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When Ancillary Care Clashes with Study Aims

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In medical and health care studies, “ancillary care” refers to any burden or cost that researchers may take on to address study participants’ medical needs in ways not required for the study’s safety or validity.^{1,2} Providing ancillary care is sometimes obligatory.^{1,2} Its provision may, however, collide with achievement of a study’s aims. How should researchers respond when that happens?

One of us encountered this issue while conducting a multisite observational study of adherence to HIV antiretroviral therapy (ART) in sub-Saharan African. This ongoing study is assessing adherence behavior in the first year of ART in populations with both early and late stages of HIV infection, including asymptomatic pregnant women. It aims to determine whether adherence interventions are needed for each population and, if so, which interventions. These questions are practically relevant to countries currently considering programs to initiate ART at the time of HIV diagnosis regardless of immunologic status or prior symptoms (“test and treat”).

The study does not provide care; local clinics provide ART to study participants according to regional standard practices. As participants know, the study provides pill containers for their antiretrovirals that are equipped with electronic adherence monitors (EAMs); when opened, they transmit a date-and-time stamp to research staff in real time. This proxy of pill ingestion permits characterization of adherence patterns and factors associated with adherence behaviors. Per standard research practices in these settings and to protect participants’ privacy, participants’ adherence data are not routinely shared with their HIV clinicians.

To determine whether statistically significant differences had emerged that warranted an early stop to some aspects of the study, a preplanned preliminary analysis was done when approximately half of participants had at least 6 months of follow-up. Mean adherence among pregnant women at one site was found to be low: 51%, as compared with 61 to 87% in the other participant populations ($P = 0.09$ for the pre-specified comparison). Although

this difference did not reach statistical significance, such low adherence jeopardizes these women's health and risks transmission of HIV to their sexual partners and fetuses. The authors discussed this scenario in the context of a National Institute of Allergy and Infectious Diseases grant to study the ethics of electronic adherence monitoring, and we identified potential responses.

In principle, at least four types of ancillary care to improve adherence are possible in this setting: researchers could take on the role of adherence counselors during participants' study visits; adherence information could be provided to participants' own clinic for potential use by their clinicians in routine follow-up appointments or as a basis for assigning them "treatment supporters"³; researchers could set up a short messaging service (SMS)-based system to send participants reminders, provide other support when the EAM detects nonadherence, or both; or on discovering persistent nonadherence, researchers could visit participants' homes and offer adherence counseling or transportation to obtain medication.⁴ None of these interventions was required by the study design, protection against study-borne risks, or the applicable standards of care; the interventions would therefore be ancillary care,¹ raising the question of how much of this type of care is owed to participants.

None of these interventions was certain to improve adherence, and all would cost researchers some — potentially prohibitive — amount of money and labor, with an uncertain prospect of success. Some risked unwanted disclosure of HIV serologic status (e.g., through witnessed home visits or SMS). An overarching worry, however, emerged as well: any effective intervention to improve adherence would compromise the study's main goal of unbiased, objective measurement of adherence.

Which, if any, of these options is most ethical? Alternatively, might it be preferable for researchers not to respond to evidence of nonadherence, because ancillary care is not always ethically mandated when it would interfere with a study's purpose?

According to a leading theory, ancillary care obligations depend on how clearly the care that researchers might provide falls within the investigator's "scope of entrustment." The permissions that participants must give researchers to collect information about their bodies and health are what gives rise to that entrustment and defines its scope. These obligations are sensitive to contextual factors such as the costs (material and scientific) of providing ancillary care.¹ Because the study under discussion relies on participants' having given researchers permission to observe adherence behavior, ancillary care pertaining to that behavior falls clearly within the scope of entrustment. That is why we draw on the entrustment-based theory: it makes the study a prime candidate for ancillary care obligations. Initially, then, this theory tends to support active intervention to address detected non-adherence, favoring any safe, effective, and affordable adherence intervention over doing nothing.¹

The theory does not treat ancillary care obligations as absolute, however, and on further interrogation, the case for an obligation faltered here. Because ancillary interventions to improve ART adherence would seek to affect the very behavior that the study is measuring, they would skew the primary outcome data. That would undercut the study's validity and

ability to provide useful information. If researchers intervened after the preliminary analysis, any later adherence information would no longer indicate “true” adherence behavior in the relevant population; the study would no longer be observational. Rather, adherence data might well reflect the interventions’ effects. That would compromise the study’s purpose of assessing the underlying need for such interventions in other communities. If the study provided adherence support upon discovery of nonadherence even before establishing the finding’s statistical significance, it might burden participants or place some at risk of unwanted serostatus disclosure, without yielding any scientific gain. So to proceed with interventions would violate the ethical requirements in all clinical research for scientific validity and genuine social value,⁵ rendering it wrongful to continue conducting the study in the affected group. And to have started the study determined to provide ancillary care in such circumstances would have made it nearly impossible for the study to have scientific value. To have gone ahead on such a basis would have potentially burdened study participants and inefficiently spent resources without clear scientific justification.

One might be tempted to cancel the study and provide enhanced care instead. But the ability to characterize nonadherence rates in populations living with HIV matters greatly in these early days of rolling out test and treat. It may, for example, alert public health systems to the need for adherence support targeted to specific populations. Achieving a study’s original aims may defeat ancillary care obligations.¹ In this study of adherence behavior, we believe that participants’ claims to ancillary efforts to improve adherence generally give way to the importance of gathering objective, unbiased adherence information.

The researchers, however, ultimately decided that a third factor — the fact that fetuses were at risk of HIV transmission but had not consented to study participation and could not otherwise seek medical care — superseded the scientific interests of the study. After discussion with the local ethics committee, whenever pharmacy refill data confirmed a pregnant participant’s likely non-adherence (>28 days during which there was no electronic evidence of adherence), the investigators began alerting her local clinic. The response to this intervention is not yet known. Future data for these participants will need to be censored because their subsequent adherence behavior may now reflect this added intervention. The decision to intervene may limit the extent of potentially useful information generated about the asymptomatic pregnant participants and about the need for targeted interventions to improve the adherence of similar populations elsewhere.

We propose that when provision of otherwise obligatory ancillary care clashes with a study end point, researchers should first determine whether there is a compromise solution that would meet both the study’s scientific aims and ancillary care obligations. Advance planning and budgeting may make that prospect more feasible. When that’s impossible, researchers and oversight bodies should reexamine the study aims in light of the human costs and risks posed by not providing ancillary care. Where study aims matter greatly, it may be permissible to prioritize study completion over ancillary care provision, as determined by an oversight body tasked with protecting participants’ rights. Whether prioritizing the study is permissible in a given case may depend on additional factors, including the interests of third parties.

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