The American Journal of Bioethics

ISSN: 1526-5161 (Print) 1536-0075 (Online) Journal homepage: http://www.tandfonline.com/loi/uajb20

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To cite this article: Amritava Das, Krishanu Saha & Pilar N. Ossorio (2018) Fairness in Manufacturing Cellular Therapies, The American Journal of Bioethics, 18:4, 68-70, DOI: 10.1080/15265161.2018.1445792

To link to this article: https://doi.org/10.1080/15265161.2018.1445792

Published online: 05 Apr 2018.

The American Journal of Bioethics, 18(4): 68–82, 2018

ISSN: 1526-5161 print / 1536-0075 online
DOI: 10.1080/15265161.2018.1445792

Open Peer Commentaries

Fairness in Manufacturing Cellular Therapies

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Recent successes of cellular immunotherapies, specifically chimeric antigen receptor T (CAR T) cell products, have generated excitement among patients, researchers, and investors. There are now hundreds of immunotherapy clinical trials underway, and many more are planned (Hartmann et al. 2017). Unfortunately, there is not enough specialized manufacturing capacity to meet the demand for patient-specific, engineered cells for early-stage clinical trials (Levine et al. 2017). Federally funded cell manufacturing initiatives are driving improvements in manufacturing (NSF Engineering Research Center for Cell Manufacturing Technologies 2018), but immunotherapy products for trials are still scarce resources. In this issue, Jecker and colleagues (2018) identify immunotherapy production facilities (manufacturers) as important, undertheorized components of the immunotherapy clinical trials infrastructure, components with previously unappreciated bioethical significance. They outline a novel framework for allocating scarce manufacturing resources to clinical trials, using four criteria and a three-stage process for determining which immunotherapy trials would receive resources.

Jecker and colleagues identify an issue that transcends immunotherapy products. For instance, viral gene therapies are similarly difficult to manufacture—their manufacturing runs sometimes produce virus sufficient to treat only one patient (U.S. Food and Drug Administration [FDA] 2017). A framework for allocating manufacturing resources could be applicable to many types of gene and cell therapy trials.

Jecker and colleagues' four criteria for allocating manufacturing resources to trials are equal opportunity, magnitude of medical benefit, resources required, and random selection. These criteria were chosen because they can be backed by empirical data and could be fairly and transparently implemented. However, we question whether the framework as currently envisioned would produce a fair distribution of manufacturing resources to trials, or would produce optimal levels of scientific knowledge for society.

Consider, for instance, the framework's equal opportunity criterion, which attempts to provide the "minimal amount of production capacity necessary" for each trial by specifying "the number of participants and amount of product required to produce *scientifically meaningful results* in a *reasonable time frame*" (Jecker et al. 2018, 61, emphasis added). Manufacturers would allocate production capacity on the basis of a power calculation for each trial—for example, finding the number of participants needed for a study to have a two-sided significance level of 5% and a statistical power of at least 80%. Note that power calculations incorporate one's risk tolerance, assumptions, and estimates. Empirical data cannot determine what counts as scientifically meaningful enough, or timely.

The authors presume that each trial would receive less manufacturing capacity than requested. For this presumption to be realized, manufacturers would have to recompute the power calculations of FDA-reviewed, institutional review board (IRB)-approved trials using different assumptions or risk tolerances than the sponsors, and determine that a trial could be meaningfully completed with fewer participants or a different design. We believe manufacturers would have difficulty justifying such recalculations as fair or scientifically preferable.

Given that the primary goal of clinical trials is to produce new knowledge, and that the number of participants in a study will influence its scientific value, we believe that power and sample size are morally meaningful with respect to allocating scarce manufacturing resources. However, the proposed framework could result in lower quality science overall. It could result in two or three underpowered trials instead of one properly powered trial. Arguably, three underpowered trials would result in less social value than one better powered trial. Generating low-quality data

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would be wasteful, demonstrating poor stewardship of research resources.

Manufacturing facilities should not be in the business of determining the sample size for trials that have already undergone scientific, FDA, and IRB review. Study sections and the FDA are legally tasked with assessing the scientific merit of a study's design, including its sample size and power calculations. Further, the FDA is better positioned than cell manufacturers to consider and weigh public input regarding research designs and priorities. IRBs must also assess scientific merit or ensure that somebody else has done so. If immunotherapy manufacturers could change a study's design after regulatory review, they could undermine the careful deliberations regulatory entities ought to have undertaken.

As a practical matter, permitting manufacturers to change sample sizes could require the sponsor to submit a change of protocol to the IRB, thus incurring monetary costs and study delays. Such burdens might negatively affect the lives of prospective study participants, as well as sponsors and investigators. Bureaucratic burdens on trials could impel potential research participants to seek unapproved and unproven interventions.

Sponsors have financial and ethical incentives to use resources efficiently in clinical trials. Most trials will have been designed to elicit the maximum amount of information from the minimum number of participants before the sponsor seeks a contract with a cell manufacturer. Thus, under the proposed framework it is not clear that each study would receive fewer manufacturing resources than requested. But if a manufacturer's review rarely changed resource allocations, then the process would impose costs on the clinical trial enterprise without adding ethical or other social benefit.

For all of the reasons just described, we conclude that manufacturers should not determine the minimum size of studies, or otherwise require changes in protocols, during a process for allocating scarce manufacturing resources to trials. We also note that sponsors and investigators often co-develop practices in multidisciplinary teams that include manufacturers (Levine et al. 2017). Trial designers and sponsors should, and often already do, consider the availability of cell manufacturing resources when designing immunotherapy trials.

Jecker and colleagues' proposed framework also motivates questions about the appropriate conceptualization of manufacturing resources. Specialized manufacturing of individualized immunotherapy products is a complex process for obtaining, activating, modifying, expanding, and transporting each participant's cells and cellular product, and current trials use a variety of manufacturing methods (Vormittag et al. 2018). The manufacturing capacity required by any trial will not be determined solely by its number of participants. Manufacturing for immunotherapy trials is not a linear process and the resources per future trial often cannot be estimated and compared with precision.

For some trial designs, manufacturers and investigators will have difficulty estimating *ex ante* how many and which types of cells to engineer for each participant. For instance, a trial might first dose participants with CAR T cells that target CD22. If some participants do not achieve remission or relapse by a designated date post infusion, those participants would receive another infusion of CAR T cells, but these would target CD19 and would therefore require a different manufacturing process (Huang et al. 2017). Another two-stage design would offer participants who did not achieve remission after the first infusion a second infusion of the same CAR T cells, if tests indicated that cells from the first infusion had not engrafted or were not operating effectively, and the previous infusion was well tolerated (Maus et al. 2013). In a third example, a Bayesian immunotherapy trial where each arm comprised immunotherapy to target one of three or four different cancer-cell antigens, neither trial investigators nor manufacturers could know at the outset how many participants would receive each type of immunotherapy—the numbers of people assigned to each arm would change as the trial proceeded. These examples illustrate some difficulties of estimating and comparing the amount of manufacturing resources required for a given trial.

Under the Jecker and colleagues framework, trials with two-stage or Bayesian designs might be disfavored compared to trials with simpler or frequentist designs because the more complex trials would likely use more manufacturing resources per person and create more uncertainties for manufacturing. However, more complex trial designs sometimes produce more knowledge and more social benefit. Two-stage and Bayesian trials may also have a higher likelihood of directly benefiting participants than other trials. Perhaps the prospect of both high social value and participant benefit could be weighed against a high demand for manufacturing resources when prioritizing trials for access to manufacturing resources.

Inherent variability between cells and manufacturing processes also makes it difficult to estimate and compare the resources required for different studies (Vormittag et al. 2018). Some cell types can be modified and expanded more easily than others, and some manufacturing processes might better suit some types of cells than others. Differences among cell types might be "mere" interindividual differences that would not affect the comparative use of manufacturing resources by trials, or they could be systematic, affecting one arm or an entire trial. Optimal manufacturing processes have not yet been identified and might vary depending on the type of cellular product.

Clinical trial recruitment also generates complexity for manufacturers who produce investigational products for immunotherapy trials. Clinical trial recruitment is inadequately mathematically modeled (Barnard, Dent, and Cook 2010). Trials do not accrue all participants simultaneously, and for early-stage trials it can be unethical to expose several people to the experimental intervention at the same time. Therefore, manufacturers cannot straightforwardly plan to fulfill the requirements of one trial before moving on to the next.

Probably, each manufacturing facility will be designed with a modular setup that can produce multiple cell and

gene therapy products, and successive batches of cells will cater to different trials. A first batch might go to trial X, a second batch to trial Y, and the third batch to trial X again. While instruments can be modified to operate in different manufacturing processes (depending on their design), a change in products under production might require changes in personnel and skill sets. For instance, people with expertise in engineering T cells might be different from people with expertise in engineering B cells. These complexities mean that a trial's use of manufacturing resources could vary depending on the mix of products simultaneously under production or the order in which different products are produced. Uncertainties of recruitment and realities of manufacturing preclude precise estimations and straightforward comparisons of the manufacturing resources that will be needed for each trial.

Despite inherent difficulties in estimating and comparing the manufacturing resource requirements for immunotherapy clinical trials, we agree with Jecker and colleagues that the community needs an ethical framework for allocating manufacturing capacity to trials. Any such framework should be grounded in sound empirical evidence, but the difficult choices will not be dictated by such evidence. A fair framework will make its underlying assumptions, methods for estimation, and value judgments apparent, and will incorporate transparent procedures for prioritizing values. It will be developed through processes that include a variety of relevant viewpoints, and will recognize that what happens between manufacturers and trial investigators or sponsors influences what happens between investigators and patients. Because trial recruitment can affect manufacturing efficiencies, and manufacturing output can influence recruitment, perhaps an ethical framework should address both allocation of manufacturing capacity to trials and participant recruitment to trials.

FUNDING

KS was supported by the National Institutes of Health (R35GM119644), National Science Foundation (EEC-1648035), National Science Foundation (CBET-1350178).

CONFLICTS OF INTEREST

Pilar Ossorio is on the ethics advisory board for Astellas Pharma U.S., Inc. She has received less than $3000 in consulting fees from Astellas each year for the past two years. To the best of her knowledge, Astellas has no active immunotherapy products on the market or in development. Astellas does have a regenerative medicine, cell therapy product in development in the US (described on the firm's website). Krishanu Saha is a member of the forum on Regenerative Medicine (NASEM) and the Center for Cell Manufacturing (CMaT, NSF). These organizations provided reimbursement for travel expenses for meetings related to immunotherapy manufacturing. ■

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