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Open Peer Commentary for Walker et al., "Ethical justifications for access to unapproved medical interventions: an argument for (limited) patient obligations"

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Title: "Right Answer, Wrong Question: Special Access, Knowledge Generation, and Clinical Trial Legitimacy"

NOTE 1: The page numbers for Walker et al. refer to the submitted manuscript, not the edited/formatted journal version, and so they need to be updated, please.

NOTE 2: The reference to Walker et al. is missing volume, issue, and page numbers.

I agree with Walker, Rogers, and Entwistle's recommendation to make access to an unapproved intervention outside of a clinical trial usually conditional on the patient's consent to reasonable data collection and reporting (DCR) for the purpose of knowledge generation. But I do not agree with some key details of their reasons why. Their argument for mandatory DCR rests on their view that special access programs (SAPs) are morally permissible only when they are not in tension with the aims of regulating medicine—namely, knowledge generation and public protection against unsafe or ineffective interventions; and that view rests on their claim that "the aims of regulation can be considered to 'trump' those of SAP provision where they are directly in tension" (Walker et al. 2014, 17). That claim is not argued for, unless the reader is meant to assume that the pursuit of a corporate good is always to be given priority over the pursuit of aggregative goods. But such an assumption is contentious. It ignores questions about what conditions there are on the legitimacy of how we pursue a corporate good like medical knowledge. In particular, it ignores whether SAP provision is one of those very conditions. In order to determine whether mandatory SAP DCR is ethically appropriate, the key question to ask is not whether this would make SAPs compatible with the aims of regulation; rather, the question to ask is whether this would be an instance of an ethically permissible way to pursue the aims of regulation.

There are good reasons to think that SAP provision is a condition on the legitimacy of society's pursuit of medical knowledge by means of randomised controlled trials (RCTs), at least when these involve terminally ill patients.[1] Walker et al. describe

[1] My argument is largely indebted to points developed by Udo Schüklenk and presented in, among other places, Schüklenk and Lowry 2009.

medical knowledge as both an aggregative good and a corporate good, since it not only yields individual benefits for people when they have treatable conditions, but also, in some sense, benefits us all. Society reasonably has an obligation to pursue such corporate goods, but there are ethical constraints on that pursuit. A prohibition on exploitation is surely among those constraints. Exploitation is a contested concept, but it includes, at least, actions where one person or group seeks to achieve an aim by securing the cooperation of another person or group in a way that lacks voluntary consent. If a regulatory authority, drug company, or medical researcher takes measures, in the name of recruitment, to make sure that terminally ill patients' only legal access to an experimental intervention is through participation in a RCT, this is exploitative. Why? We are imagining here a situation in which there is an alternative to RCT access that is (a) feasible, (b) preferred by a significant number of patients who are being recruited, and (c) closed off by the actions of an agent (a regulatory authority, a drug company, or a researcher) who is in a position of power relative to the patients. A natural or inevitable lack of alternatives is tragic but not coercive, and so does not undermine voluntary consent. If, instead, the absence of alternatives is an intentional product of the actions of the people running, funding, or regulating the trial, then this is coercive, rendering the trial exploitative.

There are at least two possible alternatives to RCT access: access in a trial that gives the experimental intervention to all participants, and special access outside of a trial. Are these always feasible? No. Regarding the first alternative, the scientific value of data in a trial with a control is usually superior to one without. Often nothing less rigorous than a randomised control will be considered adequate to fill the knowledge gap that stands in the way of regulatory approval. Hence, removing the control is not always feasible. (But it should be noted that this does not negate researchers' ethical obligation to take seriously patients' therapeutic aims by designing trials in such a way as to open up possibilities for therapeutic benefit as much as can be done without excessively sacrificing scientific aims (Schüklenk and Lowry 2009).) Regarding the second alternative, special access loses its feasibility if (i) trial funders must pay some or all of the costs of special access and this makes the trial overall too expensive, (ii) special access leads to a drop in total recruitment and this foils researchers' attempts to recruit a large enough sample to satisfy the scientific rigour of full regulatory approval, or (iii) special access slows down the rate of recruitment enough to make the trial too expensive.

The first of these problems can be avoided by allowing manufacturers to sell SAP interventions at cost. This is better than allowing profits on SAPs, which would diminish manufacturers' incentive to complete all trial phases necessary for full approval, and better than prohibiting cost-recovery fees for SAPs, which would disincentivise manufacturer participation. There is a worry that the resulting cost-to-patient difference between special access and trial access would be unjust to lower-income groups, but this is beyond the public coverage that can be expected given reasonable health resource constraints, and so is a health care inequality that is not unjust.

Problems (ii) and (iii) are more difficult. We need to think about why patients would choose special access over trial access in a situation where researchers have already acted on their obligation to take seriously patients' therapeutic aims and where

trial funders are legally required to cover the cost of experimental treatments for trial participants, but not for SAP patients. Some patients would prefer trial access, but are excluded by the trial's eligibility requirements. Whenever scientific rigour allows, these should be broadened in order to reduce conflict between SAP provision and trial recruitment. Some other patients are eligible, but cannot afford travel and accommodation costs associated with trial participation. If it is necessary for trial funders to subsidise or cover such costs in order to counteract the negative recruitment effects of SAPs, then this should be considered an additional cost that funders should be allowed to take into account when determining the cost-recovery price for SAP interventions. Hopefully, these two measures will be enough in many cases to make SAP provision feasible; and, as argued above, if it is feasible, then it is ethically required for the sake of voluntary consent. However, it is possible that even after the use of these two measures, in some cases a trial would, for either scientific or financial reasons, simply not proceed unless it were granted an exemption from the general requirement of SAP provision. In such cases, the lack of alternatives to RCT access would not be the intentional product of actions by those running, funding or regulating the trial, and so would not undermine voluntary consent.

The discussion so far has aimed to explain why in order to obtain voluntary consent for RCT participation, the experimental intervention must also be offered via special access sold at cost, except in cases where this requirement would necessitate the cancellation of the trial. Such an exemption would need to be applied only in cases where the conflict between SAP provision and trial recruitment is unusually severe. In contrast, an implication of Walker et al.'s view about trumping is that the exemption would need to be applied whenever there is any direct conflict at all between the SAP provision and the aims of regulation.

I have not yet explained why I think special access should be conditional on patient consent to DCR. One might be tempted to think that because I argue above that it is exploitative to offer only RCT access when one could instead offer a choice between RCT access and special access, I must therefore also conclude that it would likewise be exploitative toward patients who are not eligible for trial access to offer them only special access with DCR when one could instead offer them the choice between special access with DCR and special access without DCR. However, my argument above does not have that implication. I do not think mandating DCR for SAPs would be exploitative. There are two reasons for this.

First, consider the difference in justification. When a regulatory authority refuses to allow SAPs in order to make sure that patients have only RCT access, the typical justification given appeals to the importance of promoting knowledge generation for the sake of the health of future patients. Research participation is then a kind of altruism that would be praiseworthy if it were voluntary, but is exploitative because it is coerced. In contrast, if a regulatory authority were to mandate DCR for SAPs, it could reasonably justify it as a reasonable way to help make sure that patients who prefer special access would in fact have special access. As Walker et al. rightly note, if data from SAPs is allowed to play a supporting role in the approval process (a supporting role that would have to be limited enough not to threaten the primacy of trial data), then making DCR

mandatory would strengthen the incentive for drug companies to participate in SAPs. This is important, of course, because allowing SAPs makes little difference to patients unless drug company also agree to participate in them.

Second, consider the difference in the effect on access to the experimental intervention itself. RCT participants typically have a 50% chance of not receiving the experimental intervention that they regard as likely their last chance for therapeutic benefit in a terminal situation, whereas special access patients all receive the experimental intervention. That is what drives activists who fight against having only RCT access. In contrast, with or without DCR, special access patients all receive the experimental interventions. Because of this, there is no reason to expect that the requirement of DCR would lead to widespread cheating of the sort that occurs with RCT only access. After all, the demands on the patients related to data collection are described by Walker et al. as "quite limited" (Walker et al. 2014, 17). We should expect, then, that many SAP patients would accept mandatory DCR for the sake of future patients, or, at least, as a reasonable way to help secure the participation of funders, researchers, and clinicians.

REFERENCES

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