Author's response to reviews

Title: Risk of infection due to medical interventions via central venous catheters or implantable venous access port systems at the middle port of a three-way stopcock: luer lock cap vs. luer access split septum (Q-Syte)

Authors:

   Fabian Pohl (fabian.pohl@ukr.de)
   Werner Hartmann (wwhartmann@gmx.de)
   Thomas Holzmann (thomas.holzmann@ukr.de)
   Sandra Gensicke (sandra.gensicke@web.de)
   Oliver Kölbl (oliver.koelbl@ukr.de)

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Author's response to reviews: see over
Dear Mr. Nazareno,

I would like to refer to both reviewers about our manuscript entitled:

“Risk of infection due to medical interventions via central venous catheters or implantable venous access port systems at the middle port of a three-way stopcock: luer lock cap vs. luer access split septum (Q-Syte®)”

All comments were processed, the manuscript was changed in the way the reviewers suggested. We think that with all the changes suggested by the both reviewers the paper overall got a better comprehensibility.

Sincerely,

Fabian Pohl, MD
Comments to Reviewer 1

Anna Casey (1819612779100683_comment.pdf)

Major Compulsory Revisions

• The authors have previously stated that ethical committee approval was not required however, to my knowledge if patient consent is required for this work then ethical committee approval would be required, this is certainly the case in the UK. Furthermore, patients were excluded if they had received antibiotics. If determination of this factor involved review of medical records by people outside the normal care team this would also require ethical approval.

Answer:
The paper was shown to the local ethics committee to prove, if an ethical committee approval is necessary. Cases in which no ethical approval in Germany is necessary are studies where no human material (the used three-way cock was stated as "garbage", we got in addition a informal consent by all patients to use the "garbage") and where no personal data (which we did not use) was used.

You can have a look to the homepage of our local ethics committee, where you can find the full text to the upper statement.

http://ethikkommission.uni-regensburg.de/index.php/antragstellung.html

The affirmation of the local ethics committee that we do not need an ethical committee approval for our study was sent to BMC to be on hand.

• It is stated in the Background section of the abstract that contamination of the C-port is a risk that increases with the number of interventions and that lower interventions may be equated with better hygiene. For this reason a comparison of luer caps and the Q-Syte was performed. I think it would be beneficial to define here what an intervention is. The statement suggests that the use of the Q-Syte reduces the number of interventions whereas most people might assume that an intervention is the entire process of giving a particular drug.

Answer:
To specify the definition of “intervention” we modified the background section in the following way:

ABSTRACT
Even appropriate hygienic intervention maintenance carries the risk of contaminating the middle port (C-Port) of a three-way stopcock (TWC), a risk that increases with the number of medical interventions. Because of the complexity of the cleaning procedure with disconnection and reconnection of the standard luer lock cap (referred as “intervention”), we compared luer lock caps with a “closed access system” consisting of a luer access split septum system (BD Q-Syte®) with regard to hygiene (patient safety), process optimization (work simplification, process time), and efficiency (costs).
Depending on the type of cancer, one or more cytostatic drugs are intravenously administered via a CVC or a PORT, as well as parenteral nutrition or other medications, for instance, against nausea and emesis or for stomach protection. In addition, NaCl 0.9% rinsing solutions are used for cleaning catheters of cytostatic drugs and to ensure the patentcy of the catheter system. All these described administrations are designated as “intervention” in the following text.

• In the background it has been stated ‘For some time, the company BD has offered an alternative to the luer lock cap for avoiding health risks due to contamination of TWC hubs (C-ports), i.e. the Q-Syte,’……’ Many companies have offered alternatives to luer lock caps for some time and this should be stated rather than just identifying BD. Also, most of these products were developed originally to reduce needlestick injuries.

Answer:
To respond to the comment we modified the background section in the following way:

For some time, different companies offered an alternative to the luer lock cap for avoiding health risks due to contamination of TWC hubs (C-ports) or needlestick injuries, i.e. the Q-Syte® developed by BD (Becton, Dickinson and Company), a luer access system fitted with a transparent housing and a two-part silicone split septum (fig. 2).

• More detail is required in the methods section to describe the microbiological samples. I understand that no personal patient data was obtained, however were the 100 samples taken from 100 different patients?

Answer:
We got the 100 samples from 25 patients. As described in the paper we have on our ward a 24 h routine changing period of three-way cock systems. Most of the patients remained for more than two weeks on our ward for therapy. We stated this now also in the paper.

• In the methods section it was stated that the bacteria were semi-quantified however I see no results pertaining to this. If the results are reported as negative or positive then there is no requirement for this semi quantified description in the methodology, just a definition of positive and negative.

Answer:
To respond to the comment we modified the method section in the following way:

In case of a positive result [evaluated as positive sample], the bacteria were specified by means of biochemical examination. Samples without any signs of bacterial growth after 48 hours were defined as sterile and [evaluated as negative sample].

• I cannot review the process diagram in Figure 3 as it is written in German

Answer:
The process diagram should only show the complexity of the handling and cleaning process as described in the paper, therefore we felt no need to translate the diagram. The figure is now added with a translation of each step and the diagram was better explained in the paper (see page 6).

• I cannot review the NOMINAL sequence in Figure 4 as it is written in German

Answer: The process diagram should only show the complexity of the handling and cleaning process as described in the paper, therefore we felt no need to translate the diagram. The figure is now added with a translation of each step and the diagram was better explained in the paper (see page 6).

• There appears to be some problems with the referencing. References cited in the text commence with number 11, Hetem et al is reference 2, not 3 and reference 15 is mentioned in the text but does not appear in the reference list.

Answer: The reference list and referencing in the paper was revised.

Minor Essential Revisions
The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

• The sentence in the background section commencing ‘Depending on the complexity of the treatment protocol…’ would fit better following ‘…..patency of the catheter system.’

Answer: The sentence was rephrased (page 4).

• I appreciate that more detail has been given in the background regarding the three-way stopcock and luer lock cap used in the authors department however since these items are generic I think it would be suitable to just insert the manufacturer name and country in brackets without introduction into the sentence.

Answer: The proposal was converted (page 4).

• Figure 5 is not referred to in the text. In any case this could be incorporated into a key in figures 3 and 4.

Answer: The proposal was converted.
• In the discussion it is stated that measuring the contamination level of the products showed cost efficiency, however this was not directly investigated in this study.

Answer:
The main topic of the paper is the contamination level of the examined products. But we also addressed the cost efficiency (labour and material costs per use) on page 8. Excerpt of the paper: “For calculating average process costs (labour and material costs per use), we used 1000 simulations resulting in 3.92 € for luer lock caps and 2.55 € for the BD Q-Syte® access system.”

• It has been stated in the discussion that the contamination rates indicated in other trials correspond with the data obtained in the authors observation however no references are given.

Answer:

• Would it be possible to add in statistics for the comparison of meaning working times?

Answer:
The main topic of the paper is the contamination level of the examined products. We also addressed the cost efficiency with calculating the average process costs (labour and material costs per use). The main difference regarding the labour between the luer access split septum system and the luer lock cap is the smaller number of work procedures with the luer access split septum system as demonstrated in figure 3 and 4. So the meaning working time for both procedures would give no additional information.

Minor issues not for publication
• In the background ‘Infusion hose’ would better read ‘Infusion set’ or ‘Infusion line’

Answer:
The proposal was converted.

• The paragraph commencing ‘to avert injuries, each medical facility in Germany….’ This does not add anything to the paper and could be removed.

Answer:
The paragraph should show that the hygienic risk management – which is the main topic of the paper - is not only important for itself, it is also demanded by law. Therefore we does not want to remove the paragraph.
• Figure 6 is not required as a description of the process is sufficient
  Answer:
  Figure 6 was deleted.

• Figure 8 – the title is in German
  Answer:
  The title is translated to English.

• It would be more accurate to describe the microbiology element as cultures throughout rather than smears.
  Answer:
  The proposal was converted.

• The language used in this article is not really consistent with that used in infectious diseases journals, it would help to reduce jargon.
  Answer:
  The paper was written by a radiooncologist working in a university hospital, so this explains the “jargon”. Additionally the paper was revised regarding the language by Experts for medical and scientific translation.

• There are some typos and consistency issues throughout particularly regarding ‘3-way stopcock’.
  Answer:
  The name “3-way stopcock” was changed to “three-way stopcock” in the paper.

Thank you very much for your constructive review.

Sincerely,

Fabian Pohl, MD
Comments to Reviewer 2

Jun Oto (2136720451001717_comment.pdf)

Major Compulsory Revisions

Background:

1) Why were citation numbers started from (11)?

Answer:
The reference list and referencing in the paper was revised.

2) p4, line 14-19: “Figure 1 ... Heidelberg, Germany.” Please delete these sentences because almost all readers know about three-way stopcocks and luer caps.

Answer:
We wanted to show which material we use in our hospital. We think, this is necessary, so that the reader can compare it with his own material.

3) It would be preferable if the test device could be referred to generically rather than by brand name throughout the paper. The brand name and manufacturer should be listed only in the Methods section. That presents the paper as more ‘scientific’ and less just product testing.

Answer:
Whenever possible we changed the brand name to „luer access split septum system”.

Methods section:

1) p6, line 2-3:
How were the two groups assigned? Where was this study conducted? Please state ethical and consent statements.

Answer:
We compared two systems, the „conventional“ luer lock cap with the „new“ luer access split septum system. The choice which of the patients was provided with the conventional or new system was by chance. All used three-way cocks were from adult patients treated in the Department of Radiooncology, University Hospital Regensburg, Germany. All patients were asked in front to give their written informed consent. The research was in compliance with the Helsinki Declaration.
The paper was shown to the local ethics committee to prove, if an ethical committee approval is necessary. Cases in which no ethical approval in Germany is necessary are studies where no human material (the used three-way cock was stated as "garbage”, we got in addition a informal consent by all patients to use the "garbage") and where no personal data (which we did not use) was used.

You can have a look to the homepage of our local ethics committee, where you can find the full text to the upper statement.

http://ethikkommission.uni-regensburg.de/index.php/antragstellung.html

The affirmation of the local ethics committee that we do not need an ethical committee approval for our study was sent to BMC to be on hand.
We stated this also in the paper on bottom of page 7.

2) p6, line 6-10:
Unfortunately, this reviewer cannot understand how to compare these two systems because the authors did not describe the details of their study process in the methods section. As an example, for the determination of process optimization, the authors represent the workflow of intervention. However, it is unclear why they used these figures? What are they designed to show? What is the difference between these two figures? In addition, Figure 3 and Figure 4 are written in German, so this reviewer cannot completely understand.
Answer:
The process diagrams (figure 3 and 4) should only show the complexity of the handling and cleaning process as described in the paper, therefore we felt no need to translate the diagram. The figures are now added with a translation of each step and the diagrams were better explained in the paper (see page 6).

3) p6, line 13:
“we analyzed use of material and time parameters per intervention”. How did you define “per intervention”? Please explain more clearly.
Answer:
To specify the definition of “intervention” we modified the background section in the following way:

ABSTRACT
Even appropriate hygienic intervention maintenance carries the risk of contaminating the middle port (C-Port) of a three-way stopcock (TWC), a risk that increases with the number of medical interventions. Because of the complexity of the cleaning procedure with disconnection and reconnection of the standard luer lock cap (referred as “intervention”), we compared luer lock caps with a „closed access system“ consisting of a luer access split septum system (BD Q-Syte®) with regard to hygiene (patient safety), process optimization (work simplification, process time), and efficiency (costs).

PAPER
Depending on the type of cancer, one or more cytostatic drugs are intravenously administered via a CVC or a PORT, as well as parenteral nutrition or other medications, for instance, against nausea and emesis or for stomach protection. In addition, NaCl 0.9% rinsing solutions are used for cleaning catheters of cytostatic drugs and to ensure the patency of the catheter system. All these described administrations are designated as “intervention” in the following text.

4) p6, line 13-16:
“These process parameters were used...discrete event simulation (13).” Reference 13 does not describe these methods. Thus, this reviewer cannot understand how the medical costs were calculated.
Answer:
Correct reference is IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; Technischer Anhang Modellierung Seite 38, Punkt 10.2.2.; Köln Oktober 2008; www.iqwig.de, now reference number 7. The reference list and referencing in the paper was revised.
The main topic of the paper is the contamination level of the examined products. We also addressed the cost efficiency with calculating the average process costs (labour and material costs per use). The main difference regarding the labour between the luer access split septum system and the luer lock cap is the smaller number of work procedures with the luer access split septum system as demonstrated in figure 3 and 4. The medical costs are the costs of the used material and the labour time of the nurses per use based on setting in Germany (e.g. wages).

5) p8, line 5-6:
“semi-quantitatively”: This is “qualitative”, not “quantitative”, as currently described. How were “very little, little, moderate, and much” defined?
Answer:
To respond to the comment we modified the method section in the following way:
In case of a positive result [evaluated as positive sample], the bacteria were specified by means of biochemical examination. Samples without any signs of bacterial growth after 48 hours were defined as sterile and [evaluated as negative sample].

6) Please summarize about statistical analysis as a separate paragraph.
Answer:
We summarized the statistical analysis as separate paragraph on page 7.

7) Please explain how the three-way stopcock and closed system were disinfected when medical practitioners access the infusion line?
Answer:
We modified the methods section in the following way (page 8):
Before intervention the luer access split septum system connected to the C-port has been cleaned with a wiping disinfection using an antiseptic pad, the luer lock cap connected to the C-port has been cleaned with a spraying disinfection.

Results section:
1) p8, line 15 “The difference...(design, packaging, location)...” Please explain clearly what the differences between the conventional luer lock cap and the luer access split septum?
Answer:
The luer lock cap lies in different direction in the packaging, so you cannot open it „blindfolded“, which means a danger of contamination and need for a new second cap. Because of the more complex handling it can also fall down, so you need a new third cap. We think, that the reader knows these circumstances.

2) p8, line 21; “For calculating average process costs (labor and material costs per use),....” Please define what a labor cost is. How did you calculate 1000 simulations costs?
Answer:
The average process costs are the costs of the used material and the labour time of the nurses per use based on the salary in Germany.
We modified the sentence in the following way (page 9):
For calculating average process costs ([labour time multiplied with salary] and material costs per use),....
These process parameters were used for programming the process into a simulation run (n = 1000) to determine the process costs per intervention as well as their differences (ACTUAL
3) Figure 7: This reviewer cannot understand how this was calculated. Please explain this statistical analysis in the methods section and the figure legend.
Answer:
Figure 7 was changed to figure 5. A hypothesis test is a common statistical test. Statistical hypothesis tests define a procedure which controls (fixes) the probability of incorrectly deciding that a default position (null hypothesis) is incorrect based on how likely it would be for a set of observations to occur if the null hypothesis were true. We think that the explanation of the test itself in the paper would be too extensive.

4) Figure 8: This reviewer cannot understand how this was calculated.
Answer:
Figure 8 was changed to figure 6. A Break-even calculation or scatter plot is a common business analysing tool for estimating demand information and trends in revenue. In each of these, you can simplify the analysis to a straight line. We think that the explanation of the plot itself in the paper would be too extensive.

5) In addition, this reviewer cannot understand what figure 5 represents. Please explain this more clearly.
Answer:
Figure 5 is the meaning of the symbolism used in the process diagrams (figure 3 and 4). We incorporated figure 5 to figure 3 and 4.

6) p9, line 5: What is DWH? Please explain this.
Answer:
DWH means in German the same as TWC. DWH was changed to TWC.

7) “In 50 reviewed samples”: How was this sample size determined?
Answer:
In the project planning we assumed that 100 samples (50 samples per system) would be a sufficient number, anyway we also had to be careful with the project costs.

8) Where did you show your “semi-qualitative” microbiological results?
Answer:
We modified the method section in the following way:
In case of a positive result (evaluated as positive sample), the bacteria were specified by means of biochemical examination. Samples without any signs of bacterial growth after 48 hours were defined as sterile and evaluated as negative sample.
We only showed our qualitative results.

9) p10 line 6: “possible hygienic risks....NOMINAL work process (Fig 4).” How did you calculate these values? Please explain clearly.
Answer:
The possible hygienic risks were related to material, surroundings, and staff handling, that means for example that the luer lock cap lies in different direction in the packaging, so you cannot open it „blindfolded“, which means a danger of contamination with every intervention (ACTUAL process). In the luer access split septum system we connect the luer access split septum system with the C-port only once (NOMINAL process), so the hygienic risks as compared to the luer lock cap is omitted.

Discussion:
In most parts of discussion section, the authors did not discuss about their findings. This reviewer recommends the authors rewrite all parts of the discussion section.

Answer:
We think that with all the changes suggested by the both reviewers the paper overall got a better comprehensibility.

Minor Compulsory revisions:

Abstract:
1) Background: “The BD...Devices (BfArM)”. Please delete this part.

Answer:
Part was deleted.

Background:
1) p4, line 18: Please change “und” to “and”.

Answer:
„CLS Medizintechnik und Vertrieb, Adelebsen, Germany“ is the company name, therefore we can`t change it.

2) p5, line 9: Please change #closed access system” to “closed access system”.

Answer:
The proposal was converted.

3) p5, line 2-10: It is better to transfer this part to the methods section.

Answer:
We think that the explanation of the differences between the two systems belong to the background section.

Methods:
1) p7 line 8-9: “The research was in compliance with the Helsinki Declaration”. The local IRB should evaluate if your study was in compliance with the Helsinki Declaration because your study qualified as human research. If the authors state ethical and consent statements, this sentence may not be needed.

Answer:
As stated before the affirmation of the local ethics committee that we do not need an ethical committee approval for our study was sent to BMC to be on hand.
Thank you very much for your constructive review.

Sincerely,

Fabian Pohl, MD