

REVIEW

A systematic literature review to identify ethical, legal, and social responsibilities of nonprofit organizations when funding clinical trials in pediatric cancer

Vasiliki Rahimzadeh^{1,2} | Susan Wolfert^{2,3} | Vickie Buenger^{2,4} | Cindy Campbell^{2,5} | Robin French^{2,6} | Donna Ludwinski^{2,7} | Amy Weinstein^{2,8} | Caitlyn Barrett^{2,9}

¹Stanford Center for Biomedical Ethics, Stanford University, Stanford, California, United States

²Coalition Against Childhood Cancer (CAC2) Ethics Think Tank, Philadelphia, PA, USA

³Taylor Matthews Foundation, New York, NY, USA

⁴Texas A&M University, Mays Business School, College Station, Texas, USA

⁵Ty Louis Campbell Foundation, Pawling, NY, USA

⁶Morgan Adams Foundation, Denver, CO, USA

⁷Solving Kids' Cancer, New York, NY, USA

⁸Pediatric Brain Tumor Foundation, Atlanta, GA, USA

⁹CureSearch for Children's Cancer, Baltimore, MD, USA

Correspondence

Vasiliki Rahimzadeh, Stanford Center for Biomedical Ethics, Stanford University and Coalition Against Childhood Cancer (CAC2) Ethics Think Tank.
Email: vrahim@stanford.edu

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Abstract

Nonprofit organizations (NPOs) play critical roles as funding sources, research partners, and disseminators of drug developments in pediatric cancer. Yet the literature provides limited guidance about ethical best practices when NPOs make trial funding decisions in this space. We conducted a systematic review of the literature indexed in PubMed and Web of Science to identify the ethical, legal, and social responsibilities of NPOs to four key stakeholder groups in funding pediatric cancer trials: (i) patients/families, (ii) researchers, (iii) industry sponsors, and (iv) donors. We applied the lifecycle framework for patient engagement in drug research and development proposed by Geissler and colleagues to analyze themes related to NPOs' responsibilities across 54 articles that met our inclusion criteria. Emergent themes included transparency surrounding conflicts of interest, the rigor of scientific review, and communication with patients/communities about trial progress. Our research identified critical gaps in best practices for negotiating research partnerships, managing competing research priorities, and pursuing alternative financing models including venture philanthropy. Results from our review informed a set of best practices to guide NPOs in making trial funding decisions that align with stakeholder values and interests.

KEYWORDS

bioethics, clinical trials, funding, nonprofit organization, pediatric cancer

1 | BACKGROUND

Pediatric cancer patients and their families gain access to promising therapies through participation in clinical trials, but those trials

are rarely supported by the industry. Research and drug development in pediatric cancer faces substantial challenges, such as high costs, small sample sizes, uncertain market potential, and strict regulatory requirements for research involving pediatric patients.¹ Diversifying funding sources for cancer trials including from federal funding agencies and, increasingly, nonprofit organizations (NPOs),² therefore, gives patients and families hope for more trial opportunities.³ A recent landscape analysis found nearly 83% of interventional oncology trials involving children younger than 18 in the United States received at least partial funding from nonindustry sponsors, including charitable foundations, individual donors, and patient advocacy groups.⁴

The percentage of funding for pediatric cancer trials provided by NPOs is rising. Funding is generally disbursed to academic-sponsored trials—the focus of our literature review—but which do not significantly benefit commercially if trial data are used in the market authorization or regulatory approval of a new drug. This funding model contrasts with venture or entrepreneurial philanthropy projects wherein investors retain royalties and commercial interests when the investigational drug is marketed. Das and colleagues found, for example, that financing models for a hypothetical portfolio of pediatric cancer therapeutics which involve public-private partnerships had greater returns on investment from the successful sale of investigational drugs than philanthropic grants or industry megafunds alone.⁵

Charities and NPOs also differ from industry or academic sponsors in how they meet the scientific and ethical standards to which they are held. This is critical in pediatric trials because children warrant special research protections.^{6–8} The literature is sparse about what ethical responsibilities, if any, NPOs have when funding pediatric cancer clinical trials or how NPOs can sustain ethically robust relationships with patients and families, researchers, sponsors, donors, and other key stakeholder groups while expanding clinical trial opportunities.

These gaps in knowledge motivated us to conduct a systematic review of the nonprofit and clinical trial literature to address the ethical responsibilities of NPOs to (i) patients and families, (ii) researchers, (iii) donors, and (iv) trial sponsors as they relate to funding clinical trial research in pediatric cancer. The authors report results of this review, which was conducted with an equal effort by members of the Coalition Against Childhood Cancer (CAC2) Ethics Think Tank working group (the “ETT”). The results of this review aim to inform evidence-based guidance for CAC2 and other participating NPOs on how to engender community trust, maintain accountability, and promote rigorous clinical trial science when allocating donor funds to pediatric cancer drug development.

2 | METHODS

We adopted a participatory action approach^{9,10} for this work and were equal partners in the research. The ETT prioritized the research topic, developed the research question, managed data collection and analysis, and prepared results for dissemination in partnership with a research consultant (VR). To facilitate this participatory review approach, we utilized a web-based software (Covidence) that enabled asynchronous screening, data extraction, and full-text analysis.

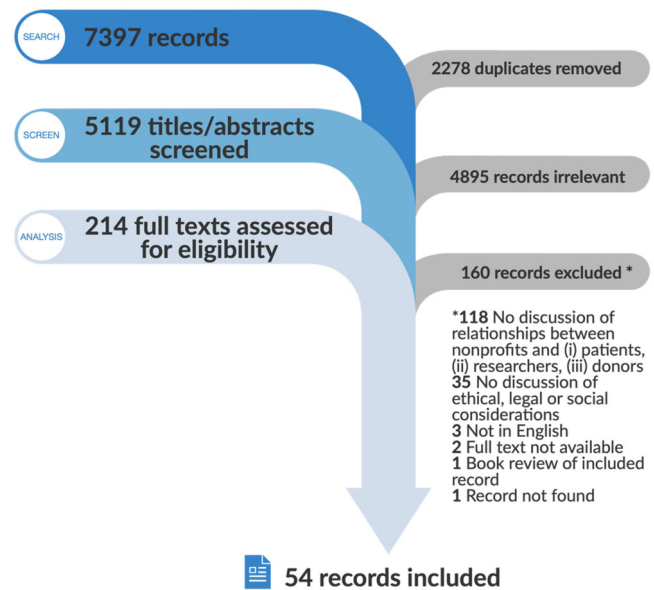


FIGURE 1 PRISMA diagram of search results

With support from a reference librarian from the Lane Medical Library at Stanford University, the ETT systematically searched the NPO and clinical trial literature to identify the ethical, legal, and social responsibilities NPOs have when funding new pediatric cancer clinical trials. A detailed search strategy is provided in the [Supporting Information](#). We were specifically interested in identifying responsibilities and understanding relationships between NPOs and the following key stakeholder groups: (i) patients/families, (ii) researchers, (iii) sponsors, and (iv) donors. Peer-reviewed articles, commentaries, published newsletters, concept papers, and white papers indexed in PubMed and Web of Science were included in the review if they:

- were published in English;
- discussed ethical, legal, and social and/or public policy considerations of partnerships between NPOs and
 - patients/families
 - sponsors
 - donors
 - researchers; and
- discussed or proposed best practices for funding clinical trials.

Given the limited number of pediatric cancer trial articles, the team broadened the criteria to include NPO funding for clinical trials broadly.

3 | RESULTS

Figure 1 details the results of the search according to PRISMA guidelines. The search returned 7,397 total articles. After screening titles and abstracts, 214 full-text articles were reviewed. Pairs of ETT members were randomly generated and assigned to screen each full-text article independently where interrater reliability agreement

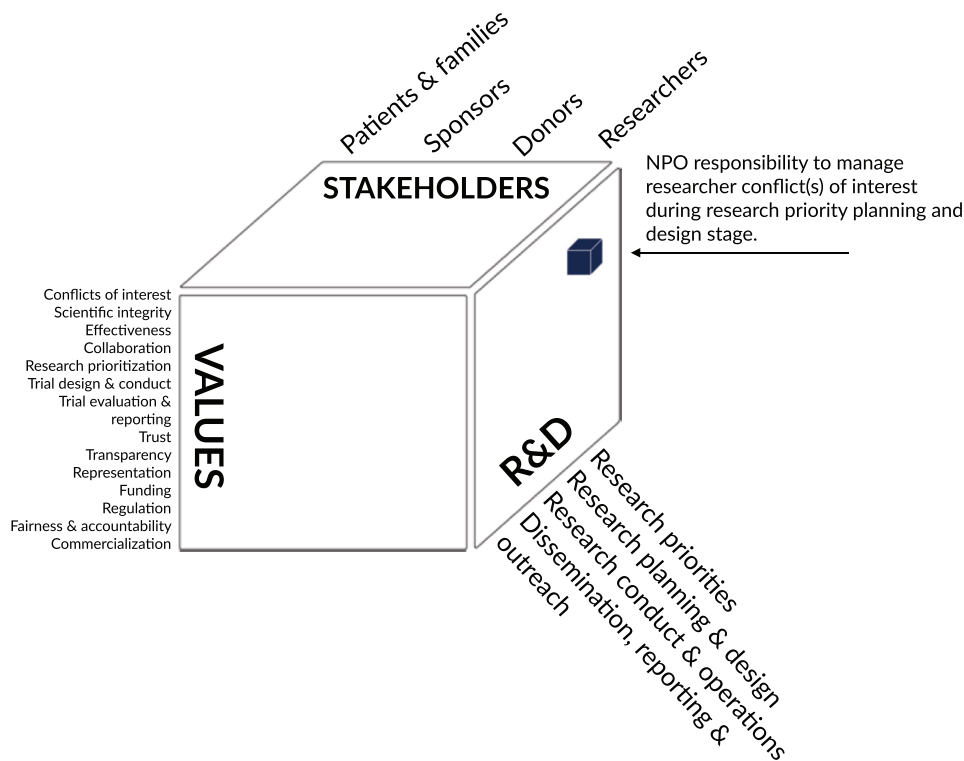


FIGURE 2 Coding matrix combining deductive and inductive codes used to qualitatively synthesize themes from 54 included records

ranged from 0.75 to 0.99. A total of 54 articles met the inclusion criteria.

4 | ANALYSIS

The reviewers synthesized themes using a framework analysis approach^{11,12} and adopted a deductive coding frame to map relevant ethical, legal, and social responsibilities onto one or more stakeholder groups across discreet stages of the drug development lifecycle. Deductive codes were drawn from the lifecycle framework proposed by Geissler and colleagues for facilitating patient involvement in drug research and development.¹³ Lifecycle stages included: (i) research prioritization, (ii) research planning and design, (iii) research conduct and operations, and (iv) dissemination, reporting, and outreach. Three independent reviewers applied the initial deductive codebook to extract relevant ethical responsibilities by relationship type from five full-text articles. Following the pilot, reviewers discussed coding discrepancies, refined the codebook, and developed additional inductive codes which emerged from the pilot analysis. The coding matrix used to analyze the dataset is provided in Figure 2. Excerpts from articles that described specific NPO responsibilities were coded and analyzed by relationship type.

5 | DISCUSSION

Myriad responsibilities emerged from the review, many of which transcended stakeholder groups. The heat map in Figure 3 displays the

coverage of themes by relationship type. Of 54 records analyzed, most responsibilities synthesized from the literature were associated with the NPO-researcher relationship. Trust was the most frequently discussed responsibility across relationship types, followed closely by transparency and conflict(s) of interest management. A discussion of the specific responsibilities of NPOs is organized below by relationship type and stage of the research development process.

The responsibility of NPOs to sustain trust with donors was referenced most among the articles reviewed. Strickland and Vaughan, for example, propose a hierarchy of values that cultivate an ethical culture between NPOs and the donors who support them.¹⁴ Financial competence sits at the top of this hierarchy, with accountability, transparency, respect, and integrity seen as foundational values necessary to enhance organizational culture. Building public trust was foundational to attracting new donor support.

6 | RESEARCH PRIORITY SETTING

In their road map for improving patient involvement in the drug research and development lifecycle, Geissler and colleagues suggest patients and their families take an active role in shaping research agendas. Terry describes how disease advocacy organizations accelerate the pace of biological understanding and drug discovery in both rare and common diseases through partnerships with patient communities.¹⁵ Involving patients early ensures that “development of novel therapies or interventions is focused on areas of patient care that require improvement as defined by patients themselves.”^{13(p614)} This

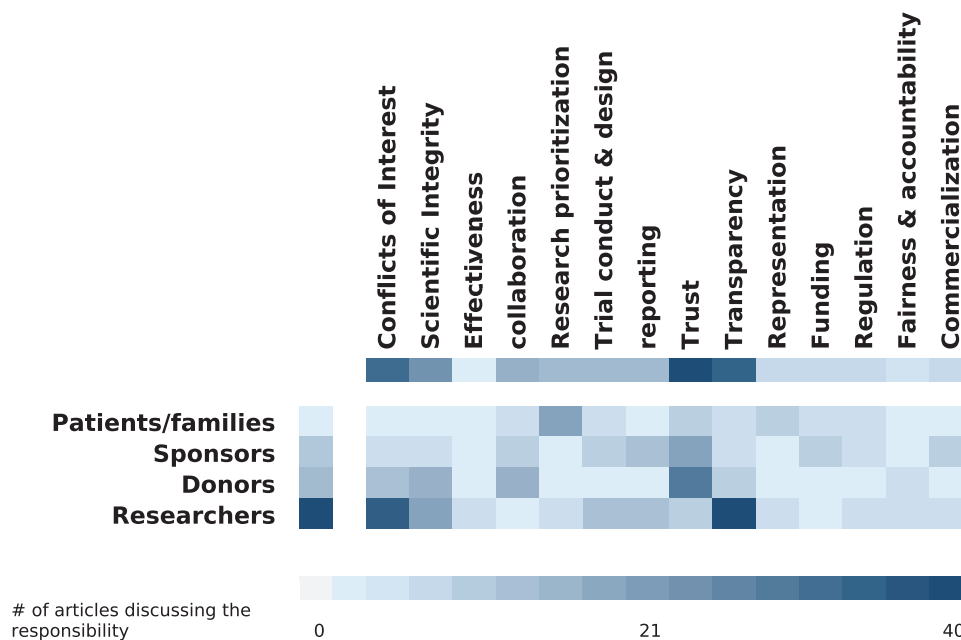


FIGURE 3 Heat map displaying thematic coverage of responsibilities of NPOs to key stakeholders in the research and drug development lifecycle

early engagement leads to a more proportionate review of anticipated benefits, harms, and resource allocation.

We coded responsibilities related to research priority setting whenever an article discussed actions, decisions, or processes used to determine research topics that would receive NPO funding. The focus was to explore how and from whom NPOs obtain input about what research should be funded. General themes analyzed from NPO responsibilities at each stage of the research lifecycle are discussed below.

6.1 | Significance of the patients' lived experience

NPOs that fund biomedical research regularly interface with patients and their families as they offer a wealth of experiential knowledge.¹⁶ Patients may also donate, advocate for research attention and funding, and provide firsthand accounts of unmet needs.^{15,17-19}

6.2 | Complex relationships

The literature described families impacted by a particular disease who establish NPOs to support research for that disease.¹⁷ NPO-affiliated patients and families may also develop special relationships with physician-investigators, creating a potential conflict of interest that can be underscrutinized. The complex nature of relationships between NPOs and patients/families warrants special consideration when prioritizing clinical trials for funding. Ethical tensions can emerge when funding is approved for trials based solely on high-priority areas for patients/families, but which may be methodologically weak. And NPOs have specific agendas pursuant to a narrow mission that may not always reflect the highest priorities of their donor base.

6.3 | Methods for identifying priorities

To enhance alignment between patient needs and available resources, the authors recommend that NPOs engage patient communities to guide funding decisions. Methods discussed in the literature for determining research priorities also included periodic systematic reviews and meta-analyses,¹⁷ surveilling clinical trial registries, interacting with researchers at scientific meetings, surveying patient communities, convening focus groups, conducting interviews, and pursuing other grassroots approaches to patient engagement.²⁰ NPOs could additionally invite patients and survivors to serve on committees that make trial funding decisions. This approach is reflected in the joint Consumers' Health Forum of Australia and the National Health and Medical Research Council model framework for embedding consumer and community participation in funding decisions to "better align health and medical research with community need, and improve the impact of research."²¹ Continued training for such research advocate roles would support these efforts.

6.4 | Transparent evaluation

The legitimacy of research agendas is enhanced when research and patient communities work together²⁰ and collaboration between researchers and NPOs avoids duplication and waste.²² Applicants for NPO funding dedicate significant time and effort to the research application, and thus should clearly understand the goals of the funder and its constituents from the outset. Clearly communicating the evaluation and selection criteria underpinning NPOs' funding decisions also helps researchers understand where their research foci lie.²

Once an NPO identifies its research priorities, it should publicize them in funding opportunity announcements. However results from a landscape analysis of pediatric cancer research funders suggest broad trends and gaps in pediatric cancer priorities.² Loucaides and colleagues determined that, despite political momentum to address pediatric cancer, global funding has stagnated, particularly for preclinical research, and is inequitably concentrated in the United States and Europe.² They add, "...global strategy on childhood cancer [requires] full transparency of all funders and their contributions to childhood cancer research is of paramount importance."²(p683) Other articles reinforced this position and argued that NPOs should hold academic researchers to the same standards as industry sponsors where transparent disclosure of conflicts of interest is concerned,²³ including social science researchers working with NPOs.²⁴

6.5 | Donor influence

Unlike federal funding agencies, donors can restrict how their gifts are used and make donation decisions based on the NPO's progress. Funding clinical research is one of several ways in which pediatric cancer NPOs demonstrate adherence to their mission.²⁵ Donations to pediatric cancer NPOs from affected patients and families may originate from gratitude and a desire to reciprocate for the care they received while participating in a clinical trial. Motivations can therefore shape expectations about how donations are allocated to support research, if at all.

Unique ethical tensions can arise when NPOs permit donor-directed funding. While donor-directed funds can enhance donor autonomy and provide more research opportunities and visibility for perpetually underfunded conditions, these trials may not undergo an adequate scientific review process and siphon limited resources away from more scientifically rigorous protocols. NPOs should therefore develop transparent policies regarding how they manage donor-directed funds.

Regularly informing donors about an NPO's scientific priorities enables donors to assess an NPO's alignment with their values.²⁶ NPOs rely primarily on public messaging and outreach to communicate how research priorities are determined and fulfilled.²² Jaroslowski and colleagues propose that NPOs consider the returns on investment when pursuing collaborations with researchers as a proxy for responsible stewardship of donor funds.²⁷ The authors discuss ethical tensions that can arise when NPOs license products to for-profit companies. Returns on donor investments in the research benefit NPOs if those proceeds are reinvested to advance drug development. Conversely, donor funds may be better used to cover the actual manufacturing and distribution costs of available therapies.

7 | RESEARCH PLANNING AND DESIGN

The focus of this stage in the research lifecycle centers on scientific methods and approaches that underpin rigorous trial design. We

coded articles under the research planning and design wherever authors discussed determining statistical endpoints, sample sizes, eligibility, participant recruitment, and retention approaches that best facilitate the responsible conduct of a trial. NPOs rely on consultative relationships with researchers, patients, donors, and sponsors to ensure only the most rigorous, feasible, and ethically robust trials are funded.²⁸

7.1 | Conflicts of interest management

NPOs must manage conflicts of interest among stakeholder groups in the research planning and design process.²⁹⁻³⁴ MacDonald,³⁴ citing Hauge, outlines the elements of an effective conflict of interest policy for NPOs. Such a policy should describe what constitutes a conflict of interest, underline a duty to disclose, detail mechanisms for follow-up, and require an audit trail and a plan for ensuring compliance.³⁴ Disclosing financial support from drug companies so as not to bias NPO recommendations is critical, particularly when sponsors are also donors. Because NPO representatives often know of other active trials investigating drugs with similar therapeutic targets, mechanisms of action, or clinical endpoints, they must declare their own conflicts.

The literature was mixed about whether industry sponsors disproportionately report favorable trial results reports. Several articles suggested biased reporting leads to trial duplication.³⁵ To protect NPO-affiliated families and patients from undue influence to participate in industry-sponsored research, research suggested adopting independent governance and decision-making processes.^{18,36} McCoy and colleagues examined tax records from 104 U.S.-based patient advocacy organizations with annual revenues exceeding USD\$7.5 million and found "at least 39% of patient-advocacy organizations have a current or former industry executive on the board, and at least 12% have a current or former industry executive in a leadership position on the board."³³(p884) Such studies suggest disclosure practices vary and have the potential to unduly influence trial funding decisions. NPOs thus rely on industry members who serve on scientific advisory boards to recuse themselves from reviewing or voting on trial proposals that align too closely with ongoing trials they manage or support in their role.

7.2 | Patient representation

Private support for biomedical research has increased over time. In addition, foundations have accelerated their support in other areas such as hospital and medical care, specific diseases, and mental health.³⁷ Meaningfully involving patients and the public in the research planning and design stages^{16,38} "has moved from a radical concept to an accepted and valued part of the research cycle."¹⁷

Patient involvement in identifying high priority areas for pediatric cancer research can also pose unique challenges. Vayena,³⁹ responding to Masters and Nutt,¹⁹ comments on the ethical appropriateness of

the plutocratic model of trial funding, whereby affected patients fund a clinical trial in exchange for participation in the study: “The patient revolution has gathered momentum but it has also generated skepticism about ... patients undertaking high risks, or studies escaping review processes.”³⁹ Trial participation can also pose time, economic, and other significant burdens that can be adequately understood only through targeted engagement with prospective participants and their families.

7.3 | Value concordance

NPOs can partner with or support academic or industry sponsors to facilitate the completion of a clinical trial. Two case studies investigating cooperative relationships between patient organizations and industry sponsors in Finland⁴⁰ and the United States³³ corroborate this. Prior to developing research sponsorship relationships, NPOs should verify that the sponsor advances the NPO’s values, purposes, and priorities. Industry sponsors are likely to prioritize trials based on the anticipated market value of the investigational drug but could share the NPO’s goals of producing safe and effective therapies for patients.⁴⁰ Tsarenko and Simpson note an assessment of “fit” is an essential component of the overall success of the relationship.⁴¹ Understanding the values that drive diverse stakeholders to engage with NPOs is conducive to new systems-based approaches to advancing drug research and development.⁴²

7.4 | Consultation with scientific experts

As NPOs’ governing boards may lack the expertise to assess a trial’s scientific merit, relationships with experts help to ensure that research planning and design ultimately benefit patients. As a representative voice for patient communities, NPOs, “can help to identify appropriate exclusion and inclusion criteria that do not prevent those at greatest need or most likely to benefit from the intervention from participating in clinical trials.”¹³ Adams and Cavanaugh, for example suggest coestablishing milestones and other benchmarks for clinical trials to support trial success.²² NPOs should also gather insight from researchers on which treatments being tested in a trial will most benefit prospective patients.⁴³

8 | RESEARCH CONDUCT AND OPERATIONS

Geissler and colleagues envision opportunities for patient representation during the research conduct and operations stages to address trial recruitment, retention, and protection.¹³ As one author notes, “accountability (in conducting trial) equates to safety in this regard because nonprofit organizations are more likely to attain security if they set up transparent procedures as well as proper oversight.”¹⁴

8.1 | Internal scientific review

Poor evidence diminishes the quality and value of clinical trials and can misguide future research.⁴⁴ NPOs should work with researchers to ensure the compensation and reimbursement models for participation do not unduly influence participation, though “incentive does not automatically promote unfairness.”³⁹ NPO representatives can also work with patient advocates to expand eligibility criteria where clinically appropriate and advise research teams on recruitment feasibility based on their experience and knowledge of competing trials.

8.2 | Responsible conduct of research

The issues of participant incentives, proportionate risks and benefits, and scientific validity require research ethics committee evaluation prior to study commencement.²³ Researchers can prepare NPOs for regulatory requirements and procedures applicable to clinical trial research in their jurisdiction.^{45–47}

9 | DISSEMINATION, REPORTING, AND OUTREACH

9.1 | Addressing bias

Publication or dissemination bias “occurs when the published literature does not reflect finished research projects in a particular subject area.”⁴⁸ Such bias distorts valuable evidence bases upon which clinical standards and best practices principally rely.⁴⁹ In the pediatric cancer space, publication biases can emerge when researchers do not report poor or inconclusive outcomes, trials that were forced to close prematurely, or findings that are outdated by the time of publication.⁵⁰ The accessibility and timeliness of trial data through publication were, therefore, a central theme emerging from the literature. Dwan and colleagues differentiate between publication and outcome reporting bias⁵¹ and found the latter was far less commonplace after assessing guidelines from 66 NPOs and charities worldwide. The authors advocate for more detailed guidance on at least four parameters to prevent biased reporting: trial registration, protocol adherence/amendment, publication, and monitoring against guidelines.⁵¹

9.2 | Publication and authorship

Several authors suggested enhancing the visibility of patients and families as research contributors by listing them as coauthors in peer-reviewed publications.⁵² Some authors called for journals and publishers to develop policies that address growing issues of opaque funding funneled through private foundations.^{44,53,54}

One article highlighted empirical research on trends in reporting trial results based on funding source, citing specific differences

between trials funded by for-profit and nonprofit entities.⁵⁵ The authors suggested performing external audits and reproducing trial analyses to serve as safeguards.⁵⁶ However, not all trials make study outcomes publicly available.^{35,56} Several articles recommended the creation of an international trial registry to support the publication of all trial results, similar to clinicaltrials.gov.^{35,55}

In addition to managing conflicts of interest during research planning and design, disclosure is likewise critical in the dissemination phase. Jacobson contends NPOs should disclose their sources of funding in all verbal and written communications.^{53(p353)} Knox and colleagues report how clinical trial results can vary when published by for-profit versus NPO sponsors.

Other authors suggest publishers develop policies to address this issue directly, citing specific examples where trial funding is provided by private foundations with close ties to pharmaceutical companies.^{30,44} In general, the literature was extremely limited on the issue of venture or entrepreneurial philanthropy, a field in which NPOs seek to maximize donor returns by funding fewer, longer term, and more commercially viable research projects.⁵⁷ Only one article discussed the implications of this trend and advocated that NPOs should refrain from seeking commercial control over the by-products of the research because this practice would heighten pressures to commercialize.⁵⁸ The authors' position conflicts, however, with the emerging practice of venture philanthropy,⁵⁹ which has shown to be highly successful for therapy development in cystic fibrosis⁶⁰ and glioblastoma.⁶¹

9.3 | Sustaining trust through transparency and accountability

The responsibility of NPOs to sustain trust with patients and donors was referenced most often among the articles reviewed. Strickland and Vaughan proposed a hierarchy of values that cultivate an ethical culture between NPOs and the donors who support them.¹⁴ The authors contend that financial competence sits at the top of this hierarchy with accountability, transparency, respect, and integrity together fostering an organizational culture of trust and trustworthiness among NPO leaders and members. NPOs have a responsibility to disclose the sources and amounts of donor funds, and donors should be transparent about the NPOs to which they donate. Building existing donor trust was also considered critical to attracting new donor support.⁶² Publishing the policies of an NPO is important to donors and several NPOs referenced a need to improve in this area.¹⁸ Such a public record should also be required to reflect any industry donations made to an NPO.

In the funding agreement, NPOs could also require investigators to list the NPOs as collaborators on trial registries, e.g., clinicaltrials.gov, to facilitate accurate reporting of NPO-supported research outcomes. An NPO with a mission to advance late-stage investigational therapies into regular clinical use should make that clear to the sponsor so that a trial is designed to position the therapy for regulatory filing.

10 | CONCLUSION

All stakeholders benefit from knowing what to expect and what is expected of them in their relationships with NPOs that fund pediatric cancer trials. We analyzed 54 articles that addressed the responsibilities NPOs have with respect to four primary stakeholder groups in the research and development lifecycle of pediatric cancer therapies. The NPO-researcher relationship generated the most responsibilities across the broadest range. Trust and transparency responsibilities transcended every relationship type and every stage in the research lifecycle. NPOs maintain trust by communicating transparently about research priorities, supporting trials based on rigorous scientific standards, and collaborating with all stakeholders across the research ecosystem.⁶³ A summary of these and other best practices is accessible in the [Supporting Information](#).

Gaps remain, however, in how NPOs, as liaisons among stakeholder groups, should navigate ethical issues. Few articles discussed how NPO responsibilities blur when stakeholders belong to multiple groups or how NPO responsibilities change, if at all, when they have financial interests in the commercialization of a drug. Measurable returns in NPO investment in trials that led to drug development for other pediatric diseases^{60,61,64} accentuate the need for consistent conflicts of interest disclosure, arm's-length recruitment strategies, and commitments to transparent trial reporting and data sharing if such models are to scale in the pediatric cancer space. Future empirical research could address these gaps by surveying NPOs about how they make research funding decisions and the ethical issues they encounter.

CONFLICTS OF INTEREST

VR is a paid bioethics consultant for the Coalition Against Childhood Cancer. All coauthors are members of the Coalition Against Childhood Cancer.

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