reporting research would limit the frequent claims for more and bigger studies, when results are already available in the literature.

Large administrative databases provide a vast amount of data reflecting our clinical practice. However, only powered, randomized, controlled trials provide unbiased estimation of treatment effect. In this clinical setting (*i.e.*, impact of intravenous acetaminophen on postoperative requirements), we do not believe that additional observational cohort analyses or additional randomized studies or meta-analyses[5] are a priority, because we already have the response.[4]

Last, although Wasserman *et al.*[1] also studied the incidence of outcome (*i.e.*, opioid-related adverse effect) and not only morphine consumption, we still consider that opioid consumption is definitely not a clinically relevant primary endpoint and could not be an intermediate outcome of a patient-related optimal one.[4] Taking into account the lack of demonstrated effect of acetaminophen on opioid-related adverse effect, this drug probably has minimal clinically relevant effects in the early perioperative period.

Competing Interests

The authors declare no competing interests.

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(Accepted for publication November 16, 2018.)

In Reply:

We welcome the thoughtful comments by Dr. Steadman and Riou *et al.*, in reply to our study.[1] We aimed to evaluate the use of IV acetaminophen and its association with outcomes including opioid utilization, opioid-related adverse effects, and cost and length of hospitalization. Dr. Steadman mentioned several limitations of our study—some justified (and mentioned in our study's Limitations section) and some less so—and observational research in general. Dr. Steadman states that "A better study would be a randomized double-blinded one in which the only variable would be the use of IV acetaminophen *versus* oral acetaminophen for 24 h in a cohort of patients that did not include chronic opiate users, and in which the multimodal regimen was standardized rather than determined by individual predilections." We agree that this would be an ideal study situation to a certain extent. However, such a study would be difficult to conduct or would significantly lack generalizability, because common practice almost never is in alignment with the control group or intervention group. Indeed, multiple (nonopioid) modalities (*e.g.*, nerve blocks, neuraxial analgesia, acetaminophen, and gabapentinoids, among others) are available for use in multimodal regimens; this results in an exponential increase in the number of potential combinations to use in practice.[2] Therefore, there currently is no universally recognized standard regimen to be used in a trial desirous of generalizability, and identifying the optimal multimodal regimen in a trial setting would be impossible given the sheer number of combinations. A more practical approach would be to use observational data to identify combinations of nonopioid modalities and timing that may result in the most optimal outcomes. This will inform trials where a selected number of multimodal regimens may be compared. Particularly the "individual predilections" noted emphasizes the difference between trial and real-world settings that provided the most thought-provoking result from our study: IV acetaminophen is mostly used as a single-dose administration on the day of surgery, which is not likely to result in a clinically relevant reduction of opioid utilization. Indeed, real-world use of drugs often differs from use in controlled trial settings where they are deemed efficacious.[3] We maintain that the value of this investigation is the demonstration of the real-world use of IV acetaminophen that was not associated with clinically significant reductions in opioid utilization. Importantly, we agree with Dr. Steadman that "Giving a single dose of IV acetaminophen and expecting a miraculous

change in opiate use is unsophisticated at best" and that "IV acetaminophen is a tool like any other in our armamentarium. If we use a tool ineffectively, then we are the problem—not the tool," and we reiterate our call for the identification of patient subgroups and IV acetaminophen administration schedules most likely to result in benefit.[1] However, in all fairness and to stay true to generally accepted scientific principles, one has to consider the possibility that no benefit may be found at all.

Riou *et al.* stated three main limitations: (1) the validity of opioid utilization from billing data, (2) heterogeneity in treatment groups based on acetaminophen doses administered, and (3) residual confounding. We agree with all three and have specifically highlighted the first in our manuscript. However, any bias attributable to mismatch between billing for opioids and administered opioids should be independent of IV acetaminophen use and thus would minimally affect our findings. Further, it is more likely that billing for opioids occurs when dispensed by the pharmacy and not when prescribed, thus increasing the correlation between billing and administration. Heterogeneity in treatments is unavoidable in studies using real-world data and actually demonstrates the value of such data over clinical trials. Here, various treatment regimens or protocols may be used, whereas trials often focus on a standard that is not generalizable as discussed above. Residual confounding will always remain when using observational data; the goal of sensitivity analyses is not to eliminate this (which would be impossible given the data used) but rather to demonstrate robustness of results using various approaches. Although we appreciate the authors' suggestion to apply a propensity score analysis or "another sophisticated multivariable matching process," given the number of treatment groups under study this would not be possible because the situation under study is more complicated than just comparing patients who received IV acetaminophen with those who did not. In our study we identified nine treatment groups based on dose of IV acetaminophen used (0, 1, or more than 1 dose) and day of use (day of surgery, postoperative day 1, postoperative day 2, or later). This was represented using three separate variables, because overlap between these groups exists. Rather than considering this a limitation, we feel that this information is valuable in that it shows the current dosing regimens in use. Resorting to an approach where just one dosing scheme would be compared with no use would entail the same limitations regarding generalizability. Thus, we respectfully disagree with Riou *et al.* that "the amount of new information is relatively limited," because our study shows real-world utilization of IV acetaminophen in a distinct surgical cohort likely to include patients who may benefit from this drug (*i.e.*, those who cannot tolerate oral medication). We found IV acetaminophen to be mostly used as a single-dose administration on the day of surgery; this does not coincide with use in trials such as the one referred to by Riou *et al.*, where the treatment regimen under study was "propacetamol 2 g every 6 h."[4]

In summary, we appreciate the comments put forward by Dr. Steadman and Riou *et al.*, because these comments are helpful to understand the results from our study in their proper context of real-world use of IV acetaminophen that revealed no benefit and possibly less than effective administration regimens.

Competing Interests

The authors declare no competing interests.

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(Accepted for publication November 16, 2018.)

Experimental Controls in Lipid Resuscitation Therapy

To the Editor:

We read with interest the recently published work by Umar *et al.*[1] The authors assert that antagonism of free-fatty acid receptor G-protein-coupled Receptor 40 (GPR40) with a G-protein-coupled receptor small