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Benefits and Burdens of Participation in a Longitudinal Clinical Trial

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Abstract

SYSTEMATIC DATA ON THE IMPACT THAT longitudinal clinical trials have on patient participants are needed to ensure that all the risks and potential benefits of participating in clinical research are properly evaluated and disclosed. Recognizing the lack of systematic data on this topic, we surveyed 582 individuals from Argentina, Brazil, and Thailand who were participating in the ESPRIT study, a Phase III randomized trial of interleukin-2 in HIV disease. Respondents were asked about the benefits and burdens of participating in ESPRIT using a self-administered survey. We found that 91% of respondents in the IL-2 treatment arm and 79% in the no IL-2 control arm reported medical benefits from their participation. In addition, 68% in the IL-2 treatment arm and 60% of the no IL-2 controls reported non-medical benefits. Thirteen percent of the IL-2 respondents and 5% of the non-IL2 respondents reported problems with their jobs due to study participation. Given that respondents, including those in the control arm, reported medical and non-medical benefits and burdens from their research participation, investigators and review committees should be aware of and respond to the potential for research participants to experience benefits and burdens that are unrelated to the intervention being tested.

Keywords

longitudinal clinical trial; benefits; burdens

TO BE ETHICAL, CLINICAL RESEARCH SHOULD OFFER an appropriate risk/benefit profile (see e.g., World Medical Association, 2008; CIOMS, 2002; NBAC, 2001; U.S. Code of Federal Regulations, 1991). To ensure that longitudinal clinical studies satisfy this requirement, it is necessary to assess what impact they have on patient participants over time. Despite the importance of this assessment, there are few systematic data on the impact longitudinal clinical studies have on patient participants. To provide data, the present study surveyed individuals who were participating

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Author Contributions.

Jaime Lazovski contributed to the conception and design, analysis and interpretation of data, drafting of the manuscript, and administrative support for this paper. Marcelo Losso made critical revisions to the manuscript. Benjamin Krohmal contributed to the analysis and interpretation of the data, and to the drafting of the manuscript. Ezekiel Emanuel contributed to the design of the study, the analysis and interpretation of the data, and to the drafting of the manuscript. Christine Grady contributed to the design of the study, to the analysis and interpretation of the data, and to the drafting and revision of the manuscript. David Wendler contributed to the design of the study, to the analysis and interpretation of data, to the drafting and revision of the manuscript, and provided overall supervision for the study. Jaime Lazovski and David Wendler had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

in the ESPRIT study, a longitudinal clinical trial that randomized individuals who were receiving treatment for HIV disease to either an experimental add-on treatment or no add-on treatment. Evaluation of participants in the ESPRIT study provided the opportunity to evaluate the experience of individuals with a serious disease in different countries who participated in a clinical research study over several years.

Methods

ESPRIT

The present data were collected as part of a larger survey of individuals participating in the ESPRIT study.[1] ESPRIT is a U.S. National Institutes of Health (NIH)–sponsored multi-national, Phase III, open-label trial comparing antiretroviral therapy plus interleukin-2 (IL-2) to antiretroviral therapy alone. Participants are HIV+ males and females 18 years or older with CD4+ cell counts of at least 300/mm^3 at baseline. Previous studies have shown that treatment with IL-2 is associated with an increase in CD4+ cells (see Ruxrungtham et al., 2000;Losso et al., 2000;Markowitz et al., 2003;Arduino et al., 2004;Youle et al., 2006). The ESPRIT study is designed to determine the significance, if any, of this increase in CD4+ cell count for disease progression and death.

ESPRIT enrolled 4,150 individuals from 25 countries. All participants are required to be on antiretroviral therapy as part of their routine treatment before randomization into the study. Antiretroviral drugs are not provided by the study. The study requires all participants to return to the clinic every four months for medical evaluation and collection of blood samples (Emery et al., 2002).

IL-2 Administration and Side Effects

Participants on the IL-2 treatment arm receive three cycles of subcutaneous IL-2 during 5 consecutive days every 8 weeks after randomization, and then additional cycles based on their CD4+ cell count response. The most prominent side effects of IL-2 are flu-like symptoms, including fever, fatigue, and myalgia, and other constitutional symptoms, such as edema, allergic reactions, hypothyroidism, irritability, insomnia, confusion, and depression. Side effects begin 2–6 hours following dosing, and typically resolve within 5 days (see, e.g., Losso et al., 2000; Arduino et al., 2004).

Survey

After a comprehensive literature review, a draft survey was developed. This draft was revised by survey professionals and pre-tested with ESPRIT participants in the United States. The final version was translated into Spanish, Portuguese, and Thai, and then back-translated into English to assess accuracy. The questions asked of participants in the control arm were the same as those asked of participants in the active treatment arm except for questions specifically related to the use and effects of the experimental treatment. For example, only those in the IL-2 treatment arm were asked about any side effects of receiving IL-2. The questions appear in Appendix A.

[1]The “Evaluation of Subcutaneous Proleukin in a Randomized International Trial” (ESPRIT) was an international, multicenter, Phase III clinical trial. The trial was designed to evaluate whether giving interleukin-2 (IL-2) to HIV-infected individuals, in addition to combination antiretroviral therapy, would reduce the rate of AIDS-related opportunistic infections and death compared to combination antiretroviral therapy alone. The ESPRIT study began in March 2000 and ended in November 2008. It enrolled over 4,000 study participants and took place at 252 clinical trial sites in 25 countries. The U.S. National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), sponsored ESPRIT. The study found that IL-2 boosts individuals’ numbers of CD4+ T cells, but does not reduce the risk of HIV-associated opportunistic diseases or death compared with combination antiretroviral therapy alone. For more information on the trial and its results, see http://www3.niaid.nih.gov/news/QA/IL_2_therapy_qa.htm and http://www.nih.gov/news/health/feb2009/niaid-10.htm.

Based on concern that clinical research raises the greatest ethical challenges when it is conducted in developing countries, the present study focused on the three developing countries participating in ESPRIT: Argentina, Brazil, and Thailand. Individuals were eligible for the survey after they had been participating in ESPRIT for at least 6 months. Individuals were invited to participate in the survey based on the availability of the survey coordinator at each site. The survey was self-administered during a clinic visit. After completion, the surveys were mailed directly to the ESPRIT coordinating center at the University of Minnesota. Site research staff did not have access to respondents' answers.

Analysis

Data reported here are from the questions related to the medical and non-medical benefits and burdens of participation in the ESPRIT Study. Questions were either multiple choice or open ended. Respondents' verbatim answers to the open-ended questions were recorded and coded independently by two authors (JL, BK). Disagreements between the two authors were settled by a third author (DW).

Respondents' reports of the benefits and burdens of participation were evaluated using a four-level Likert scale; results are shown as dichotomized responses in the tables. Significance testing was performed using Mantel-Haenszel chi square analyses of the dichotomized responses with stratification by country.

Approvals

The survey was approved by the Dr. Virgilio G. Foglia Ethics Committee in Buenos Aires, Argentina; the Emilio Ribas Institute of Infectious Disease Ethics Committee in Sao Paulo, Brazil; the Ethics Committee of the Faculty of Medicine, Chulalongkorn Hospital, Bangkok, Thailand; and the National Institute for Allergy and Infectious Disease IRB, in Bethesda, Maryland, USA. All respondents provided informed consent in writing before completing the survey.

Results

Sample Characteristics

At the time of the survey, 1,017 individuals had been enrolled in the ESPRIT study in the three countries. None of these 1,017 individuals had formally withdrawn their consent, although 6 (0.6%) were lost to follow-up. Of the 1,017 enrolled individuals, 595 (58.5%) were invited to participate over a span of 8 months. Of the 595 invited participants, 582 consented and completed the survey (response rate = 98%). Respondents had been participating in the ESPRIT study for 2 to 3 years, 292 were in the IL-2 treatment arm, and 290 were in the no-IL-2 control arm. Nearly 70% were male, the mean age was 37.6 years, and approximately 8 in 10 respondents were employed (Table 1).

Medical and Non-medical Benefits

Significantly more respondents in the IL-2 treatment arm reported medical benefits as a result of their participation in ESPRIT, although a majority of those in the no-IL-2 control arm also reported receiving medical benefits (91% to 79%; $p < 0.001$; Table 2). The three most common medical benefits cited by the IL-2 treatment participants were improvement in their health condition (41%), better access to health care services (22%), and improvement in their emotional condition (18%). The three most common medical benefits cited by the no-IL-2 control arm respondents were better access to health care services (35%), improvement in their emotional condition (18%), and savings of time and money when receiving care from the research team (12%).

Slightly more participants in the IL-2 treatment arm reported non-medical benefits compared to those in the no-IL-2 control arm (68% to 60%; $p<0.059$; Table 3). The four most common non-medical benefits cited by the IL-2 treatment and the no-IL-2 control participants respectively were emotional benefits (38% and 41%), social benefits (32% and 27%), better access to health care services (12% and 9%), and better access to medical information (8% and 10%). The only clear differences between countries involved non-medical benefits. Social benefits were regarded as the primary non-medical benefit by 52% of the Thai respondents versus 12% of the Argentinean and Brazilian respondents combined. Conversely, almost 60% of the Argentinean and Brazilian respondents regarded emotional benefits as the primary non-medical benefit versus 14% of the Thai respondents.

Burdens

Overall, 40% of the respondents in the IL-2 treatment arm, and 12% of those in the no-IL-2 control arm ($p < 0.001$) said ESPRIT participation had been “very” or “moderately” burdensome for them (Table 4). The three most common burdens cited by the respondents on the IL-2 treatment arm were side effects (43%), amount of time devoted to the study (14%), and problems at work (13%). The three main burdens cited by respondents on the no-IL-2 control arm were amount of time (22%), emotional burden (10%), and side effects (8%). In the IL-2 treatment arm, 7.5% of respondents reported that they lost their jobs as a result of their participation in the study, versus 4.5% of the non IL-2 control respondents ($p = 0.21$).

Discussion

This is one of the first studies to evaluate the impact of participating over time in a longitudinal clinical research study. A majority of respondents in both the treatment and the no-treatment control arms reported gaining at least a moderate amount of medical benefits, as well as at least a moderate amount of non-medical benefits from their participation in the ESPRIT study. In addition, 40% of the respondents in the IL-2 treatment arm, and 12% of those in the no-IL-2 control arm reported that participation in the study was at least moderately burdensome.

The present findings are based on the respondents’ self-report and were not confirmed by objective testing. As a result, it is impossible to determine precisely the extent to which the findings represent benefits and burdens experienced by the respondents versus the extent to which the findings represent respondents’ perceptions of the benefits and burdens. Nonetheless, these findings underscore the potential for participation in research to offer medical and non-medical benefits and burdens. Moreover, the perception of benefits and burdens as the result of one’s participation in clinical research, even if they do not represent actual experiences, are important because they can influence individuals’ experience with and willingness to continue to participate in clinical research.

Respondents, including those in the control arm, reported a range of medical benefits from their research participation that were unrelated to the intervention being studied. In particular, respondents reported that participation in the study provided them with access to medical professionals and improved medical services, as well as important information regarding their disease and its treatment. Non-medical benefits also were reported by many respondents. These included both social and emotional benefits. Participation in the study provided the opportunity for respondents to meet others with the same disease, allowing them to share and discuss their problems and experiences. Respondents also reported emotional benefits as the result of contributing to clinical research.

Respondents in both the active and control arms reported that participation led to significant burdens. As expected, individuals in the active treatment arm reported significant side effects as the result of taking IL-2. While a good deal of ethical concern focuses on randomizing

individuals to a no-treatment control arm, these findings highlight the concerns that trace to the side effects of experimental treatments, especially given the possibility that the experimental treatment will be found to be not efficacious. Respondents also reported a range of burdens that were not associated with the experimental treatment. In addition to the burdens of the study visits, many individuals reported job-related problems, and a surprising number reported losing their job as a result of study participation.

Attention to the benefits and burdens of participation in clinical research often focuses on the benefits and burdens of the study medication and study procedures. The present findings suggest that this focus is too narrow. Review committees and investigators should be aware of and respond appropriately to the possibility for research participants to experience benefits and burdens that are independent of the intervention being tested. Such extra benefits may include enhanced access to medical professionals and medical care, the opportunity to share information with other study participants, and an increased sense of hope and meaning as the result of contributing to efforts to find better treatments for one's disease. Burdens not related to the study treatment or procedures can include a wide range of experiences that are the result of participating in clinical research over time, including negative consequences for one's relationships and employment.

The present findings on burdens and non-medical benefits support data found in previous studies. Mattson et al. (1985) found lost time, work-related problems, and medication side effects as burdens of research participation in a survey of heart patients. In addition, the receipt of additional clinical information, access to a second opinion, and emotional reassurance were described as the main benefits of research participation. Madsen et al. (2002) reported that trial participants were burdened by the need to see many physicians at clinic visits. Another two surveys showed that research participants expect to receive psychological benefits, as well as better care and information from participating in clinical trials (Daugherty et al., 2000; Madsen et al., 2000).

The present findings raise questions about the extent to which research participants distinguish the consequences of their disease and standard treatments from the consequences of research participation (see, e.g., Joffe et al., 2001; Penman et al., 1984; Simon et al., 2004). Much of the existing literature on the conflation of research and care focuses on the failure to recognize the extent to which the methods of clinical research differ from the methods of clinical care, the so-called therapeutic misconception. The present data highlight the possibility that research participants also may have difficulty distinguishing the benefits and burdens that are the result of their clinical circumstances from the benefits and burdens that result from participation in research. For example, the no-IL-2 control participants reported study-associated improvement in health. Some individuals likely received better care while participating in the study. In addition, some respondents may have regarded their standard antiretroviral treatment to be part of the ESPRIT study. This latter possibility is supported by the finding that 8% of the control arm respondents reported side effects as a medical burden of their participation in the ESPRIT study, despite the fact that their antiretrovirals were not provided as part of the study.

The same confusion may also help to explain some of the finding that 7.5% of respondents in the IL-2 arm and 4.5% in the control arm reported losing their jobs as a result of their study participation. ESPRIT poses relatively low burdens on the control participants beyond their standard HIV treatment. In addition, the difference found between the two arms was not statistically significant. This finding suggests that some respondents may have ascribed to the ESPRIT study problems that were due to their disease and standard treatment. At the same time, the fact that reported problems with jobs were higher in the IL-2 treatment arm, while not statistically significant in this cohort, raises the possibility that some respondents

experienced significant work-related difficulties as a result of the study requirements and/or the side effects of the study treatment.

The present findings reveal that the potential benefits and burdens of participation in longitudinal clinical studies extend well beyond the potential benefits and burdens of the study medication. These findings highlight the need for investigators and ethics review committees to recognize and evaluate the full range of potential benefits and burdens of research participation. This recognition is important both for the evaluation of the risk/benefit profile of the study and for the purposes of informing potential participants. The ethical requirement to minimize risks and enhance potential benefits of clinical research participation implies that investigators and ethics review committees should consider steps to minimize non-medical harms and enhance non-medical benefits that arise during the course of study participation. This may require a process for evaluating and responding to the impact that clinical research is having on participants in real time. To ensure that treatment trials yield valid data, it is vital to retain participants over time and minimize the number of dropouts. To this end, Hussain-Gambles (2004) recommends that investigators should regularly attempt to identify and address non-medical harms that may lead participants to withdraw or to refuse to participate in clinical trials.

The ethical requirement to obtain valid informed consent also implies that it may be useful to consider ways to expand the standard informed consent process to address study-related benefits and burdens. For example, potential participants might be encouraged to explore these issues prior to research enrollment, a process that could be facilitated, where possible, by discussion with individuals already participating in the study. Investigators and review committees will need to consider carefully which risks and potential benefits are disclosed to potential participants and how they are discussed. For example, failure to disclose or discuss non-medical benefits and burdens may result in individuals having an inaccurate understanding of the impact that research participation will have on them. At the same time, overemphasis on non-medical benefits and burdens may have the potential to inappropriately entice or dissuade individuals from research participation.

Future research will be needed to answer questions raised by the present findings regarding which risks and potential benefits should be included when evaluating the appropriateness of the risk/benefit profile of clinical research studies, and which risks and potential benefits should be included when discussing the study with potential participants. Evaluation and description of clinical trials often focuses on the risks and potential benefits that are due to the intervention being evaluated. Future research will be needed to evaluate the appropriateness of this practice, the extent to which it might underestimate the risks and potential benefits of participating in longitudinal clinical research studies, and how this underestimation affects the approval and consent processes.

Best Practices

These findings highlight the need for investigators and ethics review committees to evaluate and address the actual and perceived benefits and burdens of research participation, including the benefits and burdens that are unrelated to the specific medical intervention being tested. Potential participants should be encouraged to explore these issues when deciding whether to enroll in clinical research and investigators and review committees should develop methods to track and minimize research-related burdens over the course of a given study. It is important to recognize that cultural and financial differences between countries may influence the benefits and burdens of research participation. In addition, the perception of benefits and burdens, even when not the result of actual experiences in clinical research, may influence individuals' views regarding clinical research and their willingness to participate in it.

Research Agenda

Since the present study findings are restricted to a single HIV treatment study, it will be important to evaluate the perceptions and experiences of individuals participating in clinical trials for other diseases, and in other places. This is especially important given that the degree of stigma attached to HIV differs from country to country and differs from other diseases, and that the experience and perception of burdens and benefits may be different in countries with higher and lower levels of development. The present study relied on self-administered quantitative surveys. As a result, we were not able to discuss respondents' answers in-depth and were not able to explore respondents' perceptions of the benefits and burdens of the research study versus the benefits and burdens of their condition and treatment. Focus groups and other kinds of qualitative research should be considered to address these limitations and to evaluate research participants' experiences and perceptions. We also did not attempt to objectively confirm respondents' reports regarding the benefits and burdens of participation in the study. Future research should address this important limitation. Finally, recognition of the broad range of possible benefits and burdens associated with research participation raises the question of which benefits and burdens should be included when evaluating the risk/benefit profile of clinical research studies, and when discussing research with potential participants.

Educational Implications

This study has important implications for the education, via workshops or group discussions, of those who are planning longitudinal clinical trials. The findings of this study are relevant to several stages of clinical trials. Investigators who are planning a trial should be urged to consider how participation will affect the physical and mental health status, as well as the ordinary life of potential participants. Ethics committee members who are evaluating a research project should be instructed to take into account the entire spectrum of benefits and burdens of trials. In addition, investigators as well as ethics committee members should be made aware that these non-medical benefits and burdens can also be affected by variations in the research conditions. Investigators and review committees should consider developing methods to identify and address research-related burdens over the course of a given study.

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APPENDIX A. Verbatim Questions

1	Overall, how much medical benefit (including increased CD-4 counts, improvement in your physical health, and/or increased access to medical services) do you think you are getting from participating in the ESPRIT study? Answer options: A great deal of medical benefit/A moderate amount of medical benefit/A small amount of medical benefit/No medical benefit.
2	In your view, what are the primary medical benefits of participating in the ESPRIT study?

Open-ended question.

3 To what extent do you get non-medical benefits from participating in the ESPRIT study, such as the opportunity to meet new friends, feelings of support, hope, or satisfaction?

Answer options: A great deal/A moderate amount/A little/None.

4 Please describe what these non-medical benefits are.

Open-ended question.

5 Overall, considering the time you spend and any anxiety, discomfort, or side effects you may have experienced in ESPRIT, how burdensome has it been for you to participate in the ESPRIT study?

Answer options: Very burdensome/Moderately burdensome/Slightly burdensome/Not burdensome at all.

6 What are the most significant burdens for you of participating in the ESPRIT study?

Open-ended question.

7 Has your participation in the ESPRIT study caused you any of the following problems?

Answer options: Loss of a job/Other problems in your job/Family conflicts/Conflicts with your primary health care provider.

Biography

Authors' Biographical Sketches

Jaime Lazovski is a physician who specializes in infectious diseases, medical research, and the ethics of medical research. He is one of the national study coordinators for ESPRIT in Argentina.

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Ezekiel Emanuel trained as an oncologist and political theorist. He is the chief of the Department of Bioethics at the National Institutes of Health in the U.S.

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David Wendler trained as a philosopher. He heads the unit on vulnerable populations in the Department of Bioethics at the National Institutes of Health in the U.S.

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TABLE 1

Respondents' Baseline Characteristics (N = 582)

	IL-2 Active Treatment Respondents (N = 292)		Non IL-2 Control Respondents (N = 290)	
	No.	**%**	**No.**	**%**
Male	196	67.1%	203	70.0%
Female	96	32.9%	87	30.0%
National health coverage	114	39.0%	119	41.0%
Employer insurance	57	19.5%	61	21.0%
Self pay	66	22.6%	60	20.7%
Other	30	10.3%	20	6.9%
Not available	25	8.6%	30	10.3%
No schooling	2	0.7%	2	0.7%
<12 years schooling	68	23.9%	61	21.6%
High school graduate	95	33.5%	99	35.0%
College or university	77	27.1%	80	28.3%
Graduate/professional school	42	14.8%	41	14.5%
Age (mean years)	37.7		37.5	
CD4 (median)	421		427	
Employed	78.5%		80.4%	

TABLE 2

Medical Benefits of Participation in the ESPRIT Study

	Beneficial[#]	Primary[*] Medical Benefit of Participating (Open-ended Question)								
		Health Improvement	Access to Health Care	Emotional Benefits	Access to Information	Quality Team	Save Money/Time	Other	None	Total
IL-2	91%	41%	22%	18%	7%	6%	3%	3%	0%	100%
Arm	248/272	99	54	43	16	14	8	6	0	240
Non IL-2	79%	11%	35%	18%	11%	7%	12%	4%	2%	100%
Controls	200/253	26	82	43	25	16	27	10	4	233

[#]Percentage who answered they are getting “a great deal of medical benefit” or “a moderate amount of medical benefit” from the study. Table does not include respondents who skipped the question.

[*]Respondents were asked to provide their views on the primary medical benefit of participating in the ESPRIT study. However, many respondents provided more than one benefit. In these cases, all the benefits listed by the respondent were included.

TABLE 3

Non-Medical Benefits of Participation in the ESPRIT Study

	Beneficial[#]	Primary[*] Non-medical Benefit of Participating (Open-ended Question)								
		Emotional Benefits	Social Benefits	Access to Health Care	Access to Information	Quality of Life Improvement	Save Money/Time	Other	None	Total
IL-2	68%	38%	32%	12%	8%	3.5%	1%	3.5%	2%	100%
Arm	182/267	64	53	20	13	6	2	6	3	167
Non IL-2	60%	41%	27%	9%	10%	2%	6%	4%	1%	100%
Controls	156/259	64	42	14	15	3	10	8	2	158

[#]Percentage who answered they are getting “a great deal of non-medical benefit” or “a moderate amount of non-medical benefit” from the study. Table does not include respondents who skipped the question.

[*]Respondents were asked to provide the primary non-medical benefit they received from participating in the ESPRIT study. However, many respondents provided more than one benefit. In these cases, all the benefits listed by the respondent were included.

TABLE 4

Burdens of Participation in the ESPRIT Study

	Burdensome[#]	Most Significant[*] Burdens of Participating (Open-ended Question)								
		Side Effects	Time Spent at Visits	Problems at Work	Emotional	Other Problems with IL-2	Blood Drawing	Other Answers	None	Total
IL-2	40%	43%	14%	13%	7%	4%	0%	9%	10%	100%
Arm	142/277	94	30	28	16	8	0	20	21	217
Non IL-2	12%	8%	22%	5%	10%	0%	3%	14%	38%	100%
Controls	29/262	9	23	5	11	0	3	15	40	106

[#]Percentage who stated that the study was “very burdensome” or “moderately burdensome.” Table does not include respondents who skipped the question.

[*]Many respondents cited more than one burden. All the burdens listed by the respondent were included.