *It was determined in the study protocol that the optimal preparation of the wound for subsequent therapy aiming to achieve complete wound closure requires a granulation area of at least 95%...*Is this a definition of the healing out – should this be in the outcome section. But then in the outcome section you have a different definition of healing – this is confusing. Later on it becomes clearer this is about optimal wound bed prep but it's just a bit disjointed.

	FROM NOW ON WILL ONLY FOCUS ON KEY METHODLOGICAL ISSUES RATHER THAN CONTENT ISSUES PER SE. WOULD ADVISE THE AUTHORS TO CAREFULLY CONSIDER THE FLOW OF CONTENT AND TO FOCUS ON THE KEY ELEMENTS OF THE METHODS TO REPORT HERE. *Wound* closure *could also be achieved by secondary intention or by surgical intervention at any time during the study treatment period.* It is ***vital*** to clarify how wound closure via surgery was defined. Was a wound considered healed once it had been surgically closed or was the definition of 100% epithelisation etc. also applied? I assume that it was but it needs to be very clear so that the reader knows this. It is also important to clarify or discuss whether the decision to close wounds via surgery was made by people who had knowledge of the treatment allocation as this could introduce bias. All the details on factors included in adjustment can just be listed I think – current section too detailed and also should be in analysis. Elements of the analysis are unclear – in terms of the sub-group analysis described and also not sure why a Cox-regression was not undertaken adjusting for some of the factors that have been highlighted earlier in the paper. No clear information about how missing data were dealt with I don't think. Censored is fine for time to event but not for other types of analysis I don't think. **Results** Issue with linked references in this section. **Baseline table:** I think that the ITT baseline table should be presented with the PP in the appendices. There needs to be consistency – the ITT needs to be presented as the primary analysis – will all information consistent with this. Nicotine – is this smoking – this isn't that clear. Or does it include vaping. Does it mean current intake of nicotine? Needs to be clear to the reader from the table. Could baseline table also report Wagner grades by group and wound area at baseline? These are key prognostic factors. The presentation of results is currently difficult to follow. It needs to follow a more logical order – in terms of the findings for the primary outcomes in the form of the point estimates the 95% CIs and then the p-value. I think that the p-value is the least important bit of information: the other elements of the results need to be clear in the text. *Wounds treated with NPWT had a slightly lower risk of remaining open than those of patients receiving SMWC (RR 0·97 [95% CI: 0·89-1·06)]).* I am not clear whether result is the same as the one support by the p-value 0,53 or if it is a different one. Also the risk is no significant so that needs to be considered in how this is reported.

	The time to healing data then needs to follow: supported by median time to healing (not sure why the 95% epi outcome is presented in table 2 rather than the 100% which was defined as complete healing). Exploring the factors associated with healing is a different and secondary analysis and I would push to later in the results. There are no sub-headings in the results which makes the general follow hard to follow. I think more information about the flow of participants and study is required. Also information about those that were excluded from the ITT analysis and why. *Since the cumulative number of patients with open wounds was more than 70% after 16 weeks, we were not able to calculate medians for time to wound closure.* This doesn't make any sense. The section that starts…*NPWT-arm values for the wound surface area decreased faster during the beginning of the treatment time*…doesn't seem to have any data to accompany it and I don't think there are methods to support this type of analysis in the methods. With this repeat testing I think specific methods would need to be used to test the pattern of change in size. What is presented seems almost like a qualitative assessment of the change in size and I am not sure how valid this is. *There were 45 amputations in 35 (20·5%) patients in the NPWT group and 57 amputations in 36 (20·7%) patients in the control group.* Useful to know the number of people with amputations by groups also. *Patients treated with NPWT have a slightly lower risk of undergoing an amputation or resection than patients treated with SMWC (RR: 0·99 [95%CI: 0·65- 385 1·50]).* I think that care needs to be taken with interpretation – the RR is almost 1 and the 95% span one. The statement that those treated with NPWT have a slightly lower risk it too strong without any further clarification. **Discussion** *In the DiaFu-study wound closure rates were higher in the NPWT group but did not significantly differ from 472 those in the SMWC group, although optimal preparation of the wound bed (95% granulation tissue) was achieved significantly earlier when using NPWT in both populations.* I do not agree with the interpretation of the results. There was no clear difference between groups is the main finding. There is huge focus here on change to treatment, adherence to therapy – however this as an outcome is not really detailed from what I could see in the methods. Not are data clearly presented on this in the results. I HAVE STOPPED MY REVIEW HERE. THE PAPER HAS A LOT OF POTENTIAL BUT A FURTHER DRAFT NEEDS FURTHER

	REVIEW

REVIEWER	Alex Reyzelman UCSF USA
REVIEW RETURNED	16-Sep-2018

GENERAL COMMENTS	clinically relevant study weaknesses well described in the paper

REVIEWER	Pirkka Vikatmaa Helsinki University Hospital, dep vascular surgery Finland
REVIEW RETURNED	25-Dec-2018

GENERAL COMMENTS	Negative Pressure Wound Therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT Review This preregistered rct addresses an important clinical question, whether NPWT has an effect on wound healing rates and time to heal. As the authors point out the strength of this study is generalizability, however, when not selecting a specific group, it also creates a major weakness to the reliability of the study. For which groups of patients can this result be used? The study is planned in a meticulous way and statistics seem professional, the power calculations are reported. It was a bit difficult to follow the big difference in the ITT and PP groups. Generally one would assume that the ITT analysis puts the patients in groups they were planned be included in and PP according to the treatment they actually received. In this report, however, a different method has been used (Fig1) please explain. In the reporting, a more logical order should be followed. First, analyse the differences between the groups i.e. the reliability of the comparison. Then give the result regarding primary endpoints and then the secondary endpoints. The ITT and PP analysis should be reported separately. If the PP describes what could actually be analyzed, then the dropout rate was well above 20%. The introduction includes a lengthy discussion on medicolegal and funding aspects. This is relevant but should be shortened significantly. The paper should focus on evidence first, then on the implications. The name and introduction of the study gives an assumption that all patients had diabetes, but this is poorly described. Type 1 and 2 numbers are not stated. Also, there is a paucity of demographic data in the subgroup analysis (table1). Many significant confounding factors may not be controlled. Neuropathy, retinopathy, nephropathy or other means of describing the severity of the DM should be given. Did you analyze long term glucose metabolism, insulin treatment, po medication, chargot feet and other weight bearing deformities? On ischeamia: 70.7% of the patients had PAD and 70.9% (n=173) had Rutherford class I/3 or higher, 68.4% an ulcer (n=167). Yet only 6 patients were stated to have critical limb ischaemia, how come? How did you define the perfusion to the feet? Toe pressure, tcpo2? For example in the studies by Armstrong et al, ref 72.4% of patients in the NPWT group vs 57.5% had a Rutherford III/5 ulcer, typically present in the neuroischemic foot. It is generally accepted that wound healing is significantly impaired in the presence

	of ischemia and this is further impaired with increasing severity of neuropathy. Indeed, could the fact that 15% more patients in the NPWT group had a CLI ulcer explain the fact that many significant differences were seen? Ulcer location. Heel ulcers have significantly worse prognosis than forefoot ulcers. Did you register the ulcer location and were the groups similar? Smoking significantly impairs ulcer healing. Was the difference in the "nicotine" groups significant and could it explain some of the findings? Comorbities. You give the number of patients on dialysis and it is important that the groups do not differ in this detail. However, other comorbidities, like coronary artery disease, pulmonary diseases and different rheumatoid diseases could have an effect. Also, some medications like warfarin should be compared. Many of these "covariates" are mentioned in the introduction, but I failed to see the effect in the analysis? Maybe I was too superficial? Table 2 and 3 seem to be the same, how come? Please be careful when reporting non-significant results, like the lines 375-379. If the difference is not significant a chapter should not start with "…were more than twice as likely to…". A simple statement that there was no difference, would be more accurate. One exception is when there is a trend like p0.07, but it seems that the groups were too small. This should be carefully stated as suggestive but not significant. The result section should be rewritten with this in mind. From the PP Kaplan-Meier curves it seems possible that NPWT works in big, but not small ulcers. It is somewhat confusing that 80% in the big and 80% in the small group remained open, but only 60% in the total population, fig5, please check and explain.

REVIEWER	Hongyan Xu Augusta University, United States
REVIEW RETURNED	12-Apr-2019

GENERAL COMMENTS	The manuscript is well-written. The study is important for would care in patients with diabetic foot ulcers. The description is clear. I have some minor comments. 1. In lines 63 to 64, premature treatment cessation was reported as significant from statistical test. The p-values should be given. 2. Lines 194-195. The name/reference of the web-based tool for randomization should be given. 3. Line 324, the error for reference should be fixed. 4. Table 1, the comparison of the baseline characteristics between the NPWT and SMWC should be performed with appropriate statistical tests to make sure the randomization is sufficient. 5. Table 2 and Table 3 are duplicated. 6. Line 408. "Table 1" is wrong and should be renumbered. The AE rates should be compared with appropriate statistical tests between the NPWT and SMWC.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Jo Dumville

Institution and Country: University of Manchester

Please state any competing interests or state 'None declared': Co-author of Cochrane Reviews in this area

Please leave your comments for the authors below
See attached files

→

This is a very important trial in an area with high quality evidence is lacking. I have the following comment for the paper's authors

Overall: The written English would benefit from editing in terms of readability and also ensure that the correct terms are used in some places and that the report is presented in as succinct and clear way as is possible.

Suggest looking at papers from EVRA study, VenUS IV study and other large published wound trials to see the volume of information presented and the detail given. The flow of the paper is hard to follow in places and there is some detail that is not required and then soprocme important information that is not given.

There are points in the papers where results are presented for elements for which there are no or limited methods I think.

The interpretation of findings needs to be improved in places.

There is a really important trial paper here: the important detail just needs to be extracted, presented in a linked and logical way with appropriate analyses also with suitable interpretation of data.

Answer:

Thanks for your review and the advices. We appreciate it. The article has been revised taking into account the recommendations whenever possible.

Background: Epidemiological statements such as *Acute and chronic wounds affect at least 1% of the*

population worldwide [1] needs better clarification: for example is this a point prevalence or a period prevalence? The fact that lots of people in the world at any one time might have a surgical wound healing by primary intention which require little additional care seems somewhat extraneous to the focus of this paper.

Answer:

The first two sentences were intended to introduce the topic in general. We agree that the presentation is not effective and misses the focus of the article. We also see that the articles by

Gohel et al. and Ashby et al. also do without such general introductions. We have therefore deleted the first two sentences of the background.

Consider use of the term foot ulcer(s) in people with diabetes rather than diabetic foot ulcer as it is the person who has diabetes not the wounds. Although – reading on in the paper – if people could have an amputation – is this not foot wounds rather than ulcers. If the ulcer has been amputation – surely it is the post-surgical wound that is being treated?

Answer:

An ulcer is an atraumatic loss of tissue substance (reaching at least into the dermis) that is typically accompanied by signs of inflammation. This substance defect shows up clinically as an infected, often painful wound. It is therefore legitimate to use the two terms synonymously in a background

presentation. Whenever useful, the description can be adjusted to use the term “patients with diabetic foot ulcers” or “patients with diabetic foot wounds”. In many cases, however, the use of the terms “diabetic foot ulcer” or “diabetic foot wound” is useful and correct. Ultimately, the therapy is applied to the wound.

Only a few of the available modern moist wound dressings and topical agents have been convincingly shown to achieve higher wound closure rates compared with traditional wet gauze dressings [6, 7]” The references for this seem a little old and also not focused specifically on foot ulcers in people with diabetes. There is a Cochrane overview of reviews for dressings for foot ulcers in people with diabetes, also reviews on various topical agents. There are also NMAs on dressings and topical agents for pressure ulcers and VLUs – these body of work seems more recently and relevant to the points being made.

Answer:

We updated the reference. At this point citing only the overview of Wu et al. seems to be sufficient, as this is focused on patients with DFU.

Negative pressure wound therapy (NPWT) is one of the most commonly used and well-established advanced therapies to facilitate wound healing [8]. I think that the choice of words used throughout needs to be checked carefully. I think we can only say that NPWT is used with the aim of promoting healing, not suggest that we know it facilitates healing. Whether NWPT does actually improve healing is still an uncertainty – see the several Cochrane Reviews in this area.

Answer:

The wording has been adjusted. → Negative pressure wound therapy (NPWT) is one of the most commonly used and well-established technologies with the aim to promote wound healing.

Positive effects of NPWT on wound healing have been SUGGESTED ~~demonstrated~~ in various basic Studies.

Answer:

The wording has been adjusted.

The detail on the German-specific evaluation and approval process and how it lead to the reported trial could be edited so it is shorter with just the key details as the motivation for the trial is of relevance but I don't think the reader need as much information as is presented. In general the structure of the background could probably be honed to introduce the clinical issue: the background to NPWT; the motivation for the trial from the German perspective; a summary of the current evidence base and finally the aims of the trial that is going to be reported.

Answer:

The background has been restructured and shortened.

Methods: I am not sure what a *cross-sectoral* trial is? Could be me – is this the same as a multicentre trial?

Answer:

Cross-sectoral means that the trial was performed in both medical sectors in Germany (in and outpatient care). In Germany, the providing medical services in hospitals are subject to other regulations than in the outpatient sector. As this is a very German-specific problem, we decided to delete the term cross-sectoral. Anyway, the following sentences explain the setting. We added "German-national" and multicenter.

Rather than describing as blinded analysis of wound photographs – if correct this could more informatively be described as blinded assessment of wound healing – I think it is the outcome being assess that is of relevance rather than the process used.

Answer:

If it serves the better understanding, we gladly follow the suggestion. However, we prefer the description: "blinded assessment of wound closure, wound size and wound tissue qualities using photographs". Anyway, wound healing is the process and wound closure is the result.

"In order to answer the overall question if NPWT is eligible to be reimbursed in clinical practice without any limitation" I am not sure this is the question per se. It might be more logical to present the research question that relate to the trial which is used earlier re the conduct of a pragmatic trial to evaluate the relative clinical effectiveness and safety of NPWT compared with standard moist wound care (SMWC) in those with foot wounds and diabetes.

Answer:

The wording has been adjusted.

The structure of the participant section could be edited to enhance its flow. I suggest listing all inclusion/exclusion elements and then listing addition statements such as *written informed consent was obtained from every participant after being informed about all aspects of the trial and before randomization and any trial-related procedure* after or before the eligibility criteria 'list'. Again I think less words can be used to describe the exclusion criteria more succinctly.

Answer:

The description of the participants has been restructured and shortened.

It would be useful to clarify re the inclusion of those with ulcers – who then underwent an amputation. So to be included the patient had an ulcer – but it was removed via limb amputation and it was the post-surgical wound that was treated.

Answer:

The description has been adapted and we hope that the inclusion process is clearer now.

Within this healthcare research study, clinical diagnoses rather than surrogate parameters were recorded to describe the patient population Not clear what this means.

Respective available evidence-based guidelines were referred to in the study protocol again the relevance of this sentence to the study is not clear.

Answer:

These explanations are not necessary for the description of the patient population and can, if at all, be better taken up in the discussion. The corresponding sentences have been deleted.

In the randomisation and masking section it would be really useful to make it completely clear whether allocation concealment was facilitated. It sounds like the use of the web based system meant the investigators would be unable to subvert the allocation in anyway but it would be useful to confirm this – since understanding sequence generation and allocation concealment are so important when assessing the risk of bias of any trial.

Answer:

A note on allocation concealment has been added.

Confirmation of wound closure was performed by independent, blinded assessment of wound photographs. Check consistent use of wound healing or wound closure in the paper.

Answer:

As stated above, we would like to use the term wound closure instead of wound healing. Wound closure was chosen to be endpoint of this study and we do not want to switch terms now. We added the blinded assessment of the outcomes wound size and percentage tissue quality.

Suggested rewording: All patients underwent one or more of the following no longer than six hours before randomistion: amputation, debridement or thorough wound cleansing.

Answer:

We adopted the suggested rewording.

There are elements of *Procedures* section that are quite hard to follow. I think it is talking about measuring baseline and other 'co-intervention' details to ensure balance for key possible prognostic factors but it is quite hard to follow. Again, I am not sure that the amount of detail supplied is needed – rather the key points need to be pulled out and summarised clearly.

Answer:

The text section for the procedures has been revised.

Before study start, the participating study sites were allocated to the manufacturers .It is not clear if this was randomisation or some other process – it is mentioned but not with enough clarification to understand the process.

Answer:

A more detailed explanation has been added.

Direct comparison of the used products was explicitly not planned, since the therapy method and not the medical products are to be evaluated. NPWT as interim therapy needed to be discontinued once the condition of a wound was suitable for closing, either spontaneously by epithelialization or surgically. As above – it is not totally clear what is being talked about here.

Answer:

The content of the first sentence will be taken up again in the discussion and was deleted here. The description has been adapted.

*It was determined in the study protocol that the optimal preparation of the wound for subsequent therapy aiming to achieve complete wound closure requires a granulation area of at least 95%...*Is this a definition of the healing out – should this be in the outcome section. But then in the outcome section you have a different definition of healing – this is confusing. Later on it becomes clearer this is about optimal wound bed prep but it's just a bit disjointed.

Answer:

The description has been adapted.

FROM NOW ON WILL ONLY FOCUS ON KEY METHODLOGICAL ISSUES RATHER THAN CONTENT ISSUES PER SE. WOULD ADVISE THE AUTHORS TO CAREFULLY CONSIDER THE FLOW OF CONTENT AND TO FOCUS ON THE KEY ELEMENTS OF THE METHODS TO REPORT HERE.

Wound closure *could also be achieved by secondary intention or by surgical intervention at any time during the study treatment period.* It is ***vital*** to clarify how wound closure via surgery was defined. Was a wound considered healed once it had been surgically closed or was the definition of 100%

epithelisation etc. also applied? I assume that it was but it needs to be very clear so that the reader knows this.

Answer:

The sentence was deleted from the outcome description and an explanation was added to the procedures because it fits better there. We added the clarification how wound closure by surgery was defined.

It is also important to clarify or discuss whether the decision to close wounds via surgery was made by people who had knowledge of the treatment allocation as this could introduce bias.

Answer:

A statement has been added.

All the details on factors included in adjustment can just be listed I think – current section too detailed and also should be in analysis.

Answer:

Description of covariates has been shortened, but we think listing them is still important.

Elements of the analysis are unclear – in terms of the sub-group analysis described and also not sure why a Cox-regression was not undertaken adjusting for some of the factors that have been highlighted earlier in the paper.

Answer:

Information on the statistical methods used for the analysis of the influence of the co-variates and the subgroups was added.

No clear information about how missing data were dealt with I don't think. Censored is fine for time to event but not for other types of analysis I don't think.

Answer:

Information on dealing with missing data was added.

Results

Issue with linked references in this section.

Answer:

This was an automatic link to figure 1, which was destroyed during conversion of the word document into a pdf file. We removed all automatic links from the manuscript.

Baseline table: I think that the ITT baseline table should be presented with the PP in the appendices.

Answer:

In most RCTS results publications, the baseline table is shown in the article itself and not in the appendix. Online journals are increasingly using scroll-down versions of the tables, which has the advantage that they are no longer so bulky. We changed the one big table into 3 smaler ones. We would like to take the suggestion to move the baseline Table(s) to the editor.

There needs to be consistency – the ITT needs to be presented as the primary analysis – will all information consistent with this.

Answer:

We removed the reference to the baseline table of the PP population from row 392 and corrected the legend of table 1. In the further course of the manuscript, a separate representation of ITT and PP analysis has already been implemented.

Nicotine – is this smoking – this isn't that clear. Or does it include vaping. Does it mean current intake of nicotine? Needs to be clear to the reader from the table.

Answer:

That meant smoking. This was translated unfavourably. At the start of the study, vaping was not yet an issue. However, smoking was documented in the CRF.

Could baseline table also report Wagner grades by group and wound area at baseline? These are key prognostic factors.

Answer:

Wagner grades and wound surface area at randomization were added to the Baseline table.

The presentation of results is currently difficult to follow. It needs to follow a more logical order – in terms of the findings for the primary outcomes in the form of the point estimates the 95% CIs and then the p-value. I think that the p-value is the least important bit of information: the other elements of the results need to be clear in the text.

Answer:

The presentation of results has been revised.

Wounds treated with NPWT had a slightly lower risk of remaining open than those of patients receiving SMWC (RR 0·97 [95% CI: 0·89-1·06)]).

I am not clear whether result is the same as the one support by the p-value 0,53 or if it is a different one. Also the risk is no significant so that needs to be considered in how this is reported.

Answer:

This is an indication of the relative risk of still having an open wound at the end of the treatment period. Thus, it is a different representation of the primary endpoint. You are right, that the presentation of the result was not adequate. We adapted it.

The time to healing data then needs to follow: supported by median time to healing (not sure why the 95% epi outcome is presented in table 2 rather than the 100% which was defined as complete healing).

Answer:

The 95% epi outcomes have been removed from table 2. It was not intended to show it like this.

Exploring the factors associated with healing is a different and secondary analysis and I would push to later in the results.

Answer:

The presentation of the results of the analysis of covariates was pushed more down in the text.

There are no sub-headings in the results which makes the general follow hard to follow.

Answer:

Subheadings have been added

I think more information about the flow of participants and study is required. Also information about those that were excluded from the ITT analysis and why.

Answer:

Figure 1 (referenced on page 15 in line 386) includes all information about the flow of participants. This includes a detailed listing of reasons for excluding study participants after randomization from the ITT population.

Since the cumulative number of patients with open wounds was more than 70% after 16 weeks, we were not able to calculate medians for time to wound closure. This doesn't make any sense.

Answer:

We contacted the trial statistician and this is his answer: For those patients who achieved wound closure we would of cause be able to provide descriptive statistics like mean and median. For Kaplan Meier Curves however, the median survival time or here median time to wound closure) is determined as the time point were 50% of patients have reached the outcome. At this time point the Kaplan Meier Curve crosses the 50% line (y-axis) . In our study only 30% of all patients achieved a WC. Therefore we are not able to report the median time to wound closure, since more than half of the wounds were still open after 16 weeks.

The section that starts…*NPWT-arm values for the wound surface area decreased faster during the beginning of the treatment time*…doesn't seem to have any data to accompany it and I don't think there are methods to support this type of analysis in the methods. With this repeat testing I think specific methods would need to be used to test the pattern of change in size. What is presented seems almost like a qualitative assessment of the change in size and I am not sure how valid this is.

Answer:

The presentation of the results of the wound size and the wound tissue has been completely revised.

There were 45 amputations in 35 (20·5%) patients in the NPWT group and 57 amputations in 36 (20·7 %) patients in the control group. Useful to know the number of people with amputations by groups also.

Answer:

The number of study participants with amputations for each treatment arm was already described but we added a table in which more details are provided.

Patients treated with NPWT have a slightly lower risk of undergoing an amputation or resection than patients treated with SMWC (RR: 0·99 [95%CI: 0·65- 385 1·50]). I think that care needs to be taken with interpretation – the RR is almost 1 and the 95% span one. The statement that those treated with NPWT have a slightly lower risk it too strong without any further clarification.

Answer:

You are right. The wording has been adapted.

Discussion

In the DiaFu-study wound closure rates were higher in the NPWT group but did not significantly differ from 472 those in the SMWC group, although optimal preparation of the wound bed (95% granulation tissue) was achieved significantly earlier when using NPWT in both populations. I do not agree with the interpretation of the results. There was no clear difference between groups is the main finding.

Answer:

We adapted the interpretation.

There is huge focus here on change to treatment, adherence to therapy – however this as an outcome is not really detailed from what I could see in the methods. Not are data clearly presented on this in the results.

Answer:

Poor documentation quality and the lack of therapy compliance were identified to be important negative influences on the treatment outcome within an additional error analysis. For the participating clinicians troubleshooting and a critical review of the treatment process was of high importance, which did lead to the results presentation and the discussion. We have now clearly identified the presentation of the treatment compliance and the shortcomings in the documentation in the results as an additional analysis.

I HAVE STOPPED MY REVIEW HERE. THE PAPER HAS A LOT OF POTENTIAL BUT A FURTHER DRAFT NEEDS FURTHER REVIEW

Reviewer: 2

Reviewer Name: Alex Reyzelman

Institution and Country: UCSF, USA

Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below
clinically relevant study

weaknesses well described in the paper

No answer necessary.

Reviewer: 3

Reviewer Name: Pirkka Vikatmaa

Institution and Country: Helsinki University Hospital, dep vascular surgery, Finland

Please state any competing interests or state 'None declared': No competing interest

Please leave your comments for the authors below Negative Pressure Wound Therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT

Answer:

Thank you very much for your review. We appreciate it! We tried to adapt the manuscript according to your recommendation whenever possible. Please don`t hesitate to comment again, if we misunderstood anything.

Review

This preregistered rct addresses an important clinical question, whether NPWT has an effect on wound healing rates and time to heal. As the authors point out the strength of this study is generalizability, however, when not selecting a specific group, it also creates a major weakness to the reliability of the study. For which groups of patients can this result be used?

Answer:

Patients with diabetic foot ulcers were included in the study regardless of their concomitant diseases and the risk factors that led to the development of foot ulcers. As in the clinical routine, both patients with peripheral neuropathy and peripheral arterial occlusive disease were included in the study. For this typical mixed target group, adequate therapy of the underlying disease that led to the development of the foot ulcer has the highest priority. This is also assumed in the study. The section on the strengths and weaknesses of the study has been revised to make the presentation clearer and more balanced.

The study is planned in a meticulous way and statistics seem professional, the power calculations are reported. It was a bit difficult to follow the big difference in the ITT and PP groups. Generally one would assume that the ITT analysis puts the patients in groups they were planned be included in and

PP according to the treatment they actually received. In this report, however, a different method has been used (Fig1) please explain.

Answer:

The primary analysis was performed based on a modified ITT-population. Patients falsely included in the study and without any assessment after randomization were removed from the ITT population. We used this variant of the ITT approach, what Polit and Gillespie (2010) term a 'modified ITT' analysis, which maintains the conditions to which people were randomly assigned and attempts to follow-up all participants, regardless of their participation in the intervention. However, only those successfully followed are included in the analyses. With this modified approach, however, the balance in pre-existing characteristics across conditions sought through random assignment is less likely to hold, but our study baseline is still similar for both treatment arms. Excluding patients who do not have any post

randomization wound assessment and did not receive any therapy at all, means exclusion form the study not only from the therapy. We added the information that a modified ITT approach was used.

In the reporting, a more logical order should be followed. First, analyse the differences between the groups i.e. the reliability of the comparison. Then give the result regarding primary endpoints and then the secondary endpoints. The ITT and PP analysis should be reported separately. If the PP describes what could actually be analyzed, then the dropout rate was well above 20%.

Answer:

The presentation of results has been revised.

The introduction includes a lengthy discussion on medicolegal and funding aspects. This is relevant but should be shortened significantly. The paper should focus on evidence first, then on the implications.

Answer:

We adapted the introduction and shortened the text part about the German-specific political and assessment background.

The name and introduction of the study gives an assumption that all patients had diabetes, but this is poorly described. Type 1 and 2 numbers are not stated. Also, there is a paucity of demographic data in the subgroup analysis (table1). Many significant confounding factors may not be controlled. Neuropathy, retinopathy, nephropathy or other means of describing the severity of the DM should be given. Did you analyze long term glucose metabolism, insulin treatment, po medication, chargot feet and other weight bearing deformities?

Answer:

The presence of diabetes mellitus as the relevant underlying disease was defined as an inclusion criterion and was 100% met. Diabetes 1 and 2 were not assessed. When planning the study, the medical experts stated that this was irrelevant for the outcome and therefore did not have to be collected.

We are not able to provide any information on retinopathy or nephropathy.

We are able to provide baseline data for DNOAP, presence of neuropathy (sensation loss according to the PEDIS classification system) and presence of extreme foot deformities and malpositions of toes, foot or the entire limb. We included this information in the baseline table.

Furthermore, during screening we did ask the clinical investigators to provide information on presence of extreme deformities of the foot and malpositions **that interfere healing of the study wound**, but this was poorly documented. Laboratory data were only documented if analyzed in clinical routine, thus we are not able to provide HbA1c [%] values for all patients. Only for 32 patients baseline HbA1c [%] values are available.

On ischeamia: 70.7% of the patients had PAD and 70.9% (n=173) had Rutherford class I/3 or higher, 68.4% an ulcer (n=167). Yet only 6 patients were stated to have critical limb ischaemia, how come? How did you define the perfusion to the feet? Toe pressure, tcpo2? For example in the studies by Armstrong et al, ref 72.4% of patients in the NPWT group vs 57.5% had a Rutherford III/5 ulcer, typically present in the neuroischemic foot. It is generally accepted that wound healing is significantly impaired in the presence of ischemia and this is further impaired with increasing severity of

neuropathy. Indeed, could the fact that 15% more patients in the NPWT group had a CLI ulcer explain the fact that many significant differences were seen?

Answer:

You are right that the information on the PAD is contradictory. We had taken the presentation from the statistical report without questioning it critically. Initially, only a simple question was asked about the existence of critical limb ischemia. No guidelines were given for the diagnosis. Later during screening Rutherford classification was introduced and the basics of the diagnostic classification were explicitly communicated. The information on the Rutherford classification is therefore (diagnostically) more accurate. The simple answer to the question of critical limb ischemia is purely subjective and we should not report the result. We have deleted the critical limb ischemia data (Yes, No) from the baseline table. It is likely that the examiners initially made an assessment without objective measurement. After consultation with some examiners this was affirmed. There are also special circumstances in diabetes patients. Patients with diabetes mellitus often lack the usual symptoms of PAD (intermittent claudication, rest pain) due to simultaneous neuropathy. In contrast, patients with diabetic foot wounds may have a therapy-resistant, patient intolerable rest pain, which may be a sign that the extremity of the diabetic is threatened in its preservation. Both make diagnosis more difficult. On the other hand, ABI is also considered less reliable in patients with diabetes.

The documentation of the screening took place at two different times. It is quite possible that (also because of the abundance of documentation and an unfortunately not very well functioning electronic CRF) the examiners did not further question their initial statement after extended diagnostics. The study also requested further diagnostic and surgical measures after the initial diagnosis, which could lead to a reassessment of the wound situation before randomization. However, we only want a well-founded and clear presentation and remove the subjective assessment. Since we only observed the routine, the responsibility for carrying out the diagnostics was with the investigators. We only asked for the result. To query all diagnostic steps would have completely overloaded the documentation, which was already too much anyway. The aim is to show that there is no difference between the treatment arms that could influence the study results. It would go too far to discuss the entire diagnosis and its influence on the baseline and to question the results of other studies. We are, however, open to any further advice after telling the background of the baseline assessment!

Ulcer location. Heel ulcers have significantly worse prognosis than forefoot ulcers. Did you register the ulcer location and were the groups similar?

Answer:

Yes, we did. We added an overview of the ulcer location in the baseline table. There were no relevant differences between the treatment arms.

Smoking significantly impairs ulcer healing. Was the difference in the “nicotine” groups significant and could it explain some of the findings?

Answer:

The difference of patients who smoke is very small between the treatment arms (NPWT 144 (84·3%) and SCWT 149 (85·1%). It cannot be assumed that this very small difference has an effect on any of the outcomes (difference between the treatment arms), but the high number of smoking patients could be one of the reasons, why the overall wound close rate is low.

If baseline data is reported correctly, details of participants’ baseline characteristics should be provided (in a table), but a formal statistical comparison (p value) should not be given because any differences between groups at this point must arise by chance (if randomized properly). The reader of the article can easily notice differences between the treatment arms by the representation in the table. Please have a look in the current CONSORT 2010 guidelines on the publications of clinical trials:

"Unfortunately significance tests of baseline differences are still common; they were reported in half of 50 RCTs trials published in leading general journals in 1997. Such significance tests assess the probability that observed baseline differences could have occurred by chance; however, we already know that any differences are caused by chance. Tests of baseline differences are not necessarily wrong, just illogical. Such hypothesis testing is superfluous and can mislead investigators and their readers. Rather, comparisons at baseline should be based on consideration of the prognostic strength of the variables measured and the size of any chance imbalances that have occurred." http://www.consort -statement.org/checklists/view/32-consort/510-baseline-data Thus, we will not do any significance testing for the baseline characteristics.

Comorbities. You give the number of patients on dialysis and it is important that the groups do not differ in this detail. However, other comorbidities, like coronary artery disease, pulmonary diseases and different rheumatoid diseases could have an effect. Also, some medications like warfarin should be compared.

Answer:

Within the planning of the DiaFu study, the relevant factors influencing the study objective of wound closure were identified and discussed. It was decided which influencing factors should be investigated. These results are presented. Since the number of possible influencing factors is very large, not all factors could be taken into account. We would like to report only the predefined influencing factors. Further concomitant diseases and specific medication were not systematically evaluated. Is there a particular reason why the above-mentioned diseases and warfarin should be explicitly evaluated? In several publications we found different listings of relevant comorbidities. It was often not clearly distinguished whether these were factors influencing the development of the ulcer or wound healing in the case of an existing ulcer. During the study planning phase, our medical experts decided that other influencing factors are of high relevance and that further concomitant diseases play a less important role in patients with the uniform underlying disease diabetes. In the end, randomization should ensure an equal distribution of the influencing factors and only particularly relevant factors should be considered separately.

Many of these "covariates" are mentioned in the introduction, but I failed to see the effect in the analysis? Maybe I was too superficial?

Answer:

We added the results of the covariate analysis and hope it becomes more clear now, that there were no factors influencing the outcome.

Table 2 and 3 seem to be the same, how come?

Answer:

I'm so sorry for this mistake. In an earlier version of the manuscript I wanted to pool the tables in order to save space, but later I decided to display the endpoints separately again. The tables have been corrected.

Please be careful when reporting non-significant results, like the lines 375-379. If the difference is not significant a chapter should not start with "…were more than twice as likely to…". A simple statement that there was no difference, would be more accurate. One exception is when there is a trend like

p0.07, but it seems that the groups were too small. This should be carefully stated as suggestive but not significant. The result section should be rewritten with this in mind.

Answer:

The result section has been reworked.

From the PP Kaplan-Meier curves it seems possible that NPWT works in big, but not small ulcers. It is somewhat confusing that 80% in the big and 80% in the small group remained open, but only 60% in the total population, fig5, please check and explain.

Answer:

The subgroup analysis was performed based on the ITT population. Study participants of the ITT population were assigned to a group of small wounds and a group of big wounds using the median of all wound surface areas. As this was maybe not clear in the results presentation, we added a respective sentence. We checked the Kaplan-Meier curves. The results are displayed correctly. As a secondary analysis we performed a per protocol analysis, which shows a lower number of open wounds after 16 weeks, but also (unfortunately) contains a lower number of study participants.

Reviewer: 4

Reviewer Name: Hongyan Xu

Institution and Country: Augusta University, United States

Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below

The manuscript is well-written. The study is important for would care in patients with diabetic foot ulcers. The description is clear. I have some minor comments.

1. In lines 63 to 64, premature treatment cessation was reported as significant from statistical test. The p-values should be given.

Answer:

You are right, but after consultation with our lead statistician it turned out that a significance test is not appropriate here. This analysis was not planned a priori and does not represent an outcome to be tested. We therefore report the results without p values. The hint that this is a significant result has been removed from the summary.

2. Lines 194-195. The name/reference of the web-based tool for randomization should be given.

Answer:

The information has been added. The tool was self-developed especially for this study because it was integrated directly into the website.

3. Line 324, the error for reference should be fixed.

Answer:

This was a link to table 1, which was destroyed during conversion of the word document into a pdf file. We removed all links from the manuscript.

4. Table 1, the comparison of the baseline characteristics between the NPWT and SMWC should be performed with appropriate statistical tests to make sure the randomization is sufficient.

Answer:

If baseline data is reported correctly, details of participants' baseline characteristics should be provided (in a table), but a formal statistical comparison (p value) should not be given because any differences between groups at this point must arise by chance (if randomized properly). The reader of the article can easily notice differences between the treatment arms by the representation in the table.

Please have a look in the current CONSORT 2010 guidelines on the publications of clinical trials:
"Unfortunately significance tests of baseline differences are still common; they were reported in half of 50 RCTs trials published in leading general journals in 1997. Such significance tests assess the probability that observed baseline differences could have occurred by chance; however, we already know that any differences are caused by chance. Tests of baseline differences are not necessarily wrong, just illogical. Such hypothesis testing is superfluous and can mislead investigators and their readers. Rather, comparisons at baseline should be based on consideration of the prognostic strength of the variables measured and the size of any chance imbalances that have occurred."
http://www.consort-statement.org/checklists/view/32-consort/510-baseline-data

Thus, we will not provide p-values for the baseline characteristics.

5. Table 2 and Table 3 are duplicated.

Answer:

I'm so sorry for this mistake. In an earlier version of the manuscript I wanted to pool the tables in order to save space, but later I decided to display the endpoints separately again. The tables have been corrected.

6. Line 408. "Table 1" is wrong and should be renumbered. The AE rates should be compared with appropriate statistical tests between the NPWT and SMWC.

Answer:

The numbering of the tables has been corrected.

VERSION 2 – REVIEW

REVIEWER	PIrkka Vikatmaa Department of vascular surgery, Helsinki University Hospital, Finland
REVIEW RETURNED	28-Sep-2019

GENERAL COMMENTS	This is a rct looking at wound closure rates and times (within 16 weeks) in 345 diabetics. The endpoint was reached in 46 (12.5%) and there were no differences between the NPWT and SMWC (abbreviation not opened in the abstract, which should be added). The manuscript is too long and would benefit from significant shortening. The authors should consider consulting PRISMA and PICO reporting standards in order to make it easier to follow for the reader. Patient groups, intervention, comparison and outcome should be easily available for the reader. The introduction is lengthy and partly irrelevant to this “routine praxis” study. Nevertheless, it is important to have this negative result available for the wound care community and I encourage the authors to shorten and clarify the report. L123-133 leaves somewhat open how this study and G-BA´s tender interact L139- the authors state that this study unlike previous studies tries to show that the treatment is effective and safe. I do not understand what the previous studies have tried if not the same? Therefore, the wording should be changed so that the focus on routine conditions, is clear. “Routine” is also a quite unspecific word as routines between countries and centers vary substantially. Also, the primary and secondary endpoints should be clearly communicated. L169 “exposure of blood vessels” should be further clarified. You include DM “foot wounds” and probably most in the foot itself. So bypasses to adp and atp are clear, but what other blood vessel exposure was a contraindication? L178 the patient sample is restricted due to economical reasons. Could this have had an effect on the results, please discuss in the discussion. Methods. Did you consider using the WiFi classification? L201 One of the most relevant issues would be the arterial perfusion. How was this assessed? How was the grade of infection defined? L231- primary outcome(s) should be included in the methods and the wording shortened. L239- these are not outcomes, but maybe confounding factors and the chapter on outcomes should be shortened L241- please add references to the classification systems used L265 for power calculations it is sufficient to state the assumed difference. The references 16 and 17 had as you point out not “routine” conditions or at least not the same as yours and therefore it

	is sufficient to just refer to them and shorten the text significantly. Table 1 is lengthy and much of it could be presented as supplementary material, it should be clearly stated whether or not there were any significant differences between the groups? Table 3, what was the definition of an insufficient or sufficient revascularization result? The wound healing rates show that the population was significantly different from the studies that were the basis for your power calculations (see comment above) L404- the information is available also in the table and should not be repeated in length in the manuscript L429 again the significances added to the table would give this information and the chapter could almost be omitted Figures 2- should include the statistical information and abbreviations. I would also consider inversing the curves 1-, starting down from 0.

REVIEWER	Hongyan Xu Augusta University, United States
REVIEW RETURNED	03-Jul-2019

GENERAL COMMENTS	This is a revision. The authors have answered most of my concerns. However, the following questions are not answered. 1. Line 339, the error for the reference is not fixed. 2. The AE rates in Table 7 should be compared with appropriate statistical tests between the NPWT and SMWC.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4
Reviewer Name: Hongyan Xu
Institution and Country: Augusta University, United States
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This is a revision. The authors have answered most of my concerns. However, the following questions are not answered.

1. Line 339, the error for the reference is not fixed.

Authors` answer:
Our answer is now referring to the new, revised, actual version of the manuscript (marked copy). In line 365 (former 339) we refer to Table 2: "The baseline of the identified factors possibly influencing wound closure is shown in Table 2." The legend of Table 2 states the content: "The table shows the baseline of the identified factors possibly influencing wound closure in the ITT- population. Findings, diagnoses and procedures documented by the investigators are presented. Data are N (%), Mean (SD), and Minimum – Maximum [Min – Max]." The reference is correct. The reference for Table 1 can be found in line 357. Anyway, we realized that we did not reference Table 3. We added the reference in line 371.

2. The AE rates in Table 7 should be compared with appropriate statistical tests between the NPWT

and SMWC.

Authors` answer:
First of all, we apologize for not having answered this comment before. The safety results were presented as planned in the study protocol and the SAP. The AE rates were compared between the treatment arms with appropriate statistical tests and the results were presented in the text of the manuscript. In the former Table 7 we presented details on the AEs. This was intended to be descriptive only and not to be compared with statistical tests between the treatment arms. The application of statistical tests is only adequate / applicable for the comparison of patients with AE or SAE with respect to the population of included study participants (AE rate). In particular, a statistical comparison of the number of AEs and all following information is not appropriate due to the fact that more than one AE occurred per patient.
However, since another reviewer noted that the manuscript was too long, we checked the manuscript to see whether part of the presentation could be transferred to the appendix. This applies to the additionally provided details on the AEs in table 7 and some of the results presented in the text. The results of the (statistical) comparison of the treatment arms is now summarized in the new table 7! The text has been shortened. This makes the presentation clearer and the results of the statistical tests, which were carried out as planned and with adequate methods, are now shown in the Table (as requested). This representation immediately shows that the number of AEs and the subsequent details are additional, purely descriptive information.
We also noticed that for all other tables the totals were given, but not in the former Table 7. The totals have been added to the table that provides the additional information on the AEs, which is now in the appendix.

Reviewer: 3
Reviewer Name: PIrkka Vikatmaa
Institution and Country: Department of vascular surgery, Helsinki University Hospital, Finland
Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below
Review: bmjopen-2018-026345.R1

This is a rct looking at wound closure rates and times (within 16 weeks) in 345 diabetics. The endpoint was reached in 46 (12.5%) and there were no differences between the NPWT and SMWC (abbreviation not opened in the abstract, which should be added).

Authors` answer:
The explanation for the abbreviation SMWC (standard moist wound care) has been added in the abstract in line 52.

The manuscript is too long and would benefit from significant shortening.

Authors` answer:
We have revised the manuscript once again and tried to shorten it on the basis of the reviewers` suggestions. We would, however, like to bear in mind that the aim is to produce a complete report, which sufficiently illustrates the necessary interrelations. Furthermore, we had to consider the comments and wishes of other reviewers as well as the requirements of the BMJ open.

The authors should consider consulting PRISMA and PICO reporting standards in order to make it easier to follow for the reader. Patient groups, intervention, comparison and outcome should be easily

available for the reader.

Authors` answer:
We assume that this comment refers to the methods section of the manuscript.
PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. The PICO tool focuses on the Population, Intervention, Comparison and Outcomes of a (usually quantitative) article. It is commonly used to identify components of clinical evidence for systematic reviews. PICO is a useful tool for asking focused clinical questions.
The adequate reporting guideline for randomized controlled trials is CONSORT, which we followed. Furthermore, we followed the guidelines for authors of the BMJ open.
Anyway, once again we checked the manuscript regarding the correct implementation of the guidelines.

The introduction is lengthy and partly irrelevant to this “routine praxis” study.

Authors` answer:
Already during the first review the reviewers requested a shortening of the introduction, which we provided. We shortened the introduction one more time and we hope that the information provided now is adequate for the general reader to understand the study.

Nevertheless, it is important to have this negative result available for the wound care community and I encourage the authors to shorten and clarify the report.

Authors` answer:
N/A.

L123-133 leaves somewhat open how this study and G-BA´s tender interact

Authors` answer:
It was the European tender of the statutory health insurance companies. We adapted this text part.

L139- the authors state that this study unlike previous studies tries to show that the treatment is effective and safe. I do not understand what the previous studies have tried if not the same? Therefore, the wording should be changed so that the focus on routine conditions, is clear. “Routine” is also a quite unspecific word as routines between countries and centers vary substantially.

Authors` answer:
You are right “routine” is not a good wording. The DiaFu-study had the aim to evaluate effectiveness and safety of NPWT in German clinical practice. The best way to clarify the aim was to shorten it.

Also, the primary and secondary endpoints should be clearly communicated.

Authors` answer:
Following the guidelines for authors of the BMJ open we report the primary and secondary endpoints of our study in the methods section in the chapter “outcomes” (lines 234–266).

L169 “exposure of blood vessels” should be further clarified. You include DM “foot wounds” and probably most in the foot itself. So bypasses to adp and atp are clear, but what other blood vessel exposure was a contraindication?

Authors` answer:
Of cause, this is mainly relevant for the posterior tibial artery (Atp) and dorsalis pedis artery (Adp),

because only higher caliber arteries may cause in significant bleeding. We added this information in brackets but we would like to keep the rest of the wording. This exclusion criterion has been set during study planning: "… with exposed blood vessels within or directly surrounding the wound not possible to be sufficiently covered or with an increased risk of bleeding with hemodynamic consequences, and outpatients receiving anticoagulation therapy or suffering from a highgrade impaired clotting function with a heightened risk of bleeding with hemodynamic consequences … "
We understand that especially for a vascular surgeon this exclusion criterion is most likely to appear a little "over dimensioned". Additionally, many of the patients have a peripheral arterial disease. Due to fact that the DiaFu-study was set up as a real-life clinical practice trial, we adapted the real-life clinical practice conditions. If NPWT is used in clinical practice, the user is confronted with the medical product and the manufacturers` guideline. The guidelines of S&N and KCI contain very general contraindications of which this item is one. We adapted the wording into our exclusion criteria (keeping it general like in clinical practice). As we already published this exclusion criterion with the study protocol and it is shown like this in the registry, we have to report it in the results the same way.

L178 the patient sample is restricted due to economical reasons. Could this have had an effect on the results, please discuss in the discussion.

Authors` answer:
We assume that this comment refers to: "As the statutory health insurance funds provided integrated care contracts for outpatient NPWT, it was only possible to include patients in the study who were members of a participating health insurance fund.
This is not right. The sample size was calculated a described in the chapter "Statistical analysis" and was not restricted due to economic reasons. If a patient was not a member of a health insurance company supporting this study, it was simply not possible to include this patient. This is simple another exclusion criterion and that`s why we mentioned it with the other exclusion criteria in the chapter "Participants".

Methods. Did you consider using the WiFi classification?

Authors` answer:
The WIfI system merges existing classification systems, including the Infectious Diseases Society of America (IDSA) classification for diabetic foot infections, into single concise system. After grading each category, one can then clinically stage the affected limb to estimate risk of amputation at one year. Prediction of patients most likely to require and to benefit from revascularization can be based on the SVS WIfI lower extremity threatened limb classification.
Thank you for this information. This is an interesting system and useful when focusing on revascularization. We did not consider using the WIfI system. The classification systems we used were all selected during study planning and are reported alike. Thus, we are not able to adopt another system during reporting of the results.

L201 One of the most relevant issues would be the arterial perfusion. How was this assessed?

Authors` answer:
Pedal perfusion was assessed by Ankle Brachial Index (ABI), ankle and pedal Doppler arterial waveforms, and either toe systolic pressure or transcutaneous oxygen pressure (TcPO2).
We added this information in the manuscript.

How was the grade of infection defined?

Authors` answer:
For classification of a wound infection and the severity and outcome of treatment of a DFI, there is no

empirical evidence that one classification system (Meggit-Wagner, PEDIS [perfusion, extent/size, depth/tissue loss, infection, and sensation], SAD/SAD [size (area, depth), sepsis, arteriopathy, and denervation], SINBAD [site, ischemia, neuropathy, bacterial infection, area, and depth], or UT [University of Texas]) or one wound score (USI, DUSS [Diabetic Ulcer Severity Score], MAID [palpable pedal pulses (I), wound area (A), ulcer duration (D), and presence of multiple ulcerations (M)], or DFI Wound Score) is better than any other.
[Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2004;39:885-910]
In fact, during study planning we considered using the PEDIS classification I=infection, but the acceptance by the clinical investigators was poor, which resulted in documentation deficiencies. Thus, in the DiaFu-study infection diagnosis followed the approach involving clinical evaluation and laboratory testing, and in case of suspected diabetic foot osteomyelitis (DFO) a probe to bone test to aid in diagnosis and a stepwise approach to imaging modalities in order to confirm and to determine the best treatment regimen for the study participants.
We report the parameters at baseline accordingly in Table 2.
We added the relevant information in the manuscript.

L231- primary outcome(s) should be included in the methods and the wording shortened.

Authors` answer:
The chapter “outcomes”, which includes a description of the primary outcomes, is part of the methods section of the manuscript. We arranged the chapters following the guideline for authors of the BMJ open. We shortened the wording.

L239- these are not outcomes, but maybe confounding factors and the chapter on outcomes should be shortened

Authors` answer:
We moved the list of possible confounders to the chapter “Statistical analysis” as methods for analysis are described here and list should be most useful in connection with that. We shortened the chapter outcomes. Please note that some of the descriptions made here are due to comments of other reviewers that we have to keep in the chapter.

L241- please add references to the classification systems used

Authors` answer:
We added the references to the classification systems (now lines 297-303).

L265 for power calculations it is sufficient to state the assumed difference. The references 16 and 17 had as you point out not “routine” conditions or at least not the same as yours and therefore it is sufficient to just refer to them and shorten the text significantly.

Authors` answer:
We shortened the text accordingly.

Table 1 is lengthy and much of it could be presented as supplementary material, it should be clearly stated whether or not there were any significant differences between the groups?

Authors` answer:
We transferred parts of table 1 in the appendix and adapted the wording in the text.

Table 3, what was the definition of an insufficient or sufficient revascularization result?

Sufficient revascularization result was defined as successful recanalization of the tibial artery in which the foot lesion is located or, if it is technically impossible to recanalize the respective artery, achievement of an unhindered inflow into at least one of the tibial vessels.
W added this information in the legend of the table.

The wound healing rates show that the population was significantly different from the studies that were the basis for your power calculations (see comment above)

Authors` answer:
This comment refers to the following previous comment: “L265 for power calculations it is sufficient to state the assumed difference. The references 16 and 17 had as you point out not “routine” conditions or at least not the same as yours and therefore it is sufficient to just refer to them and shorten the text significantly.”

Not the wound healing rates show that the populations are different, but differences in the populations are a possible reason for differences in the wound healing rates. This can only be shown by a direct comparison of the populations. We compared the populations and summarized the most important parameters:
Other than the studies of Armstrong and Blume, the DiaFu-study included patients with Wagner stage four. In both studies, proof of adequate perfusion was an inclusion criterion, whereas the DiaFu-study, according to clinical practice, did not exclude patients with impaired perfusion, but required adequate therapy of the circulatory disorder according to clinical guidelines. However, baseline data show that the proportion of patients with critical limb ischemia is low and does not differ significantly between the treatment arms. Furthermore, both studies excluded patients with active Charcot, uncontrolled hyperglycemia and therapy with glucocorticoids, immunosuppressants or chemotherapy. Additionally, patients with venous insufficiency were excluded from the Armstrong study. The DiaFu study included more than twice as many patients as the Armstrong study and the patients were older than in both other studies. Wound size at inclusion was similar in the Blume and DiaFu studies. The Armstrong study included significantly larger wounds, which is explained by the exclusive inclusion of amputation wounds.
However, the probably most serious difference between the studies is that the DiaFu-study was performed in (German) real-life clinical practice including all factors that affect therapy.

We added this information to the discussion. Furthermore, we shortened other parts of the discussion.

L404- the information is available also in the table and should not be repeated in length in the manuscript

Authors` answer:
This refers to the results presentation of amputations or resections. We shortened the text.

L429 again the significances added to the table would give this information and the chapter could almost be omitted

Authors` answer:
This comment refers to the presentation of the safety results. We added a new Table 7 on the adverse events (AEs) and serious adverse events (SAEs) in the manuscript and shortened the text. We moved the old Table 7, reporting details on the AEs, to the appendix.

Figures 2- should include the statistical information and abbreviations. I would also consider inversing the curves 1-, starting down from 0.

Authors` answer:
We included the statistical information in the figures (2-5). The abbreviations could be included in the legends, but it seems like the BMJ open does not provide any legends for figures. Anyway, the figures still will be read in connection with the text and all abbreviations are explained in the manuscript, thus we will not provide explanations for abbreviations in the figures.
The curves are the correct and planned representation of the results. Starting from open wounds at the time of randomization / start of study therapy, the course is displayed. Kaplan Meier curves are normally used to show survival. In this case, the survival of the open wound over time is displayed correctly. Accordingly, the axes were also designated. The number of open wounds decreases in the course of the treatment time / the observation period. With a reversal of the curves, one could show the increase in the number of closed wounds, which, however, is contrary to the principle of the Kaplan Meier curves. We have opted for this representation together with our statistician, who has many years of experience in the evaluation of clinical studies, and will thus retain it.

VERSION 3 – REVIEW

REVIEWER	Pirkka Vikatmaa Helsinki University Hospital Department of vascular surgery Finland
REVIEW RETURNED	30-Nov-2019

GENERAL COMMENTS	Thank you for the clarifications and answers to my latest questions. I am sorry if some of them were doubled from the previous ones, but I jumped in in the middle. I also apologize for my stubbornness in questioning some issues in the study. Although I still do not agree with all of the answers the manuscript has improved. I still have some basic worries about the study. There is a substantial work included and I do agree with the authors that the negative answer should be opened to the public. However, also a negative answer should be open to critical review and if the negative answer depends on lacking power or structural problems in the study, then the readers should be made aware of these facts. It may be as harmful to give out a false negative conclusion as is stating a false positive one. The authors have conducted a rct for patients with diabetic foot ulcers, an unselected group. The idea is that by not restricting the inclusion criteria, the applicability of the study result will increase. The unavoidable consequence of this decision is the increased diversity of the patient material decreasing the specifity of the findings. As discussed previously, the power calculation is based on studies that have more strictly defined patient groups. When the authors made the decision to include “real life” material, then the number of patients should have been increased substantially and power calculation based on more specific studies is inevitably too weak. Indeed, this diversity problem is further underlined by some big difficulties, the authors faced with 58% dropout rate (after randomization 74% in the SWT and 14% in the NPWT group). The reasons were various, mainly protocol violations and losses to follow up. A dropout of more than 20% in a rct should be regarded as

	significant jeopardizing the interpretation of the result. The 7.6% cross over rate is acceptable. However, for the pp analysis the final groups are too small and for the itt the dropouts too many. The diversity in the patients is also noted in the extensively detailed reporting. As I tried to emphasise during the previous comment round the main findings should be easier to understand, “no difference in the main outcomes...”. A lot of the reporting could still be omitted as irrelevant to the simple question, although I understand that the open platform offers a possibility to extensive and detailed reporting, my personal opinion still is that less is more. The lack of difference is most probably caused by this lack of power, suggested e.g. in the pp analysis in figure 5. I also still have difficulties in understanding the definition of the critical ischaemia, a major player in the DM foot. The authors claim that there is a “small amount of critical limb ischaemia”, yet 65% of the patients are stated to have rest pain or worse (61,5% Rutherford III), usually a definition for CLTI (Supplementary Table). Also, after asking now it is stated that the foot perfusion is assessed with toe pressure or tcpo2 (as you know ABI is futile in this diabetic group), but no data is shown, on the contrary a previous study performed by Armstrong is claimed to have a weakness in securing that the perfusion is sufficient (>40mmHg TCPO2 in Armstrong et al). Only 9 patients in the per protocol group underwent revascularization prior to randomization, supporting the claim, but how did you make sure that the perfusion was even theoretically sufficient for wound healing? A DSA image showing a patent artery is not enough if no perfusion data is evaluated. The patency may last just a few hours after the image is taken. Sucking an ischemic wound will then remain futile. The primary outcome “wound closure rate”, should read “total epithelialization” or “wound closure”, not a rate or proportion as this describes the cohort and not an outcome of an individual patient. The authors state that PICO is not used to evaluate randomised studies, indeed it is a very good, simple and used method in meta-analysis (analyzing many rcts) and actually most research when trying to define if the study in question asks and answers the question at hand in a logical way. The Patients were ill specified leading to a need for more included patients, the Intervention was standardized (NPWT, were intermittent or different suction powers allowed?) in the study group, but many patients did not receive the intervention as planned. The Comparison was any treatment, thus introducing a problem if the treatments would happen to have a difference within themselves (it is thought that all wound dressings are the same, but there is no definite data to show this). The Outcome of complete epithelialization was well defined, but only a small proportion of the initial patients were available for this analysis. minor issues: L424- the recurrences. How many patients did you have in the recurrence analysis? Not all were analysed, so the recurrent rates should be adjusted accordingly. L426 a strange sentence: “For 9 of 244….the outcome death was documented arm.” The last “arm” is a typo, but death is final and

	serious and should read something like "…xx (xx%) patients died in the NPWT group…" The same for major amputation. The table on adverse events now moved to the supplementary material is still difficult to understand as the AEs are not defined. Table 1 wound area should read mm2

REVIEWER	Hongyan Xu Augusta University, United States
REVIEW RETURNED	26-Nov-2019

GENERAL COMMENTS	This is a revision. The authors have addressed my previous concerns sufficiently.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 4
Reviewer Name: Hongyan Xu
Institution and Country: Augusta University, United States
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
This is a revision. The authors have addressed my previous concerns sufficiently.

No answer necessary.

Reviewer: 3
Reviewer Name: Pirkka Vikatmaa
Institution and Country: Helsinki University Hospital, Department of vascular surgery, Finland
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

Thank you for the clarifications and answers to my latest questions. I am sorry if some of them were doubled from the previous ones, but I jumped in in the middle. I also apologize for my stubbornness in questioning some issues in the study. Although I still do not agree with all of the answers the manuscript has improved. I still have some basic worries about the study. :: There is a substantial work included and I do agree with the authors that the negative answer should be opened to the public. However, also a negative answer should be open to critical review and if the negative answer depends on lacking power or structural problems in the study, then the readers should be made aware of these facts. It may be as harmful to give outa false negative conclusion as is stating a false positive one.
Authors' reply: We fully agree with this statement.
The authors have conducted a rct for patients with diabetic foot ulcers, an unselected group. The idea is that by not restricting the inclusion criteria, the applicability of the study result will increase. The unavoidable consequence of this decision is the increased diversity of the patient material decreasing the specifity of the findings. As discussed previously, the power calculation is based on studies that have more strictly defined patient groups. When the authors made the decision to include "real life" material, then the number of patients should have been increased substantially and power calculation based on more specific studies is inevitably too weak.
A small restriction of the study population by inclusion and exclusion criteria supports the aim of the study to investigate effectiveness and safety of NPWT and SMWC in German clinical practice. An advantage is the easier transferability of the results into clinical practice. In lines 573 until 582 we already discuss the differences in the populations of the Armstrong &

Blume studies and the DiaFu-study! The patient population of the DiaFu-study was less restricted. It is possible, that the assumed difference for the outcome wound closure was too large due to the smaller restriction of the patient population. We would have had to assume a smaller difference, which would have led to a higher number of cases. However, we would have to assume that the included patients have a significant negative influence on the outcome wound closure, but during study planning we didn`t. On the contrary, we assumed that in clinical practice an adequate therapy of the relevant concomitant diseases is provided and these patients receive the specific wound therapy according to their needs. Furthermore, it was assumed that the proportion of these patients in the total population is not relevantly large. However, since there was a risk of an influence such as that described by you, we decided to include the relevant concomitant diseases in an additional confounder analysis (see also statistical methods). As you also suspected, a significant influence was found for PAOD and also for the infection (results section lines 479 – 484 in the version with highlighted changes). However, both confounders were approximately equally distributed over the treatment arms, so that it cannot be assumed that the difference between the treatment arms was impaired. However, there is a significant influence of POAD on the wound closure time and of infection on the overall wound healing rate. Thank you for pointing out this possible influence, which needs to be more strongly emphasized and adequately discussed in the right context.
Indeed, this diversity problem is further underlined by some big difficulties, the authors faced with 58% dropout rate (after randomization 74% in the SWT and 14% in the NPWT group). The reasons were various, mainly protocol violations and losses to follow up. A dropout of more than 20% in a rct should be regarded as significant jeopardizing the interpretation of the result. The 7.6% cross over rate is acceptable. However, for the pp analysis the final groups are too small and for the itt the dropouts too many.
The term “drop out” generally describes study participants who leave a clinical trial before the planned end. Our problem is the lack of documentation although the majority of patients had not left the study. But in the end, it's the same. If a participant withdraws from the trial for any reason, it is considered a protocol violation. Drop-outs are problematic if they are related to the therapy (and then distort the results of the study), or if they make the sample too small. As described in the paragraph on statistical analysis and as planned a priori, the primary analysis in our study was based on the ITT population. The intention-to-treat analysis is a conservative approach that tends to underestimate the effect of treatment. Using the "last observation carried forward" the open wound status was “carried forward” until the EOMTT. However, in practice not all patients adhere to therapy prescription, so that the intention-to-treat analysis also partly reflects everyday conditions. Per-protocol and as-treated analyses, on the other hand, tend to overestimation of the therapeutic effect. In fact, 23 patients who were incorrectly randomized were directly excluded from the ITT population. However, the total number of patients required for the analysis according to the sample size calculation was not influenced by this. However, there was a high loss of study participants in the PP population, which represents the secondary analysis population. In the NPWT arm 127 of 171 (74%) study participants were excluded (49 Not documented till end of maximum treatment time (EOMT) 3 No wound closure confirmation visit available 64 Premature end of therapy 11 Unauthorized therapy change to SWT). In the SCWT arm 64 of 174 (37%) study participants were excluded (39 Not documented till end of maximum treatment time (EOMT) 4 No wound closure confirmation visit available 4 Premature end of therapy 17 Therapy change to NPWT). For a high number of patients, documentation was lacking until the end of the maximum treatment period (Total=88, NPWT=49, SMWC=39) (see also Figure 1 CONSORT), which led to the exclusion of these patients from the PP population. In the primary analysis based on the ITT population, which included patients with protocol deviations, it was assumed that these patients did not achieve wound closure within 16 weeks study treatment and observation time. This may have led to a false negative bias in the outcome wound closure in the ITT population. Due to the high loss of patients, the validity of the PP analysis is very limited. We added these important facts to the discussion. Furthermore, we have already examined and presented the protocol violations by means of additional analyses with regard to their effect on the primary endpoint! Please see lines 544 – 570 in the results paragraph (treatment compliance and documentation quality).
The diversity in the patients is also noted in the extensively detailed reporting. As I tried

to emphasise during the previous comment round the main findings should be easier to understand, “no difference in the main outcomes...”. A lot of the reporting could still be omitted as irrelevant to the simple question, although I understand that the open platform offers a possibility to extensive and detailed reporting, my personal opiniontill is that less is more.
The manuscript was revised once again and shortened as far as possible. However, we would like to point out that some aspects, even if not in the focus of this reviewer, are important for the reader's understanding (who may not have the background knowledge). Furthermore, some descriptions have been requested by other reviewers and we would like to report the results of the study completely.
The lack of difference is most probably caused by this lack of power, suggested e.g. in the pp analysis in figure 5.
As mentioned in the above commentary and in the discussion of the article, the inclusion of patients with fewer inclusion and exclusion criteria has led to a different population. The highlighted relevant factors PAOD and infection were found to have a relevant influence on the wound closure time and the total wound closure rate, but were equally distributed in both arms. We accept the importance of this influence and added it to the discussion. However, we were able to highlight a strong influence of the deviations from the treatment guidelines and documentation deficits, which in our opinion have a stronger influence on the outcome wound closure.
I also still have difficulties in understanding the definition of the critical ischaemia, a major player in the DM foot. The authors claim that there is a “small amount of critical limb ischaemia”, yet 65% of the patients are stated to have rest pain or worse (61,5% Rutherford III), usually a definition for CLTI (Supplementary Table). Also, after asking now it is stated that the foot perfusion is assessed with toe pressure or tcpo2 (as you know ABI is futile in this diabetic group), but no data is shown, on the contrary a previous study performed by Armstrong is claimed to have a weakness in securing that the perfusion is sufficient (>40mmHg TCPO2 in Armstrong et al). Only 9 patients in the per protocol group underwent revascularization prior to randomization, supporting the claim, but how did you make sure that the perfusion was even theoretically sufficient for wound healing? A DSA image showing a patent artery is not enough if no perfusion data is evaluated. The patency may last just a few hours after the image is taken. Sucking an ischemic wound will then remain futile.