Response to reviewer comments on manuscript ID: 56046

Date: 17th of August 2020

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: Comments Manuscript NO: 56046 Title: Introduction of novel Total Knee Arthroplasty system influences surgery related factors and implant positioning immediately following implementation Manuscript Type: Retrospective Study Dear authors, Thank you to give me the opportunity to review your article. You will f ind some comments in the reviewed manuscript enclosed. the topic is very interesting and innovative specialy in the context of the new regulations applied in the European community " medical device regulation". In the introduction it would be helpful to cite an article dealing with this topic. Klar E. Medical Device Regulation als aktuelle Herausforderung für die rechtssichere Einführung neuer Technologien [Medical Device Regulation as current challenge for the legally safe introduction of new technologies]. Chirurg. 2018;89(10):755-759. doi:10.1007/s00104-018-0705-3 Melvin T, Torre M. New medical device regulations: the regulator's view. EFORT Open Rev. 2019;4(6):351-356. Published 2019 Jun 3. doi:10.1302/2058-5241.4.180061 Martelli N, Eskenazy D, Déan C, et al. New European Regulation for Medical Devices: What Is Changing?. Cardiovasc Intervent Radiol. 2019;42(9):1272-1278. doi:10.1007/s00270-019-02247-0 Material and methods The study is nicely constructed but for a better understanding of the selection process please provide to the lector a flow chart of the selection to identify each group of patients. If we consider that the patient factors are the same, that the surgical factor is not biased by a study with 3 surgeons, that the prosthesis is almost conceptually identical (CR design), what are the factors that can significantly influence this lengthening of operating time and bleeding? What was the fixation of Persona compared to control group cemented or cementless? What about the instruments? What are the main differences between Persona and the other instruments you regularly used in the control group? You need to analyze the concept of the ancillary which may be the "roots" cause of this difference? Intramedullary rods? Difficulties in locating the axes and cutting levels etc... Basically the implant alone cannot disturb an experienced surgeon as much. The work is very interesting but the analysis of the root causes of these differences is not reported in the study. There is simply an analysis of the side effects but no analysis of the causes. You have to look in detail for differences that may exist between the two systems outside the implant. However, if the implant is fundamentally different (e.g. fixation method) this factor can be considered as discriminating in the differences in results. Have you abandoned this system? The work is very interesting but the analysis of the root causes of these differences is not reported in the study.

Reply:

Dear Reviewer #1,

Thank you for the comments. We appreciate your valuable input and reflections on our study.

As medical devices is a field undergoing rapid advances with high output of new devices with many purported benefits, we agree with your reflections on incorporating the stricter scrutiny in regulatory environment seen in recent years. As such please refer to line 47-50

where we have addressed this. Thank you for supplying suitable references which we have read and included.

Thank you for the remarks regarding the nice construction of our study and its interesting aspects. As per your request, we have further added a flowchart depicting the patient selection process for this study to enhance any readers initial overview (Figure 1).

Both knee implants had the same conceptual basis through their shared CR design. Both were fully cemented and made use of patella resurfacing along with use of intramedullary and extramedullary guide for femur and tibia, respectively. Yet the novel system's (Persona) different instrumentation combined with wider range of adjustment options compared to the conventional system constituted significant changes and considerations during TKA surgery when comparing systems.

The Persona system differed with respect to anatomical baseplate, option for 1mm increment adjustment for tibial bearing size, option for adjusting gaps through anteriorized and posteriorized instrumentation of the femur, option to adjust distal femoral resection in 1mm increments and option to adjust distal femoral resection angle in 1-degree increments. We have now specified this in the main text on line 109-114. We consequently believe the differences between systems largely can be attributed to the differences in instrumentation. Hence, we believe the subsequent increase in operation time of ~14 minutes in the beginning of the learning curve is a direct consequence of a more complex instrumentation (or a more variable instrumentation if you will). Increases in blood loss may be a result of the increased operation time as surgical time shows a positive correlation with increased blood loss (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2267526/). This point has now been added to the manuscript on line 258-264 we also find it important to address in the main text.

We now no longer use the older AGC system at our institution.

Reviewer #2:
Scientific Quality: Grade D (Fair)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: The article "Introduction of novel Total Knee Arthroplasty system influences surgery related factors and implant positioning immediately following implementation" does not have any new message. Any new procedure is bound to have a learning curve and some difficulties. The title mentions about Novel system but have evaluated only one new implant viz Persona® (Zimmer-Biomet, Warsaw, Indiana, USA). The title "Outcomes after first 75 consecutive unilateral primary TKA using Persona® (Zimmer-Biomet, Warsaw, Indiana, USA)"..would be more appropriate. Increase the operation time by 14 minutes, though statistically significant, is clinically insignificant. Blood loss increase of 50 ml..or 25% may sound a lot but is totally insignificant in ASA II adult patients. Also, were patient blood management (PBM) measures for decreasing blood loss were same in all groups? Was tranexamic acid was used in all patients? Was the type of anesthesia same in all patients.. regional or general anesthesia? The authors need to look at the post-operative pain factor too, especially as the LOS in the hospital was halved. These patients should be followed up after 1 year, 2 years and 3 years (and 5 years if possible) for the degree of movement and any other complications and compared with the control group. Line 106…? 71-, 54-, and 75 % by the….do you mean 71%, 54% and 75%

Reply:

Dear Reviewer #2,

Thank you for the input and we appreciate your fine reflections on our study.

We agree with your remarks regarding the title of the study. While it doesn't carry any new information by itself and any procedure is bound to have a learning curve, we believe it adequately represented the issue which this study revolves around. Nevertheless, after further consideration we agree the title manages to come off as trivial, and we have as per your request changed it. We would like to thank you for your title proposal and hope that you can accept we have chosen a combination of your suggestion and our suggestions. The new title is: "Early clinical outcome and learning curve following unilateral primary total knee arthroplasty after introduction of novel TKA system".

It is indeed very true that this study only evaluated introduction of one novel implant at our institution. However, in accordance with the aim of this study, it was deemed sufficient to demonstrate short-term clinical outcomes for patients with emphasis on how surgery related factors and implant positioning were affected by introduction of a novel TKA system. As surgical skill, experience and caseload varies across orthopeadic surgeons we ensured a study design which accounted for these variances by studying the same experienced othropeadic surgeons throughout the study. Furthermore, attention was also given to examining utilization rate for a novel system across surgeons, and how surgical experience with the implant affects outcome by including a follow-up group.

While investigating introduction of a range of novel TKA systems could likely have given us a better understanding of the intra-class variance in Introduction- and follow-up groups, we believe the overarching goal is not to demonstrate the variance between different novel systems and their mutual relation. Rather we aim to explore the early clinical outcome, implant positioning and adaptation of a novel system during its introduction.

We would like to respectfully disagree with the proposed claims of mean increase in operation time of 14 minutes is clinically insignificant as it constitutes a 28 % increase. With 3 and 5 cases daily, this difference sums up to 42 minutes and 1 hour and 10 minutes, respectively. In relation to blood loss we agree that 50 mL increase is a minor difference with little clinical relevance. This is likely a consequence of the increase in operation time as a positive correlation has been documented in other studies (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2267526/). We have now specifically included a description of the clinical relevance of operation time and blood loss in the main text, as it is an important element to address. Please see line 258-264 where we have addressed this.

Blood loss management was similar across TKA systems with bone plugging of femoral canal, 1 g tranexamic acid administered at start of operation and readministered 3 hours later. No drain or tourniquet was applied, and spinal anesthesia was given to all patients. This was not directly stated in the manuscript which we now have corrected. Please refer to line 114-117.

With respect to comments about the post-operative pain factor and length of stay was halved, please refer to line 276-280 in the manuscript where we have explained the probable cause.

This finding is most likely unrelated to the implant, as continuous evolvement of the fast-track setup in our institution with continuously decreasing LOS may explain the differences in LOS between groups (https://pubmed.ncbi.nlm.nih.gov/28918788/).

While a longer-term outcome could be interesting to follow, this study is neither designed nor aimed at accounting for longer-term outcome to TKA surgery in a comprehensive manner. We are exclusively interested in the early logistical challenges posed by introduction of a novel system.

This study is consequently exclusively aimed at short-term clinical outcomes for patients with emphasis on how surgery related factors and implant positioning were affected by introduction of a novel TKA system. Also, focus was also given to examining utilization rate for a novel system across surgeons and how surgical experience with the implant affects outcome. As an example, a longer-term study on learning curves following TKA(https://pubmed.ncbi.nlm.nih.gov/24306696/) examined a total of +46.000 TKAs using the 10 most common TKA models across a range of institutions. Follow-up analysis was conducted after 3,5 and 10 years. We are convinced our study on short term outcome, alignment and novel component utilization should be seen as a complement to long-term follow-up studies such as the one mentioned, as long-term follow-up learning curve studies are well described in the existing literature.

Thank you for the correction on line 106 (it is now line 171-172 in the revised manuscript). We have corrected the changes as per your request.

Reviewer #3:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: This manuscript describes a study on how implementation of a new TKA system influences perioperative and surgical outcome. The authors found an increase in operation time of 14 minutes (from 50 to 64 minutes) immediately after introduction, with a median intraoperative blood loss significantly increased from 200 mL to 250 mL following the introduction. The differences diminish one year after the introduction of the new implant. The manuscript is well written. The study design is reasonable. The study was well conducted and analyzed. The discussion is balanced. The findings support previous published data. The study does add new information to the field. This is a clinical study therefore if it were done in the United States it would need IRB review and approval. The authors stated “No approval from the National Ethics Committee was necessary as this was a non-interventional observational study. Permission to store and review patient data was obtained from the Danish Data Protection Agency Jr, No. 2007-58-0015.”, so please double check that this will meet the criteria by Danish regulatory agency, and meet the standard of publication by the Journal. It is not clear if surgeons used tourniquet or not during surgery. With recently almost universal use of tranexamic acid, intra-op blood loss is truly minimal. Please add this info and briefly discuss why patient in the study had average of 250 ml blood loss. Thanks for submitting your study to WJO.

Reply:

Dear Reviewer #3,

Thank you for the kind comments. We appreciate your valuable input.

We are happy you find the study well written and that it adds new information to the field. We are also pleased to hear the study design is reasonable and the discussion balanced.

As you suggest, we have double checked that this study meets the criteria by the Danish regulatory agency and the standards of publication by WJO.

No drain or tourniquet was applied. Blood loss management was similar across TKA systems with bone plugging of femoral canal, 1 g tranexamic acid administered at start of operation and readministered 3 hours later. We have now described this in the manuscript on line 114-117. We agree that universal use of tranexamic acid has reduced intra-op blood loss during TKA. A median blood loss of 200 mL is regarded relatively normal. It possibly deviates slightly to the larger side but not in any abnormal fashion, as other studies show 200 mL median blood loss and ~150 mL mean blood loss. (https://pubmed.ncbi.nlm.nih.gov/27194493/, https://www.nature.com/articles/s41598-018-31791-x, https://www.arthroplastyjournal.org/article/S0883-5403(19)31006-X/fulltext). The subsequent increase from 200 mL to 250 mL in mean intra-operative blood loss in Introduction Group, may partly be a result of the increased operation time as it shows a positive correlation with increased blood loss(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2267526/). We have now stated this on line 262-264.

Reviewer #4:
Scientific Quality: Grade D (Fair)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Major revision
Specific Comments to Authors: the paper need an abstract The authors need to clarify in the paper text any fund from the manufacturers or suspected bias that could affect the methodology or results and conclusions longer follow-up is needed and that need to be a very clear point of weakness in the discussion

Reply:

Dear Reviewer #4,

Thank you for the feedback.

We did supply an abstract to WJO in our submission and as such we are unsure what is meant by your comment: *"the paper need an abstract".* We uploaded the abstract in the "abstract window" during the online submission process and therefore did not include it in the "main text document". To avoid any further confusion, we have now added the abstract to the start of the revised main text document as well (Line 5-41).

We very much agree with your point on transparent funding and explaining any subsequent bias it may have caused. It is an important element not to be overlooked in any study. However, this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. We have now stated this specifically on line 158-159 in the paper text. Also, information bias seems unlikely as all the surgeons operated as business per usual without any knowledge of later comparisons or of the mere existence of this study. As mentioned in line 296-297 we used secure local registries which ensure that data is collected unbiasedly. Only after the study period ended was the surgeons informed and consent obtained. No data or analysis has been handled by any of the surgeons in any way.

As for selection bias specifically, we believe it can be regarded as negligible. Baseline characteristics shown in Table 1 indicates the 3 groups (Control, Introduction and Follow-up) were largely similar across gender, BMI, varus/valgus outliers and pre-operative tibio-femoral angle. If anything, the patients in Introduction Group were healthier than controls due to slightly younger age (~4.5 years) and smaller prevalence of ASA-III patients (24 % in Control group and 13 % in Introduction group).

A possibility exists that it could mask a slightly worse early clinical outcome for the first adaptors to the novel TKA system (Introduction Group) than documented in this study, caused by these small differences in baseline characteristics. This would in turn exacerbate the differences in found in early clinical outcome, and further bolster our conclusion of small gains in alignment should be held up against worse early clinical outcome. In summary, while we believe this study is minimally affected by selection bias which baseline measurements chiefly support, we believe our findings if anything leans more to a conservative side. For reference, ASA-III is a predictor for poor surgical outcome with studies finding increased readmission rates and length of stay (https://pubmed.ncbi.nlm.nih.gov/25575729/ and https://pubmed.ncbi.nlm.nih.gov/26685683/).

While a longer-term outcome could be interesting to follow, this study is neither designed nor aimed at accounting for longer-term outcome to TKA surgery in a comprehensive manner. We are exclusively interested in the early logistical challenges posed by introduction of a novel system. This study therefore focused on short-term clinical outcomes for patients with emphasis on how surgery related factors and implant positioning were affected by introduction of a novel TKA system. Additionally, focus was also given to examining utilization rate for a novel system across surgeons and how surgical experience with the implant affects outcome.

In the existing literature thorough studies on longer term outcome have been conducted where focus traditionally centers around implant survivorship, loosening and revisions, whereas the immediate short-term clinical outcome focuses on blood loss, length of operation/stay, intra-operative complications and readmissions within first 90 days. For reference, a longer-term study on learning curves following TKA by Peltola et al (https://pubmed.ncbi.nlm.nih.gov/24306696/), examined a total of +46.000 TKAs using the 10 most common TKA models across a range of institutions. Follow-up analysis was conducted after 3,5 and 10 years. Based on the long term follow up, they concluded when implant excellence is assessed for survival and implants are compared with each other, there may be a learning curve and the results achieved may be poorer for the first patients. They further emphasize the need for managed uptake of new technology in clinical practice including quantitative assessment of individual performance. We are convinced our study on

short term clinical outcome, alignment and novel component utilization should be regarded as a complement to these long-term follow-up studies. Even with concentrated effort to highlight specific longer-term outcome variables in our study, we believe this study would be insufficiently powered to state anything conclusive.