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## ***Evaluating Implant Fractures with the Premiere Hospital Databank***

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As investigators of the same implant in the US and Australia we were interested in ‘Comparative Safety of the TFN-ADVANCED Proximal Femoral Nailing System’ by Wallace et. al. (1) This study found no difference between breakage rates of TFNA and non-TFNA nails.

There are some concerns regarding the data in the premiere hospital databank (PHD). If the patient was referred to a higher level of care for their revision procedure breakage is not captured, which may be relevant considering 60% of the hospitals in the data set are small community hospitals. At one author’s 800+ bed academic institution, five implant fractures in the Gamma 3 and TFNa implants were referred from outside institutions within the same time interval. The location of the breakage is unidentified and could be variable, so that breakage of the proximal nail body in one group could be compared to the breakage of a different component in another. (2-5) The studies by Lambers et al and Johnson et al demonstrate that nail breakages occurred almost exclusively in unstable fracture patterns. (2,6) Here there was no difference in breakage rates amongst different patterns which seemed unusual, and likely due to errors in ICD9/ICD10 coding to classify them. (7)

Time to breakage in our previous studies suggested earlier failures in the TFNA than is typically seen of nail breakage. (2,4) In the survival curve presented in this study there appeared to be a higher rate of TFNA failures before 6 months which wasn’t commented on. We questioned why breakage during the index episode of care was one of the exclusion criterion as this would be exceedingly rare.

We accept the declared conflict of interest from the authors who are employees of the company that manufactures the TFNa implant, and we commend their efforts in assessing post market surveillance with their publication. The study provides further data on breakage rates of the TFNA, however does not

answer the question about breakage rate comparisons due to the study design limitations.

Disclaimer: e-Letters represent the opinions of the individual authors and are not copy-edited or verified by JBJS.

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Conflict of Interest: None Declared

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## Article Author Response

8 November 2021

*Article Author(s) to Letter Writer(s)*

**Letter in response to the eLetter by Klima and Lambers about our TFNA study published in JBJS.**

Jennifer Wood, PhD, Guy Cafri, PhD, Anna Wallace, PhD, Paul Coplan, ScD

We thank Drs. Klima and Lambers (hereafter referred to as ‘the authors’) for their interest in our study (1). We appreciate the opportunity to discuss the topics that they raised as they pertain to our study and to understanding and interpreting real-world evidence studies more generally.

The primary objective of our study was to evaluate the comparative safety of TFNA vs. comparable devices (hereafter referred to as ‘non-TFNA nails’). As it relates to the outcome of nail breakage, *comparative* means that interest is in evaluating the difference in risk between the groups (as opposed to

the risk in an individual group), and *safety* means an assessment of how safe the device is for general use. Our study used state-of-the-art real-world data methods (2,3,4) to compare breakage rates in a cohort of femoral fracture patients treated with the TFNA nail compared to a cohort treated with non-TFNA nails (Stryker Gamma3 and Zimmer Natural Nail). The active comparator cohort design enabled us to identify large cohorts (i.e., 14,370 patients implanted with TFNA and 8,260 patients implanted with Gamma3 and Natural Nail) with known denominators and the propensity score method ensured that cohorts were similar on baseline measured characteristics to reduce confounding. These rigorous methods overcome important limitations of other published studies that used case series of nail breakages to make inferences about safety. Below we provide point-by-point responses explaining how the points raised by the authors are addressed by our study design and analysis approach.

*Point 1. If the patient was referred to a higher level of care for their revision procedure, breakage is not captured in the hospital database.* As described in our article, a limitation of the Premier Healthcare Database (PHD) is that nail breakages that present to a facility different from the one in which the original implantation took place are not captured. This has the impact of underestimating the absolute risk of breakage within each study group. In addition and which is more relevant to the objective of the study, is the potential impact on the difference in risk between the two cohorts. The authors comment that up to 60% of hospitals in our study are small community hospitals and imply that they would not treat a nail breakage. Therefore, patients who had index procedures performed in these hospitals may not have all breakages recorded in the PHD. Missing 60% of breaks corresponds to a true risk of breakage of 2.5 times the observed risk, which is less than 3 times the observed risk used in the sensitivity analysis performed in our paper, resulting in a small risk difference of 0.025% at 18 months (5,6). While our data indicate that approximately 60% of patients had index procedures performed in smaller hospitals (i.e., hospital bed size < 400), it is unlikely that among patients with index procedures performed in these hospitals, who had subsequent nail breakages, *all* would have been referred to a different hospital for their revision procedures. Therefore, given that the results from the sensitivity analysis are similar to those based on the data, even after making an extreme assumption about data capture, the results suggest that our findings are robust to this concern.

In addition, in our main analysis, it is important to point out that hospital bed size was among the baseline covariates that were balanced using the propensity score analysis. Given the similarity between TFNA and non-TFNA cohorts on this covariate after balancing, there is relatively little concern that it would have led to confounding of the study results.

*Point 2. Location of the breakage is unidentified and could be variable, so that breakage of the proximal nail body in one group could be compared to the breakage of a different component in another.* The

authors are correct that the location of nail breakage could not be identified in PHD. However, the intent of our study was to assess the overall comparative risk of nail breakage, regardless of the location of the break, as this is more informative and more impactful to understanding patient safety.

Point 3. *The studies by Lambers et al and Johnson et al demonstrate that nail breakages occurred almost exclusively in unstable fracture patterns. Here there was no difference in breakage rates amongst different patterns which seemed unusual, and likely due to errors in ICD9/ICD10 coding to classify them.* First, we did not categorize patients according to stable or unstable femur fracture patterns, as ICD9/ICD10 coding does not contain this level of detail. It is unclear what the authors are referring to regarding errors in ICD9/ICD10 coding. Second, we did not report breakage rates amongst different femur fracture patterns; we did, however, categorize and analyze patients according to the location of the femur fracture at the time of index procedure as a subgroup analysis. This subgroup analysis reported the risk difference of nail breakage between TFNA and non-TFNA patients *within* specific femur fracture locations to evaluate the robustness of our conclusions.

Point 4. *Time to breakage in previous studies suggested earlier failures in TFNA and in the Klima (7) and Lambers et al (8) studies there appeared to be a higher rate of TFNA failures before 6 months, which was not commented on in the Wallace et al. paper.* Our choice to focus on the risk difference at 18 months reflects a focus on a broader evaluation of the safety of the TFNA nail, which is better ascertained after longer (rather than shorter) follow-up to ensure capture of most nail breakages. This time-period was pre-specified prior to study execution in a publicly-posted protocol and statistical analysis plan (SAP). Post-hoc evaluation of differences along the survival curve is susceptible to investigator bias and should be done with caution. Nevertheless, we note that within the first 6 months, after adjusting for patient covariate differences, the breakage rate was 0.13% and 0.10% in the TFNA and comparator groups, corresponding to a risk difference of 0.03%. We also note that the largest risk difference within the first 6 months was at 4 months when it was 0.07% (95% CI: -0.01% to 0.14%), which can be inferred from Figure 3.

Point 5. *A question of why breakage during the index episode of care was one of the exclusion criteria as this would be exceedingly rare.* This exclusion was pre-specified in the protocol because we would not be able to distinguish whether the breakages coded in the index procedure were of nails that were used in prior procedures that were not observed in the PHD. We would not know, for these patients, what type of nail was implanted during the prior procedure, the time from index procedure to nail breakage, or any of the other patient characteristics at the time of index procedure (e.g., femur fracture type). Since these patients would not be informative to our analysis, we applied an exclusion criterion to remove them.

Point 6. *The authors state they “accept the declared conflict of interest from the authors who are employees of the company that manufactures the TFNa implant”.* We appreciate the authors’ acknowledgement of our conflict of interest disclosures, as we feel it is important for all researchers to declare any conflicts of interest. We would like to clarify that we are employees of Johnson & Johnson within the office of the Chief Medical Officer, a corporate group that was created to be independent of commercial and R&D functions in order to provide impartial evaluation of patient safety data. The protocol for this study was posted publicly (<http://www.encepp.eu/encepp/studySearch.htm>) and all published analyses were pre-specified in a statistical analysis plan. The objective of our study was to evaluate the comparative safety of TFNA vs. non-TFNA nails. Collectively, the points raised by the authors do not represent meaningful challenges to the design, analyses, or conclusions of our study. Moreover, the propensity score-balanced active comparator cohort approach that we used helps to overcome common limitations of real-world data, which is why it has become the methodological standard for real-world safety evidence generation for medical products over the last two decades (9).

## References

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