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Cultivating ethically sustainable relationships with stakeholders when nonprofits fund pediatric cancer trials

WHITE PAPER

Prepared by the CAC2 Ethics Think Tank

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Cultivating ethically sustainable relationships with stakeholders when nonprofits fund pediatric cancer trials: A white paper. Coalition Against Childhood Cancer (2021).

Executive Summary

This white paper provides guidance to charities and nonprofits in sustaining ethical relationships with patients/families, researchers, donors, and sponsors when funding drug research and development projects in pediatric cancer.

What are the ethical obligations of charitable organizations to i) patients/families, ii) researchers and iii) donors, iv) industry and academic clinical trial sponsors as they relate to funding clinical trial research?

Children with cancer often gain access to the most promising treatments by participating in clinical trials. Drug development research for pediatric cancer—an area that has been understudied and underfunded by industry—has expanded in recent years because private, nonprofit funding for clinical trials has increased steadily. Unlike in the case of clinical trial sponsors, federal reporting standards do not apply to nonprofits. The lack of formal oversight raises questions about the ethical, legal, and social commitments to the patient communities that nonprofits serve. Nonprofits may need to consider how to prioritize trials that meet high standards of scientific integrity, identify and report both perceived and real conflicts of interest, and address research priorities in patient communities.

The literature has little to say about what obligations, if any, charitable organizations have when sponsoring pediatric oncology clinical trials. Nor is consideration given to how they might cultivate ethically robust partnerships between patients and relevant stakeholders within the pediatric cancer community. The Ethics Think Tank Working Group of the Coalition Against Childhood Cancer conducted a systematic review of the literature to answer four questions: *What are the ethical obligations of charitable organizations to i) patients/families, ii) researchers, iii) donors, and iv) industry and academic clinical trials sponsors as they relate to funding clinical trial research?*

The review revealed several practices that nonprofit organizations which make research grants and support drug development in pediatric cancer should consider. They include:

- articulating and adhering to their mission and values;
- maintaining open communications with researchers and patient communities; and
- identifying areas of inappropriate donor influence.

These themes informed practices at every stage of the pediatric cancer research lifecycle, from the scientific advisory step through to the dissemination of trial results and public communication. At a minimum, nonprofits and charities should:

- select trials that meet the highest ethical and scientific rigor;
- identify and disclose all real and perceived conflicts of interest; and
- mandate regular reporting of all trial progress and open access results reporting.

Who we are

The Coalition Against Childhood Cancer (CAC2) is a collaborative network of nonprofits, corporations, and individuals from 38 states and five countries that supports and serves the childhood cancer community. CAC2 members successfully advance a variety of childhood cancer initiatives by unifying their efforts. Through networking, partnering, exchanging information, and building and supporting collaborative projects, members achieve goals together that would be beyond their individual reach.

What we do

CAC2 members work across the continuum of care in the childhood and adolescent cancer experience—from prevention, diagnosis, and treatment to survivorship and bereavement—funding research at all stages of development and supporting families financially, emotionally, materially, and psychosocially. Together, we promote national and international awareness campaigns and support unified advocacy efforts.

CAC2 has grown steadily since its incorporation as a 501(c)(3) membership organization in 2013. Current membership includes 120 organizations of all sizes, 260 associates, and 80 individuals. The 13-member board of directors is drawn from membership and serves on a volunteer basis.

CAC2 views collaboration among members as a viable way to build real solutions to the myriad of challenges children with cancer and their families face. We support our members and the childhood cancer community through action-oriented, member-directed projects and a variety of educational outreach initiatives. CAC2's primary values are to put children with cancer and their families first in everything we do and to support organizations active in the fight against cancer.

Where we are now

One of the main ways CAC2 carries out its mission is by identifying and completing projects that individual organizations cannot do as easily or as effectively on their own. Our Project Incubator enables members to propose, review, select, and work on great ideas together. Since its inception in 2013, CAC2 has initiated, approved, and completed seven of seven member-proposed and member-driven projects. This Bioethics Think Tank White Paper is the 8th successful collaborative project undertaken.

In June 2017, interested CAC2 members began trying to understand the ethical issues nonprofits that fund research might encounter. They concluded that the existing literature was not adequately developed to guide CAC2 member organizations to build ethically sustainable relationships among the diverse stakeholder groups when funding research. This white paper is the result of a collaborative effort to fill this gap and to build ethics capacity among nonprofit organizations that fund pediatric cancer research.

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Glossary of terms and abbreviations¹

Clinical study. A research study involving human volunteers (also called participants) that is intended to add to medical knowledge. There are two types of clinical studies: interventional studies (also called clinical trials) and observational studies.

Clinical trial. Another name for an interventional study. A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

Collaborator. An organization other than the sponsor that provides support for a clinical study. This support may include activities related to funding, design, implementation, data analysis, or reporting.

Condition/disease. The disease, disorder, syndrome, illness, or injury that is being studied. On ClinicalTrials.gov, conditions may also include other health-related issues, such as lifespan, quality of life, and health risks.

Data Monitoring Committee/Board (DMC/B). A group of independent scientists who monitor the safety and scientific integrity of a clinical trial. The DMC can recommend to the sponsor that the trial be stopped if it is not effective, is harming participants, or is unlikely to serve its scientific purpose. Members are chosen based on the scientific skills and knowledge needed to monitor the particular trial. Also called a data safety and monitoring board, or DSMB.

Enrollment. The number of participants in a clinical study. The "estimated" enrollment is the target number of participants that the researchers need for the study.

Health Insurance Portability and Accountability Act (HIPAA). The Health Insurance Portability and Accountability Act of 1996 (HIPAA) is a federal law that requires the creation of national standards to protect sensitive patient health information from being disclosed without the patient's consent or knowledge. The US Department of Health and Human Services (HHS) issued the HIPAA Privacy Rule to implement the requirements of HIPAA. The HIPAA Security Rule protects a subset of information covered by the Privacy Rule.

Human subjects protection review board. Also called **institutional review board, IRB, or ethics committee.** A group of people who review, approve, and monitor the clinical study's protocol. Their role is to protect the rights and welfare of people participating in a study (referred to as human research subjects), such as reviewing the informed consent form. The group typically includes people with varying backgrounds, including a community member, to make sure that research activities conducted by an organization are completely and adequately reviewed.

¹ Definitions excerpted from official glossary available from [Clinicaltrials.gov](https://www.clinicaltrials.gov)

Informed consent. A process used by researchers to communicate to potential and enrolled participants the risks and potential benefits of participating in a clinical study.

Investigator. A researcher involved in a clinical study. Related terms include site principal investigator, site sub-investigator, study chair, study director, and study principal investigator.

National Institutes of Health (NIH). The National Institutes of Health (NIH), a part of the U.S. Department of Health and Human Services, is the national medical research agency in the United States comprising 27 different Institutes and Centers, including the National Cancer Institute.

Observational study. A type of clinical study in which participants are identified as belonging to study groups and are assessed for biomedical or health outcomes. Participants may receive diagnostic, therapeutic, or other types of interventions, but the investigator does not assign participants to a specific interventions/treatment.

Phase. The stage of a clinical trial studying a drug or biological product, based on definitions developed by the U.S. Food and Drug Administration (FDA). The phase is based on the study's objective, the number of participants, and other characteristics. There are five phases: Early Phase 1 (formerly listed as Phase 0), Phase 1, Phase 2, Phase 3, and Phase 4. Not Applicable is used to describe trials without FDA-defined phases, including trials of devices or behavioral interventions.

Phase 1. A phase of research to describe clinical trials that focus on the safety of a drug. They are usually conducted with healthy volunteers, and the goal is to determine the drug's most frequent and serious adverse events and, often, how the drug is broken down and excreted by the body. These trials usually involve a small number of participants.

Phase 2. A phase of research to describe clinical trials that gather preliminary data on whether a drug works in people who have a certain condition/disease (that is, the drug's effectiveness). For example, participants receiving the drug may be compared to similar participants receiving a different treatment, usually an inactive substance (called a placebo) or a different drug. Safety continues to be evaluated, and short-term adverse events are studied.

Phase 3. A phase of research to describe clinical trials that gather more information about a drug's safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs. These studies typically involve more participants.

Phase 4. A phase of research to describe clinical trials occurring after FDA has approved a drug for marketing. They include postmarket requirement and commitment studies that are required of or agreed to by the study sponsor. These trials gather additional information about a drug's safety, efficacy, or optimal use.

Protocol. The written description of a clinical study. It includes the study's objectives, design, and methods. It may also include relevant scientific background and statistical information.

Registration. The process of submitting and updating summary information about a clinical study and its protocol, from its beginning to end, to a structured, public Web-based study registry that is accessible to the public, such as ClinicalTrials.gov.

Sponsor. The organization or person who initiates the study and who has authority and control over the study.

Study design. The investigative methods and strategies used in the clinical study.

Study type. Describes the nature of a clinical study. Study types include interventional studies (also called clinical trials), observational studies (including patient registries), and expanded access.

U.S. Food and Drug Administration (FDA). An agency within the U.S. Department of Health and Human Services. The FDA is responsible for protecting the public health by making sure that human and veterinary drugs, vaccines and other biological products, medical devices, the Nation's food supply, cosmetics, dietary supplements, and products that give off radiation are safe, effective, and secure.



Introduction

With the incidence of childhood cancer on the rise² and the secondary health impacts of cancer and its treatment protocols having a significant negative impact on survivors' adult quality of life³ safe and effective care is critically important. Families have to make important and time sensitive decisions about their children's treatment plans when their time, emotional energy, and financial capacity may be in short supply. Patient advocacy organizations can help families find relevant research and information on the latest treatments and lighten their burdens.

Only one percent of all cancers arise in children⁴, but cancer continues to cause more childhood deaths than any other disease⁵ even when considering that survival has improved steadily over the past several decades. Increased survival rates owe much to the efforts of well-organized, multi-national cooperative groups that conduct phase three clinical trials for frontline therapy and the high percentage of children who enroll in those studies. Nevertheless, outcomes for some pediatric cancer types remain dismal. The need for more effective and less toxic treatment options drives the evaluation of new agents and approaches in phase one and phase two trials conducted in refractory and relapsed settings.

While pediatric cancer clinical trials are crucial to progress, finding significant numbers of children with complex disease characteristics is a challenge. Trials typically involve numerous stakeholders, such as the patients and their families, academic investigators and institutions, industry partners, regulatory agencies, nonprofit funders, and large donors who support clinical research. As a result, clinical trial consortia, rather than single-entity sites dominate the landscape in pediatric clinical research.

Only 1% of all cancers arise in children. Yet cancer remains the single most leading cause of childhood deaths despite advances in clinical trial science and survival outcomes.

One of the earliest consortia, established by the NIH in 2000, was the Children's Oncology Group (COG). This group, primarily funded by government sources, represents over 200 member institutions worldwide, conducts over 100 clinical trials at any given time, and enrolls

² National Institutes of Health Annual Report 2020 <https://www.nih.gov/news-events/news-releases/annual-report-nation-cancer-death-rates-continue-decline-2020>

³ National Cancer Institute. <http://www.cancer.gov/research/areas/childhood>; https://www.cancer.gov/research/areas/childhood/fda-approved-drugs-childhood-cancers?cid=eb_govdel

⁴ Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.

⁵ National Vital Statistics Report, vol. 62.6, December 20, 2013. <http://www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet>

thousands of children in trials each year. Since COG's inception, over 36 consortia have begun conducting clinical trials in pediatric oncology in the US alone—many that are supported through nonprofits.

The mix of funding for the consortia varies significantly with government, industry, and foundations contributing different proportions depending on the entity. With fierce competition and long application timelines for government support of early phase clinical research and a slow response from industry to initiate such trials, nonprofit funders are called upon to support early phase trials that test novel agents quickly and efficiently.

According to the International Cancer Research Partnership (ICRP) database, roughly half of the funding for research in childhood cancer currently comes from nonprofits. While this figure includes funding for basic science, translational projects, and clinical studies, it does not provide insight about the breakdown of each. In the United States alone, there are hundreds of charities focused on childhood cancer. Many of these nonprofits support clinical research and many charity representatives are also active advocates in patient communities. A large portion of such foundations represents people who have had or who have known a child with cancer. The NIH clinical trial listing shows funding sources and sponsors of clinical trials but does not indicate how many trials are supported by nonprofit funding or how much funding is provided.

While investigators and institutions must abide by institutional review board (IRB) or ethics board oversight of any patient-facing information or recruiting materials for clinical trials, there are no such guidelines for the interaction between charity representatives and patient families with respect to clinical trial recruitment.

Nonprofit funders of clinical research may also have relationships with pharmaceutical companies with products in clinical trials as well as with academic investigators. Engaging patient advocates in drug development, especially in the rare disease space, is now considered necessary by industry. But serious ethical concerns can arise when pharmaceutical or biotechnology companies engage influential advocates to bolster clinical trial recruitment.

For nonprofit organizations to support both families and researchers, there must be a high level of mutual trust. Philanthropic funders need a means to identify conflicts of interest, to evaluate the scientific and ethical quality of research proposals, and to ensure the trials they support address the research needs and priorities of the communities they serve. With little guidance on these ethical issues, charities have had to do their best and hope for the best.

Nonprofits are a growing and critically important source of funding and information for clinical pediatric cancer research. These organizations have built relationships in the pediatric cancer ecosystem with patients, families, researchers, and donors. But navigating the multiple stakeholder relationships at the highest level of ethical standards has to date been an under-considered area of inquiry.

Working Group Approach

Genesis of the Working Group

As early as June 2017, CAC2 members began exploring how to provide the wider membership with information about various ethical considerations they might face as they operate their charities. Those conversations led the CAC2 Annual Summit program planning team to invite and feature Dr. Yoram Unguru, a pediatric oncologist and bioethicist from the Herman and Walter Samuelson Children's Hospital at Mt. Sinai and the Johns Hopkins Berman Institute of Bioethics as its 2018 Annual Summit Keynote Speaker and for CAC2's Research Interest Group to consider a collaborative project in this space.

As a result of that working meeting, Research Interest Group members Amy Weinstein (Pediatric Brain Tumor Foundation), Donna Ludwinski (Solving Kids' Cancer), and Robin French (The Morgan Adams Foundation) began to explore the relationships among pediatric cancer charities, the clinical researchers who benefit from their funding, and the patients for whom those charities advocate. After a preliminary investigation, the group realized that currently published information to address these questions was sparse and presented CAC2 with an opportunity to be a thought leader in the area. The group set as its goal to study these issues and produce a paper that would be a novel contribution to the literature and a help to the community.

Process for identifying research needs

In early 2019, the group proposed the project to the CAC2 Project Incubator to assess members' interest in researching ethical issues and best practices with a goal of clarifying the opportunities and potential constraints going forward. The project title was *"CAC2 Think Tank: Exploring the Potential Ethical Issues & Best Management Practices for Childhood Cancer Charities Funding Research."*

The members thus considered whether CAC2 should organize a team to develop a working paper identifying both the potential ethical issues charities face when funding research as well as the best management practices (BMPs) charities should use in dealing with those issues. The working paper would be shared with CAC2 membership as a tool, would be presented by CAC2 at medical conferences as appropriate, and would be a living document maintained and updated by the project team.

Results of the member polling for support for the CAC2 think tank proposal:

- **63** members **participated** in the Project Incubator process
- **58 (92%)** indicated they would **support** the project
- **5 (8%)** indicated they would **not** support the project
- **15 (24%)** requested to serve in a project volunteer role
- **33 (52%)** committed to providing input, if asked, about their organization's practices
- **38 (60%)** indicated they would attend a webinar reporting the think tank's findings
- **12 (19%)** said they would help in other ways
- **2 (3%)** provided financial assistance for the project

Members from organizations nationwide volunteered to be part of the think tank dedicated to examining these issues. As envisioned, the project would include scanning current practices in comparable arenas and conducting a thorough literature review. The team would then assess and report their findings about current trends and best practices in ethical standards to guide interactions among the funding organizations, donors, and recipient organizations.

Decision to pursue the white paper

The think tank team engaged Vasiliki Rahimzadeh, PhD a postdoctoral fellow with the Stanford Center for Biomedical Ethics at Stanford University, to help refine the topic of its research. Following significant discussion, think tank members identified two areas to investigate. The first concerned research advocates and the need for clarification about their roles, particularly regarding whether they represent patients or researchers. Secondly, organizations that both fund clinical trials and help with patient recruitment for those trials may have legitimate questions about how to harmonize those practices. A literature review showed little research illuminating these two ethical issues, indicating a clear need for a working paper that outlined best practices and options for nonprofits grappling with these issues.



Systematic literature review

Methods

The Ethics Think Tank used the two research questions to guide a systematic review of the literature using a participatory consensus approach. Peer reviewed articles, commentaries, published newsletters, concept papers, and white papers indexed in PubMed and Web of Science were included if they:

- were published in English
- discussed ethical, legal, and social and/or public policy considerations of partnerships between not-for-profit patient advocacy organizations and
 - patients/families
 - researchers
 - sponsors
 - donors
- proposed research funding for a clinical trial

Articles were excluded if they discussed strategies and practices related exclusively to corporate social responsibility or if they commented on financial conflicts of interests without addressing underlying ethical, legal, or social considerations for nonprofit organizations. Eight members of the working group screened titles based on inclusion and exclusion criteria using the Covidence platform. A total of 54 articles met the inclusion criteria. Three independent reviewers analyzed all full text articles and applied thematic content analysis to code article information based on Patient Involvement in Medicines Research and Development " framework proposed by Haerry and colleagues (2018)⁶.

A detailed search strategy and flow diagram are available in **Appendix 1** and **Appendix 2**, respectively.

Results

Trust and Transparency

Trust and transparency are key factors in any research funding endeavor, but human-centered clinical trials require special focus on these elements. During every stage of a trial—the review of protocols, the decision to fund, the monitoring of progress, and ultimately, the dissemination of results—all stakeholders should have trust in the processes. Stakeholders should anticipate transparency throughout the trial lifecycle as stipulated by the Health Insurance Portability and Accountability Act (HIPAA).

Clarity regarding conflicts of interest is an important component of transparency. Conflict of interest policies have broad implications for public trust and the extent to which trust is

⁶ Haerry, D., Landgraf, C., Warner, K., Hunter, A., Klingmann, I., May, M., & See, W. (2018). EUPATI and patients in medicines research and development: guidance for patient involvement in regulatory processes. *Frontiers in Medicine*, 5, 230.

maintained throughout the trial. As funders, nonprofits should evaluate conflicts at multiple times including, but not limited to, partnership negotiation, trial conduct, publication, and reporting. Organizations should outline processes for updating conflict of interest policies on a regular basis and as may arise from regulatory changes, advances in science, changes in leadership, special circumstances, or known instances of breach.

When supporting clinical trials, nonprofits have a responsibility to maintain trust between the patient community and donors. They must also ensure that relationships with researchers and sponsors are transparent and reflect their own mission and values. Furthermore, internal policies relating to funding decisions, conflict of interest evaluation, and reporting should be transparent. A checklist of best practices that maximizes transparency in trial funding and that addresses the aforementioned and subsequent recommendations from this section can be found in Appendix 3. The topic of trust is a focal point of this literature review. This section will introduce trust and transparency as it pertains to each of the relationships between nonprofit research funders and stakeholders, including patients, researchers, and donors.

Nonprofits and Patients

As patients are most directly impacted by clinical trials, it is critical to maintain their trust throughout all stages of the trial. Nonprofits should also consider how the perceptions of conflicts at all levels of the organization have trust implications. The maintenance of public trust, specifically within patient and family communities, should guide all organizational policies and research partnerships.

Nonprofits and Researchers

Clinicians are most often the research scientists that spearhead trials. Because trial sponsors, particularly those in industry, do not regularly have relationships with nonprofits, it is critical for nonprofits to establish and maintain them to advance the nonprofits' own knowledge of the research that is taking place. In addition to engaging with clinical researchers, nonprofits have a responsibility to review and assess conflicts that may exist among researchers and sponsors, patients, and donors. Potential nonprofit partners should demand that all recipients of their funding disclose any real and perceived researcher conflicts and any additional funding sources prior to initiating the partnership. Academic partners, trialists, and others can have conflicts akin to those that may exist in for profit or industry; similar standards of disclosure should apply irrespective of organizational structure. Nonprofits are not obligated to dictate or manage other research partnerships, but can mandate disclosure.

Nonprofits and Donors

Donor support of a nonprofit is predicated on trust in the organization as well as on an alignment of values. Donors have many options in terms of nonprofit organizations to support and should be provided with the information they need to make informed decisions about how best to spend their money. A nonprofit organization's mission and values should be clearly and

regularly articulated to donors and constituent members through timely, accurate, and transparent communications. Responsible donor outreach through annual reports and the systematic updating of outward facing communication is critical to establishing and maintaining trust.

The goal of transparency may come into conflict with other important ethical considerations, however. A nonprofit that funds a clinical trial may have access to research information about efficacy, responses, or side effects while the trial is still in process that would violate confidentiality agreements if shared with donors or patients.

As patients, their families, and members of their social circles may feel a desire to express gratitude to researchers for the care they provided, direct relationships may develop among them that warrant oversight. People outside of the nonprofit may not have the expertise and resources with which to make scientifically rigorous, financially responsible, and ethically sound funding decisions. Since nonprofits that fund clinical research should already have peer review processes in place, they are well-suited to assist patients and families in understanding the scientific feasibility and impact of a particular clinical trial. Similarly, nonprofits should dissuade preferential treatment for donors on the basis of their contributions to the organization. Research funding that is donor-designated should undergo rigorous peer scientific review. A project selection plan that prioritizes science over available funds for a given project or disease type should be developed and shared.

There are donors other than individuals whose priorities may align with the nonprofit organization. Entrepreneurial philanthropy, wherein funds are invested with the expectation of an economic return to eradicate specific problems, is an emerging practice in the nonprofit world including in the pediatric cancer community. Nonprofit organizations should consider the ethical implications of engagement with entrepreneurial philanthropists and organizations. And as more companies adopt Environmental, Social, and Corporate Governance (ESG) policies, contributions to nonprofits are an increasing factor in this space. Nonprofits should report all corporate donations and fully disclose the nature and amounts of donations. This should also include donation of scientific agents, such as drugs, for clinical trials.

Research Priorities

As defined by our group at the outset of this project, research prioritization describes the actions, decisions, or processes used to inform how specific research topics compare. The focus of our review was to identify ethical frameworks within the literature that relate to how clinical trial funding prioritization is determined within a nonprofit. The goal of this work was to explore why, how, and from whom organizations obtain input on what research should be funded and to broaden stakeholder engagement relevant to trial design. The subsequent discussion will provide an overview of the extant literature on the topic of research prioritization as it relates to those relationships.

Nonprofits and Patients

Nonprofit organizations that support biomedical research regularly associate with patients impacted by the disease(s) of focus for the nonprofit. Patients may form the donor base, promote advocacy around the disease, or contribute a firsthand understanding of unmet needs. In fact, families impacted by a particular disease start many of the nonprofit organizations that support research for the disease. Because they are often intertwined, nonprofits and patients must carefully navigate their relationship when prioritizing clinical trial funding.

Conversely, research prioritization and nonprofits' agendas may not align with those identified by patient communities. Tension arises when patient advocacy organizations (PAOs) are oriented around a specific agenda that is in line with a narrow mission and/or their donor base that may not be shared by the research community. To ease this tension and develop a greater alignment of needs and available research, PAOs should adopt methods of identifying the ongoing and unmet needs of its patient communities. Methods for making these determinations may include reviewing the literature, surveilling the current trial landscape, engaging with clinical research leaders at scientific meetings, surveying stakeholders, and convening focus groups. Funding organizations that value the patient perspective could invite patients and survivors to serve on committees that make trial funding decisions. If patients' lived experiences are represented in the research agenda-setting process from the beginning, clinical trial funding decisions are optimally focused on the needs of the community.

Nonprofits and Researchers

When researchers apply for research funding through a nonprofit organization, they are dedicating significant time and effort to the process. It is imperative that the researcher is aware of and clearly understands the goals of a given funder for their work to address the needs of the nonprofit. Nonprofits that fund research should develop disciplined and transparent strategies for determining research funding priorities. Requests for proposals or funding opportunity announcements should clearly state the funding organization's goals and outline the methods it uses to prioritize and select projects.

The selection process should be transparent, and nonprofits should ensure an equitable and inclusive prioritization process regardless of donor support targets. As research can disproportionately reflect the priorities of high-dollar donors or individual families, nonprofits can work to ensure prioritized projects emerge from an inclusive process. For example, a pan-childhood cancer organization might prioritize leukemia projects because of fund-raising considerations or donor interest rather than because they have the most scientific merit or best meet the organization's funding goals. Establishing a transparent and inviolable strategy for prioritizing research decisions—such as selecting, first and foremost, based on science—enables researchers to develop projects that adhere to the organization's mission and criteria.

In accordance with a PAO's mission and scope, there should be a disciplined approach taken to the types of research that the organization supports. PAOs should consider various types of

research aligned with their defined funding strategy and within their funding capacity. For example, diversified support of interventional, observational, qualitative, investigator-driven, basic, preclinical, clinical, patient outcome research, and other translational research encompasses the complete research continuum. If research support is limited to a narrower spectrum, the reasoning behind that decision should be shared with all stakeholders.

Nonprofits and Donors

Donors drive the success of a nonprofit organization, and their support reflects alignment between their goals and the organization's activities. Nonprofit organizations should therefore regularly inform donors about the organization's scientific priorities when funding clinical trials such that donors can assess this alignment directly. This means developing transparent strategies for how research priorities are determined and communicating these priorities with donors and patient communities through public messaging and outreach. Based on good stewardship of donor funds, nonprofits should also consider the benefits and returns on research investment when pursuing collaborations with researchers. A defined prioritization and selection process that takes potential research outcomes into account will support that goal.

Donors contribute with the aim of supporting the PAO's stated research goals and mission. But donor funds are rarely earmarked to specific research projects. Rather they are allocated based on the nonprofit's needs and assessment of alternatives. Nonprofits could consider improving how donor funds are distributed by making *some* contributions research- or project-specific. In addition, to ensure good stewardship of donor funds, organizations with similar research funding priorities should collaborate to focus on funding unmet areas of need. In this way, duplication is reduced and funds become available for other worthy research. Funding collaborations enable greater impact for donors and reduce the burden on investigators as they are able to obtain more money while writing fewer grant applications.

An established and transparent research funding prioritization schema can reduce donor concern about conflicts of interest between nonprofits and researchers. When conflicts of interest unavoidably arise, parties should address them openly. As previously noted, individual donors and families who lend financial support to nonprofits may do so out of deep gratitude and a sense of reciprocity for the care they received from a clinical trial. Families may also develop special relationships with physician-investigators and other trial personnel that may not undergo scrutiny when assessing conflict of interest. Nonprofits should apply the same rigor in assessing conflicts of interest among donors and families as they do with researchers and sponsors when funding clinical trials.

Nonprofits and Sponsors

Nonprofits can partner with or support academic or industry sponsors to ensure completion of a clinical trial. Prior to developing such partnerships, it is important that the nonprofit organization and the sponsor are aligned with respect to purpose, research priorities,

philosophy, and values. For instance, an organization with a mission to support drug development and move new therapies into regular clinical use should express those goals to the sponsor to ensure that the clinical trial is designed to position the therapy for regulatory filing. In the funding agreement, nonprofits should stipulate that investigators list them as collaborators on clinicaltrials.gov. Early and frequent alignment between the parties can ensure that their respective needs and goals are met.

Research Planning and Design

Research design is the actions, decisions, and processes that comprise trial method. This includes determination of statistical endpoints, sample sizes, patient populations, eligibility criteria, and other factors. Nonprofit research funders play an important oversight role in the clinical trials they support. Not only should these organizations perform a thorough review of the research plan prior to committing donor funds to the work, as described in the previous section, but they have a responsibility to keep abreast of optimal trial designs and track alterations to research plans.

Relationships between nonprofit organizations and each of the stakeholders in the ecosystem contribute to the research process. Properly leveraging these relationships helps to ensure that research planning and design ultimately benefit patients. As nonprofit representatives are not typically research design experts, they should consult other professionals who can review and suggest modifications to research design. Nonprofits can also provide the perspective of patients for whom the trial may present time, travel, economic, and other burdens.

Nonprofits and Patients

One area that is sparse in the current ethical literature is the relationship between nonprofits and patients in relation to research planning and design. This will likely be an area of future exploration for our group as we consider future actions relating to this project.

Nonprofits and Researchers

As nonprofits may not know the scientific standards that lead to optimal trial design, they should regularly update their scientific knowledge and understanding relevant to the needs of pediatric cancer patients. To do so, funders may consider engaging experts to ensure a trial is ethically and scientifically robust. In addition to the Institutional Review Board (IRB) and the Data Safety Monitoring Board (DSMB), nonprofits should address the principles of design thoroughness, efficiency, and quality at the funding stage of a trial. It is important that patient advocacy groups collaborate with researchers at institutions with robust regulatory and ethics infrastructures. This is especially pertinent for partnerships with international research.

Nonprofits and Donors

As with the nonprofit-patient relationship, the ethical literature on research planning and design does not explore the relationship between nonprofits and donors. This will likely be an area of future exploration for our group as we consider future actions relating to this project.

Nonprofits and Sponsors

Financial support of clinical research carries a responsibility to ensure ethical trial design by sponsors, whether academic or industry. Nonprofit funders should ensure that research collaborators have obtained appropriate approvals from institutional review boards prior to negotiating partnerships. This saves time for nonprofits and sponsors and presents a milestone for funding disbursement.

Research Conduct and Operations

Nonprofit organizations that fund childhood cancer research, especially those founded by patient families and those for which patient families fundraise, are often in contact with parents, relatives, and friends of children in treatment. There are hundreds of rare diagnoses within pediatric cancer and navigating the small number of clinical trials that are both available to children and that target a specific disease can be overwhelming. It is not uncommon for those patient families to seek information and guidance from nonprofit organizations that fund research. It is the ethical responsibility of those nonprofits to maintain trust within the patient community and across all stakeholders in the trial.

Nonprofits and Patients

Folded within the trust to be maintained within the patient community is an obligation by PAOs to refrain from marketing or promoting a clinical trial that they themselves fund. When nonprofits are contacted by patient families seeking help in understanding clinical trials, the organization should be clear to inform rather than advise. Sharing information is quite commonplace under the banner of patient advocacy and proves crucial for these families. However, there is a difference between informing and influencing treatment decisions and it is incumbent upon the nonprofit to avoid even the appearance of influencing families. Organizations that consciously and knowingly market a clinical trial targeted to its constituents can be problematic. Nonprofits can make families aware of trials, but patients should seek the advice of the healthcare provider when deciding whether to participate. All discussions between nonprofits and families seeking treatment should be documented in writing.

It is a best practice for nonprofit funders to establish clear roles with researchers about who is charged with participant recruitment. In addition, nonprofits should be aware if the trial offers any extraneous benefits such as subsidies for housing, daily expenses, or travel to incentivize recruitment. While such offerings are not common in the childhood cancer community, it is important to be mindful of the possibility and to evaluate any incentives from an ethical

standpoint. Patients should be made aware of such offerings, but guided toward selecting the most appropriate trial based on clinical eligibility first.

Nonprofits and Researchers

The success of the last decades of pediatric cancer research has been largely driven by targeted funding for which rigorous peer review is essential. Without it, targeted support could enable excessive academic freedom and bias that threatens scientific integrity—especially in the distribution of 'soft' money for trials and other funded research. A rigorous scientific review should always precede project funding, especially for projects that recruit from patient communities. Funding for childhood cancer research is scarce and should be dedicated to the best science with the most favorable benefit-to-risk ratio. A lack of strong scientific review results in less strategic and lower impact spending of limited funds.

Nonprofits should establish clear milestones to report on trial conduct, progress, and results. Milestones include the completion of pre-clinical data collection, status of IRB approval, enrollment numbers, and others. A funding structure based on objectives can be developed when researchers and nonprofits agree on process, infrastructure, resources, and other criteria. The funding plan should have some built-in flexibility, reflect input from both researchers and funders, and allow for challenges that may arise during the trial. Nonprofits should ensure continuing oversight during the conduct of the trial, including the continuation of IRB review and engagement with DSMBs to maintain the highest standards of ethical research.

When evaluating trial findings at completion, nonprofits should consider conflicts of interest, fairness, and patient advocacy in their review. Results should be reported accurately and consistently irrespective of funding source.

Real and perceived conflicts of interest, as discussed earlier, can arise at multiple stages in the research process and are not limited to the partnership negotiation and trial conduct phases. Nonprofits should be aware of such possibilities throughout the clinical trial—including at publication and when reporting results through various media channels.

In rare cases when there is an opportunity for reimbursement or compensation, the ethically appropriate approach is that the distribution of funds is either equivalent for all participants or in accordance with stated and well-defined criteria irrespective of the funding source. Future policy work is needed to develop guidance regarding fair approaches to compensation.

Increasingly, POAs are called upon to counsel families about trial enrollment. Nonprofits should develop programs and strategies that guide families on trial selection and offer advice in an unbiased manner. They should not promote a given clinical trial just because they support it financially.

Nonprofits and Donors

As mentioned previously, donors, particularly those with a specific personal interest in a research area or clinical trial, may wish to influence research decisions. Nonprofits can and

should guard scientific integrity and other criteria when supporting research as it would be unethical for donors to become involved in this area. Influencing enrollment or buying a place in a clinical trial should be expressly prohibited as it is unethical based on wealth discrimination and affects scientific integrity.

Nonprofits and Sponsors

The appointment of a professionally appropriate, unbiased, and balanced team of reviewers to assess the scientific integrity of a clinical trial is as important as the development of stringent review policies and protocols. Nonprofits should ensure their own steering committees and those of the sponsor are recognized medical and scientific experts. The experts should review trials for scientific integrity and maintain responsibility for making major decisions on scientific, medical, statistical, ethical, and practical issues. Nonprofit funders should also clearly define roles, responsibilities, and parameters of sponsors in project grant agreements. Being proactive on these matters can result in fewer roadblocks as the sponsor relationship grows.

Trust is not only important within the patient community but also among collaborating sponsors, especially when considering the nonprofit's role in endorsing a trial. Industry sponsors often seek nonprofit endorsements of ongoing trials to encourage participant recruitment but may be unaware that this practice can diminish nonprofits' credibility with patient communities and create problems for patient engagement. Nonprofits should develop endorsement policies and media protocols for disseminating information about trial opportunities to ensure preparedness should this issue arise.

Dissemination, Communication, and Post Approval

Clinical trials exist to determine whether new drugs, diagnostics, or treatments are safe and effective. They can demonstrate what works and does not work in humans—information not revealed in the laboratory or from animal studies. Additionally, clinical trials allow patients to contribute to the scientific process. Even negative results add to the understanding of the disease. Regardless of the results, clinical trial findings should be openly, clearly, and completely shared with both scientific and lay audiences.

Nonprofits and Patients

Nonprofit organizations have a responsibility to share clinical research results in a manner that is both understandable and easily accessed by patient populations. Sponsors will disseminate information to the scientific audience through publications, presentations at meetings, and updates to clinicaltrials.gov. Nonprofits that support research must then communicate with patient and donor groups in a manner that is both accurate and clear to that audience. Nonprofits should be transparent about trials that have resulted in unforeseen circumstances, closures, or failure, but should not be held liable or be required to attest to the integrity of the trial. Trial findings should be reported accurately and consistently irrespective of funding source.

Nonprofits and Researchers/Sponsors

When a trial is prioritized for funding, nonprofit organizations should establish and document milestones for reporting and success metrics such as numbers enrolled, numbers treated, unanticipated hurdles, adverse events, anticipated and unanticipated successes, and a timeline for submitting manuscripts for publication. The administrative overhead of managing clinical trials can be prohibitive and motivates forming consortia such as CAC2 to support young foundations that may not have the capacity and resources to take on this oversight.

Trials that demonstrate a particular drug is either unsafe or ineffective may inform future investigations. As such, they are as important to share as trial results that demonstrate a safe and effective impact. Nonprofits can develop a negative outcome database to encourage and simplify such reporting. Nonprofits are also encouraged to include royalty agreements in grant documentation. Further perceptions about conflict of interest can be eliminated by designing agreements with the sponsor in mind and in anticipation of commercialization. Nonprofits bear the responsibility of communicating their role and any financial interest in a clinical trial.

The accessibility and transparency of trial results are critically important. Nonprofits should encourage investigators they fund to publish in open access journals and should consider helping with publication costs when they are prohibitive. At a minimum, nonprofits should require registration of the trial at clinicaltrials.gov. Nonprofit funders should also encourage routine updates to the published information. As researchers cannot be separated from their respective institutions, commercial agreements must take the institution's requirements into account. In addition, raw and analyzed datasets should be placed in public repositories that are private and secure, such as those maintained by the National Institutes of Health. This enables other researchers to access and mine the data developed with nonprofit funding and optimizes the investment return of the nonprofit's support.



Conclusion and Future Direction

With pediatric cancer clinical trials increasingly dependent on private philanthropy for funding, questions arise as to both the opportunities and the constraints nonprofit organizations face. As nonprofits fill a gap created by the low level of government or industry interest in pediatric

When nonprofits both articulate and adhere to their mission and values when funding clinical trials, donors know precisely what they are supporting.

cancer research, they enter a space where their role and path forward are not always clear. This paper was born of the growing need to address both the obligations of funding organizations and the concomitant need to cultivate and maintain ethically robust relationships among all stakeholders in the pediatric cancer community.

In researching these areas and developing this paper, we have sought to guide nonprofit funders in identifying and addressing ethical grey areas, maintaining a reliable and transparent flow of information among stakeholders, ensuring scientific and ethical rigor, and disseminating results openly and widely. We address the issues that can arise between and among nonprofits, the donors who sustain them, the patient communities they represent, and the scientists who conduct the research families need.

Paramount among our findings is the importance of ongoing trust and transparency among all stakeholders. When nonprofits both articulate and adhere to their mission and values, donors know what they are supporting. When they maintain relationships with researchers, they can evaluate and prioritize the most relevant and scientifically rigorous trials. And when they have the trust of patients and families, they can assist researchers in knowing where the unmet needs lie.

Trust and transparency are critical when nonprofits are considering funding a trial and throughout its lifecycle. Specifically, trust is maintained when, nonprofits (1) select trials that sustain rigorous scientific and ethical evaluation without regard to extraneous interests, real or perceived; (2) identify and disclose real or perceived conflicts of interest with researchers or other entities that support their work; (3) have a scientific review committee to evaluate proposals; (4) mandate the regular reporting of all trial progress, milestones, and results; (5) develop an agreed-upon framework for the sharing of results in open access journals; and (6) keep donors informed about the impact their support is having.

Nonprofits are the central switchboards that raise money, fund trials, and know the marketplace of patients' needs and ongoing research. As such, the onus is on them to maintain a trustworthy ecosystem of stakeholders.

Living at the center of the ecosystem, nonprofits are uniquely situated in a variety of ways. They can:

- evaluate the ethical, regulatory, and scientific rigor of research;
- inform patients and families of all available research that may address their needs;
- identify and reduce donor influence in the choice of area to study or patients to enroll; and
- maintain funding agreements that clearly define the roles and responsibilities of all parties.

As the role, opportunities, and influence of private philanthropy in the pediatric cancer community continues to grow, so too will the demand for an articulated set of guiding ethical principles. This paper should serve as a tool for all nonprofits that fund pediatric cancer research to engender and maintain the necessary trust among patients, donors, and researchers to keep desperately needed trials funded and give families with sick children meaningful hope.

The paper will be disseminated via open access channels and be available at conferences to all stakeholders in the childhood cancer space. As a living document, this body of knowledge will evolve along with any technological, ethical, financial, legal, and regulatory changes that affect the pediatric cancer community in the years ahead.

Two ethical considerations were notably sparse in our literature review but are important for responding to evolving trends in the nonprofit clinical trial funding space. First, few records differentiated the ethical implications of a nonprofit's relationship with patients from those with donors, particularly in the research planning and design phase. While nonprofit boards may not have expertise in research design, the organizations themselves must monitor developments in this area and track changes to the trials they fund to ensure they are structured in a way that maximally benefits patients.

Second, ethical issues surrounding nonprofits with a financial interest in the commercialization of a specific drug, known as venture or entrepreneurial philanthropy, were not well captured in the literature. Nonprofit organizations and charities have recognized opportunities for earning a return on their initial investment in clinical trial research if that research results in a new drug proven to be safe and effective by regulatory agencies. Both issues warrant further exploration and organizational attention to guide nonprofits in navigating new financial partnerships and methods of sustainability while maintaining their ethical obligations to patients and their families.

Charities, patients, researchers, trial funders, and clinicians will all benefit from knowing both what to expect and what is expected of them. When trustworthy communication is maintained, research meets the needs of the patient community, promising studies are funded, patients find clinical trial matches, and like-minded charities share information, collaborate on funding, and maximize their efficiency in helping families in need.

Going forward, it is the clear delineation of roles, expectations, and obligations that create the trust required to maximize the flow of funds into life-saving clinical trials. Pediatric cancer patient advocacy organizations fill a critical funding gap and can be sources of accurate information, community and support for patients and families in their clinical journeys.



Appendices

Appendix 1. Systematic literature review search strategy.

PUBMED

1. Charities + clinical trials

("Charities"[mh] OR "Charities"[tw] OR "charity"[tw] OR "organizations, nonprofit"[mh] OR "nonprofit organization"[tw] OR "nonprofit organizations"[tw] OR "nonprofits"[tw] OR "philanthropy"[tw] OR "philanthropic"[tw]) AND ("Clinical Trials as topic"[mh] OR "clinical trials"[tw] OR "clinical trial"[tw])

2. Charities + ethical obligations

("Charities"[mh] OR "Charities"[tw] OR "charity"[tw] OR "organizations, nonprofit"[mh] OR "nonprofit organization"[tw] OR "nonprofit organizations"[tw] OR "nonprofits"[tw] OR "philanthropy"[tw] OR "philanthropic"[tw]) AND ("guidelines as topic"[tw] OR "guidelines"[tw] OR "guiding principles"[tw] OR "biomedical research/ethics"[mh] OR "ethical guidelines"[tw] OR "mission statement"[tw] OR "ethical obligations" [tw] OR "principles"[tw] OR "values"[tw] OR "Research support as topic/ethics"[mh] OR "conflict of interest"[mh] OR "conflict of interest"[tw])

3. Charities + ethical obligations + clinical trials

("Charities"[mh] OR "Charities"[tw] OR "charity"[tw] OR "organizations, nonprofit"[mh] OR "nonprofit organization"[tw] OR "nonprofit organizations"[tw] OR "nonprofits"[tw] OR "philanthropy"[tw] OR "philanthropic"[tw]) AND ("guidelines as topic"[tw] OR "guidelines"[tw] OR "guiding principles"[tw] OR "biomedical research/ethics"[mh] OR "ethical guidelines"[tw] OR "mission statement"[tw] OR "ethical obligations" [tw] OR "principles"[tw] OR "values"[tw] OR "Research support as topic/ethics"[mh] OR "conflict of interest"[mh] OR "conflict of interest"[tw]) AND ("Clinical Trials as topic"[mh] OR "clinical trials"[tw] OR "clinical trial"[tw])

WEB OF SCIENCE

1. Charities + clinical trials

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2. Charities +ethical obligations

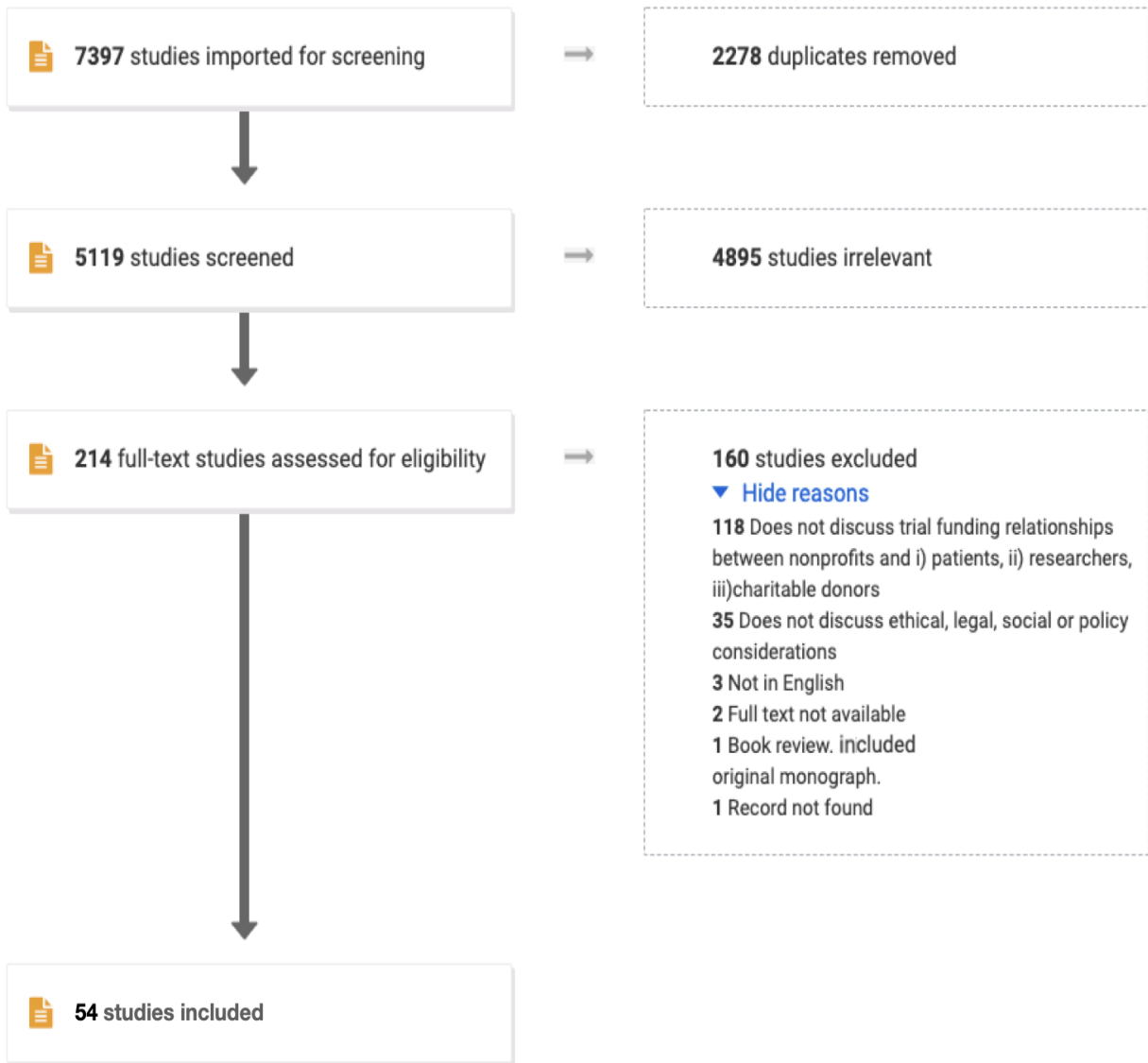
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Appendix 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of literature review.



Appendix 3. Checklist of best practices in nonprofit trial funding as synthesized from the literature review.

The following checklist should be used to support ethical non-profit clinical trial funding. These best practices do not constitute an exhaustive list, nor are they required. They are intended to provide an ethical framework for non-profit selection, funding, and monitoring of clinical trials.

Research Prioritization, Selection, and Partnership Negotiation

- Evaluate conflicts of interest for each stakeholder involved in the clinical trial, including but not limited to the researcher, non-profit funder, and industry or academic sponsor.
- Ensure transparency of internal policies relating to funding decisions, conflict of interest evaluation, and reporting.
- Avoid preferential treatment for donors on the basis of their contributions to the organization, especially with regard to the selection of clinical trials to support. Decisions on project prioritization should be made according to the non-profit organization's mission and after a scientific peer review process is conducted.
- Develop disciplined and transparent strategies for determining research funding priorities. Requests for proposals and funding opportunity announcements should articulate the funding organization's goals clearly and outline the methods it uses to prioritize and select projects.
- Communicate research funding priorities with donor and patient communities through public messaging and outreach.
- Adopt methods of identifying the ongoing and unmet needs of patient communities. Such methods may include systematic literature reviews, regular surveillance of the current trial landscape, engagement with clinical research leaders at scientific meetings, stakeholder surveys, and the convening of focus groups.
- Report all corporate donations and fully disclose the nature and amounts of donations. This should also include donation of scientific agents, such as drugs and any other gifts-in-kind, for clinical trials.
- Consider funding partnerships with organizations with similar priorities.
- Ensure alignment with respect to purpose, research priorities, and organizational mission with all partners.
- Ensure that research collaborators have obtained appropriate approvals from institutional review boards prior to negotiating partnerships.
- Clearly define roles, responsibilities, and parameters of sponsors in project grant agreements.

Research Planning and Design

- Evaluate conflicts of interest for each stakeholder involved in the clinical trial, including but not limited to the researcher, non-profit funder, and industry or academic sponsor.
- Engage experts to ensure that trials are ethically and scientifically robust. Consult with academic and/or industry professionals to review and suggest modifications to research design.
- Address the principles of design thoroughness, efficiency, and quality at the funding stage of a trial.

Research Conduct and Operations

- Evaluate conflicts of interest for each stakeholder involved in the clinical trial, including but not limited to the researcher, non-profit funder, and industry or academic sponsor.
- Inform patient communities about available trials for which they may be eligible, including but not limited to, those trials in which your organization has a role or financial interest.
- Establish clear roles with researchers about who is charged with participant recruitment.
- Establish clear milestones to report on trial conduct, progress, and results. Milestones may include the completion of pre-clinical data collection, status of IRB approval, and enrollment numbers among others.
- Ensure continuing ethics oversight during the conduct of the trial to maintain the highest standards of ethical research.

Dissemination, Communication, and Post Approval

- Evaluate conflicts of interest for each stakeholder involved in the clinical trial, including but not limited to the researcher, non-profit funder, and industry or academic sponsor.
- All clinical trial findings including positive, negative, and inconclusive, should be published via open access to the extent possible and disseminated to both scientific (e.g. publication, conference presentations) and public audiences (e.g. town halls, public outreach initiatives, organization newsletters).
- Be transparent about trials that have resulted in unforeseen circumstances or closures.
- Mandate in funding agreements the routine reporting of numbers enrolled; numbers treated; and anticipated and unanticipated hurdles, adverse events, and successes. Also mandate a timeline for submitting manuscripts for publication.
- Support publishing results in open access journals through cost sharing.
- Require registration of the trial at clinicaltrials.gov.

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