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Letter to the editor

Response to letter to the editor on "Survivorship of a modular acetabular cup system: medium- to long-term follow-up"

In reply:

This is a response to a Letter to the Editor (LTE) which was submitted to *Arthroplasty Today* by Dr. David Egilman et al., concerning a previously published manuscript [1] on a clinical study involving the DePuy Pinnacle Acetabular Cup System (PIN Study). As described in detail below, Dr. Egilman's LTE contains numerous factual inaccuracies, and the authors' conflict disclosure does not fully convey their involvement in litigation surrounding the Pinnacle Metal on Metal Hip System (Pinnacle MOM; no longer marketed).

The following list comprises the factually inaccurate statements within Dr. Egilman's LTE (italics, in quotes) and our respective responses:

> *"Drs. Kindsfater and Lesko acknowledged that at least one site enrolled patients into the PIN Study retrospectively, but [DePuy] included ninety-three patients total across ten separate sites who signed informed consents after their surgery [LTE References 1, 5, 6]".*

Response

This is incorrect, and the contextual misrepresentation of retrospective enrollment is misleading. Most importantly, the initial enrollment documents when the PIN study began more than 16 years ago required patients to consent to a "Release of Medical Records" to participate in the study. Only after the protocol was amended several years later did it require patients to sign something called an informed consent for study participation. The language Dr. Egilman uses here may lead a reader to believe that patients in the study underwent surgery without first providing informed consent for that surgery. DePuy is aware of nothing to suggest that any patient in the study failed to provide informed consent for the surgery.

DePuy is aware that up to 3 sites may have had subjects who provided consent to a release of medical records retrospectively for study participation; Dr. Egilman's earlier article [2] states that he is aware of only 2 such sites. Regardless of when consent to a release of medical records was provided, patients who were enrolled into the PIN Study received substantially the same standard of care that they would have received if not enrolled in the study, and obtaining consent to the release of medical records was the initial procedure to allow investigators the ability to provide patient data to DePuy.

> *"Dr. Kindsfater testified to non-consecutive enrollment at his own site, stating that he would not include "the street person" [LTE Reference 7]."*

Response

This is an inaccurate and unfair characterization of Dr. Kindsfater's testimony, in which he stated as follows: "If you enlist a bunch of patients, ie, the street person who comes in to me who falls down and breaks their hip and I put a Pinnacle total hip in them, I'm not going to enroll that patient in the study because he's never going to come back. Somebody who's gonna move away, those aren't a good person to put in the study. I want someone who is going to be reliable, come back, so we can get the follow-up. That's the most important thing about the study." It is a well-understood practice in prospective, long-term studies to only enroll patients who may be reasonably expected to return for follow-up. Dr. Kindsfater's testimony refers to that practice.

Moreover, elsewhere in his deposition, Dr. Kindsfater explained that there were periods of time during which his site was not enrolling patients in the study because he had already fulfilled his enrollment requirements. When the study was later expanded, he resumed enrolling patients. All of this was consistent with the applicable study protocol and his enrollment obligations. To reduce all of that testimony to a single-sentence summary is unfair and misleading. It certainly does not bring "clarity and transparency" to the discussion.

> *'Had Dr. Kindsfater enrolled patients consecutively, he would have at least four additional revisions [LTE Reference 8]. Thus the "cherry-picking" of healthy survivors was not just a theoretical problem, but one which impacted the study findings'.*

Response

No subjects were "cherry-picked" in this study as potential healthy survivors. There were pauses in enrollment when Dr. Kindsfater reached his enrollment quotas. Consecutive enrollment of eligible patients resumed once new enrollment quotas were properly reestablished with DePuy. During these pauses in study enrollment, there were patients who were treated

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under Dr. Kindsfater's standard of care. We would expect any revisions among nonstudy patients who were not enrolled because of these pauses in enrollment to be in proportion to the numbers of PIN Study patients who were revised in the course of the study.

'Drs. Kindsfater and Lesko excluded thirteen failures among PIN study participants: ten identified in [DePuy]'s medical complaints database and three reported in PIN investigator testimony [LTE References 5, 8-10]. Drs. Kindsfater and Lesko omitted [sic] these failures because including them "…without also including further follow-up on all unrevised hips from a similar search of sources outside data collection methods in this study would have introduced bias [LTE Reference 1]"'.

Response

All revisions that were made known to DePuy through data-collection efforts of the PIN Study (case report forms) were included in the analysis of data. Moreover, knowledge of additional revisions through sources outside data-collection methods of the PIN Study was properly disclosed in the manuscript [1]. None of the thirteen revisions to which Dr. Egilman refers were reported to DePuy through the mechanisms of PIN study data collection. Some of these thirteen revisions occurred in subjects who were lost to follow-up, and others occurred after their study participation ended or PIN Study data collection had ceased. It is inherent in Kaplan-Meier (KM) methodology, and scientifically sound, to assume that some revisions will continue to occur among subjects after the time of their last known follow-up (the time at which their follow-up time was censored). KM methodology assumes that such revisions will be in proportion to revisions that occurred among subjects who continued to be followed. To illustrate this, consider that the PIN Study reported follow-up on 720 subjects (out of N = 1592 enrolled) at 5 years, and altogether, there were 41 reported revisions throughout the study. Hence, there were $1592 - 41 - 720 = 831$ subjects with no follow-up beyond 5 years, in whom there were no reported revisions. The PIN Study reported a KM survivorship estimate of 97.0% at 5 years and a KM survivorship estimate of 94.7% at 10 years, which is a difference of 2.3%. Hence, it might therefore be expected that 2.3% of the 831 subjects (which is $0.023 \times 831 \approx 19$) without follow-up beyond 5 years to have had a revision. Thus, it is consistent with the reported results that 13 revisions could be discovered among PIN Study subjects after their last known follow-up.

'Contradictorily, [DePuy] included external data when they transferred thirty-one patients from a stem study into the PIN study [LTE References 6, 11]'.

Response

There is no contradiction. These 31 subjects are among the N = 1592 PIN Study subjects who were reported in the PIN Study manuscript. Data for these subjects were obtained through clinical study data-collection methods (case report forms).

'One case report form suggests that [DePuy] transferred data from a third source: a company registry called 'Captureware' [LTE Reference 5]'.

Response

We do not know what this claim refers to because LTE Reference 5 is a very large document collection of PIN Study CRFs within the MDL Docket. However, the statement is self-contradictory because it references '*One [PIN Study] case report form…*', which means that the data were received through data-collection efforts (case report forms) of the PIN Study.

'Drs. Kindsfater and Lesko claimed that the inclusion of the additional revisions would have introduced study bias [1]. In an uncontrolled prospective study such as the PIN study — where data analysis by KM accounts for variable follow-up times — these failures cannot create differential reporting bias. Rather, their exclusion biased the study towards more favorable survivorship results [LTE References 1, 8, 10]'.

Response

This is an unscientific statement with an incorrect conclusion. In our previous response to the statement that '*Drs. Kindsfater and Lesko excluded thirteen failures among PIN study participants…*', we illustrated how KM methodology properly accounts for possible revisions among subjects after the time of their last known follow-up by assuming that such revisions will be in proportion to revisions that occur among subjects who continue to be followed up. In our illustration, from the PIN Study results in the manuscript, we showed that 19 such revisions might be expected between years 5 and 10 among PIN Study subjects after their last known follow-up; consistent with this, Dr. Egilman's LTE points out 13 revisions that occurred beyond the patients' last known follow-up in the PIN Study. Dr. Egilman's statement that "[including] *these failures cannot create differential reporting bias*" is incorrect. The additional revisions noted by Dr. Egilman were identified outside of the study's data-collection methods or the study's data-collection time period. If we were to include such revisions as Dr. Egilman suggests, without also including information regarding the lack of revision among all other study subjects under similar conditions, we would have a biased estimate of the proportion of revised subjects in the study. What Dr. Egilman proposes would likely lead to an over-representation of revisions, which is the differential reporting bias that he claims is not possible.

'Drs. Kindsfater and Lesko reported a data entry cut-off date of January 2013, but [DePuy] changed the date retrospectively in 2015 and did not sign the study freeze and lock form until March 2016 [LTE References 12,13]'.

Response

The statement that DePuy changed the date retrospectively in 2015 is unfounded. The last date of a data record within PIN Study data was in January 2013, as reported in the manuscript. The database lock on March 2016 was a formal procedural activity, which does not imply data collection continued after January 2013.

'Drs. Kindsfater and Lesko included one revision that came to their attention in December 2015 [LTE References 13,14]. This selective reporting constitutes cherry-picking'.

Response

We do not know what the stated date of December 2015 is in reference to, and it is not clear why Dr. Egilman considers this inclusion of a revision to be '*cherry-picking*'. In June 2015, while reading radiographic reviewer comments in preparation for the final study report, it was observed that a radiograph that was submitted to DePuy in July 2004 revealed a previously

unknown revision. Because this revision was among data which had been submitted to DePuy through data-collection efforts (case report forms) of the PIN Study, it was included in the final study results. This type of data clarification after a study has concluded is not unusual and is not "cherry-picking".

'[Drs. Kindsfater and Lesko] reported no revisions for osteolysis, but PIN investigators recorded two such revisions [LTE References 1, 5]'.

Response

This is an unfounded statement. The reference on which Dr. Egilman relies on for this statement is a large document collection within the MDL Docket which is too broad to serve as a verifiable reference source, as no specific documents are identified. Nevertheless, we infer that this statement refers to 2 Pinnacle MOM subjects who were reported in the PIN Study manuscript [1] with an adverse event of osteolysis (Table 6 in the manuscript). Both of these patients were revised and are summarized among those who were reported with a revision for adverse local tissue reaction (Table 2 in the manuscript).

'The device related death of Dr. Kindsfater's patient — who suffered a dislocation and died under anesthesia — and 109 other recorded patient deaths were not disclosed in the paper [1, 5, 15]'.

Response

This statement, which is apparently based on a misinterpretation of the cited phone call log [LTE Reference 15] regarding a patient who was revised by a different surgeon, is incorrect in several ways. To DePuy's knowledge, there was no device-related death in the study. No patient in the study died under anesthesia, most notably under Dr. Kindsfater's care. Regarding the referenced patient, Dr. Kindsfater has reviewed the patient's records and confirmed unequivocally that the death was not device related. The suggestion that one of Dr. Kindsfater's patients died under his care because of the device and that Dr. Kindsfater failed to report it is reckless and unjustifiably impugns Dr. Kindsfater's professional reputation. Deaths that occurred among other study subjects were not device related and were not reported because this was not one of the purposes of the study.

Conclusion

In summary, Dr. Egilman's LTE contains many factual inaccuracies, which undermine his stated purpose to '*bring greater clarity and transparency to Drs. Kindsfater and Lesko's findings*'. Drs. Kindsfater and Lesko stand by their original manuscript and the results reported therein.

Finally, while claiming his purpose is to bring greater clarity and transparency to Drs. Kindsfater and Lesko's findings, Dr. Egilman's conflict disclosure is less than transparent. The disclosure states that "*None of these authors were compensated for work on this article and the lawyers for the injured plaintiffs did not review this article and had no input into the content of the article*". Moreover, Dr. Egilman states on his LTE conflict of interest form that "*We received no funding for work on this paper*". However, his conflict disclosure confirms that he has been paid for his litigation-related work, which included writing an expert report in which plaintiffs' lawyers were involved, and that they did review. Dr. Egilman's expert report forms the basis for the article written by Dr. Egilman et al. [2], and Dr. Egilman's LTE coauthors were all paid to assist him with this expert report. Readers will want to consider this apparent conflict of interest when evaluating the reasons for the many inaccuracies in Dr. Egilman's LTE. From our perspective, whatever the purpose of Dr. Egilman's LTE may be, it certainly does not bring greater accuracy, clarity, or transparency to the discussion.

As should be clear from the aforementioned responses, the undersigned are not neutral observers of the LTE or the PIN Study. Rather, Dr. Lesko is employed by DePuy Synthes, Inc., and he has been involved in the PIN Study as a statistician and coauthored the article that Dr. Egilman's letter addresses. DePuy Synthes, Inc. and Johnson & Johnson (a separate entity) are involved in ongoing litigation brought by parties who have retained Dr. Egilman and his coauthors as experts. Dr. Kindsfater was an investigator in the PIN Study. He coauthored the article that Dr. Egilman addresses and has other research and consulting relationships with DePuy Synthes, Inc. and related entities. Dr. Kindsfater also gave a deposition in the Pinnacle MOM litigation, at which Dr. Egilman was present. Because the topics discussed herein are subjects of ongoing litigation involving the Pinnacle MOM device, DePuy's lawyers were also consulted about the foregoing.

References

[1] Kindsfater K, Lesko J. Survivorship of a modular acetabular cup system: medium- to long-term follow-up. Arthroplasty Today 2017. ISSN 2352-3441, https://doi.org/10.1016/j.artd.2017.07.001.

[2] Steffen JE, Fassler EA, Reardon KJ, Egilman DS. Grave fraudulence in medical device research: a narrative review of the PIN seeding study for the Pinnacle hip system. Account Res 2018;25(1):37.

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