Balancing Benefits and Complexities of Pediatric Clinical Research

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Bachelor of Science, University of Pittsburgh, 2022

Submitted to the Graduate Faculty of the

Department of Human Genetics

School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2024

UNIVERSITY OF PITTSBURGH

SCHOOL OF PUBLIC HEALTH

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April 19, 2024

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Abstract

Pediatric clinical research and clinical trials are pivotal in advancing medical knowledge to improve health outcomes for children with complex medical needs. However, there are many challenges associated with conducting research in pediatric and rare disease populations. These challenges require careful planning and strategic solutions by all individuals involved in the research process. Despite the challenges, there are also numerous benefits for patients involved; researchers must find the optimal balance to achieve the desired health outcomes in such a vulnerable population. To gain a more thorough understanding of this process interviews were conducted with healthcare providers in clinical research to gather qualitative in-depth information about their experiences. This data was compared to benefits and challenges of pediatric research that was documented in existing literature.

Results showed that some of the top challenges included recruiting patients that perfectly fit the eligibility criteria for each study, working with extremely strict protocols, and ensuring patient compliance with the research. There are also many health disparities such as underrepresentation of minority groups, scheduling complications due to parental work obligations, and a lack of reliable medical resources in rural areas. Individuals eligible to participate in research benefit by being connected with top-rated specialists, experiencing empowerment through sharing personal experiences, staying informed about the latest available treatments, and improving their quality of life. Additionally, people working in the field of clinical

research enjoy the direct connection with patients and contributing to the future success of healthcare.

Understanding the benefits and challenges of pediatric clinical trials is significant to the field of public health as the aim is to safely advance evidence-based medicine, unravel disease mechanisms fundamental for the development of new treatments, and promote health equity to ensure comprehensive representation and care for patients.

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1.0 Introduction

In recent years, there has been a significant expansion in the number of treatments available for genetic disorders due to the increasing knowledge of disease mechanisms. One critical way to make advancements and gather data about genetic disorders is by utilizing clinical trials to research the efficiency and efficacy of potential new treatments. Many rare genetic conditions have limited treatment options and require complex management. When there are no approved medications to treat these conditions, some patients decide to participate in clinical trials in hopes of finding a new treatment to slow disease progression. This is particularly noticeable in pediatric populations, as children and their families seek methods to enhance survival rates and quality of life. While studies using clinical trials are essential to furthering the understanding of genetic disorders, they come with an abundance of challenges for both the patients and researchers involved.

1.1 History of Clinical Research

The earliest documented clinical trials can be traced back to biblical times where accounts recorded how experiments controlling diets impacted the public health of specific communities (Bhatt, 2010). In the modern era, James Lind is considered to be the first physician who conducted a controlled clinical trial in which he studied treatments for scurvy among sailors in 1747 (Bhatt, 2010). Although rudimentary compared to modern clinical trials, conducting a study of this nature marked a significant milestone in the advancement of medicine and research. After the initial development of clinical trials, more notable milestones include the development of placebo

controls, double blinded studies, randomization, and the creation of ethical frameworks for the protection of participants in the studies. These developments provide the foundation for successful research that can produce reliable results.

In studies testing new pharmaceutical agents as treatments for genetic conditions, placebos are often used as a control to prove that the new treatment is effective beyond just the belief that it has the ability to produce a cure (Gupta & Verma, 2013). Using a placebo-controlled study is now seen as a standard practice that will showcase the efficacy of the new treatment. While this holds significance for conditions lacking other approved treatments, additional ethical concerns arise when patients must be deprived of existing treatments to participate in a new placebo-controlled study. In these situations, it becomes increasingly more important to consult institutional review boards (IRBs) to protect patients and their wellbeing.

There have been numerous instances of unethical research being conducted on human subjects in the past, so the development of IRBs was a necessary step in the history of clinical trials. IRBs are ethics committees which provide protection for human research participants. The committees must evaluate if proposed research is meeting ethical standards, have researchers checked for any potential biases, and ensure that participants are reasonably protected (Grady, 2015; "IRBs and Assurances,").

One of the most notable examples of discrimination in healthcare and research was the Tuskegee syphilis study (Scharff et al., 2010). This study is widely acknowledged as a key factor contributing to distrust in research due to the extent of deception endured by participants. During this study, researchers intentionally withheld lifesaving treatments from 400 African American men and deliberately infected many Guatemalans with syphilis and gonorrhea. The goal was to find ways to prevent these infections in the future, but doing so without gathering informed consent

and deceiving participants led to major ethical concerns (Tobin, 2022). Following the detrimental aftermath of this study, racial minority groups have become more reluctant to participate in clinical research due to concern of improper medical care. IRBs must now review proposed research activities to check for biases and unjust treatment.

With genetic studies specifically, the Havasupai case highlighted many concerns surrounding improper use of DNA in research. The Havasupai Tribe filed a lawsuit against Arizona State University in 2004 for using their DNA in more genetic studies than what they originally consented to (Garrison, 2013). During the initial consent, researchers verbally explained to participants how their DNA would be used to examine reasons why a large percentage of Havasupai adults had type 2 diabetes. The wording in the written consent documents was much more vague, stating that the DNA could be used to research "behavioral/medical problems" (Garrison, 2013). This was both misleading and culturally insensitive as the Havasupai Tribe and many other Native Americans view DNA and other biological samples as sacred materials. While no formal regulations were imposed after this case, it prompted many researchers to carefully evaluate their protocols for obtaining consent while minimizing discrimination and distrust in research.

1.2 Clinical Trial Structure

There are multiple types of clinical trials, each with a very specific study design process. Some of the most common designs include prevention trials, treatment trials, and quality of life trials ("The Basics," 2022). Prevention trials aim to find ways to stop disease from initially manifesting or returning. Treatment trials, which this project will focus on most, are used to test

new therapies or drugs that could be beneficial to patients. Quality of life trials focus on how to maximize comfort and quality for patients with chronic conditions ("The Basics," 2022).

Clinical trials are conducted in four different phases to gather information about the safety and effectiveness of the treatment being studied ("The Basics," 2022). Phase I studies are conducted in a small group of subjects with the goal of learning about the safety and side effects of the drug or treatment when first introduced to humans. Phase I is often open to healthy volunteers, but that is not always the case with specialized rare disease trials. After Phase I is completed, only affected patients will be included in the study. Phase II trials expand the treatment to a larger group of people and continue to evaluate the safety and effectiveness. A trial progresses to Phase III when previous results were promising. Phase III trials require an even larger sample size to confirm effectiveness, monitor side effects, and compare to other available treatments. If the study passes Phase III and is eligible for approval by the Food and Drug Administration (FDA), then it can enter Phase IV, where the treatment is available to the general public and researchers will track how the population responds to the new treatment ("The Basics," 2022). The goal of each phase is summarized below in Table 1.

Table 1: Phases of Clinical Trials

Phase I	Phase II	Phase III	Phase IV
Goal: Learn about safety and determine proper dosing	Goal: Evaluate effectiveness and continue to gather information on safety	Goal: Continue with previous goals, monitor side effects, compare to other treatments	Goal: Observe long-term responses and effects in the targeted population

Recruitment protocols are one of the most important study design choices that set guidelines for the rest of the clinical trial. Balancing benefits and potential harms, setting the proper inclusion and exclusion criteria, and determining enrollment procedures are all integral components of study design that will result in optimal recruitment rates. Recruitment rate is determined by factors impacting both patients and investigators (Thoma, Farrokhyar, McKnight, & Bhandari, 2010). Additionally, many research sponsors will require certain levels of diversity in the enrolled population to ensure inclusive participation is achieved. Many people experience the same disease in different ways, so including individuals with a variety of lived experiences allows all groups to benefit from clinical research and treatment advancements ("Diversity and Inclusion in Clinical Trials,"). While taking the extra time to carefully plan studies may not eliminate all barriers to recruitment, it will help to greatly reduce some challenges.

1.3 Overview of Clinical Trials' Benefits

Pediatric clinical trials can seem overwhelming to many patients and their families, but there are several benefits associated with participation. One of the most noteworthy benefits is obtaining early access to treatments that can improve health outcomes. This is especially important for conditions with limited treatment options outside of the clinical trial. Patients will be monitored closely by the research team conducting the trial and progress will be carefully documented. The resulting data can then be used to help others who face similar health challenges by increasing survival rates and quality of life. Some patients may also find gratification in actively participating in their health management; this is frequently observed when individuals face an unfavorable heath prognosis and seek to exert control over their wellbeing. While not always considered a primary benefit in pediatric populations, many children with complex medical histories perceive their conditions to be part of their identity and wish to take control. Parents may also assist their children in taking measures to prevent disease progression when possible.

Additionally, researchers and pharmaceutical companies strive to make sure that participants do not face any negative consequences during participation. One example of this is seen when pharmaceutical companies reimburse participants for any costs that are incurred during a study visit. This financial compensation is paid to make sure that participation in the study is not causing any extra hardships for patients and their families. However, this can also cause ethical concerns about coercion in the study. To avoid this, many sponsors have decided to reimburse participants for expenses incurred, but no additional money is paid as an incentive to participate.

1.4 Overview of Clinical Trials' Challenges

Despite the benefits, many individuals still express reluctance to participate in clinical research, or to allow their children to do so. The reasons could include fear of unknown side effects, the extensive time commitment needed for many studies, or the travel required to clinic sites, to name a few (Nathe, Oskoui, & Weiss, 2023).

Limited health and genetic literacy is another factor that may lead to hesitation to participate in clinical research. The study protocols for clinical trials are often long and complicated, which makes it difficult for some individuals to grasp the rationale behind the research. When protocols are not written in plain language, many participants will rely on the members of the study team to explain the steps in simpler ways. Members of the research team must continually build a relationship with patients and their families to strengthen trust and ensure patients know that their best interest is always in mind.

Another important consideration in pediatric clinical research is obtaining consent from parents or guardians, and assent from children, when possible. This is an essential aspect of conducting ethical research but does occasionally come with challenges.

Finally, there are several logistical challenges associated with clinical research. This includes limitations with funding sources, strict protocols and IRB guidelines, and coordination of all study-related activities with patients, company sponsors, and different departments in the hospital.

1.5 Other Types of Clinical Research

In addition to interventional clinical trials, another important type of clinical research includes observational studies and patient interviews. Choosing the proper research design often depends on the outcome of interest in a particular study. As clinical trials are often used to test new treatments, interviews and observational studies are more commonly used as a simple and noninvasive way to gather first-hand information. Asking patients detailed questions allows for insight about how new treatments, or lack thereof, are impacting their lives. These interviews provide an opportunity to expand on challenges that may not be documented in other structured studies while sharing important considerations from a patient's perspective (Dibenedetti et al., 2018). Incorporating patients' needs and experiences in the drug development process can also help determine if compliance with a new treatment regimen is reasonably expected once it is available to the public (Michel et al., 2023). Overall, interviews pertaining to clinical research offer an invaluable glimpse into patients' experiences.

1.6 Specific Aims

⇒ **Aim One**: Identify challenges that pediatric patients face when participating in clinical research.

⇒ **Aim Two**: Identify challenges that researchers face while conducting pediatric studies.

⇒ **Aim Three**: Highlight benefits of participating in pediatric clinical trials for rare genetic conditions that have limited treatment options.

⇒ **Aim Four:** Conduct interviews to incorporate knowledge from experienced healthcare professionals into a review of the current state of pediatric clinical research.

⇒ **Aim Five:** Analyze existing literature about health disparities in pediatric populations.

2.0 Background

2.1 Literature Search Criteria

To determine what information had already been published about challenges in pediatric clinical trials and pediatric health equity, search queries in PubMed included:

- Clinical trial design
- Clinical research challenges
- Clinical research benefits
- Pediatric clinical trials
- Pediatric health equity
- Social determinants of health
- Rare disease clinical trials

Searches were primarily focused on articles published in the past ten years, but some exceptions were made for background information pertaining to clinical trials. This review excluded neonate and infant populations as there is minimal clinical research conducted in these groups and finding relevant information to the project would be challenging. Excluding these groups focused the review to patients aged 5-18. Many articles found through this search were not about the clinical trial process, but rather about specific trials for specific conditions. These papers were also excluded as the literature review primarily focused on identifying overarching themes and challenges that are not specific to just one study or condition.

2.2 Social Determinants of Health

Social determinants of health are factors that are unrelated to medical care that can influence health outcomes and contribute to different responses among groups receiving the same treatment (Hahn, 2021). Economic stability, education access and quality, healthcare quality, neighborhood and build environment, and social and community context are all categories of social determinants of health. Social determinants of health influence individuals of all ages, but children are a particularly important population as many physical, emotional, and social factors that develop early in life set a foundation for future health outcomes (Sokol et al., 2019). It can be hard to accurately examine all social determinants of health in children as researchers must consult the parents, and there is a possibility of influence of social desirability bias (Sokol et al., 2019).

While clinical trials are not considered traditional healthcare, they still influence health outcomes and social determinants of health should be considered in research contexts. Understanding the impacts of social determinants of health is a key component of understanding some of the challenges associated with pediatric clinical research. Socioeconomic status and access to quality healthcare are two factors that can have drastic impacts on pediatric health outcomes, but more research is required to understand how these influence clinical trial results.

Table 2: Social Determinants of Health

Economic Stability	Education Access and Quality	Healthcare Quality	Neighborhood and Build Environment	Social and Community Context
- Employment - Income - Debt - Medical bills	- Literacy - Language - Early childhood education - Higher education	- Distance to medical facilities - Provider availability - Quality of care	- Access to healthy foods - Housing - Public transportation - Recreation - Safety	- Support systems - Discrimination - Community values

2.3 Pediatric Health Equity

Health equity, as defined by the Centers for Disease Control and Prevention (CDC), is the state in which everyone has a fair opportunity to attain their highest level of health ("What is Health Equity?," 2022). In order to achieve such a state, there must be ongoing efforts to address inequities and determine the influence of social determinants of health. Addressing these health disparities in children is particularly important considering the lasting impact on adult health and economic success. Developing pediatric-focused health equity indicators is still an unmet priority (Montoya-Williams, Pena, & Fuentes-Afflick, 2020). There is a strong push to improve population health and health-related social justice in academic health centers, which is also where a large amount of clinical research is being conducted. There is an “institutional responsibility” to monitor these

issues and promote health equity. This is especially applicable to pediatric populations as children tend to have more frequent medical appointments than adults (Montoya-Williams et al., 2020). Identifying health inequities, directing children to proper resources, and collaborating with other public health stakeholders are a few of the many ways in which researchers can contribute to pediatric health equity.

2.4 Rare Disease Communities

A rare disease is classified as any disease that affects less than 200,000 individuals in the United States at a given point in time ("Rare Disease FAQ," 2020). This definition still leaves a wide range for prevalence of rare diseases; some conditions may affect just under 200,000 people while others may only affect a small handful of individuals in the country. These small populations lead to a very limited sample size that is eligible to participate in research. Traditionally, most clinical trials are done with a large enough sample size to make sure that results will be statistically significant and generalizable to the population of interest. With rare conditions, there are sometimes exceptions that must be made due to the limited sample size, and this introduces some new challenges into clinical research for these communities. Especially with the ultra-rare conditions, it is harder to gain an adequate amount of data to determine safety protocols for new treatments and maintaining funding with limited data can further exacerbate the issues at hand (Sardella & Belcher, 2018).

2.5 Special Considerations in Pediatrics

There are limited studies addressing the needs of pediatric populations in research separately from the needs of adults. With between 50 to 75 percent of rare diseases starting in childhood, many of which are chronic, this population deserves increased attention (Bavisetty, Grody, & Yazdani, 2013). This gap in knowledge between children and adults has been recognized by authorities and legislators, with policies now being implemented to lessen this gap (Lagler, Hirschfeld, & Kindblom, 2021). Because children are considered a vulnerable population for research, many clinical trials are first started in adults before they progress to include younger participants. This is a practical way of reducing risk of unnecessary harm in children, but the lack of safety and efficacy data in children arises when the studies do not progress to pediatric populations (Lagler et al., 2021). It is complicated to extrapolate data from adult clinical research and use information to treat children without proper protocols. Children are not simply smaller adults; their bodies have different physiological processes and administration of new drugs must be studied accordingly (Kern, 2009). To ensure progress is being made towards the goal of labeling new drugs for pediatric use, the Pediatric Research Equity Act (PREA) was established in 2003. This gives the FDA authority to require pediatric studies when applications for new drugs and biologic therapies are submitted ("Pediatric Research Equity Act,").

2.6 Importance for Public Health Genetics

Clinical research is a key topic in the world of public health genetics. Pharmaceutical clinical trials are one of the most important ways that new information is gathered to make

advancements in the treatment of rare genetic conditions. To ensure the health and wellness of all participants and future patients, researchers must weigh the benefits and harms when assessing the best way to conduct the clinical trials. This is especially true in pediatrics as children are a particularly vulnerable population that requires extra considerations, as mentioned in the previous section. Additionally, public health can influence clinical research by highlighting important health issues that require more investigation, promoting diversity and inclusion efforts, and determining best practices for communication regarding both recruitment and sharing results. Interviews between patients and researchers are a useful outlet to voice concerns about areas in which healthcare may be lacking. Addressing these inadequacies with policy makers is another important practice in public health that aims to promote health equity.

3.0 Methods

3.1 Interviews

To assess some of the various challenges in pediatric clinical research, five one-on-one interviews were conducted with a variety of healthcare professionals involved in clinical research. Participants were identified through encounters during the interviewer's practicum experience and other related activities during graduate school. These healthcare professionals included a genetic counselor, a nurse from the Pediatric Clinical and Translational Research Center (PCTRC), two medical students, and a clinical research coordinator. Each interview lasted around 30 minutes. During interviews, the following questions were asked:

1. How long have you been working in pediatric clinical trials?
2. What are your favorite parts of working in pediatric clinical trials?
3. What are some of the benefits of these trials for patients?
4. What makes a good research patient in your opinion?
5. What are some of the biggest challenges you face in pediatric clinical trials- both with recruitment and during the study?
6. Do you think researchers and/or healthcare providers create bias in studies when choosing patients to enroll?
7. What role do parents play in pediatric clinical trials? Do they pose any barriers and how do you work with them to benefit their child and the research being done?
8. What health disparities have you noticed that patients often experience?
9. Do you have any suggested solutions to minimize these health disparities?

10. Are there any changes you would like to see in future study design protocols?

11. What is your best advice for new people starting to work with pediatric clinical trials?

Clarifying questions were asked when necessary to gain a comprehensive understanding of the opinions and experiences being discussed. Except for two interviews that took place via phone due to the participants' locations, interviews were conducted in person at the University of Pittsburgh or at UPMC Children's Hospital of Pittsburgh. To maintain confidentiality, interviews were not recorded but notes were taken by the interviewer, and the roles of participants were not linked with their responses. No other identifiable data was collected.

3.2 Ethical Considerations

The University of Pittsburgh Institutional Review Board (IRB) determined that the study met regulatory requirements for exempt research. All interview questions were reviewed, and an introductory script was written to explain the purpose of the study to participants while emphasizing that participation was voluntary. Supporting documents are included in Appendix A and Appendix B. Verbal consent was received at the start of each interview.

4.0 Results

4.1 Provider Experiences in Clinical Research

Participants had work experience in clinical research that ranged from one year up to 30 years, with some having worked in clinical research for the entirety of their career and others previously being involved in other areas of healthcare or preclinical research. All participants agreed that they valued the research being done and they were satisfied with their decision to be working in this sector of healthcare.

Table 3: Interview Participant Demographics

Job Type	**Time in Clinical Research**
Medical Student	1 year
Clinical Research Coordinator	2 years
Nurse	3 years
Medical Student	4 years
Genetic Counselor	30 years

When asked about their favorite parts of working in clinical research, all participants mentioned direct patient care and relationships being the most valuable aspect of their work. One participant mentioned how they like spending time talking to patients and learning what is important to them. By building rapport in this way, trust is established, and it becomes easier for patients to communicate with researchers. Another participant mentioned how they really enjoy

teaching patients about genetics and sharing wisdom in a way that other healthcare professionals may not have in the past. Many patients and their families already know a lot about their medical condition(s) but explaining things in a new way may shift perspectives and offer hope for the future. For studies with multiple follow-up visits, it is meaningful to researchers when they see improvements in their patients over time. Many genetic conditions have extremely limited treatment options, and the sense of fulfillment derived from contributing to future success was a shared sentiment among several participants in this study. All participants mentioned how they admire the commitment and dedication of their patients. It was also mentioned how special it feels when patients recognize the contributions made by researchers as well. Individuals working in clinical research are part of the patients' diverse care team and they provide an important perspective into the overall treatment process.

Table 4: Participants' Favorite Aspects of Research

1. Building meaningful relationships with patients
2. Teaching patients and other providers about current research
3. Developing new approaches and treatments where prior information is lacking

4.2 Ideal Clinical Research Patients

Outside of the set inclusion and exclusion criteria for each study being conducted, there are several factors that contribute to a patient being a good fit for a particular study. When working with pediatrics, many participants acknowledged that it is more about the parents than the children participating in the study. Some of the most helpful qualities in patients and families include being

organized, detail oriented, and compliant with medications and the research timeline. This is especially important with clinical trials where results can be compromised if compliance is not perfect or adverse events are not properly shared and documented. This also leads into the importance of patients and families being communicative with researchers and continually following up on previous appointments with any relevant updates. It can be hard to expect every family to rearrange their lives to accommodate the demanding schedule associated with certain research studies. However, incorporating some degree of flexibility is always advantageous.

Multiple participants mentioned how they also enjoy when patients and their families are interested in the research being done. This is typically seen when patients ask many questions about why things are being done and what type of information is gained from the tests. For studies that are more conversation based with less intervention, one of the best qualities in a patient is simply being willing to talk to researchers and share experiences openly. Additionally, more than one participant mentioned how it is very admirable that some of the patients are participating in research even though there is no direct benefit to them. This shows that many patients are altruistic in their reasons for contributing to the overall knowledge and future success of clinical research.

Table 5: Qualities of Ideal Research Patients

1. Organized and detail oriented
2. Compliant with research protocols
3. Communicative
4. Inquisitive

4.2.1 Parental Role in Pediatric Research

Working alongside parents is an important part of the research process, especially when children are very young. Children are asked for assent when appropriate, but ultimately parents are the ones making final decisions in many cases. Depending on the child's current medical state, some parents are very receptive to participation in research while others are more hesitant to agree to any unnecessary procedures which lack guaranteed successful outcomes. One participant really emphasized how most of the parents they work with are very inspiring as they go above and beyond to care for their children. Participating in ongoing trials is a significant commitment, but many parents are committed to taking any necessary measures to help their children. However, it can still be difficult to schedule study visits when parents have demanding schedules. There may also be times when parents are frustrated with the timing of certain steps in the study or about decisions made by industry sponsors, but clinical researchers are the ones placed in the middle. Another participant mentioned how this often leads to them advocating for the balance of what is best on both sides.

One participant who was conducting interviews as part of their research mentioned how they love seeing different interactions between the parents and children in the study. Some parents were able to explain and anticipate all their child's needs, but others didn't really know the full story about what their child was really experiencing. This is most noticeable with older teenagers who opt not to share certain things with their parents but do feel comfortable talking with researchers.

4.2.2 Bias in Recruitment

When participants were asked if they believed that researchers and/or healthcare providers create bias in studies when choosing patients to enroll in studies, the answer was always yes. There are many steps taken to reduce bias and conduct ethical studies in clinical research, but participants still believe that implicit and explicit bias does exist in many cases. One individual mentioned how there are patient registries for many of the conditions being researched and after getting to know the patients, there are some instances when individuals are asked to enroll in a study only if researchers believe they would be a good fit. While researchers may choose patients based on how difficult or compliant they are, this is not always a bad thing. Patients who are less compliant will typically face more difficulties successfully completing a study, so researchers are ensuring that no additional hardship is faced. However, there are also instances when one healthcare provider may label a patient as difficult, but then an outside researcher comes in and disagrees with this assessment. One participant mentioned how they noticed the patients labeled as difficult were actually very open to discussing their experiences in research settings and they only felt uncomfortable when they did not fully support their doctors' decisions. Additionally, perfect compliance may be an essential part of certain clinical trials, but other studies may be more inclined to focus on what an average patient looks like.

4.3 Benefits for Patients in Clinical Research

The benefits for participating in clinical research are dependent on the type of study being done. For clinical trials that are investigating new treatments, participants mentioned that some of

the biggest benefits for patients include being connected with top specialists for their condition and following a strict care management schedule with more direct monitoring than what would be seen in a typical clinic setting. Researchers must document every positive or negative change in health status during the trials, so they must be extra attentive to the patients enrolled in the study. Additionally, if the new treatment is working successfully, patients will experience positive changes in their health and they will contribute to improved conditions for future patients. Often, this improvement in health leads to greater quality of life and encouragement for the future. One participant noted how many patients feel that it is easy to give up hope after so many years of unsuccessful treatment attempts. Any improvement can feel like a big success and staying up to date with the latest medical advancements can be one way to take control of a challenging medical situation.

Multiple participants also mentioned how some patients and families also grow their support network through interacting with others in the study that they are involved in. This helps to have others who share common experiences and want to support each other. Occasionally, this support can also lead patients to join forces and lead advocacy groups or reach out to legislators for increased awareness and funding in their area of interest. This is one important way to have their voices be heard by powerful individuals. Additionally, many patients in interview-based research mention that having the opportunity to share their experiences is a meaningful part of the process and it brings a large sense of fulfillment.

One final benefit that was mentioned by many participants was the fact that patients are often paid or reimbursed by the research team or pharmaceutical companies sponsoring the study. The reimbursement is a good tactic to ensure that patients do not decline participation in research due to financial concerns. This offsets many inconveniences that patients may face, and it also

improves retention rates in ongoing studies. There are some studies that will also pay patients as an incentive to participate, but some are moving away from this to reduce any ethical concerns of coercion. Especially for experimental therapies with unknown outcomes, researchers want to ensure that patients understand the risks associated with the study and their decision is not fully influenced by financial incentives.

Overall, there are many benefits that patients experience while participating in clinical research. The studies offer individuals access to new breakthrough treatments, and they can also feel empowered to contribute to the collective progress of healthcare, ultimately benefiting both current and future patients.

Table 6: Top Five Benefits of Clinical Research Participation for Patients

1. Connect with top medical specialists
2. Extra attentive care plans
3. Positive health outcomes
4. Expanded support network
5. Opportunity to openly share experiences

4.4 Challenges and Limitations of Pediatric Clinical Research

Identified challenges exist in all aspects of the clinical research process, starting with planning and recruitment and lasting through sharing of results after completion of the study. Almost all participants noted how finding the perfect patients for each study can be challenging. The severity of disease often impacts the willingness of individuals to participate in various

research studies. Some patients may see research as the only option for new treatment opportunities and are therefore more willing to participate. Others may not think research is important to them if they are healthy and will not receive direct benefits. One researcher expressed frustration about the lack of responses from potential research patients to recruitment invitations, which leaves the reasoning behind their decision unclear. Additionally, some patients change their mind during the consent process, and they must work around this. Another participant mentioned how they struggle to recruit medically complex patients when there are very strict inclusion and exclusion criteria that limit the pool of eligible patients.

After the initial recruitment challenges, most difficulties with conducting research studies are related to the available protocols. The biggest complaint was that many protocols written in industry settings do not always translate well to practice in a clinical setting as the fine details and nuances are not considered. Following a strict protocol can become complicated when there are discrepancies in how the procedure should be carried out. It was also discussed how relearning protocols to reduce the likelihood of errors becomes incredibly time consuming when there is a large duration of time between study visits. It is easier to establish a routine with larger studies that are frequently performed.

Moreover, ensuring compliance during the studies is an essential task. There is a lot of organization and preparation that goes into a successful study, and it is the responsibility of researchers to confirm patients are completing their responsibilities. One participant talked about this being more difficult when working with high-risk and special needs children, but it is an essential part of the job. Another participant discussed how they often experience non-compliance from other healthcare workers that are assisting in the study but not typically involved in research. Due to the detailed documentation process, a member of the research team should be present even

when doing simple activities, such as taking vitals. This participant explained how they frequently ran into issues with this communication and would have to request a redo of vitals when they could be present to ensure accuracy. This is one example of the many ways in which scheduling and communication with multiple care teams in the hospital can cause difficulties.

Table 7: Top Five Challenges of Clinical Research for Providers

1. Finding the perfect patients to recruit in each study
2. Working with strict inclusion and exclusion criteria
3. Protocols written in industry do not always translate well into clinical practice
4. Ensuring compliance from patients and other providers
5. Scheduling and communicating with multiple care teams

4.4.1 Health Disparities in Clinical Research

Participants reported witnessing numerous health disparities when interacting with a diverse range of patients in research settings. In general, it is crucial to ensure research remains unbiased towards specific demographics while still acknowledging disparities that exist beyond the scope of medical interventions. Varying socioeconomic differences exist between patients and while it may be challenging to work with this when it impacts scheduling abilities, solutions must be determined so more disadvantaged individuals are not excluded from research.

One participant discussed how geographic location is one of the biggest factors influencing care of the patients that they work with. Some hospitals serve large regions of the country and patients must travel far distances to reach quality healthcare. This becomes difficult without reliable transportation, but otherwise patients in rural areas lack access to reliable medical

resources. For patients that do not have access to routine or emergency medical care, there are often far more health complications that they face, thus creating more issues within research.

Some patients are very hesitant to participate in any type of unnecessary research. Depending on the type of study being conducted, research may not be seen as a top priority by some patients. Especially in emergency or other high stress situations, adding research to a patient's schedule could feel daunting. Additionally, some individuals may refuse to participate in research due to distrust in medical systems. One participant mentioned that they often help treat individuals from an underserved community and must establish additional trust while completing the consent process. Another participant discussed how they frequently encounter language barriers that make explanations of complex medical topics quite difficult. Ensuring that patients understand the ethical considerations that are included when designing research studies is essential and protocols must be explained in a way that can be understood by patients. Researchers must practice compassion and respect the wishes of patients regardless of the decision that is made about participation.

Table 8: Health Disparaties Impacting Clinical Research

1. Difficulties planning research visits with parents' work schedule
2. Geographic distance from healthcare facilities
3. Lack of reliable transportation to appointments
4. More health complications for patients with lack of routine and emergency medical care
5. Lack of trust in medical systems due to past discrimination in research

4.4.2 Suggested Solutions for Health Disparities

Finding solutions for broad health disparities is no easy task and would likely require large-scale interventions at institutional or policy levels. Multiple participants mentioned that there are limited options on an individual level, but being accessible to patients as much as possible is a start. In addition to this, doing community outreach and education combined with advocating for improved healthcare will help spread knowledge of the issues that do exist. As one participant noted, including underserved communities in research and doing more intentional recruiting to gain a representative sample of the population being targeted will help to reduce potential disparities.

Within healthcare systems, two important suggestions to limit health disparities would be having more specialized care available at satellite campus locations and having increased access to interpreter services. These would both allow for more patients to receive quality access to care and research. On an even larger level, disparities would be further minimized with improved public transportation, universal childcare, and universal healthcare. These are unfortunately all large undertakings which are unlikely to be refined in the near future.

Table 9: Proposed Solutions for Health Disparaties

1. Being accessible to patients as much as possible
2. Community outreach and education
3. Intentional recruiting for optimal diversity
4. Improved public transportation
5. Universal healthcare and universal childcare

4.5 Desired Changes in Future Protocols

To minimize challenges faced by researchers, there are some changes that could be made to future study design protocols. They must be written in a way to eliminate as much bias as possible while also having clear inclusion and exclusion criteria. Sometimes the strict exclusion criteria make it difficult to get a representative sample of participants, but having these criteria and making sure to understand the population being studied will allow for the ideal balance during recruitment. To ensure the research is representative of the population, there are usually certain levels of diversity that researchers aim to achieve. Knowing your target population is a key skill as researchers must consider that certain conditions or hardships are faced in certain demographic groups more than others.

Many participants emphasized the importance of organization throughout the studies. Some protocols do not allow for preparation prior to the start of the visit, but having materials available ahead of time would be ideal so researchers are not rushing to organize materials in front of patients during an appointment. Protocols must have some flexibility and allow researchers to exercise their best judgement regarding outcomes of the study. One participant mentioned how

they occasionally notice certain steps in a protocol may lead to compromised results if done exactly how it is written. In this case, finding the right balance between following the protocol and making good judgment calls is important so long as everything is properly documented. Another participant mentioned how the proposed timing in protocols is not always realistic. Collecting data for research during a lifesaving surgery means that the team must prioritize healthcare and research is secondary. If there are complications during a surgery, the team does not want to interrupt surgeons to collect their sample. Recognizing the complexity of research and being understanding of challenges is essential in clinical research. One participant also suggested having a centralized location to upload results from study visits. It becomes complicated to learn and manage multiple different systems for sharing results with study sponsors.

Table 10: Research Protocol Changes

1. Allow for preparations ahead of time, when possible
2. Allow researchers to exercise best judgment
3. More realistic timing for data collection
4. Centralized location for reporting results
5. Collaboration between industry sponsors and individuals gathering data

4.6 Advice for Working in Pediatric Clinical Research

All participants in the interviews expressed how much they enjoyed working in pediatric clinical research. When reflecting on their experiences, participants had a lot of advice to share with individuals who are just starting their career in the field. This advice ranges from inspiration

for personal growth to ways that will best help patients. Being passionate about the studies being done and invested in producing the best results will ultimately lead to a rewarding experience for all individuals involved. It also helps to be extremely knowledgeable about the research being done and to be prepared for when patients start asking question. Learning how to communicate effectively both with patients and other providers is a crucial skill in clinical research. Being part of a multidisciplinary team can be both rewarding and challenging, but it is important to remember that working together with the patients' best interests in mind is the goal.

Continuing with the theme of communication with patients, being empathetic and comforting towards your patients is another important skill. Participating in research can be scary at times, so researchers must do their best to address these fears appropriately. One participant also mentioned how important being sensitive with the timing of research discussions during the recruitment process is. Some patients are experiencing new diagnoses or complications and participating in research may not feel like the most pressing issue in that moment. If patients say no to participating, researchers must respect that decision while still expressing care towards that patient. Once patients are enrolled in a study, continuing to build that trusting relationship will allow the patients and families to feel more comfortable opening up and sharing their experiences. This open communication will greatly increase compliance with the study and help with improved outcomes in the research process. Being open minded is essential as well, as one participant mentioned how patients can say very unexpected things during interviews, but you must remain a trustworthy and non-judgmental individual who is invested in their care.

Overall, thinking about the big picture with why you chose to work in clinical research along with how it is helping patients should be a motivating factor. Several participants mentioned how there are too many people doing the bare minimum and just following step by step protocols

without much additional effort. Instead, be inquisitive, look up why things are done the way they are, what different tests mean, and what the implications for patients are.

Table 11: Advice from Providers in Clinical Research

1. Be passionate and knowledgeable about the studies you are conducting
2. Learn how to communicate effectively with patients and other providers
3. Practice empathy and compassion with patients
4. Build trusting relationships with patients
5. Be open-minded
6. When possible, do more than the bare minimum required for your job

5.0 Discussion

There were many similarities regarding the benefits and challenges in pediatric clinical research when comparing findings from the initial literature review with the responses from interviews. This includes challenges that exist because of a lack of resources in certain communities, distrust in research, and insufficient health equity. The most common advantage mentioned in the literature and interviews was access to new treatments. Analyzing themes that emerged from the interviews focused on many specifics of pediatric research which received less emphasis in previously published work, such as scheduling conflicts and frustrations with study protocols. These interviews prompted interesting conversations with numerous topics for future exploration. Gaining insight from hearing healthcare professionals' opinions on ideal research candidates, parent-child dynamics, and advocacy stemming from family support groups provides new opportunities to further investigate the social aspects of clinical research. Furthermore, they built upon known barriers by discussing the challenges with strict inclusion and exclusion criteria, ways in which healthcare and research differs across geographic locations, and the necessity of more communication between researchers and industry sponsors. Finally, participants shared insightful advice for other individuals working in clinical research.

5.1 Limitations and Future Directions

This study was conducted with a small sample size of healthcare professionals in clinical research. Additionally, several of these participants work within the same hospital system in

Pittsburgh. To get a more diverse range of experiences, it would be beneficial to recruit participants from more locations. Geographic location and access to quality healthcare were factors discussed throughout this project and it would be interesting to see how much impact they have on the clinical research process in different locations.

Another consideration for future investigation could be including parents in the interviews. This would provide another perspective into the benefits and challenges in pediatric clinical research. Directly interviewing these parents will allow researchers to gain more insight regarding social determinants of health, which were frequently found to be correlated with challenges in clinical research participation. With this parental point of view in mind, redesigning study protocols will optimize outcomes for all individuals involved.

6.0 Conclusion

Pediatric clinical research is a topic receiving insufficient attention despite recognition of the challenges that exist. There are limited published articles specifically focusing on pediatric populations when discussing challenges in research and healthcare disparities. A majority of the focus is on adults and typically articles only include a small section on the importance for children. Due to the increased vulnerability and lasting impacts of health inequities faced by children, more direct research is needed to understand the full scope of challenges. When interviewing healthcare professionals involved in clinical research, they shared some of the benefits and challenges associated with their own studies. The benefits for children in these studies include being connected with top-rated specialists, having extra attention from a healthcare team to manage clinical care, and having a safe space to openly share experiences related to their health and wellbeing. Challenges for patients were mainly focused on social determinants of health such as socioeconomic status, lack of reliable transportation to medical appointments, and distrust in medical systems. Researchers also face their own challenges during these studies from finding the perfect patients for recruitment to working with poorly written protocols. Therefore, while clinical research has profound benefits and helps to advance medical discoveries, addressing the challenges and placing more emphasis on pediatric health indicators remains critical for promoting equitable healthcare practices and improved outcomes in this population.

Appendix A IRB Exemption Letter

University of Pittsburgh | Institutional Review Board
Office of Research Protections

EXEMPT DETERMINATION

Date:	January 17, 2024
IRB:	STUDY23120132
PI:	Caroline Wallendal
Title:	Challenges and Health Disparities in Pediatric Clinical Research
Funding:	None

The Institutional Review Board reviewed and determined the above referenced study meets the regulatory requirements for exempt research under 45 CFR 46.104(d).

Determination Documentation

Determination Date:	1/17/2024
Exempt Category:	(2)(i) Tests, surveys, interviews, or observation (non-identifiable)
Approved Documents:	• Interview questions.docx, Category: Data Collection; • Introductory Script.docx, Category: Recruitment Materials;

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Carolyn Baker. **NOTE**: Modifications are only required if they will affect the exempt determination. However, it is important to **close your study when finished** by submitting a Continuing Review.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

The University of Pittsburgh has a Federal Wide Assurance approved through the Office of Human Research Protections (FWA00006790).

Appendix B Introductory Interview Script

⇒ The purpose of this research study is to identify challenges and health disparities that exist in pediatric clinical research.

⇒ We will be asking a handful of healthcare professionals to participate in short interviews that will help identify common challenges.

⇒ There are no foreseeable risks associated with this project. There are no direct benefits to you.

⇒ Your participation is voluntary. You can stop participating at any time by informing the interviewer.

⇒ If you choose not to participate, or if you do not complete the study, this will have no effect on your relationship with the University of Pittsburgh, UPMC, or any other associated institutions.

⇒ This study is being conducted by Caroline Wallendal, who can be reached at cew63@pitt.edu if you have any questions. Additionally, faculty mentor Wenndy Hernandez can be contacted at weh119@pitt.edu.

⇒ Would you like to participate?

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