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Views of IRB Members regarding Phase 1 Pediatric Oncology Trials

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Abstract

There is significant debate over whether phase 1 pediatric oncology trials are ethical and approvable. We thus surveyed IRB members to answer four questions. First, do IRB members think the potential medical benefits of average phase 1 pediatric oncology trials outweigh the risks? Second, do they think these trials are ethically appropriate? Third, do they think these trials are approvable? Fourth, how do the views of IRB members on the first two questions compare to the views of the US public? Of the 107 respondents who met the inclusion criteria, 18.8% stated that the potential medical benefits of average phase 1 pediatric oncology trials outweigh the risks, 32.5% stated that the potential medical benefits and risks are about equal, and 48.8% stated that the risks outweigh the potential medical benefits. Compared to the general public, IRB members were significantly more likely to think the risks outweigh the potential medical benefits ($p= 0.01$). Finally, 68.8% of IRB members indicated that average phase 1 pediatric oncology trials are approvable, and 56.3% indicated that these trials are appropriate in children. These findings suggest two-thirds of IRB members believe average phase 1 pediatric oncology trials are approvable. Yet, almost half regard the risks as outweighing the potential medical benefits and almost half think these trials are inappropriate. These findings raise important questions regarding why IRB members and the general public evaluate the same risk/benefit profile differently, and whether it is possible to reconcile the two perspectives.

Keywords

Phase 1; risks; potential benefits; institutional review boards

Phase 1 pediatric oncology trials are vital to improving treatments for pediatric cancer. Yet, there remains significant debate over whether these trials are ethical and approvable.[1–3]

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Critics express concern that these trials expose children with advanced cancer to excessive risks in order to collect data to benefit future patients. They conclude that these trials are not ethical, and they are not approvable under US regulations, which permit IRBs to approve pediatric research that poses significant risks only when it offers a prospect of direct benefit which justifies the risks. Proponents counter that the potential medical benefits these trials offer participants justify the risks.

To try to resolve this debate, some commentators consider whether the investigators of phase 1 trials *intend* to benefit participants [3–5] or whether their *goal* is to benefit participants.[6,7] Others consider whether these trials offer *any* chance for medical benefit.[8] Yet, these factors do not determine whether pediatric trials that pose significant risks are ethical and approvable. That depends on whether they have important social value, their risks are "justified" by the potential benefits to participants, and the risk-benefit profile is "at least as favorable" as the available alternatives.[9]

Recent collection of data on the risks and potential medical benefits of phase 1 pediatric oncology trials offers the opportunity to assess for the first time whether IRB members think the risks of these studies are justified by their potential medical benefits.[10] Using these data, along with data from prior studies [11–20], we estimated the risks and potential medical benefits of average phase 1 pediatric oncology trials. We then conducted a survey to address four questions: Do IRB members think the potential medical benefits of average phase 1 pediatric oncology trials justify the risks? Do they think these trials are ethically appropriate? Do they think these trials are approvable under US regulations? How do the views of IRB members regarding the first two questions compare to the views of the US public? [21]

Methods

Risks and potential medical benefits of average phase 1 pediatric oncology trials

In a recent analysis, Waligora et al. (2018) found a partial or complete response rate of 10.3% in phase 1 pediatric oncology trials. This is similar to the 9.6% response rate found by Lee et al. (2005), which analyzed pediatric phase I studies, and the 10.6% response rate Horstmann et al. (2005) found in adult phase I oncology studies. Based on these results, we described the chance for medical benefit in an average phase 1 pediatric oncology trial as follows:

> For 1 in 10 children who enroll in the study, the experimental treatment causes their tumor to shrink. For most children, this does not lead to a better or longer life. For a few children, it leads to a better and possibly longer life.

In terms of risks, Waligora et al. found a **drug-related** death rate of 2.09% and a **drug-related** grade 3 or 4 adverse event rate of 1.32 per person. This is higher than other pediatric meta-analyses which found **drug-related** rates of 0.4%[20] and 0.5 %[22], but is consistent with the **drug-related** (adult) rate of 1.9–2.3% found by Schwaederle et al. (2016). We thus described the risks of an average phase 1 pediatric oncology trial as follows:

Most children who enroll in the study experience a serious side effect from the experimental treatment, such as significant nausea, pain, or hospitalization. Also, 1 in 100 die as a result of taking the experimental treatment.

Survey Development

We drafted the survey based on a comprehensive review of the literature. Following input from experts in these fields, we created two versions, one for the US public and one for IRB members. The version for the general public was piloted in four rounds of testing using Amazon Mechanical Turk (MTurk) with 555 respondents. Revisions were made after each round. We then revised the IRB survey based on the final version of the US public survey.

Both surveys addressed four domains: 1) respondent characteristics; 2) risks and potential medical benefits of average phase 1 pediatric oncology trials; 3) risks and societal benefits of net-risk pediatric research; and 4) attitudes toward research (adapted from Rubright et al. 2011 [23]). This article reports the results from the first, second, and fourth domains in the survey of IRB members. It also compares these results to the analogous results obtained in the survey of the US public.

The two versions of the survey described the risks and potential medical benefits of an average phase 1 pediatric oncology trial in the same way, and then asked respondents whether the potential medical benefits outweigh the risks, and whether the trial was appropriate to conduct in children. The IRB survey also asked respondents whether they thought the described trial was approvable under U.S. regulations whereas the survey of the US public asked whether respondents would enroll their child.

IRB Survey

The IRB survey asked respondents to imagine their IRB is reviewing a phase 1 study testing the safety of an experimental cancer treatment which has the aforementioned risks and potential medical benefits (see supplemental information for verbatim wording). The study proposes to enroll children with advanced cancer whose only alternative is to be kept as comfortable as possible until they die, which is likely to occur in a few months. Following this description, respondents were asked three test questions to ensure they understood the risks and potential medical benefits. They were then asked how the risks and potential medical benefits compare.

To be ethical and approvable, pediatric clinical trials need to have important social value and pose acceptable risks.[24] Consistent with this approach, US regulations permit IRBs to approve pediatric trials that pose ‘minimal’ or a ‘minor increase’ over minimal risk. Under US regulations, IRBs may approve pediatric trials that pose greater than a minor increase over minimal risk only when: 1. the potential medical benefits “justify” the risks; and 2. there is no available alternative that offers participants a more favorable risk-benefit ratio.

The goal of the present survey was to assess whether IRB members think average phase 1 pediatric oncology trials satisfy the first condition of the potential medical benefits justifying the risks. However, we were concerned that some respondents might be unfamiliar with the idea of potential medical benefits “justifying” risks. As a result, we worded the answer

options as follows: “The potential medical benefits definitely outweigh the risks”; “The potential medical benefits probably outweigh the risks”; “The potential medical benefits and risks are about equal”; “The risks probably outweigh the potential medical benefits”; and “The risks definitely outweigh the potential medical benefits.”

Combining the first three responses provides an estimate of how many respondents believe that participation in the trial poses no ‘net’ risks in the sense that the risks do not exceed the potential medical benefits.[24] We regard this group as believing that the potential medical benefits ‘justify’ the risks. Combining the last two responses provides an estimate of how many respondents think the study poses net risks to participants. We regard this group as believing the potential medical benefits do *not* justify the risks.

Participants were next asked whether they thought the described study was approvable under US regulations for pediatric research, specified as 45CFR46, subpart D, and whether it was ethically appropriate to conduct the study in children. This question was followed by an open-ended question asking participants to explain why, in their view, the described study was or was not appropriate. To analyze the responses, one of the authors developed preliminary themes, which were modified by a second author. The two authors discussed the themes together and developed a list for coding. Based on this list, the two authors independently coded the responses, with no limit on the number of themes permitted per respondent. Disagreements were settled by discussion until consensus was reached. During this process several themes were clarified, and two new themes were added. The themes we report are based on the final list.

Finally, we asked respondents whether they thought that, when the risks *definitely outweigh* the potential medical benefits, it can still be appropriate to approve studies in children for non-medical reasons. Those who indicated that this can be appropriate were asked about the appropriateness of five specific non-medical reasons that have been discussed in the pediatric research ethics literature (see supplemental information, questions 9–13).

Participants

We solicited the participation of a convenience sample of IRB members using two approaches. First, we posted a description of the study and a survey link on *Ampersand*, the official blog of Public Responsibility in Medicine and Research (PRIM&R), a professional organization composed of human research protection professionals. The study was also featured in two email blasts to PRIM&R members. Second, we wrote a post on the IRB Forum inviting members to complete the survey and sent two reminders over a two-month period.

Participants had to be 18 years or older and have English language proficiency. They also had to be a current member, or member within the previous five years, of an IRB that was US-based or an IRB that reviewed studies subject to US regulations. We regard individuals who did not answer the questions needed to determine eligibility as not eligible.

Participant Protection

This survey was deemed exempt from US regulations by the NIH intramural IRB. No personally identifiable information was collected. Potential participants were informed that participation was voluntary, they could skip any questions, and they could stop at any time. No compensation was offered. We regarded answering the questions as indicating respondents' consent.

Data Analysis

Categorical variables were summarized as counts and percentages. The chi-square test or Fisher's exact test was used to compare the categorical variables between groups. All analyses were performed using SAS (version 9.4. SAS Institute Inc., Cary, NC, USA). To assess whether respondents think the potential medical benefits of phase 1 pediatric oncology trials justify the risks, whether these trials are approvable, and whether these trials are appropriate, we limited the analysis to respondents who answered all three test questions correctly indicating that they understood the risks and potential medical benefits of the described trial.

Results

Participants

A total of 126 individuals accessed the survey, 16 of whom did not meet the eligibility criteria. In addition, 3 respondents did not answer the questions necessary to determine eligibility, leaving 107 respondents for analysis. Overall, 86.8% of the 107 respondents self-identified as white, 70.6% as female, and 3.9% as Hispanic (Table 1). For comparison, it is estimated that 86.8% of IRB members in the US are white, 58.9% are female, and 5.6% are Hispanic.[25]. Finally, 67.7% had been an IRB member for 5 or more years and 73.4% had reviewed 10 or more pediatric studies.

Views of Average Phase 1 Pediatric Oncology Trials

Overall, 80 of the 107 respondents (74.8%) answered all three test questions correctly. Of these 80 respondents, 18.8% indicated that the potential medical benefits probably or definitely outweigh the risks, 32.5% indicated that the potential medical benefits and risks are about equal, and 48.8% indicated that the risks probably or definitely outweigh the potential medical benefits (Table 2).

Combining respondents who indicated that the potential medical benefits probably or definitely outweigh the risks with those who considered the potential medical benefits and risks to be about equal, 51.3% thought these trials do not pose net risks. We regard these respondents as believing that the potential medical benefits *justify* the risks. In contrast, 48.8% indicated that the risks probably or definitely outweigh the potential medical benefits. We regard these respondents as believing that the potential medical benefits *do not justify* the risks, hence, the described trial does not satisfy US requirements for approval by an IRB. In addition, 68.8% of the 80 respondents indicated that the described study is approvable under US regulations and 56.3% indicated that the study was probably or definitely ethically appropriate (Table 2).

Of the 80 respondents who answered all three test questions correctly, 79 provided an explanation for why they thought the described study was appropriate, or not appropriate in children. Among the 46 respondents who thought the study was appropriate, the potential for participants to benefit medically was mentioned 12 times (themes 3, 4; see supplemental information). In contrast, the potential to benefit future children/need to test interventions in children was mentioned 22 times (themes 1, 1a, 2). One respondent stated: “Children are NOT small adults. Drugs need to be tested in children in order to identify appropriate doses and to determine potential side effects.” In addition, eight respondents cited the possibility of approving the study in the regulatory categories 406 or 407, which require that a study has the potential to collect valuable information for improving care for children. Finally, eight respondents stated that parents should be given the opportunity to decide whether to enroll their children.

The 33 respondents who thought the study was not appropriate mentioned the risks/potential harms 33 times in total (themes 2, 3, 4, 6, 10, 11). One respondent stated: “For so little risk and given the pain the child is already suffering it seems too much to ask that the child suffer more for little benefit.”

Predictors

Given the demographic homogeneity of our sample, we were not able to assess whether there were any associations between the findings and a number of sociodemographic variables, including race, ethnicity, and gender. We did assess whether there were any associations between the findings and the following variables: length of time as an IRB member, number of pediatric studies reviewed, whether the respondent has children, and whether any of the respondent’s children had a serious illness. No statistically significant associations were found.

Acceptability of Non-medical Reasons for Participating

With respect to studies whose risks were specified as outweighing the potential medical benefits, 60 (56.1%) of the 107 total respondents indicated that it could still be appropriate to enroll children for non-medical reasons. Of these 60 respondents, 87.5% thought it was probably or definitely appropriate in order to help other children with cancer, 80.4% because there are no other options, and 69.6% to bring meaning to a bad situation (Table 3).

Comparison of the Views of IRB Members and the General Public

IRB members were significantly more likely than the US public (in our prior survey) to think the risks of average pediatric phase 1 oncology trials outweigh the potential medical benefits (48.8% versus 32.9%; p= 0.01). In contrast, the percentage of IRB members who indicated that these trials are probably or definitely appropriate, 56.3%, is slightly higher than the percentage of the US public who expressed the same view, 53.4%.

For studies whose risks were specified as outweighing the potential medical benefits, 56.1% of IRB members versus 58.3% of respondents in the general public survey indicated that these studies can be appropriate in children for non-medical reasons. Of these respondents, the percentage who thought the studies are probably or definitely appropriate because they

offer a way to help other children with cancer was almost identical between IRB members and the general public (87.5% versus 88.0%). In contrast, IRB members were significantly less likely than the general public to endorse the following reasons: offers a way to fight the disease and maintain hope (58.9% versus 88.1%; p= < 0.0001); provides a way to bring meaning to a bad situation (69.6% versus 86.1%; p= 0.0019); there are no other options (80.4% versus 90.9%; p= 0.018).

Discussion

Proponents and critics agree that phase 1 pediatric oncology trials are important to improving treatment for pediatric cancer. Debate over whether these trials are ethical and approvable thus focuses on whether they offer participants sufficient potential medical benefits to justify the risks. In a prior survey of the US public, 66.1% of respondents indicated that the potential medical benefits of average phase 1 pediatric oncology trials justify the risks.[21] This finding suggests these trials can be ethical and approvable.

The present survey supports the conclusion that these trials are approvable. Specifically, 68.8% of IRB members indicated that phase 1 pediatric oncology trials are approvable under US regulations. At the same time, almost half of IRB respondents indicated that the potential medical benefits do *not* justify the risks. This finding raises the question of why some IRB respondents think the trials are nonetheless approvable.

Four respondents indicated that these trials may be approved as posing a minor increase over minimal risk. While the regulations do not define a ‘minor’ increase over minimal risk, qualifying interventions are typically understood as ones where: “The increase in the probability and magnitude of harm is only slightly more than minimal risk” (https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2005-july-28-letter-appendix-b/index.html). A high chance of experiencing a serious side effect, and a 1 in 100 chance of death do not qualify as only slightly more than minimal, suggesting these trials cannot be approved as minor increase over minimal risk. Alternatively, respondents might interpret the US regulations as sufficiently flexible to permit IRBs to approve studies that they regard as socially valuable, even when they do not satisfy the strict letter of the regulations.

A third possibility is that some respondents assumed studies which do not offer sufficient potential benefit to participants for approvable by an IRB may be approved by the Secretary in the category of studies “not otherwise approvable” (subpart D, section 407/50.54). Yet, in the open-ended responses, only four respondents mentioned this possibility.

Finally, 56% of respondents indicated that it can be appropriate to enroll children in trials which have an unfavorable risk/benefit profile for non-medical reasons. Some respondents may have believed IRBs can approve pediatric trials that pose higher risks on this basis. Yet, this approach is inconsistent with standard interpretations according to which non-medical benefits do not qualify as ‘direct’ benefits as required by the US regulations.[26, 27]

The present survey also found that 56.3% of IRB members regard these trials as ethically appropriate in children. This finding suggests that 10–15% of IRB members believe

trials which are approvable under US regulations are *not* ethically appropriate. This is a concerning finding that merits future research.

The present findings raise the possibility that IRB members may have a different perspective on the ethics of pediatric research compared to the general public and parents. In our prior survey, members of the public, and parents in particular, emphasized the fact that participation in phase 1 trials offers the potential for medical and non-medical benefits (e.g. a way to do something and maintain hope). In contrast, IRB members who think average phase 1 pediatric oncology trials are appropriate emphasize the potential benefits for future children while IRB members who think these trials are inappropriate emphasize the risks.

Given their different roles, it is perhaps not surprising that parents and the public emphasize the potential benefits to participating children, whereas IRB members emphasize protecting participating children and helping future children. Future research will be needed to assess whether these two perspectives can be reconciled. For example, some commentators argue that the design and review of clinical trials would benefit from the input of research subjects [28]. The present findings suggest it might also make sense to include the parents of children with cancer on IRBs to ensure their perspective is represented.

Limitations

Our results are based on responses to a hypothetical study. IRB members may have different views in response to actual studies reviewed during convened meetings. Second, most of our respondents were white, non-Hispanic and female. While this profile appears to reflect the demographics of IRB members in the US, it limited our ability to assess any associations between respondents' sociodemographic characteristics and the results. Third, a significant number of respondents skipped one or more questions. This may have affected our findings.

Conclusion

The present findings suggest that, compared to the public and parents, IRB members are significantly less likely to think that the potential medical benefits of phase 1 pediatric oncology trials justify the risks, and significantly less likely to endorse non-medical reasons as appropriate for enrolling children. These findings raise the possibility that IRB members may have a different perspective on the ethics of pediatric research compared to the public and parents. Future research should consider whether these two perspectives can be reconciled and whether this difference points to the need to ensure that the views of the public and parents are represented when pediatric clinical trials are reviewed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Sociodemographics (N=107)

	N	%
IRB Role (check all)		
Chair	24	22.4
Lawyer	1	0.9
Ethicist	9	8.4
Researcher	22	20.6
Clinician	13	12.2
Community member	12	11.2
Patient advocate	5	4.7
Non-scientist	29	27.1
Other	18	16.8
Missing	24	
Years of IRB membership		
Less than 5 years	33	32.4
5–10 years	27	26.5
11–15 years	16	15.7
More than 15 years	26	25.5
Missing	5	
Number of pediatric studies reviewed		
None	5	4.9
Less than 10	22	21.6
10–20	13	12.7
21–50	13	12.7
More than 50	49	48.0
Missing	5	
IRB affiliation (check all)		
Academic/university	56	52.3
Government	7	6.5
Hospital	60	56.1
Commercial	6	5.6
NGO	10	9.4
Tribal	0	0.0
Other	2	1.9
Gender Identity		
Man	30	29.4
Woman	72	70.6
Missing	5	
Race (check all)		
White	92	86.8
Black or African American	3	2.8

	N	%
American Indian or Alaska Native	2	1.9
Asian	5	4.7
Native Hawaiian/Pacific Islander	0	0.0
Other	3	2.8
Prefer not to say	1	.94
Missing	1	
Ethnicity		
Hispanic	4	3.9
Non-hispanic	97	95.1
Prefer not to say	1	1.0
Missing	5	
Any children?		
No	30	29.4
Yes	72	70.6
Missing	5	
Any children have a serious illness?		
No	46	64.0
Yes	26	36.0
No children	30	
Missing	5	
Enrolled yourself in research?		
No	50	49.0
Yes	52	51.0
Missing	5	
Enrolled a child in research?		
No	54	75.0
Yes	18	25.0
No children	30	
Missing	5	

Table 2:

Views of Phase 1 Pediatric Oncology Trials (N=80 respondents who passed all 3 test questions)

	N	%
Potential medical benefits outweigh risks?		
Potential medical benefits definitely outweigh risks	1	1.3
Potential medical benefits probably outweigh risks	14	17.5
Benefits and risks about equal	26	32.5
Risks probably outweigh potential medical benefits	22	27.5
Risks definitely outweigh potential medical benefits	17	21.3
Study approvable under US regulations?		
Yes	55	68.8
No	25	32.5
Study appropriate in children?		
Definitely not appropriate	10	12.5
Probably not appropriate	25	31.3
Probably appropriate	36	45.0
Definitely appropriate	9	11.3

Table 3:

Appropriateness of non-medical reasons (of those who thought non-medical reasons could be appropriate, N=60)

Offers a way to help other children with cancer	**N**	**%**
Offers a way to help other children with cancer		
Definitely not appropriate	0	0.0
Probably not appropriate	7	12.5
Probably appropriate	40	71.4
Definitely appropriate	9	16.1
Missing	4	
Offers a way to fight the disease and maintain hope		
Definitely not appropriate	8	14.3
Probably not appropriate	15	26.8
Probably appropriate	29	51.8
Definitely appropriate	4	7.1
Missing	4	
Provides a way to bring meaning to a bad situation		
Definitely not appropriate	1	1.8
Probably not appropriate	16	28.6
Probably appropriate	35	62.5
Definitely appropriate	4	7.1
Missing	4	
Provides a way for parents to make some money		
Definitely not appropriate	53	94.6
Probably not appropriate	1	1.8
Probably appropriate	2	3.6
Definitely appropriate	0	0.0
Missing	4	
There are no other options		
Definitely not appropriate	2	3.6
Probably not appropriate	9	16.1
Probably appropriate	36	64.3
Definitely appropriate	9	16.1
Missing	4	