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The American Journal of Bioethics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/uajb20

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To cite this article: Tobias B. Polak , Joost van Rosmalen & Carin A. Uyl – De Groot (2020) Response to Open Peer Commentary "Making It Count: Extracting Real World Data from Compassionate Use and Expanded Access Programs", The American Journal of Bioethics, 20:11, W4-W5, DOI: 10.1080/15265161.2020.1820113

To link to this article: https://doi.org/10.1080/15265161.2020.1820113

Published online: 26 Oct 2020.

THE AMERICAN JOURNAL OF BIOETHICS
2020, VOL. 20, NO. 11, W4–W5
https://doi.org/10.1080/15265161.2020.1820113

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Response to Open Peer Commentary "Making It Count: Extracting Real World Data from Compassionate Use and Expanded Access Programs"

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In their open peer commentary: "Making It Count: Extracting Real World Data from Compassionate Use and Expanded Access Programs" (Rozenberg and Greenbaum 2020), Rozenberg and Greenbaum discuss important matters concerning the added value of extraction of real-world data from expanded access programs. The authors address practical concerns and provide recommendations for the collection, analysis and interpretation of such data. However, we feel four points warrant further clarification.

First, extracting real-world data from expanded access programs is not as novel as the authors presumed. In our recent review of drug approvals that incorporated real-world data from expanded access programs, we identified 49 approvals relying on these data (Polak et al. 2020). Remarkably, some approvals date back to the 1990s. Back then, they were simply called observational, epidemiological studies, or "expanded access studies:" far less fancy nomenclature than "real-world data," yet perhaps equally effective.

Second, the authors seem to underestimate the conflicting interest expanded access brings to clinical trial recruitment. Similarly alluding to SARS-CoV-2 as the authors do, the Mayo Clinic authors of the convalescent plasma expanded access program point out that "*Physicians, hospitals and patients have the choices of this program (red: the expanded access program) versus a RCT. It is clear that over 90,000 patients and over 10,000 physicians elected to participate in the pragmatic, real-world evidence study design*" (Joyner et al. 2020). Hence, the expanded access program was actually competing with ongoing clinical trials. Randomizing only a fraction of the patients that participated in the expanded access program would have yielded far more actionable insights—urgently needed in times of a pandemic (Kalil 2020).

Third, at first sight it seems natural to extract real-world data from expanded access programs. It might be more appropriate to ask the question why that data is not being collected. Indeed, other scholars have argued it is ethically imperative to collect data when patients are treated with investigational medicine (Chapman et al. 2019). Taking a closer look, data collection requires infrastructure, such as well-designed and validated databases, but also legislation that facilitates data collection. It is for example unclear in what regulatory perspective expanded access data collection, or subsequent analysis of that data, should be seen. Even more provoking is the fact that some European Union member states simply do not allow data collection within compassionate use programs (Polak et al. 2020).

Fourth, the authors state that one might avoid using (placebo) controls, i.e., "putting a real patient at risk," by using statistical techniques. Advanced statistical techniques may attenuate biases in analyses of observational (expanded access) data. However, their results are not as robust as those of randomized controlled trials—and robust results are needed in times of crisis. Statistical methods applied to observational data cannot fully replace randomized controlled trials (Banerjee and Prasad 2020). Furthermore, a majority of drugs still fail to demonstrate effect in randomized controlled trials, hence, patients might have been better off being randomized to a control group.

We support the authors in their call for regulatory guidance and alignment regarding the opportunity expanded access programs bring to collect real-world data. We should not fail to learn from expanded access data, but by failing to randomize patients in the first place, we might learn nothing at all.

DISCLOSURE STATEMENT

Joost van Rosmalen declares no conflict of interest. Tobias B. Polak is part-time employed by myTomorrows. Carin A.

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Uyl de Groot declares no conflict of interest. All authors work on a grant provided by HealthHolland.

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