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In Reply Many of the questions raised by Chapple and Blackston and by McDonald and colleagues about our recent Original Investigation[1] are addressed in Pocock and Stone's recent review on what to do when the primary outcome fails.[2] Certainly, a trial in which the primary outcome falls short of statistical significance can be distressing to investigators. However, as highlighted by Chapple and Blackston, the interpretation of trial results may be colored by undue attention to a single primary outcome and arbitrary *P* value cut points. These constraints make sense in confirmatory studies of new drugs and devices (where the consequences of false positives can be dire) but not necessarily in more exploratory studies (like the Personalized Research for Monitoring Pain Treatment study[3]).

Both letters raise a number of other methodological issues, including lack of statistical power, underemphasis of important secondary outcomes, problems with application of the n-of-1 intervention, and potentially poor patient adherence. As we noted in our article,[1] the study fell 12% short of enrollment goals, but it is not clear that reaching the planned sample size of 244 would have resulted in a significant *P* value. Single studies rarely provide definitive estimates of effect size, and for this reason we believe further studies (and subsequent meta-analyses) are warranted.

We agree that statistically significant between-group differences were seen in medication-related shared decision making and in the probability of achieving a 5-point pain interference score reduction. These findings are clinically important and deserving of further study. Likewise, although certain n-of-1 trial design choices (eg, offering nonpharmacologic treatments and relatively short treatment periods) may have contributed to the large proportion of inconclusive n-of-1 trials, our goal was to balance experimental rigor with patient choice and convenience.

Finally, although patients randomized to the n-of-1 arm adhered well to their assigned treatment regimens (averaging 1.4 on a 1-5 scale, with 1 indicating "always" following the directed treatment), we did not track adherence to the "winning" treatment following the trial. If the benefit of n-of-1 trial participation (if any) is mediated purely through the identification of clinically superior treatments, poor adherence to the "winner" in the aftermath of an n-of-1 trial could, as McDonald and colleagues suggest, limit the potential benefit. However, we suspect that other potential mechanisms are operative (eg, creating a more therapeutic physician-patient relationship, enhancing patients' self-efficacy as autonomous agents) and may deserve more attention than previously recognized.

Richard L. Kravitz, MD, MSPH
Christopher H. Schmid, PhD
Ida Sim, MD, PhD

Author Affiliations: University of California, Davis, Sacramento (Kravitz); Brown University, Providence, Rhode Island (Schmid); University of California, San Francisco, San Francisco (Sim).

Corresponding Author: Richard L. Kravitz, MD, MSPH, University of California, Davis, Department of Internal Medicine, Division of General Medicine, 4150 V St, Ste 2400, Sacramento, CA 95817 (rlkravitz@ucdavis.edu).

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Inconsistencies in Reporting Studies of Lactic Acidosis

To the Editor In their recently published Original Investigation regarding metformin use, renal function, and acidosis, Lazarus and colleagues[1] explained why their findings were different than ours[2] and wrote that our study "was limited by sparse [estimated glomerular filtration rate] data and did not account for changes in [estimated glomerular filtration rate] over time."[1(909)] This is not true. Table 2 in our article[2] summarized that we were able to classify more than 90% of metformin exposure time to renal function. In addition, our methods section clearly stated that we determined renal function during follow-up time and ran our analysis using a time-varying Cox regression analysis in which we modeled both changes in metformin exposure and changes in renal function over calendar time.

Nevertheless, because both studies[1,2] used routine health care data, renal function recordings were probably a proxy indicator of the true renal function during the development of lactic acidosis. A more sensible explanation for the differences between the studies is that Lazarus and colleagues[1] were more likely to measure metabolic or respiratory acidosis instead of lactic acidosis. The authors used *International Classification of Diseases, Ninth Revision, Clinical Modification* codes to define their outcome. This coding system, in contrast with UK Read terminology, cannot define lactic acidosis; therefore, we feel that the words *lactic acidosis* should have been replaced by *acidosis*. In a recently published follow-up letter, Lazarus and colleagues[3] wrote that our study[2] evaluated acidosis. This is not true either; we evaluated the risk of lactic acidosis.

Frank de Vries, PharmD, PhD

Author Affiliation: Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands.

Corresponding Author: Frank de Vries, PharmD, PhD, Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, Utrecht 3584 CA, the Netherlands (f.devries@uu.nl).

Conflict of Interest Disclosures: Dr de Vries is employed at Maastricht University Medical Centre in Maastricht, the Netherlands, and in his role supervises 2 PhD students who are employed by F. Hoffmann-La Roche. The topics of the students' PhDs are not related to this article nor did Dr de Vries receive any fees or reimbursement for his supervision.

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2. Eppenga WL, Lalmohamed A, Geerts AF, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care*. 2014;37(8):2218-2224. doi:10.2337/dc13-3023

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In Reply We thank Dr de Vries for his letter and, overall, agree with his comments. Limitations of diagnostic codes exist in both studies.[1,2] In the future, we believe that advancements in the design and structure of electronic health records will allow for more sophisticated algorithms to accurately identify exposures and outcomes. Such advances will be fundamental to the assessment of the risks and benefits of medications and clinical care processes, and ultimately, improvement in patient outcomes.

Benjamin Lazarus, MBBS, MPH
Morgan E. Grams, MD, PhD

Author Affiliations: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Lazarus, Grams); Division of Nephrology, Monash Medical Centre, Clayton, Australia (Lazarus); Department of Medicine, Johns Hopkins University, Baltimore, Maryland (Grams).

Corresponding Author: Morgan E. Grams, MD, PhD, Department of Medicine, Johns Hopkins University, 2024 E Monument St, Baltimore, MD 21205 (mgrams2@jhmi.edu).

Conflict of Interest Disclosures: None reported.

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Association Between April 20 Cannabis Celebration and Fatal Crashes

To the Editor In our Research Letter[1] examining crash risks on the "4/20" counterculture holiday, we identified drivers (rather than crashes) as the unit of analysis because one or more drivers may contribute to a crash. This approach also helps optimize interpretability for clinicians and policymakers around driving risks despite breaching strict assumptions for statistical independence. Furthermore, as Aydelotte and colleagues[2] point out, similar results were obtained whether the driver (OR, 1.12; 95% CI, 1.05-1.19) or the crash (incidence rate ratio, 1.10; 95% CI, 1.02-1.20) was the unit of analysis. The observed difference in calculated absolute risks simply indicates the average crash involves more than one driver.

Aydelotte and colleagues[2] also introduce some secondary analyses to test the robustness of our original results. In particular, limiting the control days to just April 13 or just April 27 also yielded similar estimates of relative risk (incidence rate ratios, 1.12 and 1.09, respectively). Naturally, each point estimate has a broad confidence interval, because halving the number of control days reduces statistical power. We believe the use of 2 flanking control days (not solitary control days) is preferable because the approach increases statistical power and also helps account for seasonal trends in crash risk.[3,4]

Another new secondary analysis offered by Aydelotte and colleagues[2] involves restricting the analysis to the years since 2010. However, the choice of this 7-year interval seems arbitrary and prone to selection bias. In particular, the secondary analysis excludes 2008 and 2009, the years in our study interval with the highest relative risk of fatal crashes on April 20. Furthermore, the observed relative risk of fatal crashes on April 20 may appear blunted if impaired driving on control days has become more common. This illustrates a larger point that absolute increases in crash risks are likely to reflect the prevalence of impaired driving. We hope that countermeasures designed to limit impaired driving will mitigate these risks.

Some countries, such as the Netherlands, decriminalized cannabis years ago yet have generally safer roads than the United States. To achieve similar success, effective safety measures should be deployed in the United States to reduce fatal traffic crashes on 4/20 and throughout the year.[5]

John A. Staples, MD, MPH
Donald A. Redelmeier, MD, MSHSR

Author Affiliations: Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada (Staples); Centre for Clinical Epidemiology and Evaluation, Vancouver, British Columbia, Canada (Staples); Centre for Health Evaluation and Outcome Sciences, Vancouver, British Columbia, Canada (Staples); Department of Medicine, University of Toronto, Toronto, Ontario, Canada (Redelmeier); Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada (Redelmeier).

Corresponding Author: John A. Staples, MD, MPH, Department of Medicine, University of British Columbia, 1081 Burrard St, Room 5910, Burrard Building, St Paul's Hospital, Vancouver, BC V6Z 1Y6, Canada (john.a.staples@gmail.com).

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CORRECTION

Error in Editorial Note: In the letter titled "Re-examining the Association Between '4/20' and Fatal Crashes—Doobie-ous Data?" by Aydelotte et al,[1] the Editorial Note