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What can the lived experience of participating in risky HIV cure-related studies establish?

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Abstract

This response to Gail Henderson et al argues that they were right that interviewees' appraisals of cure study participation should inform (future) protocol review decisions, but wrong to take these appraisals at face value.

Gail Henderson and colleagues report intriguing results from interviews with participants of an HIV cure trial in Thailand.⁽¹⁾ That trial gives participants little chance at getting cured and imposes what might seem like significant risks and burdens—from drug toxicity, therapeutically unnecessary exams and analytical antiretroviral treatment interruption ('ATI'). But interviewed participants seem happy that they joined it. Why? Participants point to the intense attention and testing within the trial, the manageable nature of risks from ATI, the fun break from restrictive antiretroviral regimens, curiosity about their bodies' responses to experimental approaches, their special suitability to this study's needs, community with fellow participants and altruism.⁽¹⁾ Interesting psychological and socio-logical lessons abound. Henderson et al instead claim evaluative and regulatory lessons, which I shall assess critically.

RATIONAL CHOICE

The authors write:

When the context of specific cure trials is brought in, the decisions of our participants appear rational because their appraisal of factors such as ATI differ from experts; because more consequences figure in their decisions than appeared from the outside; and because the standard of practical rationality against which these choices are evaluated needs to adapt to include considerations beyond consequences...⁽¹⁾

That moves too fast. The fact that people have different and surprising appraisals does not show their appraisals to be right and their decisions rational. We need an argued assessment of these appraisals. In the case of ATI risks, potential harms like developing drug resistance and reseeded of viral reservoirs need not be symptomatic or known before or during the

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Competing Interests

None declared.

trial. While the short pause from antiretrovirals in this type of ATI study may indeed be manageable,(2) that is because experts not patients say so. Nor does it apply universally: ‘In some [cure-related studies with ATI], a longer period of viraemia would be needed’.(3) In these riskier ATI studies, currently on the increase, participant assessments arguably fail to clarify that participation boosts personal prospects. Conversely, the fun break from antiretrovirals is from a relatively undemanding one-pill-a-day regimen that these recently infected patients must learn to live with anyhow. (Might that break so appeal because of shame, or prejudice, which can precede adaptation to a recent medical condition(4) and which trialists could try to reduce rather than exploit? Might it reflect false hope that taking antiretrovirals for life is avoidable?) The authors cite Buchak’s view that there is no right and wrong about decisions on risk. Intuitively, however, taking very high risk for a petty gain (a break from a one-pill-a-day regimen?) is irrational, and even Buchak would reject a participant appraisal that parts ways with that same participant’s decisions on unrelated risks.(5)

Henderson et al sometimes imply that listening to participants’ assessments is necessary (not sufficient) for discovering the rationality of their decisions: ‘judging risk/benefit ratios without appreciating these lived experiences can lead to false determinations of irrational decision making’.(1) But they cite a clear refutation of that necessity—a Journal of Medical Ethics symposium I guest-edited.(1, 6) We lacked Henderson et al’s input on lived experiences, yet easily hypothesised that participants’ choice to join the studies, which is ‘at least prima facie a bad gamble’, need not be irrational and may reflect instead indirect medical benefits, psychosocial benefits, a ‘Buchakian’ approach to risk or altruism—spanning what Henderson et al’s interviews establish.(7)

In discussing whether participants’ decision was rational, Henderson et al emphasise that it was fully informed: ‘The consent form informed participants that the trial included ATI and described the risk of the three experimental drugs in detail’.(1) One wonders: Were ATI risks described in detail? While participants provide general assurances that all risks were divulged and understood, stronger assurance would come from testing comprehension. The article rarely considers the possibility that interviewees’ assessments were incorrect because of sour grapes, social approval bias, or other distortions. Why refer to participants’ ‘experiences’ not their ‘perceptions’ or ‘reports’? Upbeat participants apparently considered non-therapeutic blood tests, MRIs and lumbar punctures to be ‘benefits’, but the latter tests, to pick one, are painful and when historic studies deliberately misrepresented them as benefits, abusive.

Finally, the authors emphasise that study risks were preconditions for certain study benefits. But that does not prove rationality, either. A gambler may drive a beneficial thrill, or her very identity, from financial risk, yet gambling often remains a bad idea overall, and potentially irrational.

PROTOCOL REVIEW

Henderson et al add that participant experiences should ‘also be taken into account when ethically assessing whether a trial should be offered’.(1) I agree. The current blanket refusal

of many regulators and review boards to consider indirect benefits is unwarranted. Strongly suspected indirect benefits to participants could inform review boards' risk to benefit ratio assessments. They could permissibly figure on consent forms. And because indirect benefits make intelligent consent likelier, firmly established indirect benefits could sometimes justify relaxing verification of consent validity.

While regulators and ethics reviewers assessing protocols cannot know the exact indirect benefits to specific participants, evidence could be collected and assessed on indirect benefits in various study types, and various site and study population types, informing review of similar later studies. Until that happens, cruder proxies could be used. For example, in most trials, an arbitrary, small positive number representing 'overall indirect benefits' could be presumed. While crude, that presumption is more accurate than presuming absence of indirect benefits.

To count in favour of protocol approval, indirect benefits need not make decisions to participate into 'good gambles' or 'rational'. Research on human subjects can be legitimate even when participation is expected to be somewhat disadvantageous overall. Such research asks people to volunteer, with full consent, for a socially important mission. Medical research is not for the participant's sake, but for social good. While certain missions are so risky and serve such a trivial societal need that seeking volunteers for them would be unethical, many others worsen participants' prospects overall while remaining legitimate.⁽⁸⁾ By analogy, it is often legitimate for doctors acting as hospital administrators to solicit financial donations even when they expect the benefits of donating (tax deductions, increased self-worth...) to remain smaller than the financial and non-financial costs to the donor.

So I agree on the regulatory bottom line. Many studies whose direct medical impacts on participants are expected to be negative are legitimate. For me, however, that is not because these studies are necessarily beneficial to participants, in ways that a 'narrow vision' of the reasons that should motivate participants may miss. Rather, studies can be legitimate when they are not beneficial to participants.

Thus, a perfectly manageable short pause from antiretroviral treatment should not impede an important cure-related study. Not even when it runs against participants' best interests overall. A far riskier ATI, which places participants (and their fetuses and sex partners) at serious risk, is harder to justify, although with certain provisions it too may well be worth it.

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