Post-trial Access to Tested Interventions: The Views of IRB/REC Chair, Investigators, and Research Participants in a Multinational HIV/AIDS Study

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ABSTRACT

Controversy exists regarding an ethical requirement to make products proven effective in research available after the trial. Little is known about the views of several stakeholders. Phone or self-administered questionnaires were completed by 65 IRB/REC chairs, 117 investigators, and 500 research participants in a multinational HIV trial to assess their views about posttrial access to interventions proven effective in the study. A total of 83% of research participants, 29% of IRB/REC chairs, and 42% of researchers (p = 0.046) thought IL-2 should be guaranteed for every HIV-infected person in the world if proven effective. Most European and Latin American research participants thought IL-2 should be provided free, while North American, Australian, and Thai participants commonly said at a price the average person could afford (p < 0.001). Most IRB/REC chairs and researchers thought the CIOMS “reasonable availability” requirement applied to people in the country where the study was conducted and meant a drug should be available at a price the average person could afford and that host country governments had primary responsibility for making it available. Most research participants believe an HIV drug proven effective in research should be made available to everyone in the world who needs it. IRB/REC chairs and researchers were less expansive both in who and how they thought a drug should be guaranteed.

INTRODUCTION

One of the most controversial ethical issues in multinational clinical research is posttrial access to interventions, that is to what extent are research sponsors and investigators required to ensure that research participants and host communities have access to interventions proven effective in clinical trials. Guidance is provided in some existing codes of research ethics. For instance, the Council for International Organizations of Medical Sciences (CIOMS) stipulates that before undertaking research in a community or population with limited resources, sponsors and investigators must “make every effort to ensure that any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”1 Some commentators have gone further, advocating that sponsors guarantee access to interventions, even if it requires enhancements to the community’s health delivery infrastructures.2–4 Yet there remains considerable debate and uncertainty2–8 about (1) the locus of responsibility for providing the drugs or interventions, (2) the definition of “population or community” to which the drugs or interventions should be made available, and (3) what actually constitutes “reasonably available,” i.e., should drugs or interventions be provided free or at some cost.5,6

Attitudes about posttrial access held by those who regularly interpret and implement ethical requirements, namely clinical investigators of multinational clinical studies, and institutional review boards (IRBs) or research ethics committees (RECs) that review such studies are unknown. Similarly, little is known about the perspectives of those affected by posttrial access, research participants themselves. We surveyed IRB/REC chairs, clinical investigators, and research participants involved in a...
multinational HIV/AIDS study in 25 different countries to describe their views about what should be ensured to participants and host communities after a study and who should be responsible. These questions were part of a larger survey that included questions about informed consent, risks and benefits of ESPRIT, and other aspects of the ethics of research.

**MATERIALS AND METHODS**

**Site and subject selection**

ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial) is an NIH sponsored open-label, randomized trial of subcutaneous recombinant interleukin-2 (IL-2) in HIV-positive people of 18 years or older with a CD4+ cell count of ≥300/mm³. It aims to evaluate and compare the effectiveness of IL-2 plus antiretroviral therapy versus antiretroviral therapy alone in reducing the rate of disease progression, including death, over a 5-year period.9 Between February 2000 and May 2003, 4150 participants were enrolled.

From December 2000 to July 2003, we surveyed three multinational cohorts associated with ESPRIT: (1) chairs of IRB or REC who reviewed the ESPRIT protocol, (2) clinical investigators who had enrolled at least five ESPRIT participants, and (3) ESPRIT research participants.

IRB/REC chairs were contacted by telephone or email. After giving oral consent, chairs were interviewed over the telephone by trained interviewers; in four cases a language interpreter was present. If unavailable, chairs were asked to recommend a committee member familiar with the review of ESPRIT. Of 94 chairs contacted, 17 refused, 12 never responded, and 65, representing 18 countries, were interviewed (53 chairs and 12 IRB/REC members designated by the chair) (69% response rate).

ESPRIT principal investigators who had enrolled five or more participants were identified by the ESPRIT coordinating center and mailed self-administered questionnaires. A reminder and a second questionnaire were sent to investigators who did not respond after the first mailing. Of 159 investigators contacted, 117 representing 23 countries completed questionnaires (74% response rate).

ESPRIT participants who participated in this ethics substudy were from 11 countries—Argentina, Australia, Belgium, Brazil, Denmark, France, Germany, Poland, Thailand, the United Kingdom, and the United States. At all sites but Thailand, ESPRIT participants completed self-administered questionnaires after they had given signed informed consent to join ESPRIT and prior to discovering their randomization assignments. Completed questionnaires were placed in envelopes, sealed, and mailed back to the research team and not available to local ESPRIT researchers. In these 10 countries, 359 participants completed questionnaires. In Thailand, in-person interviews were conducted by trained personnel unaffiliated with ESPRIT. All 141 participants approached in Thailand were interviewed.

**Survey development**

The questionnaires were developed by the authors in collaboration with the National Opinion Research Center (NORC) at the University of Chicago (Chicago, IL), after a literature search, identification of relevant domains, and examination of the ESPRIT consent form and protocol. Questionnaires were modified after cognitive and behavioral pretesting by NORC. Each survey had six domains. The surveys of the IRB/REC chairs and investigators were in English while the surveys of the research participants were translated and back-translated into the local language. Data reported here are from a subset of questions that asked specifically about availability of IL-2 after the study (four questions each in the PI and IRB/REC chair survey and two questions in the subject survey) and about familiarity with the CIOMS guidelines (one question each in the investigator and IRB/REC surveys).

**Human subjects approval**

The ethics study protocols, questionnaires, and consent documents were approved by the IRBs of the National Institute for Allergy and Infectious Diseases (NIAID) and of NORC; the participants’ materials including the protocol questionnaire and consent document were also approved by the IRB or REC at each participating ESPRIT site.

**Data analysis**

Responses were coded as categorical variables based on response categories in the relevant questions. No summary scores were used. Outcomes of interest for all respondents included guaranteed availability and cost of IL-2 if proven effective after ESPRIT. PIs and IRB/REC chairs were also asked about familiarity with and interpretation of CIOMS guidelines regarding reasonable availability. Regional comparisons as well as comparisons among types of respondents were performed using chi-square analysis.

**RESULTS**

Respondents included ESPRIT participants (n = 500), IRB/REC chairs (n = 65), and ESPRIT clinical investigators (n = 117) from many different countries, with the largest percentage of research participants from Latin America (43%), IRB/REC chairs from North America, and clinical investigators from Europe (50%) (Table 1).

**Posttrial access to IL-2**

To a multiple choice question regarding who should be guaranteed IL-2 after ESPRIT if proven effective for HIV, most research participants (83%) said every HIV-infected person in the world should be guaranteed access to IL-2 (Table 2). Less than half of the clinical investigators (42%) and 29% of the IRB/REC chairs shared this view. IRB/REC chairs most frequently (34%) responded that HIV-infected people in their country should be guaranteed access to IL-2. There were significant differences among the three groups of respondents (p = 0.046) regarding the cost of IL-2. Half (54%) of research participants thought IL-2 should be provided free of charge to HIV-infected patients who needed it, and 34% at a price the average person could afford. Significant geographic differences were noted (Table 3). Most European (67%) and South American (74%) research participants thought IL-2 should be free, compared to less than a
third of participants from the United States, Thailand, and Australia \((p < 0.001)\).

**Interpreting the CIOMS “reasonable availability” requirement**

The IRB/REC chairs and investigators were asked how they generally interpret the CIOMS “reasonable availability” requirement (Table 4). Similar percentages of IRB/REC chairs and investigators thought CIOMS required that drugs be provided at a price the average person in the country can afford (65% and 64%, respectively), while fewer—11% of IRB/REC chairs, 18% of ESPRIT investigators—thought the guidelines required drugs be provided free. However, again there were important geographic differences. Significantly more ESPRIT investigators from Europe (25%) and South America (29%) thought reasonable availability meant free provision of drug compared to investigators from the United States (9%) or Australia and Thailand (5%) \((p = 0.005)\). Similarly, 25% of European IRB/REC chairs, but fewer Australian and Thai chairs (16%) and no U.S. chairs, thought reasonable availability meant free provision of drug.

About half (51%) of IRB/REC chairs and 35% of ESPRIT investigators said the host country government was primarily responsible for making a drug reasonably available; fewer (40% and 28%) thought the drug company should be responsible. About three-fourths of each group said the reasonable availability requirement extended to people in the country where the study was conducted, but not to people in the entire world (Table 4).

Half of the investigators and 42% of IRB/REC chairs reported a moderate to great deal of influence from the CIOMS guidelines on their review or conduct of research; fewer said they were not familiar with (27% of investigators and 9.2% of IRB/REC chairs) or not influenced at all by the CIOMS guidelines (7.8% PIs and 30.8% IRB/REC chairs).

**DISCUSSION**

This study represents one of the first attempts to assess the views of research participants, researchers, and IRB/REC chairs regarding a requirement for making interventions proven effective in clinical trials “reasonably available” after a trial. Continued debate and uncertainty surround the details of to whom products should be made reasonably available, at what cost, and by whom.5–7,10 These data indicate that research participants’ views differ from those of IRB/REC chairs and clinical investigators regarding these issues.
Very few respondents, both in the context of ESPRIT and considering the more general “reasonable availability” requirement, thought that guaranteed posttrial access to drugs or interventions should be limited to research participants. Most research participants believed that all HIV-infected people in the world should be guaranteed IL-2 if needed. IRB/REC chairs and clinical investigators were less liberal. And when asked to consider this issue more generally—as an interpretation of the CIOMS requirement—they were more likely to say access should be guaranteed for people in the country where the research was conducted. In a previous study most U.S. and developing country investigators supported making interventions available to the study population but recognized many practical difficulties in doing so.\textsuperscript{11}

Although most research participants thought IL-2 should be made available to all who need it, only half said that it should be provided free of charge as opposed to a price the average person could afford. Geographic variations were striking. Research participants, investigators, and IRB/REC chairs from Europe and South America were more likely to endorse providing drugs free of charge, whereas respondents from the United States, Australia, and Thailand said drugs should be provided

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**Table 3. Research Participants’ Attitudes About the Cost of Posttrial Drugs\textsuperscript{a}**

<table>
<thead>
<tr>
<th>If proven effective, what should the cost of IL-2 be?\textsuperscript{b}</th>
<th>Total</th>
<th>Europe</th>
<th>Latin America</th>
<th>North America</th>
<th>Australia/Thailand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free of charge</td>
<td>54%</td>
<td>67%</td>
<td>74%</td>
<td>32%</td>
<td>27%</td>
</tr>
<tr>
<td>A price the average person can afford</td>
<td>34%</td>
<td>19%</td>
<td>17%</td>
<td>46%</td>
<td>59%</td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
<td>14%</td>
<td>9%</td>
<td>22%</td>
<td>13%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}p = 0.001 according to a chi-square test with eight degrees of freedom.

\textsuperscript{b}Verbatim question from the questionnaire.

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**Table 4. Posttrial Access to Drugs Based on the CIOMS “Reasonable Availability” Requirement\textsuperscript{a}**

<table>
<thead>
<tr>
<th>IRB/REC chairs (n = 65)</th>
<th>ESPRIT clinical investigators (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The CIOMS phrase “reasonably available” requires that the drug be provided\textsuperscript{b}</td>
<td>Free of charge</td>
</tr>
<tr>
<td>At a price the average person in the country can afford</td>
<td>65%</td>
</tr>
<tr>
<td>At the cost of making the drug</td>
<td>11%</td>
</tr>
<tr>
<td>At a price set by the drug company</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
</tr>
<tr>
<td>The primary responsibility for making the drug “reasonably available” belongs to\textsuperscript{b}</td>
<td>Study sponsor</td>
</tr>
<tr>
<td>Host country government</td>
<td>51%</td>
</tr>
<tr>
<td>Drug company</td>
<td>40%</td>
</tr>
<tr>
<td>International organization</td>
<td>11%</td>
</tr>
<tr>
<td>Someone else</td>
<td>0%</td>
</tr>
<tr>
<td>The people to whom the drug must be made “reasonably available” are\textsuperscript{b}</td>
<td>Research participants</td>
</tr>
<tr>
<td>People in the area where the study was conducted</td>
<td>5%</td>
</tr>
<tr>
<td>People in the entire country where the study was conducted</td>
<td>73%</td>
</tr>
<tr>
<td>People in the country and neighboring countries where the study was conducted</td>
<td>2%</td>
</tr>
<tr>
<td>People in the entire world</td>
<td>14%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}None of these responses is statistically significant based upon chi-square tests.

\textsuperscript{b}Verbatim question from the questionnaire.
at a price the average person can afford. Such regional differences may reflect different underlying values, with Europeans and South Americans more likely to espouse communal solidarity as a core value for health care while those from the United States, Australia, and Thailand may support more individualist and entrepreneurial values. These differences could also reflect what respondents are accustomed to, as most Europeans and South Americans receive free or almost free comprehensive health care, including medications, through national health systems while Americans and Thais do not.

Both IRB/REC chairs’ and investigators’ responses suggest shared responsibility for making a drug “reasonably available,” with both groups indicating an important role for the host country government. These responses may reflect a growing recognition of the need for partnerships between host countries and sponsors in externally sponsored research, and are consistent with limited findings elsewhere.¹¹

Since all respondents were involved in an HIV/AIDS study, these findings may not be generalizable to IRB/REC chairs, investigators, or research participants in other types of clinical studies. Additionally, despite 682 respondents, geographic distribution was limited to the distribution of ESPRIT sites. Countries chosen for ESPRIT reflected concern about the ethics of conducting a trial in countries where IL-2 and antiretrovirals were unlikely to be available posttrial. Consequently, there were no respondents from Africa or poorer Asian countries. Some variability might also have resulted from the fact that IRB/REC chairs and Thai subjects were interviewed while other respondents completed self-administered questionnaires.

CONCLUSIONS

This study provides valuable data regarding the views of three different groups involved with a large multinational HIV treatment trial about the complex ethical questions of to whom, at what cost, and by whom interventions proven effective in research should be made available posttrial. In light of the ambiguity surrounding these requirements, such data help to clarify the views of important stakeholders about ethical requirements in multinational clinical research.

ACKNOWLEDGMENTS

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REFERENCES


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