Why Patients Continue to Participate in Clinical Research

David Wendler, PhD; Benjamin Krohmal; Ezekiel J. Emanuel, MD, PhD; Christine Grady, PhD, RN; for the ESPRIT Group

Background: Clinical research exposes patient participants to unproved methods and research procedures in order to gather generalizable knowledge to benefit others. While some commentators argue that this process inappropriately exploits patient participants, there are few data available to evaluate this claim.

Methods: Human immunodeficiency virus (HIV)-infected individuals from Argentina, Brazil, and Thailand who had been participating in the Evaluation of Subcutaneous Proleukin (Interleukin-2) in a Randomized International Trial (ESPRIT) study for at least 6 months were invited to complete a self-administered survey on their experience and were asked why they continued to participate. The ESPRIT study is a phase 3, multinational, randomized trial comparing antiretroviral therapy plus interleukin 2 (IL-2) with antiretroviral therapy alone in individuals with HIV disease.

Results: From a list of 12 possible reasons regarding why patient participants continue to participate, 8 options were selected as “very important” by 75% or more of 582 respondents, including the possibility of benefiting personally and the potential to help others. When asked to indicate the most important reason from this list, respondents in the IL-2 arm (n=292) selected (1) increasing their CD4 lymphocyte count (26%); (2) finding better treatments for patients with HIV in their home country (22%); and (3) getting IL-2 (12%). Respondents in the no–IL-2 arm (n=290) selected (1) finding better treatments for patients with HIV in their home country (32%); (2) finding better treatments for HIV-infected patients in other countries (12%); and (3) increasing their CD4 lymphocyte count (11%). Also, 90% of the respondents indicated that participation in ESPRIT involved making a “major” or “moderate” contribution to society, and 84% felt “very” or “somewhat” proud to be making this contribution.

Conclusions: Most respondents continue to participate in the ESPRIT study in hopes of benefiting personally. The majority also recognized that by participating in ESPRIT they were contributing to helping others; they experienced pride regarding this contribution and considered it an important reason to continue to participate. These results indicate that it is possible for patient participants, even those randomized to a control group, to recognize and embrace the goals of the research in which they participate. Future studies will be needed to determine to what extent these findings generalize to other studies and other countries and what steps can help patient participants recognize and embrace the goals of clinical research.

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A GROWING BODY OF DATA suggests that patients enroll in clinical research for multiple reasons: they hope to benefit personally, often hope to help others, and trust those who conduct the research. In contrast, there are few data on why patients continue to participate in clinical research. Why do patient participants, especially those randomized to a control group, continue to accept the added risks and burdens, eg, additional clinic visits and extra research procedures, that clinical research places on them? Answering this question is especially important given the view that clinical research inappropriately exploits patient participants by exposing them to added risks and burdens for the benefit of others. This process, it is claimed, fails to respect patient participants as persons. Instead, clinical research treats patient participants as if they were things, objects, or even guinea pigs, used for the benefit of others, without concern for the participants’ own goals and interests. For example, in a widely cited article, Jonas argues that clinical research turns patients into “a thing—a passive thing merely to be acted on.”

Exploitation involves unfairly or inappropriately taking advantage of some for the benefit of others. Most commentators agree that there are at least 2 types of...
exploitation. Outcome exploitation occurs when individuals receive an unfair level of the benefits that result from a shared activity, while process exploitation involves inappropriately taking advantage of individuals’ vulnerability to carry out an activity. The claim that clinical research inappropriately exploits patient participants typically focuses on the potential for process exploitation. In particular, critics claim that clinical research gets patient participants to undergo research procedures by inappropriately taking advantage of their lack of understanding and/or their illness and need for treatment. To help evaluate these claims, the present study collected empirical data on 2 questions related to process exploitation. Are patient participants able to recognize that they are participating in clinical research, not receiving clinical care? Can patient participants, especially those with a life-threatening illness, embrace the goals of clinical research, or do the research goals conflict with their own goals to receive treatment and to improve their health?

METHODS

ESPRIT STUDY

The present data were collected as part of a survey of individuals participating in the Evaluation of Subcutaneous Proleukin (Interleukin-2) in a Randomized International Trial (ESPRIT) study. The ESPRIT study is a US National Institutes of Health–sponsored, open-label (ie, nonblinded) trial comparing antiretroviral therapy plus interleukin-2 (IL-2) with antiretroviral therapy alone in 4000 individuals in 25 countries, mostly in Europe. Participants are human immunodeficiency virus (HIV)-positive men and women aged 18 years or older with a minimum baseline CD4 lymphocyte count of 300/µL. Participants take at least 2 antiretroviral agents. Antiretroviral agents are not supplied by the ESPRIT study. Study end points are disease progression and death. Participants return to the clinic every 4 months for medical evaluation and collection of blood samples. Because it is often claimed that the potential to exploit patient participants is greatest in developing countries, the present survey focused on the 3 developing countries participating in ESPRIT: Argentina, Brazil, and Thailand.

SURVEYS

Participants from Argentina, Brazil, and Thailand were invited to complete a baseline survey when they enrolled in ESPRIT, and they were asked to complete a follow-up survey after they had been participating in the study for at least 6 months. The present article focuses on the results of the follow-up survey, which was self-administered during a clinic visit. Participants were invited to participate in the follow-up survey based on staff availability. Research and clinic staff did not have access to the completed surveys, which were mailed directly to the ESPRIT center at the University of Minnesota, Minneapolis. The follow-up survey focused on 4 domains: (1) impact of participation in the ESPRIT study; (2) compliance with study requirements; (3) understanding of the study; and (4) motivations for continued participation. The present article reports on the fourth domain.

The follow-up survey was developed in 9 steps: (1) comprehensive literature review; (2) draft survey development; (3) review and revision by survey professionals; (4) cognitive, behavioral, and reliability pretesting with ESPRIT subjects in the United States; (5) survey revision; (6) translation into Portuguese, Spanish, and Thai; (7) back-translation into English and revision for accuracy; (8) translation into Portuguese, Spanish, and Thai; and (9) review of the translated surveys by native investigators in Argentina, Brazil, and Thailand. The survey used primarily closed-ended questions, with a few open-ended questions.

The follow-up survey asked respondents the following question: “How would you describe your role in the ESPRIT study?” “Would you say that you are (1) a participant, (2) a patient, (3) an experimental subject, (4) a guinea pig, or (5) other?” The term guinea pig was translated literally as conejillo de indias in the Argentinian survey and as cobaia in the Brazilian survey. In Spanish and Portuguese, as in English, the term commonly refers to one who is experimented on inappropriately. Because the term guinea pig does not carry the same meaning in Thai, this option was translated as “being used inappropriately” in the Thai survey.

STATISTICAL ANALYSIS

Multivariate logistic regression was used to test for associations between baseline data and whether respondents described their role as that of a guinea pig, or being used inappropriately; whether they believed they were making a contribution to society by continuing to participate in ESPRIT; and whether they believed that they were helping to advance scientific knowledge. Multivariate logistic regression was used to test for associations between baseline data and how important the following factors were in the respondents’ decision to continue to participate: the opportunity to help others in their country, the opportunity to help those in other countries, and the opportunity to contribute to a meaningful project.

Associations between participation in the baseline survey and whether respondents indicated that they were contributing to a meaningful project, helping to advance scientific knowledge, and making a contribution to society were summarized with a proportional odds model using logistic regression with stratification by country. The respondents’ answers to the open-ended questions were recorded verbatim and coded independently by 2 authors (D.W. and B.K.), with disagreements settled by a third author (C.G.).

APPROVALS

This study was approved by the Dr Virgilio G. Foglia Ethics Committee, Buenos Aires, Argentina; the Emilio Ribas Institute of Infectious Disease Ethics Committee, São Paulo, Brazil; the Ethics Committee of the Faculty of Medicine, Chulalongkorn Hospital, Bangkok, Thailand; and the institutional review board of the National Institute of Allergy and Infectious Diseases, Bethesda, Maryland. All respondents provided informed consent in writing before completing the survey.

RESULTS

At the time of the follow-up survey, 1017 individuals had enrolled in ESPRIT in the 3 participating countries. Of these 1017 individuals, none had formally withdrawn, although 6 (0.6%) were unavailable for follow-up. Of the 1017 enrolled individuals, 595 (58.5%) were invited to participate in the follow-up survey, and 582 (98%) consented and completed the survey. Of the 582 respondents, 292 were in the IL-2 arm, 290 were in the no-IL-2 arm; 329 completed the follow-up survey only, while 253 also completed the baseline survey. Respondents had
been enrolled in ESPRIT for 2.5 years on average at the
time they completed the follow-up survey. Nearly 70% were
male; the mean age was 37.6 years; and approxi-
mately 8 in 10 were employed (Table 1).

In an open-ended question, respondents were asked to
describe “the single most important reason you con-
tinue to participate in the ESPRIT study.” The most com-
mon reasons given were to obtain medical or personal
benefit, followed by a desire to contribute to science
(Table 2). Respondents were then asked in a close-
ended question to rate how important 12 possible rea-
sons were to their decision to continue to participate. From
this list, 8 options were selected as “very important” by
75% or more of respondents (Table 3). When asked to
indicate the most important reason from this list, re-
pondents in the IL-2 arm selected (1) possibly increasing
their CD4 lymphocyte count (26%); (2) contributing
to finding better treatments for HIV-infected people
in the participant’s country (22%); and (3) getting IL-2
now (12%). The 3 reasons selected as most important by
respondents in the no–IL-2 arm were (1) contributing
to finding better treatments for HIV-infected people
in other countries (12%); and (3) possibly increasing their CD4
lymphocyte count (11%).

In response to 2 close-ended questions, 89% of respon-
dents in the IL-2 arm and 90% of respondents in the no–
IL-2 arm indicated that participation in ESPRIT involved
their making a “major” or “moderate” contribution to so-
ciety (Table 4). Also, 86% of respondents in the IL-2 arm
and 83% of those in the no–IL-2 arm felt “very” or “some-
what” proud that they were helping to advance scientific
knowledge by their continued participation. Prior partici-
ipation in the baseline survey was not a predictor of whether
respondents felt that they were making a contribution to
society or whether they felt proud that they were helping
to advance scientific knowledge. Whether individuals
were in the IL-2 arm or the no–IL-2 arm and whether they had
attended college also were not predictors of their re-
sponses to these questions.

Table 1. Characteristics of 582 Respondents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IL-2 Active Treatment Respondents (n=292)</th>
<th>No–IL-2 Control Respondents (n=290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>196 (67.1)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>96 (32.9)</td>
</tr>
<tr>
<td>Health insurance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>National coverage</td>
<td>114 (39.0)</td>
<td>119 (41.0)</td>
</tr>
<tr>
<td>Employer</td>
<td>57 (19.5)</td>
<td>61 (21.0)</td>
</tr>
<tr>
<td>Self-pay</td>
<td>66 (22.6)</td>
<td>60 (20.7)</td>
</tr>
<tr>
<td>Other</td>
<td>30 (10.3)</td>
<td>20 (6.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (4.9)</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No schooling</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>&lt;12 y schooling</td>
<td>68 (23.9)</td>
<td>61 (21.6)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>95 (33.5)</td>
<td>99 (35.0)</td>
</tr>
<tr>
<td>College or university</td>
<td>77 (27.1)</td>
<td>80 (28.3)</td>
</tr>
<tr>
<td>College graduate/</td>
<td>42 (14.8)</td>
<td>41 (14.5)</td>
</tr>
<tr>
<td>professional school</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>37.7</td>
<td>37.5</td>
</tr>
<tr>
<td>CD4 lymphocyte count</td>
<td>421</td>
<td>427</td>
</tr>
<tr>
<td>at baseline, median, /µL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed, %</td>
<td>(78.5)</td>
<td>(80.4)</td>
</tr>
</tbody>
</table>

Abbreviation: IL-2, interleukin 2.

The table does not include respondents who did not answer the question. Values are given as number (percentage) unless otherwise indicated.

Table 2. “Single Most Important” Reason for Continued Participation in the ESPRIT Study (Open-Ended Question)

<table>
<thead>
<tr>
<th>Group</th>
<th>Medical Benefit</th>
<th>Personal Benefit</th>
<th>Contribute to Science</th>
<th>Help Others</th>
<th>Keep Commitment</th>
<th>Other</th>
<th>Help Investigators</th>
<th>Physician’s Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 arm</td>
<td>160 (56)</td>
<td>55 (19)</td>
<td>28 (9)</td>
<td>11 (4)</td>
<td>10 (4)</td>
<td>13 (5)</td>
<td>6 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>No–IL-2 arm (control)</td>
<td>108 (38)</td>
<td>56 (19)</td>
<td>58 (20)</td>
<td>16 (6)</td>
<td>15 (6)</td>
<td>14 (5)</td>
<td>6 (2)</td>
<td>6 (2)</td>
</tr>
</tbody>
</table>

Table 3. Reasons for Continued Research Participation in the ESPRIT Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Help Patients in Own Country</th>
<th>Increase CD4 Lymphocyte Count</th>
<th>Help Patients in Other Countries</th>
<th>Contribute to a Meaningful Project</th>
<th>Get IL-2 After Study if Effective</th>
<th>Keep Commitment</th>
<th>Get Better Care</th>
<th>Learn of New Treatments</th>
<th>Get IL-2b</th>
<th>Get Free Tests</th>
<th>Help Friends</th>
<th>Other Meds Not Working</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 arm</td>
<td>257 (91)</td>
<td>249 (89)</td>
<td>240 (85)</td>
<td>232 (85)</td>
<td>227 (83)</td>
<td>214 (78)</td>
<td>207 (76)</td>
<td>207 (75)</td>
<td>223 (75)</td>
<td>185 (68)</td>
<td>157 (62)</td>
<td>91 (46)</td>
</tr>
<tr>
<td>No–IL-2 arm (control)</td>
<td>260 (92)</td>
<td>226 (84)</td>
<td>236 (85)</td>
<td>222 (81)</td>
<td>207 (76)</td>
<td>217 (79)</td>
<td>203 (75)</td>
<td>219 (80)</td>
<td>187 (57)</td>
<td>187 (69)</td>
<td>143 (55)</td>
<td>67 (33)</td>
</tr>
</tbody>
</table>
Compared with respondents from Argentina and Brazil, respondents from Thailand were more likely to express pride that they were helping to advance scientific knowledge (odds ratio [OR], 2.14; 95% confidence interval [CI], 1.44-3.20) and less likely to indicate that they were making a contribution to society in ESPRIT (OR, 0.57; 95% CI, 0.40-0.78). Male respondents were as likely as female respondents to indicate that they were making a contribution to society, but they were less likely to express pride that they were helping to advance scientific knowledge (OR, 0.57; 95% CI, 0.37-0.86).

When asked in a close-ended question to describe their role in the ESPRIT study, 42% of respondents in the IL-2 arm and 43% of those in the no–IL-2 arm chose the term participant (Table 5); 3% of the IL-2 respondents and 1% of the no–IL-2 respondents chose the term guinea pig or being used inappropriately. Respondents’ sex, home country, race, age, and baseline CD4 lymphocyte count were not significant predictors of whether they described their role in this way. The percentage of respondents from Argentina and Brazil who chose the option worded as guinea pig was not statistically different from the percentage of respondents from Thailand who chose the option being used inappropriately. However, power is limited by the small numbers who selected this option.

This study provides the first empirical data of which we are aware on the motivations and experiences of patients who continue to participate in clinical research, including those randomized to a control group. The vast majority of respondents appear to have understood this aspect of their research participation. For example, 90% of respondents indicated that the opportunity to obtain medical or personal benefit and the opportunity to help others were very important reasons for continuing to participate. Also, 90% believed that they were making an important contribution to society, and 84% expressed pride in helping to advance scientific knowledge.

These data reveal that patients can have multiple reasons for participating in clinical research. Most importantly, the fact that respondents were motivated to obtain treatment for a life-threatening illness did not preclude them from being motivated to help others through their participation in the ESPRIT study as well. This finding provides empirical support for the claim that, given the right approach, clinical research, including research in developing countries, can be conducted in a way that allows patient participants to recognize and embrace the scientific goals of the studies in which they participate.

Exploitation occurs when some individuals are used unfairly or inappropriately for the benefit of others. Critics often charge that clinical research inappropriately takes advantage of patients’ vulnerabilities for the benefit of others. While patient participants, especially those with life-threatening illnesses, are vulnerable in a number of ways, critics typically focus on the possibility that clinical research inappropriately exploits their failure to understand clinical research and/or inappropriately exploits their illness and need for treatment.

The term therapeutic misconception has been used to describe a number of ways in which individuals can fail to understand clinical research. Empirical studies to evaluate these potential misunderstandings find that research participants often underestimate the risks of research, overestimate its potential benefits, fail to understand the purpose of phase 1 studies, and fail to recognize that research does not provide individualized treatment. In contrast, a recently proposed consensus definition of the therapeutic misconception focuses on whether individuals understand that the purpose of clinical research is to gather generalizable knowledge that may benefit others. The present survey provides data relevant to this understanding by evaluating whether respondents understood that they were contributing to a project designed to benefit others. The vast majority of respondents appear to have understood this aspect of their research participation. For example, 90% of respondents indicated that the opportunity to help others was a very important reason for continuing to participate in ESPRIT. Similarly, more than majority of these HIV-infected respondents from Argentina, Brazil, and Thailand had multiple reasons for continuing to participate in the ESPRIT study. More than 80% indicated that the opportunity to obtain medical or personal benefit and the opportunity to help others were very important reasons for continuing to participate. Also, 90% believed that they were making an important contribution to society, and 84% expressed pride in helping to advance scientific knowledge.

### Table 4. Respondents’ Views on Participation in the ESPRIT Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Making Contribution to Society</th>
<th>Proud to Help Advance Knowledge</th>
<th>Patients With HIV Have Obligation to Be in Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 arm</td>
<td>254 (89)</td>
<td>248 (86)</td>
<td>227 (79)</td>
</tr>
<tr>
<td>No–IL-2 arm (control)</td>
<td>257 (90)</td>
<td>236 (83)</td>
<td>239 (84)</td>
</tr>
</tbody>
</table>

Abbreviations: ESPRIT, Evaluation of Subcutaneous Proleukin (Interleukin-2) in a Randomized International Trial; HIV, human immunodeficiency virus; IL-2, interleukin 2.

The table summarizes the answers of the respondents who chose the following options: (1) “major” or “moderate” contribution to society; (2) “very” or “somewhat” proud to help advance knowledge; and (3) “major” or “moderate” obligation to participate. The respondents who did not answer the question or answered “don’t know” are not included.

### Table 5. Respondents’ Description of Their Role in the ESPRIT Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants</th>
<th>Patients</th>
<th>Subjects</th>
<th>Guinea Pigs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 arm</td>
<td>115 (42)</td>
<td>82 (30)</td>
<td>65 (24)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>No–IL-2 arm (control)</td>
<td>121 (43)</td>
<td>109 (39)</td>
<td>43 (15)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Abbreviations: ESPRIT, Evaluation of Subcutaneous Proleukin (Interleukin-2) in a Randomized International Trial; IL-2 Interleukin 2.

The table does not include respondents who did not answer the question or answered “don’t know.”

Guinea pig was translated literally as *cabezillo de indias* in the Argentinian survey and as *cobaia* in the Brazilian survey. In both languages, the term commonly refers to one who is experimented on inappropriately. For the Thai survey, the answer choice was translated as “being used inappropriately.”
8 in 10 regarded the opportunity to contribute to a meaningful project as a very important reason to continue to participate. These data do not preclude the possibility that respondents failed to understand other aspects of the ESPRIT study, such as the magnitude of the risks or the alternatives. However, it appears that respondents did understand that participation in the ESPRIT study involves contributing to a project designed to help others.

This finding reveals that it is possible for clinical trials to retain patient participants, including those randomized to a control arm, without exploiting the therapeutic misconception understood as the failure to recognize that one is participating in a study designed to benefit others. A survey of participants in a randomized, double-blind, placebo-controlled trial of propranolol for the prevention of heart attack reported similar results. While that survey did not explicitly evaluate individuals’ motivations for continuing to participate, it found that 73% of the participants expected other heart patients to benefit from their participation in the study.

The fact that patient participants recognize that they are contributing to helping others does not eliminate the potential for process exploitation. In particular, clinical research might get patient participants to contribute to research goals that they recognize but do not share and, perhaps, even oppose, by inappropriately exploiting their illness and need for treatment. Respondents had a life-threatening infection, and more than 75% continued to participate in the ESPRIT study in hopes of realizing medical benefit. However, more than 75% of the respondents also were motivated to help others. Furthermore, the majority of participants expressed pride that they were contributing to an effort to gather generalizable knowledge that might help others, and almost half described their role in the ESPRIT study as that of a “participant,” suggesting that they regarded themselves as active contributors to the scientific goals of the ESPRIT study, not simply as passive objects or things being experimented on.

In sum, the majority of respondents recognized that they were participating in research, embraced the goals of the research, felt pride in contributing to these goals, and regarded the possibility of contributing to the research goals as an important reason to continue to participate. These findings reveal that it is possible to conduct clinical research in developing countries without exploiting patient participants’ failure to understand that they are participating in research and without exploiting their need for medical treatment to get them to contribute to goals that they do not endorse.

At the same time, almost one-third of the respondents described their role in the ESPRIT study as that of a patient. Some of these individuals may not have recognized that they were involved in clinical research and may have been unwittingly contributing to its goals. Also, 3% of respondents in the IL-2 arm and 1% of those in the no-IL-2 arm described their role as that of a guinea pig or of being used inappropriately. This finding suggests that some individuals can feel exploited even when the vast majority of participants embrace the goals of the study and express pride regarding their role. Future research should consider what steps investigators can take to help patient participants recognize and embrace the goals of the research in which they participate and address any concerns regarding exploitation.

The present findings are subject to several important limitations. First, these findings are restricted to a single HIV treatment study. Future research will be needed to determine to what extent participants in other studies experience process exploitation and how this concern might be addressed. Second, respondents had access to treatment independent of the trial and had baseline CD4 lymphocyte counts of at least 300/μL. Those for whom treatment is available only in research, as well as those with more advanced disease, may be less motivated to help others and may be more vulnerable to exploitation. Third, while respondents embraced the goals of the ESPRIT study, participation in the no-IL-2 arm poses relatively low burdens and the IL-2 arm offers the potential for medical benefit. Future research will be needed to assess the motivations and experiences of individuals who face greater research risks and burdens for the benefit of others. Fourth, some respondents may have provided positive assessments of their participation in the ESPRIT study because they were reluctant to admit to themselves, or to others, that they were being exploited. Finally, the present study focused on whether participants recognized that they were in research and embraced its goals. Future research will be needed to evaluate whether clinical research exploits patient participants in other ways.

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Correspondence: David Wendler, PhD, Department of Bioethics, National Institutes of Health, Bldg 10, Room 1C118, Bethesda, MD 20892 (dwendler@nih.gov).

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REFERENCES