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Predictors of Early Termination of Pediatric Oncology Clinical Trials Due to Poor Accrual: An Exploratory Analysis

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Abstract

Purpose: The purpose of this dissertation is to explore factors affecting accrual and completion of pediatric oncology clinical trials. This dissertation includes a scoping review of barriers and facilitators to enrollment in pediatric oncology clinical trials, a systematic review of trial-level factors affecting accrual and completion of oncology clinical trials, and an exploratory analysis of trial-level factors affecting accrual and completion of pediatric oncology clinical trials from ClinicalTrials.gov data.

Problem/Aims: Cancer is the second leading cause of death in children. Clinical trials explore potential new therapies for children with cancer by determining safety and effectiveness of interventions. The literature demonstrates widespread inadequate accrual of trial participants and associated early termination of oncology clinical trials. This dissertation aimed to provide evidence of trial-level factors affecting accrual and completion of pediatric oncology clinical trials by reviewing the literature, identifying possible trial-level factors, and performing an exploratory analysis of the ClinicalTrials.gov dataset.

Design including theoretical basis: A modified version of the Social Ecological Model and Arskey and O'Malley's framework guided the scoping review. Bennette et al.'s framework, along with that of Knafl and Whittmore, directed the systematic review. Bennette et al.'s framework also guided the exploratory analysis using the ClinicalTrials.gov dataset.

Findings: Barriers to enrollment in pediatric oncology clinical trials exist at the trial, individual, interpersonal and organizational levels. Several trial-level barriers to

enrollment in adult oncology clinical trials previously were identified, such as enrollment, intervention type, phase, allocation, arm type, sponsor, number of participating facilities, and primary disease. The exploratory analysis indicated none of the aforementioned variables and others such as primary purpose, number of primary outcomes, interventional study model, and number of arms were predictive of early termination of pediatric oncology trials due to low accrual. However, odds for studies to terminate early were 4.7 times higher for those that used a data and safety monitoring committee compared to those that did not ($p = 0.05$).

Conclusion: Findings from the scoping and systematic reviews suggest there are trial-level factors that affect early termination of pediatric oncology trials due to low accrual. Findings from the exploratory study indicated that use of a data and safety monitoring committee plays an important role in early trial termination due to low accrual. The design of future pediatric oncology clinical trials should incorporate approaches to minimize trial-level factors that are associated with or predictive of early trial termination. Additional studies examining trial-level factors should utilize multiple trial databases and investigate pediatric oncology trials that have been conducted worldwide.

Key words – Clinical trials, oncology, cancer, pediatric, children, enrollment, accrual, recruitment

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Introduction

Cancer is the second leading cause of death in children, exceeded only by injuries. In 2020, 11,050 children ages 0-14 years are predicted to be newly diagnosed with cancer. Moreover, 1,190 children in this same age group years are predicted to die from cancer.[1] Cancer affects children of all ethnicities, socioeconomic backgrounds, and genders.[2] Available cancer therapies often result in toxicities, secondary cancers, and long-term financial challenges for affected children and their families.[3,4] Thus, new cancer therapies for children are urgently needed.

Clinical trials explore potential new therapies for children with cancer by determining the safety and effectiveness of investigational drugs, devices, surgeries, and other interventions.[5] As a result of increased public pressure for more efficacious and less toxic cancer therapies, the number and costs of oncology clinical trials have increased. Thirty-two oncology clinical trials for children were opened in 2010, increasing to 137 in 2019.[6] Clinical trials for FDA-approved oncology drugs in 2015-2017 had a median cost of $37.1 million per trial (interquartile range = $17.0 - $60.4 million).[7] Consequently, the increase in number of oncology clinical trials and their associated high cost present challenges to their successful completion.

The increase in number and high cost of oncology clinical trials present challenges to their successful completion due to required financial and human resources. Sponsors of clinical trials and cancer centers that participate in oncology clinical trials have limited resources to support the clinical and administrative operations necessary for trials.[8,9] Federal funding and monetary support from pharmaceutical companies for the

conduct of clinical trials have decreased over time, while trial activation and maintenance are often complex and require many resources. For example, the activation of a phase III trial may consist of greater than 370 processes.[10].

The Institute of Medicine (IOM) cited inefficiencies in the development and conduct of clinical trials in the United States. One of these inefficiencies is the inability to prioritize trials likely to be most successful. The IOM's report called for improvement in the speed and efficiency of the design and conduct of clinical trials, including the prioritization, selection, and completion of oncology clinical trials.[11] The lack of prioritization results in scarce resources being wasted or misappropriated to clinical trials that fail to successfully complete, thus impeding the availability of new, effective therapies for patients who desperately need them.

The literature has demonstrated widespread inadequate accrual of trial participants and associated early termination of oncology clinical trials. One study revealed 40% of National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) trials did not meet accrual goals.[12] In another study, more than 70% of phase III oncology trials reported inadequate accrual and only 37.9% of closed phase III trials reached their targeted accrual.[13] Moreover, one in five surgical randomized clinical trials is terminated prematurely because of inadequate accrual[14]. In addition, researchers have reported approximately one randomized clinical trial involving radiation failed to complete for every two of these types of trials that completed. Inadequate accrual was the main reason for the failed trials.[15] Accrual is important

because an adequate sample size is required for valid trial results.[16] Consequently, accrual is an indicator of a clinical trial's success.

In addition to lack of validity of study outcomes due to small sample sizes, inadequate accrual can have several other negative effects on a clinical trial's financial resources and participants. First, the enrollment period for a trial may need to be extended to obtain the targeted sample size, thus delaying results and increasing the trial's costs.[17] Each additional month for the conduct of a phase 3 clinical trial regardless of therapeutic indication costs a median of $671,000.[18] Second, the early termination of a clinical trial due to inadequate accrual results in significant loss of financial and human resources that were utilized in the trials' design, activation, recruitment, data collection and analysis, and management of the trial[19-21]. Consequently, those resources are not available to use for trials for the same target population that may have had a successful completion.[20] Third, the efforts of patients who participated in a clinical trial that terminates early due to low accrual have been in vain because the trial did not contribute knowledge in science.[17,19,20] Therefore, there are also ethical implications of inadequate accrual and early termination of clinical trials.

Factors that affect the successful accrual and completion of oncology clinical trials operate at the trial, individual, interpersonal, organizational, community, and policy levels. Many researchers have investigated these factors for adult oncology clinical trials [22-36]; however, limited research exists about trial level factors that may affect successful accrual for pediatric oncology clinical trials. Trial level factors (e.g., eligibility criteria, planned sample size, phase of study, study design, use of randomization, funder,

and location) have been found to be associated with, or predictive of, completion of cardiovascular clinical trials, adult oncology clinical trials, and quality of pediatric clinical trials.[37-39] However, these trial level factors have not been investigated for pediatric oncology clinical trials, lest using a robust national dataset such as ClinicalTrials.gov. Precise estimates of which types of trials will be able to successfully meet their accrual targets based upon trial characteristics will support rapid translation of bench discoveries to therapies for children with cancer.[39] Identification of trial-level factors that affect the successful accrual and completion of oncology clinical trials is necessary for precise estimates.

Over recent years, the government and public have insisted on transparency in clinical trials to facilitate drug development and safety. Subsequently, federal regulations were established to require sponsors of clinical trials to provide pre-defined data about their clinical trials in the ClinicalTrials.gov database.[6] Thus, ClinicalTrials.gov has become the largest and most inclusive database of clinical trials in the world due to it having the most predefined data[40] Changes in regulations instituted over the last two decades resulted in discrepancies in the type and amount of data that investigators submitted into the database during that timeframe.[6] As a result, the number of available variables differs among different time periods, study types (phase I, II, III, or IV), allocation (randomized or nonrandomized), and intervention model (parallel, crossover, factorial, or single-arm). Assessment of the completeness of variables in ClinicalTrials.gov may identify variables to be included in the design of future studies about clinical trials as an enterprise (studies about clinical trials as a whole based on large

databases of clinical trials rather than data from a few clinical trials at a single or few institutions).

Theoretical Models

This dissertation includes a scoping review of barriers and facilitators to enrollment in pediatric oncology clinical trials, a systematic review of trial-level factors affecting accrual and completion of oncology clinical trials, and an exploratory analysis of trial-level factors affecting accrual and completion of pediatric oncology clinical trials from ClinicalTrial.gov data. Each of these investigations utilized a theoretical model to guide the data analysis and organization of the results. The scoping review of barriers and facilitators to enrollment in pediatric oncology clinical trials utilized a modified version of the Social Ecological Model (SEM) by McLeroy et al. [41] The SEM model was used because clinical trial enrollment is affected by a myriad of factors at multiple levels, including the trial, individual/intrapersonal, interpersonal, organizational, community, and policy levels. Trial-level factors affecting enrollment include the availability of a clinical trial, the status of the trial (e.g. open or closed), and eligibility criteria. Individual factors relate to study participants and include age, sex, race, ethnicity, insurance status, cancer characteristics, and motivation. Interpersonal factors include parents' desire for continuity of care by healthcare providers, physicians' discussions with parents and children about clinical trials, and physicians' attitudes about clinical trials. Organizational factors include local availability of a clinical trial and continuity of care. Community factors include a culture of fear and distrust among minority groups because of exploitative practices in past trials, such as the Tuskegee syphilis study. Finally, policy

includes laws that mandate insurance coverage for routine patient care costs associated with participation in clinical trials, hence lessening the financial burden of trial participation.

Both the systematic review of trial-level factors affecting accrual and completion of oncology clinical trials and the exploratory analysis of trial-level factors affecting accrual and completion of pediatric oncology clinical trials utilized Bennette et al's [42] conceptual model of trial-level factors associated with low trial accrual. The model offers four critical domains for assessing trial-level factors associated with low trial accrual: background, disease-related, treatment-related, and trial design. Background factors include greater competition from other trials and less state-level coverage of clinical trial costs. Disease-related factors include less advanced disease, solid tumor setting, less compelling scientific rationale, and lower annual incidence of the eligible population. Treatment-related factors include greater deviation from standard of care, research question not relevant to clinical practice, patient or provider preference for a particular treatment, radiotherapy or surgical treatment, not an investigational new agent, more expensive treatment, higher risk for toxicity, multimodality, and less compelling scientific rationale. Trial design factors include stricter or more eligibility criteria, randomized design, placebo-controlled arm, greater trial complexity, longer follow-up, and higher patient burden.

Contributions of manuscripts

Each manuscript in this dissertation compendium contributes to the identification of barriers to enrollment and, consequently, successful completion of pediatric oncology

clinical trials. The first manuscript, *Barriers and Facilitators to Enrollment in Pediatric Oncology Clinical Trials,* is a scoping review with the purpose of determining the state of knowledge of barriers and facilitators to enrollment in pediatric oncology clinical trials. Results and discussion were organized by trial, individual/intrapersonal, interpersonal, organizational, community, and policy levels. One finding of the review was the gap in knowledge about trial-level barriers and facilitators to enrollment in pediatric oncology clinical trials. Therefore, currently known trial-level barriers and facilitators to enrollment in adult oncology clinical trials were investigated in the second manuscript.

The purpose of the second manuscript in this dissertation compendium, *Trial-level Factors Affecting Accrual and Completion of Oncology Clinical Trials: A Systematic Review,* was to explore the literature to identify trial-level factors that affect accrual and/or completion of adult and pediatric oncology clinical trials, gaps in the literature, and prospective future research. A finding of this review was that none of the reviewed studies focused solely on pediatric oncology clinical trials and only three studies included a small number of pediatric trials. The identified trial-level factors identified in the first and second manuscripts, along with the available variables in the ClinicalTrials.gov dataset, informed the third manuscript. The identified trial-level factors and variables in the ClinicalTrials.gov dataset included enrollment, primary purpose, trial phase, interventional study model, number of arms, arm type, masking, allocation, intervention type, end points, number of primary outcomes, sponsors, number of participating facilities, primary disease, and data monitoring committee.

The purpose of the third manuscript, *Predictors of Early Termination of Pediatric Oncology Clinical Trials Due to Poor Accrual: An Exploratory Analysis,* was to describe the presence of variables and completeness of data entry for variables in the ClinicalTrials.gov database over time. The frequency and proportion of pediatric oncology clinical trials with data for a given variable and data differed across four periods which were based on the effective dates of regulations affecting data requirements for ClinicalTrials.gov. The manuscript also reports on the investigation of trial-related factors that may predict early termination of pediatric oncology clinical trials due to low accrual. Results showed that use of a data and safety monitoring committee plays an important role in early trial termination due to low accrual.

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Manuscript 1

Scoping Review: Barriers and Facilitators to Enrollment in Pediatric Oncology Clinical Trials (accepted for publication by *Pediatric Nursing*)
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Scoping Review: Barriers and Facilitators to Enrollment in Pediatric Oncology Clinical Trials

Abstract

Cancer is the second-leading cause of death among children in the United States. Oncology clinical trials are designed to investigate new potential therapies. Approximately 60% of children with cancer are treated on clinical trials. The purpose of this scoping review of the literature is to explore what is known about barriers and facilitators to enrollment in pediatric oncology clinical trials. Arskey and O'Malley's methodological framework guided the scoping review. The electronic databases of PubMed and SCOPUS were searched for relevant publications. Thirty publications met eligibility criteria, which included empirical publications related to barriers and facilitators to enrollment in pediatric oncology clinical trials. The results and discussion of barriers and facilitators were organized by utilizing a modified version of the Social Ecological Model (SEM). Trial-level barriers included lack of an available trial, trials closed to accrual, and eligibility criteria. Individual factors included age, sex, race/ethnicity, insurance status, cancer characteristics, and motivation. Interpersonal factors included parents' desire for continuity of care by healthcare providers, physicians' discussions with parents and children about clinical trials, and physicians' attitudes about clinical trials. Organizational factors that influenced enrollment included local availability of a clinical trial and continuity of care. No studies of community or policy-level barriers and facilitators were found. Theoretically based studies need to be conducted to identify factors at SEM levels not previously studied and investigate interventions to address factors that adversely affect enrollment. Furthermore,

interdisciplinary collaboration among nurses and other professionals working at each SEM level is vital to surmount enrollment obstacles.

Keywords: Clinical trials, oncology, cancer, pediatric, enrollment

Scoping Review: Barriers and Facilitators to Enrollment in Pediatric Oncology Clinical Trials

Surpassed only by injury, cancer is the second-leading cause of death among children in the United States (American Cancer Society [ACS], 2020). In 2020, 11,050 children under 15 years old are predicted to be newly diagnosed with cancer, and of these, 1,190 are expected to die (ACS, 2020). As evidenced by these statistics, new effective oncological therapies are needed for children. Oncology clinical trials are designed to discover safe and efficacious means to prevent, diagnose, treat cancer and manage its symptoms (National Cancer Institute [NCI], 2020). Clinical trials are responsible for the childhood cancer cure rate increasing from less than 10% to over 80% during the past 40 years (Children's Oncology Group [COG], n.d.). There are over 1,900 active oncology clinical trials for 1 – 17-year-old patients in the ClinicalTrials.gov database (U.S. National Library of Medicine, 2020).

Enrollment is significant because it is a key metric in determining the success of a clinical trial, as optimal sample size is required for valid results (Melnyk & Morrison-Beedy, 2012). Also, if a clinical trial is extended due to poor enrollment, its costs continue to rise resulting in budget deficits and wasted resources (Steinman et al., 2017). However, enrollment of participants in oncology clinical trials is a challenge. Approximately 60% of children with cancer are treated on clinical trials (COG, n.d.). Existing literature about barriers and facilitators to enrollment in pediatric oncology clinical trials is limited. Identifying factors inhibiting enrollment is imperative so that interventions addressing enrollment challenges be developed, implemented, and evaluated to foster the successful completion of oncology clinical trials. Thus, the

purpose of this scoping review of the literature is to explore what is known about barriers and facilitators to enrollment in oncology clinical trials for children. The research question driving this review is "What are the barriers and facilitators to enrollment in oncology clinical trials for children?"

Methods

Arksey and O'Malley's (2005) methodological framework guided the scoping review. The authors chose this framework because it facilitates rigor and transparency in each stage, thus increasing the reliability of findings. The five stages of the framework that were utilized were (1) identification of the research question, (2) search for applicable studies, (3) selection of the most appropriate studies utilizing inclusion and exclusion criteria, (4) collation, and (5) summary of results.

The authors conferred with a reference librarian to determine the best approach to search the literature for relevant studies (most recent search on November 23, 2019). A PRISMA flow chart graphically detailed the identified records, included and excluded records, and reasons for excluded records (Moher et al., 2009) (Figure 1). The titles and abstracts of the publications were evaluated for relevance based on inclusion and exclusion criteria. Inclusion criteria were empirical publications related to barriers and facilitators to enrollment in pediatric oncology clinical trials. Exclusion criteria included the following: non-English speaking; children over 21 years old; diagnoses other than cancer; publications solely related to the prevention, screening, and survivorship of cancer; interventions; commentaries, statements, and recommendations. There were no publication date delimiters since 1) there were limited publications about barriers and

facilitators to enrollment in oncology clinical trials for children and 2) this scoping review was intended to summarize and analyze all applicable study results to date.

Adhering to stage 2 of Arskey and O'Malley's (2005) framework, the electronic databases of PubMed and SCOPUS were searched for relevant publications. Due to variations in terms used to describe enrollment of oncology clinical trials, the following key words with appropriate Boolean operators were utilized: (pediatric[Title/Abstract] OR children[Title/Abstract] OR adolescents[Title/Abstract] OR teenagers[Title/Abstract]) AND (cancer[Title/Abstract] OR oncology[Title/Abstract]) AND ("clinical trials"[Title/Abstract] OR "clinical research trials"[Title/Abstract] OR "therapeutic trials"[Title/Abstract]) AND (enrollment[Title/Abstract] OR accrual[Title/Abstract] OR recruitment[Title/Abstract] OR participation[Title/Abstract] OR selection[Title/Abstract]). Publications were limited to English language and peer-reviewed journal articles. The reference lists of retrieved publications were also hand searched for primary sources and additional applicable publications.

To accomplish stage 3 of Arskey and O'Malley's (2005) framework, a scoping review matrix was used to organize the selected publications. Publications were organized by the following: author/date, purpose, country, ages of children, cancer type, sample size and description, number and type of sites/number of clinical trials/phase of clinical trials, study design/data collection methods, barriers/facilitators, SEM levels, and results.

The results and discussion of barriers and facilitators to enrollment in pediatric oncology clinical trials were organized by utilizing a modified version of the Social

Ecological Model (SEM) by McLeroy et al. (1988). This model was selected because clinical trial enrollment is influenced by factors at multiple levels. The modified SEM addresses trial, individual/intrapersonal, interpersonal, organizational, community, and policy levels (see Table 1 for definitions).

Results

The initial search produced 2,335 citations. With 715 duplicates removed, 1,564 citations were removed due to ineligibility based on the review of titles and abstracts. Of the 59 remaining full-text publications, 30 met inclusion criteria (Table 2). These studies represented diverse settings, designs, and implementation strategies. The studies about pediatric clinical trials were conducted in multiple countries, with only 13 conducted in the United States. The majority of studies (n=23) specified a facility setting specializing in pediatric cancer or a database containing data about pediatric patients and/or pediatric oncology clinical trials. Almost half (n=13) did not specify types of cancers. Of those that did specify cancer type, leukemia was most frequently studied (n=15). Phase of clinical trial was specified for 17 studies (phase I or I/II=9; phase III/late phase=8). Most studies about clinical trials (n=18) did not specify number of clinical trials examined. Four studies involved only one clinical trial, while the remaining 26 studies involved anywhere from 2-26 clinical trials. Eighteen studies used quantitative methods, and 12 used qualitative methods. None of the studies used mixed methods. For the quantitative studies, the most frequent source of data were electronic databases containing data about pediatric oncology clinical trials and/or their participants (n=10) whereas for qualitative studies it was interviews (n=12).

Social Ecological Model (SEM)

Only four studies were explicitly based on a theoretical framework, and none of the studies relied on the SEM for the design or analyses. Of the 30 studies included in the final analysis, 18 addressed one level of the SEM, and seven addressed two levels. Only five studies addressed three or four levels of the SEM, and none addressed five or six levels. Most of the studies (n=26) addressed the individual/intrapersonal level of the SEM (Table 3).

SEM Levels

Trial

Five studies examined trial-level barriers and facilitators to enrollment in pediatric oncology clinical trials. Trial-level barriers included lack of an available trial, trials closed to accrual, and eligibility criteria that children did not meet (Dechartres et al., 2011; Dodgshun et al., 2014; Pole et al., 2017; Surun et al., 2018). Type of dosing in clinical trials also influenced enrollment. Adolescents were more likely to decline dose intensification trials than dose reduction trials compared to younger children (Tulstrup et al., 2016).

Individual/Intrapersonal

Twenty-seven studies examined several types of individual/intrapersonal barriers and facilitators to enrollment in pediatric oncology clinical trials. Demographic factors such as age, sex, race/ethnicity, parental language, insurance status, distance from cancer center, geographical and urban/rural residence have been examined (Aristizabal et al., 2015; Donnelly et al., 2017; Lund et al., 2009; Nooka et al., 2016; Pole et al., 2017; Shah

et al., 2014; Shochat et al., 2001; Thomas et al., 2018; Winestone et al., 2019). In general, adolescents compared to younger children and Hispanics compared to non-Hispanics are underrepresented in oncology clinical trials (Aristizabal et al., 2015; Lund et al., 2009; Nooka et al., 2016; Shochat et al., 2001). Being of Asian and Arab/west Asian ancestry and greater distance from cancer center were associated with non-enrollment (Pole et al., 2017). Males were also less likely to participate in clinical trials than females (Donnelly et al., 2017). Children who lacked insurance had lower rates of clinical trial participation (Shochat et al., 2001). Individual factors such as cancer characteristics have also been investigated in relation to enrollment of children in clinical trials (Aristizabal et al., 2015; Dodgshun et al., 2014; Donnelly et al., 2017; Eiser et al., 2005). Children with hematological cancers have higher clinical trial participation rates than those with other types of cancers (Dodgshun et al., 2014; Donnelly et al., 2017; Thomas et al., 2018).

Other individual factors such as understanding of clinical trials and motivation for enrollment into pediatric oncology clinical trials have been investigated (Eiser et al., 2005; Ingersgaard et al., 2018; Miller et al., 2013; Robertson et al., 2019). In one study, most mothers described the aim of a clinical trial as comparing old and new therapies, but they lacked understanding of randomization (Eiser et al., 2005). Parents' and children's motivations for trial participation include the following: hope for a cure, desire to try anything, continuity of care, maintenance of quality of life, increased life expectancy, less toxicity, and altruism (Barrera et al., 2005; Crane et al., 2019; Hinds et al., 2005; Ingersgaard et al., 2018; Miller et al., 2013; Oppenheim et al., 2005; Robertson et al.,

2019; Simon et al., 2006; Unguru, et al., 2010; van der Geest et al., 2016; Woodgate & Yanofsky, 2010).

Interpersonal

Interpersonal factors have been explored in relation to enrollment of children in clinical trials. Parents' desire for continuity of care by healthcare providers can influence the decision to participate in a clinical trial (Barrera et al., 2005). Also, the content and quality of physicians' discussions about clinical trials can affect parents' perceptions and understanding of clinical trials, thus affecting the decision about trial participation (Byrne-Davis et al., 2010; Deatrick et al., 2002; Miller et al., 2014; Robertson et al., 2019; Simon et al., 2006). A physician's attitude about clinical trials or belief about what is in a child's best interest can affect enrollment (Dechartres et al., 2011; De Vries et al., 2010; Dodgshun et al., 2014; Pole et al., 2017; Robertson et al., 2019). In addition, when there is a conflict between parents and an adolescent about enrollment, parents' wishes usually take precedence (Ingersgaard et al., 2018). Finally, a trusting relationship between healthcare providers and children/parents can facilitate trial participation (Woodgate & Yanofsky, 2010).

Organizational, Community and Policy

Five studies examined organizational barriers and facilitators to enrollment in pediatric oncology clinical trials. Lack of a locally available clinical trial adversely affects enrollment (Dechartres et al., 2011; Dodgshun et al., 2014; Surun et al., 2018). In contrast, one of the main reasons for participation in phase I clinical trials is that the trials provide continuity of care compared to the other option of no further treatment (Barrera

et al., 2005). No studies of community or policy-level barriers and facilitators to enrollment in pediatric oncology clinical trials were found.

Discussion

Social Ecological Model (SEM)

A key finding of this scoping review is that barriers and facilitators at several SEM levels influence enrollment of children in oncology clinical trials. According to SEM, interventions at several, if not all, of these levels will be required to substantially increase enrollment of children in oncology clinical trials.

Trial

Surprisingly, few studies examined trial-level barriers and facilitators to enrollment in pediatric oncology clinical trials. The main trial-level barriers examined were related to the availability of a clinical trial open for enrollment for children with cancer. Trial availability was influenced by the type of cancer targeted by pediatric oncology clinical trials. Determining the most prevalent childhood cancers that do not have available clinical trials is of the utmost importance. Clinical trials for these cancers can then be developed and implemented to establish the safety and efficacy of new treatments to benefit pediatric cancer patients. Also important is the coordination of opening clinical trials. Often there are multiple open trials that are competing against each other for enrollment of the same population. At other times, there are no open trials for that same population. Coordination of the opening of trials may help prevent these situations from occurring and facilitate trials with reaching their enrollment goals.

The number and types of research studies about trial-level barriers and facilitators that influence enrollment in pediatric oncology clinical trials is lacking compared to those about adult oncology clinical trials. Few characteristics of pediatric oncology clinical trials were investigated in relation to enrollment except for eligibility criteria and dosing schema. Unlike with pediatric oncology trials, much research has been conducted about trial-level barriers and facilitators that influence enrollment in adult oncology clinical trials. These barriers and facilitators include, but are not limited to, eligibility criteria, disease type, treatment type, research question, design complexity, phase of trial, planned sample size, sponsor, number of sites, and location(s) of sites (Adams-Campbell et al., 2004; Al-Refaie et al., 2011; Baum, 2002; Bennette et al., 2016; Benson et al., 1991; Cheng et al., 2010; Diehl et al., 2011; Freedman et al., 2018; Go et al., 2006; Khunger et al., 2018; Kim et al., 2015; Kornblith et al., 2002; Logan et al., 2017; Massett et al., 2016; McKane et al., 2013; Meric-Bernstam et al., 2015; Moore et al., 2004; Penberthy et al., 2012; Schroen et al., 2010; Schroen et al., 2011; Simon et al., 2004; Spiegel et al., 2017; Statler et al., 2018; Stensland et al., 2014; Swain-Cabriales et al., 2013; Tang et al., 2017; Tibes et al., 2011).

The trial-level barriers for pediatric oncology clinical trials may be different than those for adults. Children are often diagnosed with different types of cancers than adults, thus the clinical trials target these different cancer types and have different eligibility criteria and treatments. Also, since childhood cancer is less prevalent than adult cancer, there are fewer sites participating in clinical trials. In addition, pediatric oncology clinical trials have different sponsors and participating sites than those of adult oncology trials.

Most pediatric oncology clinical trials are sponsored by COG, which is supported by the NCI. Over 90% of children with cancer in the United States are treated at COG member institutions, which consist mainly of children's hospitals and academic cancer centers (COG, n.d). Unlike pediatric clinical trials, most adult oncology clinical trials are sponsored by pharmaceutical companies (Lechleiter, 2015). Also, adult cancer clinical trials are conducted at many facilities besides hospitals and academic cancer centers, such as community hospitals and private physician offices. Additional research is needed to determine if the differences in sites and sponsors between adult and pediatric oncology trials affect enrollment. For example, those trials sponsored by pharmaceutical companies may have better enrollment than those sponsored by COG since pharmaceutical companies tend to have larger financial resources for advertising and participant incentives such as travel vouchers.

Researchers have also examined many barriers and facilitators to enrollment in adult oncology clinical trials in detail. For example, the following eligibility criteria pertaining to characteristics of potential participants were related to poor accrual: the presence of comorbidities, poor performance status, advanced age, histopathology, past history of cancer, a current second cancer, inadequate laboratory results, fewer prior systemic chemotherapy regimens, and disease-specific inclusion criteria such as testosterone levels, PSA results, Gleason scores, and number of positive lymph nodes (Adams-Campbell et al., 2004; Al-Refaie et al., 2011; Bennette et al., 2016; Diehl et al., 2011; Freedman et al., 2018; Go et al., 2006; Kornblith et al., 2002; Massett et al., 2016; McKane et al., 2013; Meric-Bernstam et al., 2015; Moore et al., 2004; Penberthy et al.,

2012; Schroen et al., 2011; Simon et al., 2004; Statler et al., 2018). Even in studies where eligibility criteria were found to influence enrollment in pediatric oncology clinical trials, specific eligibility criteria were not investigated to determine which of the criteria served as barriers to enrollment. Restrictive eligibility criteria may be able to be amended to facilitate enrollment while still maintaining internal validity of pediatric oncology clinical trials.

Individual/Intrapersonal

Almost all the studies examined barriers and facilitators to enrollment in pediatric oncology clinical trials at the individual level. Overall, the studies demonstrated disparities with enrollment in pediatric oncology clinical trials in relation to age, sex, race/ethnicity, language, and insurance status, same as demonstrated in the previously discussed studies about influential factors of enrollment in adult oncology clinical trials. These disparities may indicate Healthy People 2020's objectives is to reduce health care disparities for cancer has not been met (U.S. Office of Disease Prevention and Health Promotion, 2019). Pediatric oncology clinical trials need to be developed and implemented to facilitate enrollment as they are the key to discovering and testing new, effective treatments.

Desperation for a cancer cure and/or extension of a child's life was consistently demonstrated as a motivation for clinical trial enrollment. When children and their parents receive a cancer diagnosis and/or a poor prognosis, they are overwhelmed and may not be able to think rationally about potential treatments and possible associated adverse events. Parents will often do anything to save their children. In this mindset, they

may be unable to rationally consider the possible lack of efficacy and presence of toxicities associated with treatments on clinical trials. Healthcare providers must ensure true assent and informed consent have been given before children are enrolled on clinical trials.

Interpersonal

The most commonly examined interpersonal barriers and facilitators to enrollment in pediatric oncology clinical trials were those related to parental consent. The content of physicians' discussions with parents about clinical trials affected the parents' perceptions and understanding of clinical trials, possibly affecting the parents' decisions about their children enrolling in the clinical trial (Byrne-Davis et al., 2010; Deatrick et al., 2002; Miller et al., 2014; Robertson et al., 2019; Simon et al., 2006). Therefore, healthcare providers need to provide clear and comprehensive clinical trial information to parents to facilitate enrollment.

When there was a conflict between parents and an adolescent about trial participation, parents' wishes usually took precedence (Ingersgaard et al., 2018). Therefore, healthcare providers need to provide a supportive environment that facilitates communication and understanding between parents and children to avoid continuing conflict. Healthcare providers also need to ensure proper assent and informed consent procedures are followed, especially when a child's wishes conflict with his parent(s).

Organizational

Only five studies examined organizational barriers and facilitators to enrollment in pediatric oncology clinical trials. Most of these studies found lack of an available trial

adversely affected enrollment. Besides being a trial-level barrier, lack of an available trial can also be considered an organizational barrier influencing enrollment in pediatric oncology clinical trials. Even though an appropriate oncology clinical trial may exist for a child, the trial may not be open at the institution where the child is receiving care. Also, the child's family may not have the resources to travel long distances to receive care at an institution that is participating in the trial. Grant-funded agencies and pharmaceutical companies should be incentivized to open pediatric oncology clinical trials at institutions that are strategically located to meet the needs of the most children as possible. In addition, since clinical trials are costly to operate, organizations should be encouraged to manage their limited financial and human resources, so they are able to financially open additional much-needed pediatric oncology clinical trials. When its not possible open new trials, centers can educate parents/adolescents about important trials that may be available at other institutions.

Community and Policy

None of the studies examined barriers and facilitators to enrollment in pediatric oncology clinical trials at the community and policy levels. The conduct of research about barriers and facilitators that influence enrollment in pediatric oncology clinical trials at the community and policy levels may require more time and financial resources than the conduct of research at the individual and interpersonal levels. Hence, current limited and competitive research funding may contribute to the unequal proportion of research about barriers and facilitators at the community and policy SEM levels that influence enrollment in pediatric oncology clinical trials.

Barriers and Facilitators in General

A finding of this scoping review is the majority of studies were conducted in Europe addressing barriers and facilitators that influence enrollment of children in oncology clinical trials. Barriers and facilitators investigated in this scoping review may not have the same influence as they have in other countries due to different cultures, healthcare delivery systems, and regulations. Thus, researchers and health care providers need to be cautious in applying specific study findings from one community or country to others.

Findings from some studies exploring differences in enrollment for cancer type and insurance status differed from those of others exploring the same factors. Aristizabal et al. (2015) found no significant differences in enrollment for cancer type and insurance status. However, Shochat et al. (2001) found children who lacked insurance had lower rates of clinical trial participation. These conflicting findings may be due to different types of insurance available in the different states in which the children lived. Findings from several, but not all, studies suggest hematological cancers are associated with higher clinical trial participation rates than other types of cancers (Dodgshun et al., 2014; Donnelly et al., 2017; Thomas et al., 2018). These conflicting findings could be due to different types of cancers that were examined in the studies. Hematological cancers have a higher frequency than other cancers in children. If there are more patients with a certain cancer, it may be easier to enroll a larger number of participants into a clinical trial, compared to patients with rare cancers.

Gaps in the Literature

Barriers and facilitators to enrollment in pediatric oncology clinical trials have been described in the literature. However, very few, if any, were examined at the trial, organizational, community, and policy levels. In addition, the sample of studies in this scoping review did not specify which factors were most influential on enrollment. The studies did not specify if some factors such as trial phase, age, and race/ethnicity were more influential than others based on the type of cancer targeted in clinical trials, patient demographics, and settings.

The sample of reviewed studies generally lacked a theoretical framework and large sample sizes of clinical trials. Only four of the reviewed studies were theoretically based. In future studies, the utilization of theory to explore factors at all SEM levels will strengthen internal validity and increase interpretability of results (Melnyk & Morrison-Beedy, 2012). Many of the reviewed studies also lacked a large sample size of clinical trials. In addition, many of them did not use a comprehensive database of clinical trials that includes trials conducted throughout a country or the world. Small sample sizes of clinical trials conducted in a single or few locations limit the generalizability of study results.

Limitations

This scoping review framed by the SEM presented a general synopsis of the current literature related to factors associated with enrollment of children in oncology clinical trials and identified opportunities for future research on this topic. However, the literature search may not have included all available studies in the published literature because additional terms describing enrollment may have been inadvertently omitted.

Moreover, since only one reviewer was available, selected studies included in the final review could not be assessed for inter-rater reliability based on the inclusion and exclusion criteria.

Implications for Future Research

Future research on enrollment in pediatric oncology trials should consider investigating barriers and facilitators at the trial, organizational, community, and policy levels and developing novel interventions to address factors at all SEM levels. Also, future studies on enrollment of children in oncology clinical trials can include large samples of clinical trials and utilize large databases of clinical trials conducted in multiple countries. Finally, more research is needed to understand the reasons for the contradictory findings in the sampled studies.

With an increased incidence of childhood cancers and low pediatric participation rates in oncology clinical trials that may hold promise for future treatments, it is imperative that factors addressing enrollment challenges be examined and addressed. Many factors at each SEM level affect enrollment. Following a theory-based evaluation and synthesis of research about factors that influence enrollment in pediatric oncology clinical trials, this scoping review demonstrated a lack of adequate research. To address this gap, theoretically based studies with rigorous designs and adequate sample sizes need to be conducted to address factors at SEM levels not previously studied. Finally, interventions should address factors that influence enrollment while using innovative approaches, such as trial designs that eliminate unnecessary eligibility criteria; electronic educational materials that can be adapted based on a parent's/child's knowledge of

oncology clinical trials; and organizational, community, and federal policies incentivizing the opening of pediatric oncology clinical trials in locations where they are needed.

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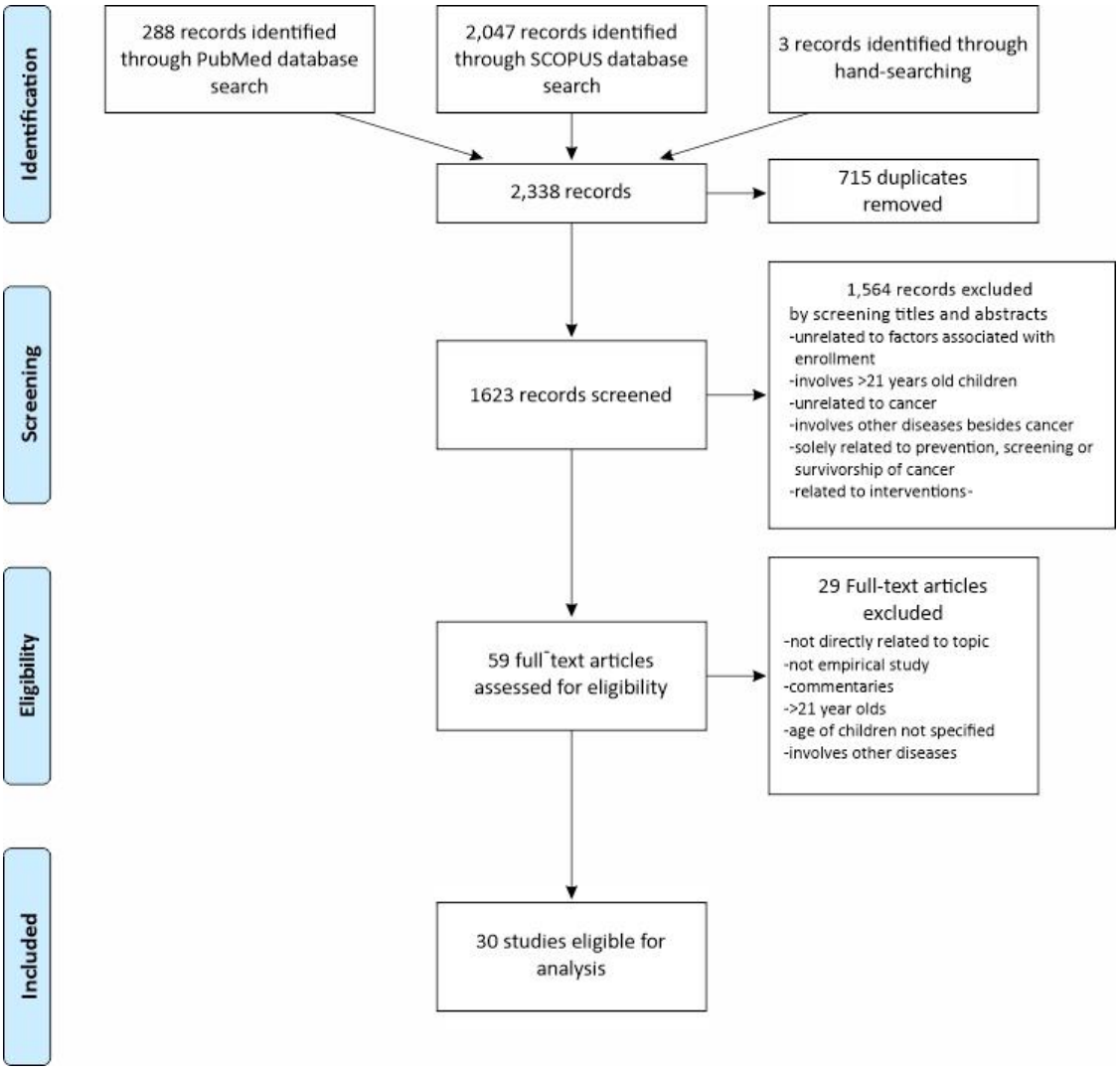

Figure 1. PRISMA flow chart

Table 1. Social Ecological Model: Levels of influence

Levels of Influence	**Definition**
Trial[a]	Characteristics of clinical trials that affect enrollment such as phase, disease indication, and eligibility criteria
Individual/Intrapersonal	Personal characteristics that affect behaviors such as age, sex, and race/ethnicity
Interpersonal	Relationships that provide social support and contribute to one's identity
Organizational	Formal institutions and informal social groups, including their policies and processes that influence members' behaviors
Community	Formal or informal networks with their own social norms among people, groups, and organizations
Policy	Local, state, and national laws and policies that promote or regulate behavior

[a]Note: Trial level added to adapted Social Ecological Model: Levels of Influence (Mitchell, 2010; Robinson, 2008)

Mitchell, J.A. (2010). Social ecological factors influencing cancer-related preventive health behaviors in African American men. Ohio State University.

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Table 2. Literature matrix for barriers and facilitators to enrollment in pediatric oncology clinical trials

Author, Date	Study Purpose	Country	Ages of Children	Cancer Type	Sample Size and Description	# and type of Sites / # of CTs/ Phase of CTs	Study Design/ Data Collection Methods	Examined Barriers/Facilitators	SEM Levels Addressed	Results
Aristizabalet etal., 2015	Evaluate differences in participation of children in cancer CTs by age, sex, race/ethnicity, parental language, cancer type and insurance status	United States	1-21 years	Unspecified	353 patients	1 Children's Hospital/ Unspecified number of CTs/ Phase unspecified	Quantitative-retrospective cohort/ Rady Children's Hospital San Diego (RCHSD) Tumor Registry and the RCHSD Hematology/ Oncology Research Center database	Age, sex, race/ethnicity, parental language, cancer type and insurance status	Individual	There was significant underrepresentation for Hispanics compared to Non-Hispanic whites, children of Spanish-speaking vs. English-speaking parents, and patients 15–21 years old versus those 0-4 years old. There were no significant differences in enrollment for other racial groups, sex, cancer type or insurance status.
Barrera et al., 2005	Examine 1) children's health-related quality of life (HRQOL)	Canada	7-15 years	Brain tumor, neuroblastoma,	7 mothers, 2 fathers, and 3 male children	1 large children's hospital/	Qualitative/Interviews	HRQOL components and reasons for phase I trial	Individual, interpersonal, organizational	The main reasons for participation in phase I trials were hope for a cure, continuity of care,

	when they are eligible for phase 1 trials and 2) their families' reasons for considering trial participation			acute lymphoblastic leukemia		Unspecified number of CTs/ Phase I		participation		maintenance of quality of life, and increased life expectancy.
Byrne-Davis et al., 2010	Determine how doctors' communication could affect Recruitment	United Kingdom	2 - 11 years	Acute lymphoblastic leukemia	20 doctor-patient duos and 30 parents [17 mothers and 13 fathers])	6 principal treatment sites/ 1 CT/ Late phase	Qualitative/Observations and interviews	Doctors' discussions about CT, parents' perceptions and comprehension of CT	Interpersonal	Doctors discussed the CT during most consultations. They discussed 1) their roles as both an investigator and clinician by utilizing vernacular aligning them to the trial and parent, and 2) the trial as a scientific study that allowed personalized treatment. Parents comprehended voluntariness, differences from standard care, and right to withdraw at any time. Some were confused about the minimal residual disease test and personalized treatment.

Crane, Haase & Hickman, 2019	Describe the meaning of phase I pediatric oncology trial participation experience from the parental perspective	United States	3 – 17 years	Unspecified	11 parents	Two pediatric academic medical centers and national childhood cancer support and advocacy groups/ 15 CTs/ Phase I	Qualitative – phenomenology/ Demographic form, interview and child's CT record	Parent's lived experiences of child's participation in oncology phase I CT	Individual	Parents' motivation for their child to participate in a phase I oncology trial was wanting to try something new and everything possible to help their child and to be a part of the research that leads to a cancer cure.
Deatrick, Angst & Moore, 2002	Describe parental perspectives about their children's participation in phase I oncology CTs	United States	2 -18 years	Solid tumors, leukemias, and other cancers	21 parents (19 mothers, 2 fathers)	One children's cancer research center/ Unspecified number of CTs/ Phase I	Quantitative-descriptive, cross-sectional using secondary analysis for qualitative data/ Interviews	Parental perspectives about their children's participation in phase I oncology CTs	Individual, Interpersonal	All parents felt they had limited or no choice for a cure regarding their children's participation in a phase I CT. Parents had several expectations for the CT such as treatment, buying time for another treatment, a miracle, altruism, and delay in death. Healthcare providers' openness and presentation of

										options helped parents make the best decision about participation. Parents also made the decision based practical issues, children's capacity, and spirituality.
Dechartres et al., 2011	Approximate prevalence of adults and children with acute leukemia who participated in CTs and determine factors associated with non-participation	Paris	3-11 years (included adults but separate analyses)	ALL and AML	164 children	3 hematological departments specializing in pediatrics/ 5 pediatric trials/ Phase unspecified	Quantitative-prospective observational /Survey	Trial availability, eligibility, parental or investigator decision	Trial, interpersonal, organizational	72% of children with AML and 68% with ALL had an available trial. Only four cases (5%) of AML and ALL were not eligible. Patient, parental or investigator decision to not participate was very low (1%).
DeVries et al., 2010	Ascertain clinicians' views, attitudes, and experiences towards adolescents' enrollment in research	Netherlands	10-18 Years	Unspecified	15 pediatric hemato-oncologists	2 pediatric oncology centers in 2 academic hospitals / unspecified number of CTs/	Qualitative-Interview	Clinicians' views, attitudes and experiences towards adolescents' enrollment in research	Interpersonal	Four central themes: Pediatric oncologists believe the following: (1) most adolescents do not have the capacities to contribute to research discussions; (2) they fail to provide adolescents with

						Phase unspecified				all research information; (3) parental consent is sufficient; and (4) research protocols are safe and in adolescents' best interests.
Dodgshun et al., 2014	Determine enrollment rate in pediatric cancer CTs in New Zealand using a dataset and identify reasons for non-enrollment	New Zealand	<17 years	Unspecified	289 children	2 sites but encompasses most pediatric oncology cases in New Zealand/ Unspecified number of CTs/ Focus on phase III	Quantitative-retrospective cohort/ New Zealand Child Cancer Registry and medical records	No trial open locally, closed to accrual, rare tumor, physician decision, technical, parental decision, emergency treatment, breach of protocol, administrative decision	Trial, individual, interpersonal, organizational	28% of children with cancer in New Zealand were enrolled on CTs. Enrollment rates differed by diagnosis, with low enrollment rates for lymphomas and neuro-oncology cancers and high rates for other solid tumors and acute lymphoblastic leukemia. The two most common reasons for non-enrollment were no locally open CT (27%) and CTs closed to accrual (20%).
Donnelly et al., 2017	Determine cancer CT participation since the Northern Ireland	Northern Ireland	< 15 years (included adults	Unspecified	317 children	All unspecified	Quantitative-retrospective cohort; Northern	Participation in interventional cancer CT, sex,	Individual	21% of children with cancer participated in a CT. 34% with hematological

	Cancer Trials Network was founded; determine population and disease factors associated with CT participation		but separate analyses)				Ireland Cancer Registry (NICR) was linked to the Northern Ireland Cancer Trials Centre (NICTC) database	deprivation, distance from cancer center, urban/rural residence, cancer site		cancers participated in a CT, which was over 70% of all trial participants. Females were more likely to participate in trials than males. Disease site, especially hematological cancers, were associated with CT participation.
Eiser et al., 2005	Describe understanding of consent by mothers of children newly diagnosed with ALL in relation to recruitment to randomized controlled trials	United Kingdom	4-16 years	Acute lymphoblastic leukemia	50 mothers	4 United Kingdom Children's Cancer Study Group centers/ 1 CT/ Phase III	Qualitative-/interviews	Mothers' understanding of CTs	Individual	47 of 50 mothers consented for their child's participation in the RCT. Reasons for participation and views about the consent process varied. Mothers' understanding of the purpose, advantages, and disadvantages of the CT greatly varied. Most mothers described the aim as comparing old and new therapies. They lacked

										understanding of randomization.
Hinds et al, 2005	Explore preferences, decisions, and influential factors of decisions of children and adolescents with advanced cancer about end-of-life care	United States and Australia	10-20 years	Solid, brain, leukemia	20 children/adolescents	2 children's hospitals/ Unspecified number of CTs and phase of CTs	Qualitative/Interviews	Factors influencing CT participation	Individual	Factors related to participating in CTs by children and adolescents included a chance for cure and relationships with others.
Ingersgaard et al., 2018	Investigate adolescents' and parents' motivations and preferences for participation in the ALL2008 trials and adolescents' partaking in that decision	Denmark	1-17 years	Acute lymphoblastic leukemia	16 (five patients 12–17 years, six parents of adolescents, and five parents of patients 1–12 years)	Unspecified number of sites/ 2 CTs/ Phase III	Qualitative-explorative/ Interviews	Reasons for decision about participation, decision-making process/roles	Individual, Interpersonal	Adolescents and parents valued adolescents' Involvement with decision-making about enrollment, with over half of the adolescents being involved with the decision-making. Parents' wishes took precedence over adolescents' wishes in cases of conflict. Motivations and preferences of parents of children did not differ from those of adolescents, which consistently included altruism. Decisions were

										based on cure, toxicity and preference for standard or experimental treatment. Thoughts of an adverse outcome caused fear about regretting a decision, yet physician's expertise was trusted.
Johnston et al., 2010	Examine factors affecting CT participation by children less than 36 months old with central nervous system tumors	Canada	<36 months	Brain tumor	579 children	16 of 17 centers that treat all children with cancer in Canada/ Unspecified number of CTs/ Phase unspecified	Quantitative-retrospective cohort/ Data bank containing survey data from pediatric oncology centers	Year of diagnosis, age at diagnosis, sex, tumor location, histology, grade of malignancy	Individual	22% were enrolled in a CT. No factor was significantly associated with CT participation. The two main reasons for non-enrollment were no available study or none open at the site.
Lund et al., 2009	Identify racial/ethnic/age/sex representation in pediatric cancer treatment trials	United States	0-19 years	Solid or lympho hemato poietic	14,188 cases	Unspecified number of sites, CTs, and phases	Quantitative-Children's Oncology Group (COG), Surveillance, Epidemiology, and End	Race, ethnicity, age, sex	Individual	Each racial and ethnic group was proportionally representative. The following were significantly under-represented

							Results (SEER), and the US Census databases			for solid tumor subgroups: whites (especially males), adolescents, and Hispanics aged <10 years. The following were significantly underrepresented for lymphohematopoietic cancers: blacks, Hispanics, and adolescents. The most significantly under-represented groups were adolescents for both solid and lymphohematopoietic cancers and Hispanic females with lymphohematopoietic cancers.
Miller et al., 2013	Investigate adolescents' perspectives of understanding and decisions about participation in a pediatric phase I cancer study	United States	14-21 years	Unspecified	20 adolescents	6 children's hospitals/ Unspecified number of CTs / Phase I	Qualitative-Interviews	Understanding, decision making process, expectations, reasons for consent/non-consent	Individual	All adolescents enrolled in the phase I study, and 85% made the final decision about participation. Most (90%) understood voluntariness, risks, and right to

										withdraw. Most believed that the trial would increase their life expectancy. The most frequent reasons for participation were clinical benefit, an option, improved quality of life, and fewer side effects than their previous treatments.
Miller et al., 2014	Describe children's and adolescents' Involvement in informed consent discussions for phase I cancer trials and test associations between involvement in the discussions and age, patients' perceptions of difficulty understanding, and pressure to participate	United States	14-21 years	Unspecified	61 patients but only 8 interviewed patients	6 children's hospitals/ Unspecified number of CTs/ Phase I	Qualitative-Interviews	Physician to patient communication, perceived pressure	Interpersonal	Patients reported low difficulty understanding and perceived pressure. Proportion of physician to patient communication was not associated with perceived pressured.
Nooka et al., 2016	Evaluate patients by race, ethnicity, sex, and age in pediatric oncology phase 1 CTs	United States	0-19 years	Lymphohematopoietic	1348 children	Unspecified number of sites and CTs/	Quantitative-retrospective cohort/ Children's Oncology	Race, ethnicity, sex, and age	Individual	The following were underrepresented in phase I CTs: LH tumors (9.3%

				(LH) and solid malignancies (128 malignancies)		Phase I	Group (COG); Pediatric Brain Tumor Consortium (PBTC); Surveillance, Epidemiology, and End Results (SEER); US Census databases			observed vs 37% expected), Hispanics (12.6% observed vs 27% expected), particularly Hispanic females (6% observed vs 18% expected), the 0- to 4-year age group (11.7% observed vs 36.5% expected).
Oppenheim et al., 2005	Explore a mother's view of issues related to pediatric oncology phase I-II trials	France	7 years	Germinal tumor	1 mother	1 institute/ 1 CT/ Phase I-II	Qualitative-interview	Reasons for CT participation	Individual	CT participation was accepted by the mother to avoid surgery and gain more time with her child. The chance for cure and altruism did not affect her decision.
Pole et al., 2017	Determine proportion of children newly diagnosed with cancer enrolled on a therapeutic CT and identify factors associated with enrollment and non-enrollment	Canada	0-14 years	Unspecified	9204 children	17 sites; unspecified number of trials and phase	Quantitative-retrospective cohort; Cancer in Young People in Canada (CYP-C) national pediatric cancer population-	Trial availability, physician decision, age at diagnosis, sex, race, cancer type, distance from care facility	Trial, individual, interpersonal	Lack of available trial (52.2%) and physician decision (11.2%) were the most frequently cited factors for non-enrollment. The following were associated with non-enrollment: Asian and Arab/west Asian race,

							based database			astrocytoma diagnosis, and greater distance from cancer center.
Robertson et al., 2019	Explore health-care professionals' (HCPs) perspectives about obtaining informed consent for early-phase pediatric oncology trials	Australia and New Zealand	Patients under age 18 years	Unspecified	87 HCPs	Number of sites and CTs unspecified/ Early phase	Quantitative-Cross-sectional/ Survey	HCPs' perceived obstacles with obtaining consent, experiences of parents' decision-making about enrollment, experiences of providing information to parents, and perceptions of parent understanding	Individual, Interpersonal	61.6% of HCPs stated they did not try to influence parents' decisions about participation in early phase trials, but 23.3% stated that they told parents that their child would benefit. The main impediment in obtaining consent (32%) was parents' desire to try anything. Many parents seemed to misunderstand fundamental concepts about trials. 25.2% of HCPs believed that unclear information affected parents' decisions and that these decisions were influenced by their beliefs that the trials was the best hope, trust in the HCP, and

										perceived medical benefit.
Shah et al., 2014	Assess CT recruitment of children in Great Britain diagnosed with leukemia during 1980–2007 and evaluate factors that may influence recruitment	Great Britain	0-14 years	Acute lymphoblastic leukemia(ALL) and Acute Myeloid Leukemia(AML)	9147 ALL and 1466 AML patients who were eligible for national CTs	Unspecified number of sites/ 20 CTs/ Phase unspecified	Quantitative-National Registry of Childhood Tumours linked to birth registrations, Children's Cancer and Leukaemia Group records, Hospital Episode Statistics and Medical Research Council clinical trial registers	Birth weight, congenital malformation, socioeconomic status, and ethnicity	Individual	Recruitment rates for ALL varied significantly with congenital malformation (Down syndrome 61%, other malformations 80%, none 82%; p<0.001) and ethnicity (South Asian 78%, other minority groups 80%, white 85%; p<0.001). Rates for AML varied with birth weight (< 2500 g 48%, 2500–4000 g 69%, >4000 g 67%; p=0.001) and congenital malformation (Down syndrome 28%, other malformations 56%, none 63%; p<0.001). For ALL and AML, no patters by SES were found.
Shochat et al., 2001	Understand the utilization of oncology CTs by	United States	</=21 years old	Unspecified	5,141 children	251 hospitals/ Unspecifi	Quantitative-Surveys from >200 hospital	Disease, age, sex, race,	Individual	The following had highest CT participation: those

	children in 1987 and 1992					ed number of trials and phase	cancer registries	insurance, and geographical region		treated at pediatric centers (53.8%) compared to other institutions (25.1%) and ≤5 years old (63.7%; others, 42.0%). Adolescents had the lowest participation. Type of insurance did not affect protocol participation but patients who lacked insurance had lower rates of participation. White, non-Hispanic patients had the lowest participation rates.
Simon et al., 2006	Explore how altruism is discussed in the clinical research setting and whether it has any effect on CT participation	United States	1-18 years	Acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML)	140 consent sessions with parents	6 institutions that routinely treat pediatric leukemia/ at least 4 CTs/ Phase III	Qualitative/Audiotaped informed consent sessions and interviews	Discussion of altruism	Individual, interpersonal	Enrollment rate was not higher among those with consent session that involved altruistic discussion. Altruism was discussed in most consent sessions, was introduced most frequently by the clinician, and was multi-thematic most often

										focusing on benefits to science.
Surun et al., 2018	Explore access to early-phase pediatric oncology CTs for refractory solid tumors and identify reasons for lack of invitation or participation	France	Below 18 years of age	Solid tumors and lymphomas (leukemia excluded)	100 children	1 site/ Unspecified number of trials/ Phases I and II	Quantitative-retrospective chart review	Reasons for not inviting patients to participate, parents' refusal, inclusion failure	Trial, individual, interpersonal, organizational	52 patients were asked to participate in an early-phase trial(s). Twenty parents declined, primarily due to concerns about decline in quality of life or constraints. Fourteen patients were not included on trial due to clinical deterioration. Five patients had no available early-phase trials. 43 patients were not enrolled mainly due to exclusion criteria, desire for standard treatment, constraints, psychological reasons, and follow-up in another hospital.
Thomas et al., 2018	Evaluate if cancer CT availability is associated with low enrollment of early AYAs and determine the	United States	0-20 years	Unspecified	216 patients (58 early AYAs and 158 children)	1 academic children's hospital/ 26 CTs/	Quantitative-prospective observational cohort study	Age, sex, cancer type, ethnicity	Individual, organizational	No significant difference in CT existence or availability at the site was found between children

	effects of age and other factors upon enrollment					Mostly phase III				and eAYAs. Overall, there was a significantly lower likelihood of eAYAs, non-Hispanics, and patients with solid tumors to be enrolled.
Tulstrup et al., 2016	Examine if type of trial (intensification vs. reduction) with different toxicity profiles is associated with parents' and adolescents' decisions about CT enrollment	Nordic countries	1-17 years	ALL	1,853 patients	Unspecified number of sites/ 3 CTs/ Phase III	Quantitative-retrospective cohort study/ Nordic Society of Paediatric Haematology and Oncology database	Trial type	Trial, individual	Parents of children preferred intensification, but parents of adolescents preferred reductions. Adolescents were more likely to decline intensification trials than children.
Unguru et al., 2010	Investigate younger and older children's understanding of oncology research and their decision-making related to it	United States	7-18 years	Several types	37 children with cancer	1 children's medical center/Unspecified number of CTs and phase	Quantitative-Quality-of-assent instrument	Understanding and preferences of research participation	Individual	More children (73%) participated in CTs to help children in the future with cancer than to get well personally (60%).
van der Geest et al., 2016	Examine why parents agreed to have their child with incurable cancer participate in a CT during palliative period	Netherlands	3-15 years at death	Unspecified	24 parents of 16 deceased children	1 children's hospital/ Unspecified	Quantitative-retrospective cross-sectional/Questionnaires	Reasons for CT participation	Individual	The most frequent reasons for CT participation were treatment for future patients (n = 16), hope for a cure (n = 9), and

						number of CTs/ Phase unspecified				prolongation of child's life (n = 6).
Winestone et al., 2019	Identify patient and institutional factors associated with enrollment on AAML1031	United States	0 - >15 years	Acute myeloid leukemia (AML)	370 children at tertiary care hospitals associated with Children's Oncology Group (COG)	Unspecified number of sites/ 1 CT/ Phase III	Quantitative - retrospective cohort/Pediatric Health Information System database (PHIS)	Race/ethnicity, sex, age, insurance type, acuity at presentation, region, zip-code poverty, zip-based low education	Individual	The following were less likely to enroll non-Hispanic Black patients compared to non-Hispanic White patients, patients with multi-system failure versus no system failure, and patients living in zip codes with lower poverty compared to zip codes with higher poverty, but this varied by race/ethnicity. Enrollment rates were similar across all age categories except infants who had a lower rate.
Woodgate & Yanofsky, 2010	Understand Canadian parents' decisions about their children's participation in cancer CTs	Canada	6 month-15 years at diagnosis and 3-17	Unspecified	31 parents from 30 families	1 outpatient pediatric cancer center/	Qualitative-Descriptive/Interviews	Reasons for CT participation	Individual, interpersonal	Six themes were noted: surrealness, the child's best interest, benefit to future families of children with cancer, acceptance

			years at time of study			Unspecified number of CTs/ Phase unspecified				of decision, single decision among several choices, trust.

CT(s) = clinical trial(s)

Table 3. Socioecological Levels Addressed

Author(s), Year	Trial	Individual	Interpersonal	Organizational	Community	Policy
Aristizabalet etal., 2015		X				
Barrera et al., 2005		X	X	X		
Byrne-Davis et al., 2010			X			
Crane, Haase & Hickman, 2019		X				
Deatrick, Angst & Moore, 2002		X	X			
Dechartres et al., 2011	X		X	X		
DeVries et al., 2010			X			
Dodgshun et al., 2014	X	X	X	X		
Donnelly et al., 2017		X				
Eiser et al., 2005		X				
Hinds et al, 2005		X				
Ingersgaard et al., 2018		X	X			
Johnston et al., 2010		X				
Lena et al., 2019		X				
Lund et al., 2009		X				
Miller et al., 2013		X				
Miller et al., 2014			X			
Nooka et al., 2016		X				
Oppenheim et al., 2005		X				
Pole et al., 2017	X	X	X			
Robertson et al., 2019		X	X			
Shah et al., 2014		X				
Shochat et al., 2001		X				
Simon et al., 2006		X	X			
Surun et al., 2018	X	X	X	X		
Thomas et al., 2018		X		X		
Tulstrup et al., 2016	X	X				
Unguru et al., 2010		X				
van der Geest et al., 2016		X				
Woodgate & Yanofsky, 2010		X	X			

Manuscript #2

Trial-level Factors Affecting Accrual and Completion of Oncology Clinical Trials: A Systematic Review (submitted for publication to *Contemporary Clinical Trials*)

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Trial-level Factors Affecting Accrual and Completion of Oncology Clinical Trials: A Systematic Review

Abstract

Background: Cancer is the second-leading cause of death in the United States. Clinical trials translate basic science discoveries into treatments needed by cancer patients. Inadequate accrual of trial participants is one of the most significant barriers to the completion of oncology clinical trials.

Objective: The purpose of this study was to investigate trial-level factors that affect accrual and/or completion of oncology clinical trials, identify gaps in the literature, and indicate opportunities for future research.

Design: A systematic review of the literature on trial-level factors that affect accrual and/or completion of oncology clinical trials was performed. Searches in PubMed and Scopus identified 6,582 studies. Based on eligibility criteria, 16 studies were selected for the review. Results were analyzed according to the following: a) background factors, b) disease-related, c) treatment-related, and d) trial design.

Results: Background factors that were investigated in relation to oncology clinical trial accrual and/or completion included sponsor, number and location of participating institutions, competing trials, time of trial opening, and fast-track status. Disease-related factors included the annual incidence and type(s) of targeted cancer. Several types of treatment such as drugs, radiation and surgery were examined in the studies. Trial design factors included trial development time, eligibility criteria, randomization, sample size, trial phase, placebo use, and required protocol procedures and their timing.

Conclusion: With low patient participation rates in oncology clinical trials that hold promise for future treatments, it is imperative that trial-level factors affecting accrual be identified and addressed to facilitate the completion of trials.

Keywords: Clinical trial, oncology, cancer, enrollment, accrual

Trial-level Factors Affecting Accrual and Completion of Oncology Clinical Trials: A Systematic Review

1. Introduction

Cancer is the second-leading cause of death in the United States with approximately 606,520 deaths expected in 2020 (American Cancer Society [ACS], 2020). As pressure has escalated to expeditiously translate basic science discoveries into treatments that are urgently needed by cancer patients, the increased number of oncology clinical trials and exorbitant costs of conducting these trials have resulted in challenges to their completion. According to ClinicalTrials.gov, approximately 2,800 oncology clinical trials opened in 2015. This number grew to over 4,600 in 2019 (National Library of Medicine [NLM], 2020). The median cost of clinical trials for oncology drugs approved by the Federal Drug Administration (FDA) in 2015-2017 was $37.1 million per trial (interquartile range = $17.0 - $60.4 million) (Hsiue et al., 2020).

With growth in the number of oncology clinical trials and limited resources to support the conduct of these trials, inadequate accrual of trial participants has become one of the most significant barriers to the completion of clinical trials. Only 3-8% of oncology patients participate in clinical trials (ACS Cancer Action Network, 2018). In addition, approximately 20% of oncology clinical trials fail to complete because of inadequate accrual (ACS Cancer Action Network, 2018). Patient accrual is a significant metric in determining the success of a clinical trial, as achieving the targeted sample size is required for valid results (Melnyk & Morrison-Beedy, 2012). Clinical trials are too frequently terminated early or extended due to inadequate accrual. This adversely impacts the financial and other resources of cancer trial sponsors and participating sites (Steinman et al., 2017). Most importantly, trials that are delayed or terminated early impede the ultimate goal of providing effective cancer therapies to patients who urgently need them.

In 2010, the Institute of Medicine (IOM) called for a substantial improvement in the efficiency, completion, and prioritization of clinical trials (IOM, 2010). To accomplish these objectives, precise predictions about a trial's accrual and completion are vital in this time of limited research funding for governmental, academic, and corporate entities (Schroen et al., 2010). These precise predictions to meet the IOM's objectives are only possible through a comprehensive understanding of the factors that affect accrual and completion of oncology clinical trials. The literature demonstrates that factors impacting accrual and completion of oncology clinical trials operate at the individual, interpersonal, organizational, community, and policy levels. Although many researchers have investigated factors at these levels and developed interventions such as patient navigation and communication training to address barriers, accrual and completion of clinical trials remain inadequate (Ahaghotu et al., 2016; Fouad et al., 2016; Hurd et al., 2017; Ling et al., 2000; National Conference of State Legislatures , 2017; Wuensch et al., 2017; Yusuf, 2004). It is unclear whether studies have adequately explored factors at the trial level that may affect successful accrual and trial completion, e.g., eligibility criteria, planned sample size, phase of study, study design, and use of randomization.

The purpose of this systematic review was to examine the empirical literature to investigate trial-level factors that affect accrual and/or completion of oncology clinical trials, identify gaps in the literature, and indicate potential opportunities for future research. The following research question guided the review: Among studies that analyzed large data sets of clinical trials, which trial-level factors influenced accrual and/or completion of oncology trials?

2. Methods

The authors consulted with a medical reference librarian to determine the best approach to search the literature for applicable studies. The PRISMA statement guided the systematic selection of literature included in the sample, and a PRISMA flow chart detailing the process was created (see Figure 1) (Moher et al., 2009). PubMed and Scopus databases were searched on February 24, 2020 for relevant publications. There were no date delimiters. The following search terms with appropriate Boolean operators in titles and abstracts were applied: (*cancer OR oncology) AND ("clinical trials" OR "clinical research trials" OR "therapeutic trials") AND (enrollment OR accrual OR recruitment) AND ("eligibility criteria" OR inclusion OR exclusion OR methodology OR design OR "randomized controlled trials" OR "randomized control trials" OR RCTs OR barriers OR challenges OR facilitators OR "facilitating factors" OR factors OR correlates OR pragmatic OR feasibility).* Publications were limited to the English language published in peer-reviewed journals. The reference lists of retrieved publications were also hand searched for additional applicable primary sources.

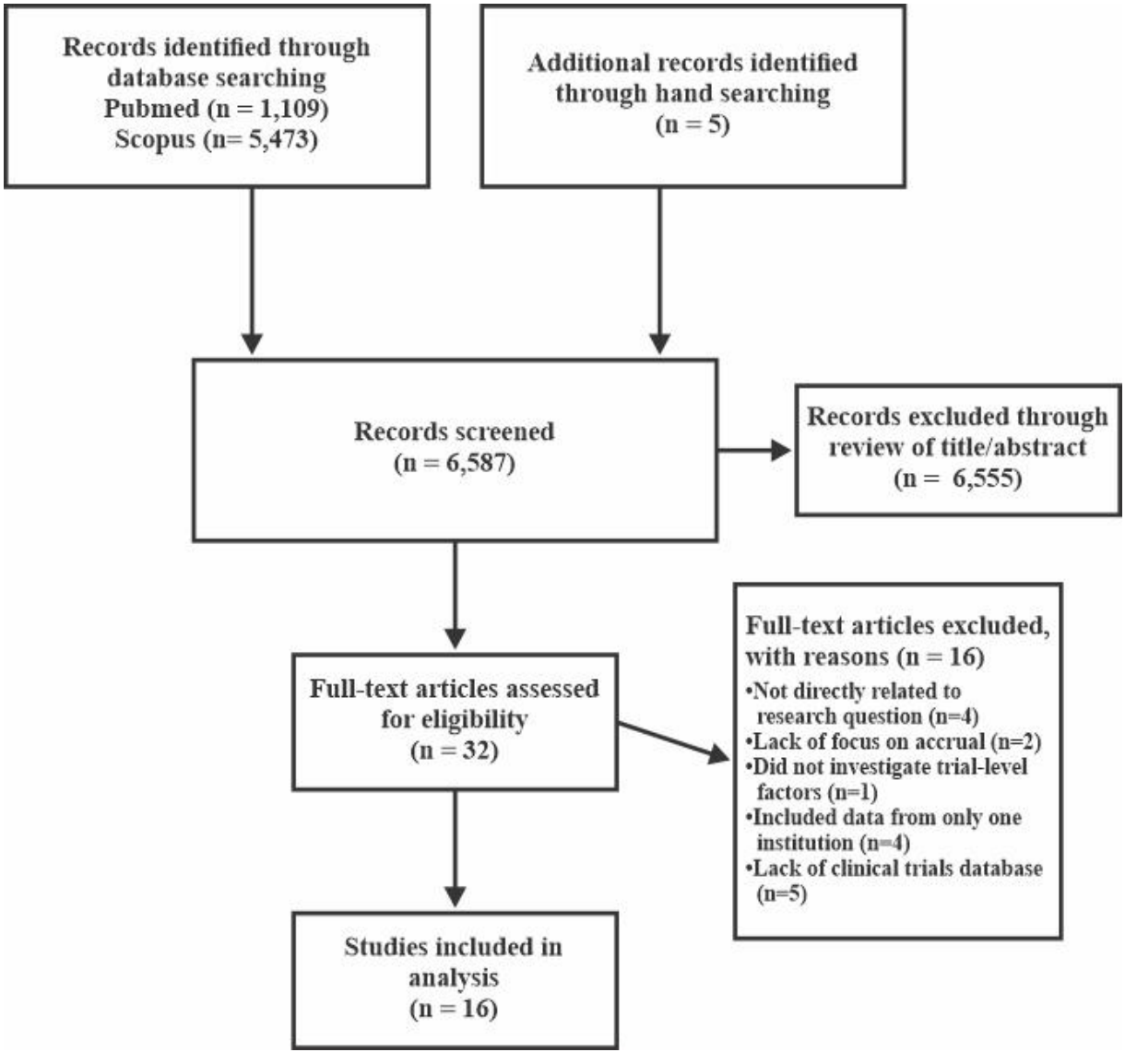

Fig. 1. Flow diagram for literature selection and inclusion.

The initial search produced 6,582 citations (PubMed = 1,109 and Scopus = 5,473). Five additional citations for peer-reviewed articles were identified from hand searching. The titles and abstracts of the publications were evaluated for relevancy based on inclusion and exclusion criteria. Studies were included if they were: a) empirical studies that analyzed trial-level factors that influenced accrual and/or completion of oncology trials and b) studies that analyzed data from state, regional, national, or

international clinical trial databases. Excluded were studies that investigated both oncological and non-oncological clinical trials, utilized a clinical trials database specific to a single institution or network of local institutions, or only examined individuals' perceptions of trial-level factors that influenced accrual and/or completion of oncology clinical trials. Also excluded were qualitative studies, literature reviews, meta-analyses, dissertations, narratives, commentaries, workshop proceedings, and expert recommendations addressing trial-level factors. Upon evaluation, 6,555 citations were removed due to ineligibility based on the review of titles and abstracts. Of the 32 remaining full-text publications, 16 met criteria to be included in the study sample. Of note, Scopus did not contain any eligible publications that were not already found in PubMed.

The results and discussion of this review were organized according to the themes of Bennette et al.'s (2016) conceptual model of trial-level factors associated with low trial accrual. The model's main themes encompass the following: a) background factors, b) disease-related, c) treatment-related, and d) trial design. Background includes factors such as competition from other clinical trials and insurance coverage of patient procedures associated with clinical trials. Disease-related include factors such as annual incidence of cancer and cancer stage. Treatment-related include factors such as type of treatment (e.g. chemotherapy or surgical) and use of a single modality (e.g. radiation) as opposed to multiple modalities (e.g. chemotherapy and radiation). Trial design includes factors such as eligibility criteria and use of randomization.

3. Results

3.1 General Overview

Trial-related factors that impact a study's accrual and/or completion were examined in several contexts such as study design, population, type of cancer, sample size, trial phase, and database (Appendix 1). Fifteen studies were quantitative, and one study had a mixed methods design. All studies (n = 16) were at level 4 (e.g. retrospective cohort study) according to Melnyk's hierarchy of evidence (Melnyk & Morrison-Beedy, 2012). Also, all studies examined oncology clinical trials for adults, with only three including trials for pediatrics. The majority of the studies (n = 10) did not limit inquiry to a specific type(s) of cancer. Three studies specified multiple types of cancer. The remaining studies (n = 3) specified one type of cancer, two of which were lung cancer. Sample size ranged from 16 to 12,875 clinical trials. Almost half of the studies (n=7) included a sample of phase I, II, and III trials. Most of the remaining studies had a sample of phase I and II trials (n = 2) or phase II and III trials (n = 3). Two studies had a sample of only phase III trials. All studies (n = 16) used a national database(s) as the source of clinical trial data. The most commonly used database (n = 8) was ClinicalTrials.gov. Only one study utilized a theoretical or conceptual framework, which was Bennette et al.'s (2016) conceptual model of trial-level factors associated with low trial accrual.

3.2 Conceptual Model of Trial-Level Factors Associated with Low Trial Accrual

To organize the results and discussion, the authors of this systematic review utilized Bennette et al.'s (2016) model that conceptualizes trial-level factors associated with low trial accrual according to themes. Of the 16 studies included in the final analysis, the following themes were addressed: background factors (n = 10), 8 disease-related (n = 11), 5 treatment-related (n = 8), and trial design (n = 14).

3.2.1 Background Factors

Background factors affecting oncology clinical trial accrual and/or completion were reported in the literature. Sponsor/funder was one of the examined background factors. Amongst published phase III oncology clinical trials, industry sponsored trials were among the fastest accruing (Ruther et al., 2015). Also, with poor accrual being the most common cause of early terminated clinical trials, industry sponsored immune checkpoint inhibitor trials were significantly less likely to terminate early compared with those that were sponsored by federal and academic institutions (Khunger et al., 2018). Worldwide, industry sponsored trials were also significantly more likely to attain accrual sufficiency than government funded trials (Paul et al., 2019). Consequently, government sponsorship was a predictor of study failure of randomized clinical trials in radiation oncology (Nguyen et al., 2018).

Clinical trial development time was another examined background factor. Cheng et al. (2010) measured trial development time from initial submission of the trial to the NCI Cancer Therapy Evaluation Program (CTEP) to the opening of the trial. Oncology clinical trials developed in < 12 months were significantly more likely to meet accrual targets than those developed in 12-18 months. In contrast, oncology clinical trials developed in > 24 months were significantly less likely to meet accrual targets than those developed in < 12 months and 12-18 months.

Other background factors affecting oncology clinical trial accrual and/or completion were the number and location of participating institutions. Clinical trials conducted at a single institution were more likely to fail to complete than those conducted at multiple institutions (Nguyen et al., 2018; Stensland et al., 2014). Regarding location of participating sites, data from one study suggested that trials performed outside of the United States or both within and outside of the United States were more likely to

complete than those conducted solely in the United States (Stensland et al., 2014). Findings from another study demonstrated that the continental location of the principal investigator and trials conducted internationally were not significantly associated with study failure (Nguyen et al., 2018). Multinational trials were among the fastest accruing. However, there were no significant differences in accrual time between trials conducted in the United States compared to Europe among phase III oncology clinical trials (Ruther et al., 2015).

Competing trials, time of trial opening, and fast-track status were background factors that were investigated in relation to oncology clinical trial accrual and/or completion. Among adult National Clinical Trials Network (NCTN) (cooperative group) cancer clinical trials, the number of competing trials was a predictor of low accrual, with a higher number of competing trials associated with low accrual (Bennette et al., 2016). Nguyen et al. (2018) examined completed and incomplete randomized clinical trials in radiation oncology that opened in consecutive time periods. Significantly more trials failed during each consecutive time period (11.8% before 2007, 34% in 2007-2008, and 39.5% in 2009-2012). Hernandez-Torres et al. (2019) found trial start date prior to 2003 was associated with lower accrual of older adults. Fast track review status designated by the Food and Drug Administration (FDA) was not associated with low accrual (Bennette et al., 2016).

3.2.2 Disease-related

Lower annual incidence of the targeted type(s) of cancer and larger required enrollment fraction of the eligible patient population were predictors of low accrual (Bennette et al., 2016). Among NCI Cooperative Group phase III clinical trials, fewer breast cancer trials terminated due to inadequate accrual (Korn et al., 2010). Also, Ruther

et al. (2015) found the fastest accruing trials among phase III oncology clinical trials were those for breast cancer. However, Hernandez-Torres et al. (2020) demonstrated breast cancer clinical trials were associated with lower accrual of older adults. Among the older population, clinical trials for central nervous system cancers were associated with higher accrual (Hernandez-Torres et al., 2020). There was no significant difference in adequate accrual between urological and nonurological trials. However, kidney cancer trials accrued the best, whereas bladder cancer trials accrued the worst among urological trials (Paul et al., 2019). Predictors of low accrual were trials for common solid cancers as opposed to rare solid or liquid tumors and those with inclusion criteria that targeted multiple types of cancer (Bennette et al., 2016).

There were mixed results for the association between accrual and metastatic disease. In two studies, metastatic disease, compared to nonmetastatic disease, was a predictor of low accrual (Bennette et al., 2016; Lemieux et al., 2008). Also, early stage cancer was significantly associated with enrollment of older persons (Gross et al., 2005). However, in another study accrual was better for trials that involved advanced disease (Lyss & Lilenbaum., 2009).

3.2.3 Treatment-related

Treatment-related factors were investigated in the literature. Clinical trials that investigated immune checkpoint inhibitors were less likely to terminate early compared to those that investigated other types of oncology drugs, but the results were not statistically significant (Khunger et al., 2018). Predictors of low accrual included non-targeted therapy and radiation therapy (Bennette et al., 2016). Accrual was poorer for Radiation Therapy Oncology Group trials than other cooperative groups and for multimodality trials that did not primarily include systemic treatment (Lyss & Lilenbaum,

2009). Whereas Bennette et al. (2016) found the use of an investigational new drug to be a predictor of low accrual, other researchers (Korn et al. 2010; Lyss & Lilenbaum, 2009) found no significant difference in inadequate accrual between clinical trials that involved a new investigational therapy and those that did not. Clinical trials involving standard therapy, with or without a new therapy, had better accrual than those that did not incorporate standard therapy (Lyss & Lilenbaum, 2009). Trials that compared surgery to other types of therapies such as drugs were associated with low accrual and/or trial failure, and multimodality clinical trials were associated with low accrual (Bennette et al., 2016; Nguyen et al., 2018).

3.2.4 Trial Design

Our findings suggest eligibility criteria, randomization, sample size, trial phase, placebo use, and required protocol procedures and their timing affect accrual and/or completion of oncology clinical trials. The main reported reasons for slow accrual for phase I oncology clinical trials were safety/toxicity (48%), design/protocol issues (42%) and eligibility criteria (41%). In addition, the main reasons for slow accrual for phase II oncology clinical trials were eligibility criteria (35%) and design/protocol issues such as required procedures, treatment schedule, and overall complexity of the trial (33%) (Massett et al., 2016). Increased trial complexity defined by a higher number of targeted diseases in inclusion criteria, interventions and study locations was associated with low accrual (Bennette et al., 2016).

Sample size and phase of the clinical trial were two trial design factors that affected accrual and/or completion of oncology clinical trials, although with mixed results in studies. Bennette et al. (2016) found larger sample size was a predictor of low accrual. However, Khunger et al. (2016) demonstrated the sample size goal (not reported)

was higher for completed trials with a median sample goal of 47 compared with that of terminated trials with a median of 9. They also found phase II and phase III trials were significantly less likely to terminate early compared with phase I trials, with low accrual being the most common reason for early termination for all trials. However, Bennette et al. (2016) demonstrated phase III was a predictor of low accrual. Other studies did not show accrual varied by trial phase (Paul et al., 2019).

Eligibility is another trial design factor that affects oncology clinical trial accrual. Overall, eligibility criteria that place burdens on patients, such as those that require the collection of tissues that are not involved with standard of care, were associated with low accrual (Bennette et al., 2016). In a study of phase I to III molecular trials, the total number of eligibility criteria was significantly associated with the enrollment period's duration in trials that had at least 35 enrolled patients (Kim et al., 2015).

Specific types of eligibility criteria, which have the potential to considerably limit accrual, were examined in the literature. In a study utilizing ClinicalTrials.gov, the following exclusion criteria were in early phase clinical trials for breast, colorectal, or lung cancers: age > 75 years (6%), history of prior malignancies (86%), autoimmune disease with exceptions of vitiligo and alopecia (48%), any central nervous system (CNS) metastasis (38%), symptomatic CNS metastasis (34%), human immunodeficiency virus (31%), hepatitis B or C (21%), and atrial fibrillation (20%). Renal and hepatic eligibility criteria were prevalent, such as creatinine <1.5 of the upper limit of normal (ULN) (35%). Compared to targeted therapy clinical trials, chemotherapy clinical trials were more likely to have exclusion criteria pertaining to CNS metastasis and history of other malignancies. Industry-sponsored trials were more likely to have liver function exclusion

criteria than those with other types of sponsors such as the NCI or universities (Duma et al., 2019).

Other specific types of eligibility criteria were examined in the literature. In a study of Eastern Cooperative Oncology Group (ECOG) -affiliated lung cancer clinical trials, 80% excluded prior cancer diagnosis: active cancer (16%), any prior cancer (14%), within 5 years (43%), and within 2-3 years (7%). These exclusions were more common for phase II and III clinical trials (85%) compared to pilot/phase I clinical trials (25%). Estimated proportion of excluded prior lung cancer patients was up to 18% (>5% for 2/3 of clinical trials and >10% for approximately 1/3 of clinical trials). Exclusion criteria related to prior cancer treatment were present in 39% (20) of clinical trials, with 29% (15) excluding chemotherapy or other therapy and 10% (5) excluding both that and radiotherapy (Gerber et al., 2014). Although in one study (Bennette et al., 2016) performance status (function, symptom burden, need for care) in exclusion criteria was not found to be associated with poor accrual in adult oncology clinical trials, performance status in exclusion criteria was significantly associated with enrollment of older persons in another study (Gross et al., 2005). However, exclusion criteria related to renal dysfunction were associated with lower accrual of older adults (Hernandez-Torres et al., 2020).

Randomization and use of placebo were other trial factors studied regarding accrual and/or trial completion. Bennette et al. (2016) found the use of randomization to be associated with low accrual. This was further supported by pediatric nonrandomized clinical trials having adequate accrual (Korn et al., 2010). However, in another study, randomization was not found to affect accrual or the early termination of studies (Paul et al., 2019). The use of a placebo also had mixed results. In a study of breast cancer clinical

trials by Lemieux et al. (2008), trials with no placebo were associated with better recruitment than those with a placebo. However, Bennette et al. (2016) found no associations between low accrual and placebo use. Also, Ruther et al. (2015) reported there were no significant differences in accrual time between placebo and non-placebo use in published phase III oncology clinical trials.

Required protocol procedures and their timing affected accrual in oncology clinical trials. The requirement of obtaining a tissue sample to assess eligibility was a predictor of low accrual (Bennette et al., 2016). Better recruitment was associated with an allowed 12 week or more interval vs. less time from diagnosis, surgery, or end of previous therapy for nonmetastatic clinical trials (Lemieux et al., 2008). There was no association between blinding and length of follow-up and poor accrual (Bennette et al., 2016).

Other trial design factors were investigated in the literature. There were no associations for accrual related to age group, sex, intervention model, therapeutic compared with nontherapeutic treatment, masking compared with open label, primary purpose, and specialty (Paul et al., 2019). Among randomized clinical trials in radiation oncology, lack of accrual was the main reason for trial failure, and a safety endpoint as an outcome was associated with trial failure (Nguyen et al., 2018).

4. Discussion

In this systematic review, we examined the empirical literature to investigate trial-level factors that affect accrual and/or completion of oncology clinical trials, identified gaps in the literature, and suggest potential opportunities for future research. One of the most striking findings was the limited number of studies that utilized large databases, lest ClinicalTrials.gov, to examine trial-level factors that affect accrual and/or completion of

oncology clinical trials. Researchers are no longer limited to studying clinical trials merely as a single trial or trials which involved a single or few institutions. ClinicalTrials.gov allows researchers to investigate clinical trials as an enterprise since it is the largest and most comprehensive clinical trial database in the world (Fain, 2018).

There was the lack of a standard definition of adequate or inadequate accrual. For example, Paul et al. (2019) appeared to define insufficient accrual as anything less than 100% of the trial's minimum projected sample size whereas Bennette et al. (2016) defined low accrual as less than 50% of the target sample size. Different definitions for the outcome variable of adequate or inadequate accrual may partially explain discrepant results in the examined studies' results.

Background factors that were investigated in relation to oncology clinical trial accrual and/or completion included sponsor, number of participating institutions, location of the institutions, competing trials, time of trial opening, and fast-track status. The literature consistently demonstrated that industry-sponsored trials outperformed trials sponsored by other entities in accrual and completion. The pharmaceutical industry may have more financial resources to manage clinical trials at multiple worldwide institutions and invest in accrual strategies such as advertising and participant incentives such as travel reimbursements. Unsurprisingly, a higher number of NCTN-sponsored competing trials was associated with low accrual. Fast track review status designated by the FDA was not associated with low accrual which would be expected, given that fast tracking involves having study sponsors and the FDA working closely together to prioritize and expedite the conduct of clinical trials to get the investigational therapy approved and released to the market.

The type of cancer and its annual incidence were disease-related factors that were investigated. Except among the older population, clinical trials for breast cancer trials consistently outperformed those for other types of cancers in accrual, possibly resulting from the high incidence of breast cancer and public awareness campaigns for these clinical trials. Predictors of low accrual were common solid cancers as opposed to rare solid or liquid tumors. Overall, there are more standard therapies available for common solid cancers than liquid and rare solid tumors. Therefore, patients with common solid cancers have more standard therapy options and do not have to rely on an investigational therapy, resulting in lower accrual in clinical trials.

Several types of treatment were examined in the studies. Clinical trials involving radiation and surgery face challenges with accrual and/or completion. Patients may choose drug regimens, whether as standard therapy or in trials involving only drugs, to avoid the invasiveness and potential complications of a surgical procedure. Also, the proposed surgical procedure in a clinical trial may not have established efficacy in itself or compared to marketed drugs. In addition, patients may prefer drug regimens over radiation clinical trials because they do not want to complete frequent visits to a radiation facility as radiation therapy often entails daily administrations for many weeks. There were mixed results about accrual between clinical trials that involved a new investigational therapy and those that did not, likely due to the difference in toxicity profiles of the investigational agents.

The following trial design factors were investigated: trial development time, eligibility criteria, randomization, sample size, trial phase, placebo use, and required protocol procedures and their timing. Eligibility criteria was the most frequently investigated factor. Although they are necessary to exclude patients who have negative

prognostic factors and a high risk of adverse events, eligibility criteria can adversely impact accrual and/or trial completion. Each eligibility criterion needs to be evaluated to ensure it is supported by the scientific literature and not included just because it was contained in previous protocols (Malik & Lu, 2019). Duma et al. (2019) also recommends eligibility criteria to be relaxed once a drug's toxicity profile is better understood.

Although trial-level factors that affect accrual and completion of oncology clinical trials have been discussed in publications, there remain gaps in the literature. Several trial-level factors have not yet been investigated utilizing ClinicalTrials.gov outside of studies that are sponsored by NCTN, focus on urological and non-urological solid cancers, and investigate radiation. These trial-level factors include primary purpose, randomization, blinding, and placebo use. In addition, there is a need for studies that characterize the relative importance of various trial-level factors driving clinical trial accrual and/or trial completion and to test the impact of including and excluding these driving trial-level factors on accrual. Research is needed to determine if trial protocols developed to minimize the inclusion of trial-related factors known to be significant barriers result in successful accrual. The reviewed studies did not indicate if some trial-related factors were more influential than others based on the type of cancer targeted in clinical trials. In addition, although this systematic review examined diverse trial-related factors, the review did not address influential trial-related factors specific to patient demographics, except for older adults. Trial-related factors may differ in the way they affect accrual in clinical trials focused on different types of cancers or populations, such as pediatrics. Interventions to improve accrual may need to be tailored to clinical trials for specific types of cancers and populations.

Studies utilizing a mixed methods design may increase knowledge about trial-level factors that affect accrual and/or study completion. Mixed methods studies could explore participants' views of, and experiences with, trial-related factors to improve accrual and/or trial completion. This knowledge could assist researchers in developing and implementing efficient trial designs and effective interventions to increase accrual and completion of oncology clinical trials. These data would be helpful in determining which trial-related factors are modifiable.

We found that several of the examined studies had conflicting results about the association between trial-level factors and accrual and/or completion of oncology clinical trials. Therefore, more research is required to further elucidate these associations. Only eight of the sample articles utilized ClinicalTrials.gov, thus future researchers should consider use of this database when studying trial-level factors that affect accrual as having a larger sample sizes of clinical trials would increase generalizability of results. Furthermore, clinical trials for different types of cancer encounter distinct challenges to successful accrual. The majority of studies included in this systematic review did not specify a specific cancer, so future research is vital to address trial-level barriers to accrual associated with individual types of cancer. Also, since most of the studies in this review focused on adult oncology clinical trials, similar research is needed for clinical trials for other populations such as pediatrics. Finally, focused efforts on the development and implementation of interventions to address the trial-level factors that adversely impact accrual are needed. This research will need to involve careful reflection about the modifiability of trial-level factors. Improved accrual may contribute to successful completion of oncology clinical trials in a timely manner, reducing the waste of financial and other resources.

This systematic review has limitations. The literature search may not have included all available studies in the published literature because additional terms describing trial-level factors may have been omitted inadvertently. Moreover, since one investigator conducted the review, selected studies included in the final review could not be assessed for inter-rater reliability based on the inclusion and exclusion criteria.

5. Conclusion

With low patient participation rates in the increasing number of oncology clinical trials, it is imperative that trial-level factors affecting accrual be identified and interventions addressing these challenges be developed to facilitate the completion of trials. Following a theory-based evaluation and synthesis of research on trial-related factors that influence accrual in oncology clinical trials, this systematic review identified gaps in research in this area. To address the gaps in the literature, theoretically-based studies evaluating the association between trial-level factors and accrual/trial completion should be conducted. The use of theory guides the evaluation, analysis, and organization of data. In addition, researchers should simultaneously address background, disease-related, treatment-related, and trial design factors that influence accrual using innovative approaches, focusing on specific types of cancer and populations.

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Appendix 1. Literature matrix for trial-level factors affecting accrual and/or completion of oncology clinical trials

Author, Date	Study Purpose(s) Specific to Trial Factors and Accrual	Type(s) of Cancer	Sample Description, Size	Phase(s) of CTs	Database	Trial-related Factors	Results Specific to Trial Factors
Bennette et al., 2016	Evaluate associations and predictors between trial-level factors and low accrual in adult cooperative group cancer CTs (clinical trials)	Multiple	787 interventional, late phase, cooperative group adult oncology CTs that started in 2000-2011	II, III	Aggregate Analysis of ClinicalTrials.gov (AACT), Drugs@FDA Database, Surveillance, Epidemiology, and End Results (SEER) Program	Number of competing trials, treatment setting, intervention modality, therapeutic, targeted therapy, new investigational agent, priority status, metastatic setting, clinical setting, sample size, randomized design, phase, placebo, number of interventions, more than one condition, blinded, number of participating sites, eligibility limited by performanc	-Predictors of low accrual included the following: higher number of competing trials, phase III, higher enrollment percentage of eligible population, non-targeted therapy, radiation therapy, lower annual incidence of clinical condition, tissue sample required to assess eligibility, non-new investigational drug, metastatic setting, sample size, more than one condition, and common solid cancer. -Other factors associated with low accrual were multimodality, surgery, arduous eligibility criteria, randomization, and trial complexity including number of interventions, number of study locations, and more than one disease. -There were no associations between low accrual and placebo use, length of follow-up, fast track review, blinding, and eligibility limited by performance status.

						e status, eligibility limited by age	
Cheng et al., 2010	Investigate trial development time on accrual to oncology CTs	Multiple	419 therapeutic, non-pediatric oncology CTs activated between 2000-2004 and sponsored by National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP)	I, I/II, II, III	CTEP Protocol and Information Office database with input from Clinical Data Update System and Clinical Trials Monitoring Service	Trial development time	-CTs developed in < 12 months were significantly more likely to meet accrual targets than those developed in 12-18 months. -CTs developed in > 24 months were significantly less likely to meet accrual targets.
Duma et al., 2019	Identify comorbidities that adversely impact recruitment of patients with breast, colorectal, or lung cancers in early phase CTs	Breast, colorectal, lung	1,103 early phase therapeutic cancer CTs from 2000-2015	I, Ib/II, II	ClinicalTrials.gov	Trial phase, target disease, anticancer therapy, line of therapy, location, sponsor, inclusion and exclusion criteria (age limits, comorbidities, organ function)	-The CTs had the following exclusion criteria: age > 75 years (6%), history of prior malignancies (86%), autoimmune disease with exceptions of vitiligo and alopecia (48%), any central nervous system (CNS) metastasis (38%), symptomatic CNS metastasis (34%), human immunodeficiency virus (31%), hepatitis B or C (21%), and atrial fibrillation (20%). -Renal and hepatic eligibility criteria were prevalent such as creatinine <1.5 of the upper limit of normal (ULN) (35%). =Compared to targeted therapy CTs, chemotherapy CTs were more likely to have exclusion criteria pertaining to CNS metastasis and history of other malignancies. -Trials sponsored by industry were more likely to have liver function exclusion criteria than those with other types of sponsors.
Gerber et al., 2014	Determine prevalence of prior cancer-related exclusion criteria and their impact on lung cancer CT accrual	Lung	51 lung cancer CTs sponsored or endorsed by the Eastern Cooperative Oncology Group (ECOG) thoracic committee	I/pilot, II, III	ECOG thoracic committee website; linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database	Eligibility criteria related to prior cancer and its treatment	=41 (80%) of ECOG -affiliated lung cancer CTs excluded prior cancer diagnosis: active cancer (16%), any prior cancer (14%), within 5 years (43%), within 2-3 years (7%)). -Estimated proportion of excluded prior lung cancer patients was up to 18% (>5% for 2/3 of CTs and>10% for approximately 1/3 of CTs). -Exclusion criteria related to prior cancer treatment were present in 20 (39%) of CTs, with 15 (29%) excluding chemotherapy or other therapy and 5 (10%) excluding both that and radiotherapy.
Gross et al., 2005	Ascertain the effect of protocol factors on enrollment of older patients in cancer CTs	Lung, breast, colorectal, prostate	36,167 patients enrolled in 33 National Cancer Institute (NCI)-sponsored	Unspecified	NCI Clinical Trial Evaluation Program database; NCI	Cancer type, performance status, comorbiditi	-Cancer type (early stage) and performance status in exclusion criteria were significantly associated with enrollment of older persons.

			cooperative group cancer CTs in 1996-2002		Physician Data Query (PDQ) clinical trial database	es excluded stage	
Hernandez-Torres et al., 2020	Determine if exclusion criteria are associated with low accrual of older adults to cancer CTs	Multiple	69 Canadian Cancer Trials Group studies that started in 1990-2010	III and randomized phase II	Canadian Socioeconomic Management System database	CT start date, cancer type, and exclusion criteria	=The following CT factors were associated with lower accrual of older adults: start date prior to 2003, breast cancer indication, and exclusion criteria related to renal dysfunction. =Central nervous system CTs were associated with higher accrual of older adults.
Khunger et al., 2018	Ascertain the frequency and factors associated with withdrawal and early termination of oncology CTs, focusing on immune checkpoint inhibitor (ICI) trials	Multiple	12,875 adult, interventional, randomized oncology trials; 350 ICI trials (2011 to 2015)	I, I/II, II, II/III, III	ClinicalTrials.gov	Type of cancer, type of treatment, sponsor, phase, accrual goal	- Low accrual was the most common reason for early termination for all trials. -5% of CTs were early terminated, and 3.5% were withdrawn. - 4% of ICI trials were early terminated, and 1.4% were withdrawn. - ICI trials were less likely to early terminate compared with all other oncology drug trials, but the results were not statistically significant. - Institution-sponsored trials were significantly more likely to early terminate compared with industry sponsored trials. - Phase II and phase III trials were significantly less likely to early terminate compared with phase I trials. - The accrual goal was higher for completed trials with a median 47 compared with terminated trials with a median 9.
Kim et al., 2015	Investigate implications of eligibility criteria in phase I to III molecular trials	Multiple	67 CTs conducted by Novartis Oncology in the United States from 2006 to 2013	I, II, III (only II and III in final analysis)	Use of ClinicalTrials.gov was not successful; Manual review of trials	Number and characteristics of eligibility criteria	Overall, the total number of eligibility criteria did not affect enrollment duration. However, it was significantly associated with the enrollment period's duration in trials that had at least 35 patients.
Korn et al., 2010	Examine accrual for National Cancer Institute (NCI) Cooperative Group phase III CTs between 2000-2007	Multiple	191 CTs activated in 2000-2007 *includes 42 pediatric CTs	III	Unspecified	Disease site, use of randomization, use of investigational new drug	An estimated 22.0% of all adult and pediatric CTs would be terminated due to inadequate accrual, with 1.7% (2,991) of the total enrolled accrued patients being on these CTs. Fewer breast cancer CTs terminate due to inadequate accrual. 2 of 42 pediatric trials had poor accrual. None of the pediatric nonrandomized CTs had inadequate accrual. There was no significant difference in inadequate accrual between CTs that involved an investigational new drug and those that did not.
Lemieux et al., 2008	Identify protocol characteristics of breast cancer CTs associated with poor recruitment	Breast	688 CTs opened between 1997-2002 in Ontario	I, II (or I and II), III (or (II and III)	Questionnaires to cooperative groups and pharmaceutical companies; missing data obtained from	Phase, randomization, control group, blinding, intervention,	The following protocol factors were associated with better recruitment: no placebo vs. placebo, nonmetastatic vs. metastatic, and allowed 12 week or more interval vs. less from diagnosis, surgery, or end of previous therapy for nonmetastatic CTs.

					publications (ClinicalTrials.gov and websites for cooperative groups and pharmaceutical companies were used only to verify if trials should be included if no completed questionnaire received)	intervention available outside the study, sponsor, location, number of participating sites, menopausal status, metastasis, minimal age limit, maximal age limit, number of eligibility criteria, premature dosing, maximum interval between diagnosis/surgery/end of therapy and enrollment, extra baseline tests, extra follow-up tests	
Lyss & Lilenbaum, 2009	Ascertain accrual patterns among cooperative group non-small cell lung cancer CTs	Non-Small Cell Lung	16 randomized CTs sponsored by the main cooperative groups in North America that closed accrual between 2000-2005	II, III	Community Oncology and Prevention Trials Research Group; National Cancer Institute of Canada	Extent of disease, trial phase, # of modalities	-Accrual was poorer for Radiation Therapy Oncology Group trials than other cooperative groups and for multimodality trials that did not primarily include systemic treatment. -Accrual was better for trials that involved advanced disease. -CTs involving standard therapy regardless of the inclusion of a new therapy had better accrual.
Massett et al., 2016	Determine reasons for slow accrual in early phase trials sponsored by the National Cancer Institute	Multiple	135 corrective action plans from 2011-2013 *11 (8%) were pediatric trials and 5 (4%)	I, II	Corrective action plans and NCI Cancer Therapy Evaluation Program	Study design/protocol, eligibility	-The main reported reasons for slow accrual for phase I CTs were safety/toxicity (48%), design/protocol issues (42%) and eligibility criteria (41%). The main reasons for phase II CTs were eligibility criteria (35%) and design/protocol issues (33%).

			were for trials for both adults and children		(CTEP) database		
Nguyen et al., 2018	Compare characteristics of completed and incomplete randomized CTs in radiation oncology and identify predictors of trial failure	Multiple	134 trials that were registered from 2007-2010	I, II, III	ClinicalTrials.gov	Cooperative group involvement, sponsor, PI location, number of open institutions, international study, PI's h-index, disease site, age, sex, main comparators, number of study arms, masking, blinding, primary purpose, anticipated enrollment, final enrollment, primary outcome	-Lack of accrual (57.5%) was the main reason for trial failure -Significantly more trials failed with each consecutive time period (11.8% before 2007, 34% in 2007-2008, and 39.5% in 2009-2012). -Predictors of failure were surgical comparator, government sponsorship, safety endpoint, and studies starting after 2006 via univariate analysis. -Via multivariate analysis, predictor of failure was surgical trials, and predictor of trial success was behavioral trials.
Paul et al., 2019	Determine predictors of adequate accrual in urological and nonurological solid cancer trials	Prostate, colorectal, kidney, bladder, testicular, breast, lung	326 trials in 2000-2006	III and IV	ClinicalTrials.gov; International Standard Randomised Controlled Trial Number Registry (United Kingdom based); online databases such as PubMed and Google Scholar	Age group, nonrandomized vs randomized, funding source, sex, intervention model, therapeutic vs nontherapeutic, masking vs open label, primary purpose, specialty, phase	-63% of trials reported sufficient accrual. -There was no significant difference in adequate accrual between urological and nonurological trials. -Kidney cancer trials accrued the best whereas bladder cancer trials accrued the worst. -Compared to government funded trials, industry sponsored trials were significantly more likely to attain adequate accrual. -No other factors (e.g. age group, nonrandomized vs randomized, intervention model, therapeutic vs nontherapeutic, masking vs open label, primary purpose, specialty, phase) were significantly associated with sufficient accrual.

Ruther et al., 2015	Determine accrual speed in published phase III oncology CTs across geographical locations and identify its influential factors	Multiple	546 phase III oncology therapeutic CTs published in 2006-2010 *included 4% pediatric/young adult CTs	III	OVID-Medline	Country, type of cancer, funder, arms, and result	-The fastest accruing CTs were those that had the following characteristics: multinational, breast cancer indication, industry sponsorship, and equivalency. -There were no significant differences in accrual time between placebo and non-placebo CTs and those CTs conducted in the United States versus Europe.
Stensland et al., 2014	Evaluate study factors associated with trials that fail to complete	Multiple	7776 adult interventional cancer trials	I/II, II, III	ClinicalTrials.gov	Number of sites, sponsor, location	-The most common reason for CTs to fail to complete was poor accrual (39%). -The following trials were more likely to not complete: ---Single center versus multicenter trials ---Industry-sponsored versus federally funded trials -Trials performed outside of the United States or both within and outside of the United States were more likely to complete than those conducted solely in the United States.

CT=clinical trials

Manuscript #3

Predictors of Early Termination of Pediatric Oncology Clinical Trials Due to Poor Accrual: An Exploratory Analysis

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Predictors of Early Termination of Pediatric Oncology Clinical Trials Due to Poor Accrual: An Exploratory Analysis

Abstract

Background: Poor accrual is a significant barrier to the completion of pediatric oncology clinical trials. Early terminated or prolonged trials have substantial financial implications and hinder the availability of new effective pediatric cancer therapies in a timely manner. The purposes of this study were to 1) describe patterns in the presence of variables and completeness of data entry for variables in the ClinicalTrials.gov database over time for pediatric oncology trials and 2) investigate trial-related factors that may affect early termination of pediatric oncology clinical trials due to low accrual.

Procedure: ClinicalTrials.gov data were extracted from Aggregate Analysis of ClinicalTrials.gov (AACT). Descriptive statistics and multiple logistic regression were used to analyze the data.

Results: The number of variables increased with each subsequent period, except the most recent period (150, 159, 160 and 139, respectively). Of the 160 examined variables, 129 (81%) variables had 100% of applicable data in each period. None of the following clinical trial characteristics were associated with or predictive of early termination of pediatric oncology trials due to low accrual: enrollment, primary purpose, intervention type, phase, interventional model, allocation, arm type, number of arms, masking, primary end points, number of primary outcomes, sponsor, number of participating facilities, and primary disease. However, odds for studies to terminate early were 3.9 times higher for those that used a data and safety monitoring committee compared to those that did not (p=0.05)

Conclusions: Knowledge of trial-level factors that may affect accrual and completion of those trials may enable researchers to strategically design trials in a manner that facilitates accrual and trial completion in an efficient manner.

Predictors of Early Termination of Pediatric Oncology Clinical Trials Due to Poor Accrual: An Exploratory Analysis

Introduction

Cancer is the second-leading cause of death among children in the United States, exceeded only by injuries.[1] In 2020, it was predicted that 11,050 children ages 0-14 years old would be diagnosed with cancer, and 1,190 children in the same age group would die from cancer.[1] Besides death, ramifications of childhood cancer include long-term complications from anticancer therapies such as secondary malignancies and financial hardships for survivors and their families.[2,3] As of 2019, only 34 drugs had been approved by the United States Food and Drug Administration (FDA) for the treatment of pediatric cancers.[4] New effective anticancer therapies are necessary as evidenced by cancer remaining a leading cause of death for children. The following types of cancers account for almost 82% of childhood cancer deaths: brain (30.0%), leukemia (24.8%), bone and articular (10.1%), endocrine (9.0%), and mesothelial/soft tissue (7.7%).[5]

Clinical trials afford new effective therapies for children with cancer by establishing the safety and efficacy/effectiveness of drug discoveries. Alongside the need for new effective cancer therapies for children, the number of pediatric oncology clinical trials and their associated costs have substantially increased. According to the ClinicalTrials.gov database, 32 pediatric oncology clinical trials were initiated in 2010 whereas this number grew to 137 in 2019.[6] Clinical trials for FDA-approved oncology drugs in 2015-2017 had a median cost of $37.1 million per trial (interquartile range = $17.0 - $60.4 million).[7]

Poor accrual is a significant barrier to the completion of pediatric oncology clinical trials. For a study's findings to be valid, an adequate sample size is required.[8] Approximately 60% of children with cancer are treated in clinical trials.[9] Consequently, pediatric oncology clinical trials that are terminated early or prolonged due to poor accrual adversely impact treatment outcomes; in addition, early termination or prolongation of trials negatively affects the financial well-being of trial sponsors such as governmental organizations, academic institutions and the pharmaceutical industry, along with that of institutions participating in the trials.[10] Most notably, early terminated or prolonged trials hinder the release of new effective pediatric cancer therapies in a timely manner.

The literature demonstrates that factors impacting accrual and completion of adult oncology clinical trials operate at the trial, individual, interpersonal, organizational, community, and policy levels.[11-16] Trial level factors include the following: sponsor, trial development time, number and location of participating institutions, sample size, competing trials, time of trial opening, fast-track status, type of cancer, incidence of the targeted cancer, and presence of metastases.[11,17-27] Other trial level factors include type of treatment, eligibility criteria, randomization, required procedures and their timing, use of a placebo, and phase of study.[11,18-26,28-32] However, a dearth of research exists about trial level factors that may affect accrual in pediatric oncology clinical trials. Trial level factors may differ between trials for pediatric and adult populations because these populations differ in their biology, types of cancer, and cancer therapies.[33]

As a result of a growing demand for transparency regarding clinical trials by the government and public to facilitate drug development and safety, many sponsors are required by federal regulations to register their trials on ClinicalTrials.gov.[34] Registration is required for clinical trials that involve an FDA investigational new drug application, have at least one participating site in the United States, or involve a drug, biological, or device produced in the United States and exported elsewhere.[35,36] Before the ClinicalTrials.gov database became accessible in 2000, researchers relied upon available data from a single trial or multiple trials within a single institution to investigate trial-level factors. ClinicalTrials.gov now allows researchers to investigate clinical trials as an enterprise. However, changes in regulations over the last two decades resulted in discrepancies in the type and completeness of data that investigators submitted into the database during that time frame.[37] As a result, the amount of available data differs among variables such as eligibility criteria and sample size and across different time periods.

To address the previously discussed gaps in knowledge of accrual and early termination of pediatric oncology trials, this study aimed to: 1) describe patterns in the presence of variables and completeness of data entry for variables in the ClinicalTrials.gov database over time; and 2) investigate trial-related factors that may affect early termination of pediatric oncology clinical trials due to low accrual.

Theoretical Framework

Bennette et al's[11] conceptual model of trial-level factors associated with low trial accrual guided variable selection, data analysis and organization of results. The model offers four critical domains for assessing trial-level factors associated with low trial

accrual: background, disease-related, treatment-related, and trial design. Background factors include factors such as greater competition from other trials and less state-level coverage of clinical trial costs. Disease-related factors include factors such as less advanced disease, solid tumor setting, less compelling scientific rationale, and lower annual incidence of the eligible population. Treatment-related factors include factors such as treatment in trials that are greatly different from standard of care, research question not relevant to clinical practice, patient or provider preference for a particular treatment, radiotherapy or surgical treatment, not an investigational new agent, more expensive treatment, higher risk for toxicity, multimodality, and less compelling scientific rationale. Trial design factors include factors such as strict or many eligibility criteria, randomized design, placebo-controlled arm, greater trial complexity, and longer required follow-up.

Methods

To examine possible trial-related predictors of early termination of pediatric oncology clinical trials due to low accrual, the authors utilized ClinicalTrials.gov data which were extracted from Aggregate Analysis of ClinicalTrials.gov (AACT). The researchers chose ClinicalTrials.gov because it is the largest and most comprehensive database of clinical trials in the world.[38]

ClinicalTrials.gov Dataset Description

Maintained by the National Library of Medicine (NLM), ClinicalTrials.gov is a database that includes information about clinical trials and other types of studies for diverse illnesses, including cancer. This database, which is accessible by the public, includes clinical trials sponsored by public and private entities, conducted in all states and

216 countries. Sponsors or primary investigators provide both, the initial information and periodic updates of the clinical trials.[6]

The National Institutes of Health (NIH) created ClinicalTrials.gov as a registry of clinical trials that examine investigational drugs' effectiveness for serious illnesses due a mandate by the Food and Drug Administration Modernization Act of 1997 (FDAMA). In 2000, ClinicalTrials.gov became accessible to the public. Subsequently, the Amendments Act of 2007 (FDAAA) required the database's expansion to include other types of clinical trials and additional information about the trials, including their results. The law also instituted penalties for failure to provide the required information. In 2016, the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) further expanded the required information for clinical trials. Thus, because of laws, the number of registered trials and amount of available information for these trials have increased over time. In addition, over the years more sponsors and investigators have provided their trial data due to other policies.[36,37] For example, in 2005 the International Committee of Medical Journal Editors instituted the requirement of clinical trial registration for publication.[39]

Aggregate Analysis of ClinicalTrials.gov (AACT) Dataset Description

Aggregate Analysis of ClinicalTrials.gov (AACT) is a database that contains all ClinicalTrials.gov data related to registered protocols and their results. Every day the data in ClinicalTrial.gov are uploaded to AACT, a relational database.[40] The AACT database was chosen for this study because it allows ClinicalTrials.gov data to be more easily downloaded and imported into statistical analysis software SPSS than the original files on

the ClinicalTrials.gov website. The files on ClinicalTrials.gov are very large zipped files, each containing a large number of sub-files in XML format that cannot easily be imported into SPSS without use of XML syntax and/or purchase of an XML to SPSS converter. In contrast, files in the AACT database have been converted to .txt, simplifying and reducing steps for the user.

Data Analysis

SPSS Version 25 (Armonk, NY: IBM Corp, 2017) was used to perform analyses of selected variables from the AACT dataset. The aims were to describe patterns in the presence of variables and completeness of data entry for variables in the ClinicalTrials.gov database over time and 2) investigate trial-related factors that may affect early termination of pediatric oncology clinical trials due to low accrual. For both aims, frequency distributions for all variables are reported in tables. For Aim 2, Chi-square statistics were obtained to determine whether a relationship between the potential predictor variables (enrollment, primary purpose, intervention type, phase, interventional model, allocation, arm type, number of arms, masking, primary end points, number of primary outcomes, sponsor, number of participating facilities, primary disease, data monitoring committee) and early termination of clinical trial due to low accrual exists. Frequencies and percentages are reported. In addition, multiple logistic regression was performed. Forward stepwise and forced entry multiple logistic regression were used to add potential predictors sequentially into the model based on a significance level α of < 0.2 to reduce the chance of a false negative result (Type II error) since this was an exploratory analysis.

Results

Characteristics of Clinical Trials

A total of 474 pediatric interventional oncology trials were identified in the AACT database. Of the different time periods examined in this study, most pediatric oncology trials (n = 222) were initiated during 2008 – 2017. Most of the trials did not specify any participating institutions within the United States (n = 258) and/or had a status other than completed or terminated/withdrawn (n = 210). Of the total pediatric interventional oncology trials, 105 were trials conducted in the United States that were either completed (n = 87, 83%) or terminated/withdrawn due to poor accrual (n = 18, 17%). Most of these trials (n = 77, 73%) enrolled 100 or fewer subjects. Over half of the trials (n = 62, 59%) had a primary aim to test a treatment, with drugs being the most frequent type of intervention (n = 48, 46%). The most common phase of trial was II (n = 27, 26%), and 49 (47%) trials had a single group study design. Forty trials (38%) involved randomization. Most trials had two arms (n = 41, 39%), with the majority of trials (n = 73, 70%) having an experimental arm versus an active, sham, placebo, or no intervention control arm. Most trials (n = 74, 70%) had no masking, i.e., neither study participants nor raters obtaining assessments were blinded to the treatment assignment. Almost half (n = 50, 48%) were sponsored internally by universities and hospitals. Even though leukemia was the most frequent primary disease (n = 25, 24%), trials (n = 34, 32%) often included patients with multiple types of cancer. The majority of trials had > 1 participating facility (n = 56, 53%) and a data and safety monitoring committee (n = 51, 58%).

Trials with a Given Variable Completed within Four Time Periods

The researchers aimed to describe patterns in the presence of variables and completeness of data entry for variables in the ClinicalTrials.gov database over time. Over time, new regulations mandated additional variables be captured within ClinicalTrials.gov. The researchers examined the frequency and proportion of pediatric oncology clinical trials with a given variable completed within four periods defined by new regulations affecting data entry in ClinicalTrials.gov (see Table 1). The number of initiated trials increased with each subsequent time period (n = 27 initiated before 21Nov1997 [Period I]; n = 120 between 21Nov1997 and 31Aug2008 [Period II]; n = 222 between 01Sep2008 and 17Apr2017 [Period III]), except the most recent time period (n = 98 between 18Apr2017 and 01May2020 [Period IV]), when the data were retrieved from ClinicalTrials.gov. In addition, the number of variables increased with each subsequent period, except the most recent period (150, 159, 160 and 139, respectively). Of the 160 examined variables, 129 (81%) variables had 100% of applicable data in each period. If a variable was included in a period, that variable was not necessarily included in a subsequent period, e.g. number of related serious events and sample size included in analysis for each outcome for each study group. The third period had the most complete data, with 99.6% compared with 84.4% in first period, 85.5% in the second, and 83.2% in the fourth period. The most incomplete data in the fourth period pertain to final analyses and results, e.g. sample size included in analysis for each outcome for each study group, number of withdrawals/drops, and number of related serious events.

Association of Clinical Trial Characteristics with Early Termination of Pediatric Oncology Trials

No statistically significant associations between clinical trial characteristics and early termination/withdrawal of pediatric oncology trials were observed (Table 4) except for use of a data and safety monitoring committee. Though *p* is not below 0.05, the odds of early termination/withdrawal were almost 4 times higher among trials with a data monitoring committee than those without one (OR = 3.9, $p = 0.05$). Also, the odds of termination/withdrawal of clinical trials with one primary outcome were almost 2 times higher than those with two or more primary outcomes (OR = 1.73, $p = .390$). Also, though not statistically significant, differences in proportions of enrollment and early terminated/withdrawn trials were observed (93% vs 7%, p = .29). These findings should be further investigated.

Predictors of Early Termination of Pediatric Oncology Clinical Trials Due to Low Accrual

Multiple logistic regression modeling was used to examine whether characteristics of clinical trials were predictive of early termination of pediatric oncology trials due to low accrual (see Table 5) when combined. None of the clinical trial characteristics were predictive of early termination of pediatric oncology trials due to low accrual in these data.

Discussion

This study aimed to 1) describe patterns of the presence of variables and completeness of data entry for variables in the ClinicalTrials.gov database over time and 2) investigate trial-related factors that may affect early termination of pediatric oncology clinical trials due to low accrual. Despite the need for new, effective therapies for

pediatric oncology patients, the number of clinical trials that can be conducted is constrained by limited financial resources and willing participants. Therefore, identification of trial-level factors associated with poor accrual is crucial, to minimize the expenditure of valuable resources for the development and conduct of trials with a high likelihood of failing to complete.[17]

Patterns of Presence of Variables and Completeness of Data Entry for Variables in ClinicalTrials.gov Database

Patterns of the presence of variables and completeness of data entry for variables in the ClinicalTrials.gov database differed over time. ClinicalTrials.gov did not exist prior to 1997 so available data about initiated trials during this period were extremely limited and entered retrospectively. The most recent period (18Apr2017-01May2020) had fewer initiated clinical trials than the previous two periods which is due to this time period consisting of only three years as opposed to the previous two periods which each consisted of approximately 10 years. The number of required variables increased each subsequent period until the third period due to increased regulations and policies mandating increased transparency of clinical trials. The decline in completed data in the most recent period is likely due to clinical trials initiated during this period still ongoing. Information for many variables, such as number of adverse events and sample size included in analysis for each outcome for each study group, is not available until after the completion of a trial. With the continued growth in number of clinical trials and increased regulations to facilitate transparency of clinical trials, ClinicalTrials.gov may become a more robust database in the future.

Predictors of Early Termination of Pediatric Oncology Clinical Trials Due to Low Accrual

Unexpectedly, none of the examined trial characteristics were found to be predictors of early termination of pediatric oncology trials: enrollment, primary purpose, intervention type, phase, interventional study model, allocation, arm type, number of arms, masking, primary end points, number of primary outcomes, sponsor, number of participating facilities, primary disease, and data and safety monitoring committee. These results are contrary to the literature that demonstrated trial-level factors impact accrual and completion of adult oncology clinical trials.[11,17-32] The difference in results compared to available adult trials may be due to small number of examined pediatric oncology clinical trials which limits testing power. Also, the combination of several categories of trial characteristics within variables necessary for analyses due to small frequencies in some categories was a limiting factor. For example, the original plan was to analyze each of the following types of interventions as has been done in studies of adult oncology clinical trials: drugs, behavioral, biological, combination product, device, diagnostic test, dietary supplement, genetic, procedure, and radiation. However, due to the small number of trials in each category, all intervention types except drugs had to be combined for testing. Even with combining categories, some of the resulting groups remained small due to the small overall sample size as well as the imbalance between completed and early terminated trials. The likelihood of type II errors increases with small groups, possibly resulting in predictors not being identified.

Strengths

This study has multiple strengths. Predictors of early termination of oncology clinical trials due to poor accrual have been understudied in the pediatric population. ClinicalTrials.gov is the largest database of clinical trials, thus this study's results are more generalizable than if the study had a sample consisting of trials conducted at a single or few institutions. Also, this study analyzed clinical trials sponsored by both cooperative groups and pharmaceutical companies as both operate differently. The cooperative group program is part of a governmental agency, the National Cancer Institute, and pharmaceutical companies are for-profit organizations.

Limitations

This study has limitations, several of which pertain to the ClinicalTrials.gov database. Existing legislation does not require all types of clinical trials, such as phase I trials, to be registered on ClinicalTrials.gov.[36] In addition, data for all examined variables are not present as the data are currently and/or were previously not required.[35] The first aim of this study was to describe patterns of the presence of variables and completeness of data entry for variables in the ClinicalTrials.gov database over time. Results could differ based on the cut-off dates for time periods as it takes time for laws and policies to be fully implemented.[19] The second aim of this study was to investigate trial-related factors that may affect early termination of pediatric oncology clinical trials due to low accrual. Results for the study's second aim could differ based on the timing of the study because sponsors and principal investigators can retrospectively update information in ClinicalTrials.gov. Also, some of the groups within variables such as type of interventions were small, possibly resulting in predictors not being identified. Additional

legislation for required data submission to ClinicalTrials.gov and enforcement of the current and future legislature could improve analyses. The use of only one clinical trials database may have introduced bias since data in ClinicalTrials.gov may be inaccurate.[25] Incorporating the use of another large database such as the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) may lessen bias in future research.

Limitations exist with the dependent variable of early termination of clinical trials due to inadequate accrual. The imbalance between the numbers of completed trials and trials terminated/withdrawn due to poor accrual is a limitation because it is more difficult to identify predictors since the terminated/withdrawn group is so small. Reason for the termination or withdrawal of a clinical trial is not a required field by ClinicalTrials.gov, thereby possibly introducing selection bias.[20] Also, all cases of early termination due to inadequate accrual may not have been captured for the analysis. For example, sponsors may have reported the reasons for termination or withdrawal as "cancellation of trial by sponsor" or "inadequate budget." Both of these reasons may have been related to poor accrual. Also, often there are multiple reasons for a trial to be terminated or withdrawn.[27] For example, a trial may be terminated for both poor accrual and inadequate budget and yet only one reason is entered into ClinicalTrials.gov.

Other limitations are related to confounding variables. The effects of variables at the individual, interpersonal, organizational, community and policy levels were not addressed in this study. Furthermore, this study did not assess trial-level factors that other researchers have found that significantly impact accrual and or early study termination

due to inadequate accrual, such as disease incidence, eligibility criteria, and tissue testing.[11,41]

Implications

This study has several implications. Identification of modifiable trial-level factors that are associated with inadequate accrual may enable future trials to be designed in a manner that facilitates accrual and their completion.[11,17] Meanwhile, healthcare providers can provide patient education about non-modifiable trial-level factors to possibly increase acceptance and trial participation.[17,22] Sponsors and institutions can prioritize clinical trials that have trial-level factors that are associated with accrual and trial completion. If sponsors and institutions develop and/or select trials with trial-level factors that are associated with inadequate accrual or early termination, they will be aware in advance that increased resources and interventions will likely be required for successful trial completion.[11,41] Sponsors should ensure the reason for early study terminations is documented in ClinicalTrials.gov so these data are available for future research endeavors about trial-level factors associated with early termination of clinical trials.

Future Research

Future research is needed pertaining to trial-level factors associated with early termination of pediatric oncology clinical trials due to inadequate accrual. Research can advance study findings by including pediatric oncology clinical trials conducted throughout the world, rather than focusing on just those conducted within the United States. Also, variables such as eligibility criteria in the ClinicalTrials.gov that were not investigated in this study but may be associated with early termination of pediatric

oncology clinical trials due to inadequate accrual, such as eligibility criteria, should be considered for future study. Finally, research can be conducted to determine if interventions such as patient education regarding non-modifiable trial-level factors can improve accrual and completion of pediatric oncology clinical trials.

Conclusions

New, effective anticancer therapies for children are necessary as evidenced by cancer being the second-leading cause of death among children in the United States. Yet, limited financial and human resources exist for the conduct of clinical trials. Therefore, sponsors and institutions must develop and prioritize clinical trials that have a high likelihood of accruing and completing. The identification of trial-level factors that are associated with accrual and/or trial completion is crucial for this to occur. This study identified patterns in the presence of variables and completeness of data entry for variables in the ClinicalTrials.gov database over time. It also investigated trial-related factors that may affect early termination of pediatric oncology clinical trials due to low accrual. Findings of trial characteristics included in this study suggest they are not predictive of early termination of pediatric oncology trials, possibly due to the small number of available trials. However, the authors did not include evaluation of trial inclusion/exclusion criteria and trial complexity because these variables were not readily available in the database, and these factors may be important drivers of failure to accrue/complete clinical trials based on the existing literature. Future studies may evaluate these factors and examine a larger number of clinical trials to further understand trial-level factors associated with

accrual and/or pediatric oncology trial completion and strategies to address the trial-level factors that have a negative impact.

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TABLE 1 Frequency and proportion of trials with a given variable completed within four periods

	Period for start date			
Variable	Before 21Nov1997 (n=27)	21Nov1997-31Aug2008 (n=120)	01Sep2008-17Apr2017 (n=222)	18Apr2017-01May2020 (n=98)
	I	II	III	IV
Sample size at baseline for each study group	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (0%)
Baseline type of units of measure of sample	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Baseline parameter for units of measure of sample	4 (14.8%)	23 (19.2%)	29 (13.1%)	0 (0%)
Brief description of study	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Intervention MeSH terms	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Number of facilities	27 (100%)	113 (94.2)	190 (85.6%)	89 (90.8%)
Number of related non-serious events	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (0%)
Number of related serious events	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (0%)
Year of registration	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Number of months between start date and primary completion date	15 (55.6%)	79 (65.8%)	144 (64.9%)	10 (10.2%)
Results reported	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Number of months between primary completion date and first received results date	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (100%)
Study has at least one facility in USA	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Study has just one facility	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Minimum age converted to an integer	7 (25.9%)	54 (45.0%)	161 (72.5%)	77 (78.6%)
Maximum age converted to an integer	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Part of minimum age info that specifies units	27 (100%)	120 (100%)	222 (100%)	98 (100%)

Part of maximum age info that specifies units	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Number of primary outcomes	15 (55.6%)	98 (81.7%)	220 (99.1%)	98 (100%)
Number of secondary outcomes	9 (33.3%)	59 (49.2%)	158 (71.2%)	65 (66.3%)
Number of other outcomes	0 (0%)	0 (0%)	9 (4.1%)	7 (7.1%)
Condition MeSH terms	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Conditions under study	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Country where facility located	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Type of arm	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Date when results were first received	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Descriptions of design groups	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Are results primary or secondary outcomes	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Measure used	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Time frame in which events were reported	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Description of design outcomes	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Type of allocation	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Interventional model	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Observational model	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Primary purpose	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Observational timing	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Type of masking	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Description of intervention	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Was subject masked?	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Was caregiver masked?	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Was investigator masked?	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Was outcome accessor masked?	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Detailed description of protocol	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Uploaded documents	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Link for study-related documents	27 (100%)	120 (100%)	222 (100%)	98 (100%)

Period of drops and withdrawals	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Reasons for drops or withdrawals	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Number of drops or withdrawals	1 (3.7%)	20 (16.7%)	26 (11.7%)	0 (0%)
Sampling method	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Gender	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Minimum age	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Maximum age	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Were healthy volunteers eligible?	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Brief description of eligible patients	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Inclusion and exclusion criteria	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Study status	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Name of facility	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Facility's city	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Facility's state	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Facility's zip code	27(100%)	120 (100%)	222 (100%)	98 (100%)
Facility's country	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Terms or phrases synonymous with intervention	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Intervention or exposure	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Name of specific intervention	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Description of intervention	27 (100%)	120 (100%)	222 (100%)	98 (100%)
URL for intervention	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Description of URL for study	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Period of study when study was not completed	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Outcome count	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (0%)
Type of non-inferiority	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Description of non-inferiority	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Parameter type of outcome	27 (100%)	120 (100%)	222 (100%)	98 (100%)

Parameter value of outcome	0 (0%)	6 (5.0%)	9 (4.1%)	0 (0%)
p value modifier	27 (100%)	120 (100%)	222 (100%)	98 (100%)
p value	0 (0%)	7 (5.8%)	9 (4.1%)	0 (0%)
One- or two-sided confidence level	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Confidence interval	0 (0%)	5 (4.2%)	8 (3.6%)	0 (100%)
Confidence interval lower limit	0 (0%)	3 (2.5%)	8 (3.6%)	0 (0%)
Confidence interval higher limit	0 (0%)	4 (3.3%)	8 (3.6%)	0 (0%)
p value description	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Statistical method	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Statistical method description	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Description of estimates	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Description of groups	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Units for outcome	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Sample size included in analysis for each outcome for each study group	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (0%)
Title of outcome measurement	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Description of outcome measurement	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Units of outcome measurement	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Parameter type of outcome measurement	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Parameter value of outcome measurement	4 (14.8%)	23 (19.2%)	27 (12.2%)	0 (0%)
Dispersion type of outcome measurement	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Dispersion value of outcome measurement	0 (0%)	7 (5.8%)	11 (5.0%)	0 (0%)
Lower limit of outcome measurement	0 (0%)	6 (5.0%)	5 (2.3%)	0 (0%)
Upper limit of outcome measurement	0 (0%)	6 (5.0%)	5 (2.3%)	0 (0%)
Outcome type	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Outcome title	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Outcome description	27 (100%)	120 (100%)	222 (100%)	98 (100%)

Timeframe of outcome	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Outcome population	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Units of outcome	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Dispersion type outcome	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Parameter type of outcome	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Details of recruitment	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Details of pre-assignment	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Date of adverse event	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Time frame in which adverse events were reported	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Type of adverse event	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Where did adverse event terminology come from	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Type of adverse event assessment	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Number of subjects with adverse events	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (0%)
Number of subjects at risk for adverse events	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (0%)
Description of adverse event	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Number of adverse events	0 (0%)	9 (7.5%)	10 (4.5%)	0 (0%)
Organ system affected by adverse event	27(100%)	120 (100%)	222 (100%)	98 (100%)
Terminology used to describe adverse events	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Frequency threshold of adverse event	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (0%)
Type of result reported	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Title of group for which results were reported	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Description of group for which results reported	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Type of sponsor	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Was sponsor the lead or collaborator?	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Name of sponsor	27 (100%)	120 (100%)	222 (100%)	98 (100%)

Date study was first submitted to ClinicalTrials.gov	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Date results were first submitted to ClinicalTrials.gov	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Date of last submission to ClinicalTrials.gov	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Submission date of version of record that met quality control criteria	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Date that submission was made public on ClinicalTrials.gov	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Is study first posted date an estimate or actual date	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Is results first posted date an estimate or actual date	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Is last update posted date an estimate or actual date	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Date study started	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Is start date an estimate or the actual date?	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Study completion date	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Is completion date an estimate or the actual date?	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Primary completion date	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Is primary completion date an estimate or the actual date?	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Type of study	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Acronym for study name	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Brief title of study	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Official title of study	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Overall status of study	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Why study was stopped	27 (100%)	120 (100%)	222 (100%)	98 (100%)

Last reported status of study	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Phase of trial	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Actual or anticipated enrollment number	25 (92.6%)	108 (90.0%)	222 (100%)	98 (100%)
Is enrollment number actual or anticipated number	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Source of study data	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Number of arms	9 (33.3%)	57 (47.5%)	162 (73.0%)	73 (74.5%)
Number of groups	1 (3.7%)	14 (11.7%)	30 (13.5%)	13 (13.3%)
Does study have expanded access	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Does study have a data monitoring committee	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Does study involve a FDA-regulated drug	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Does study involve a FDA-regulated device	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Product manufactured in and exported from US	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Is there a plan to share ipd	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Description of plan to share ipd	27 (100%)	120 (100%)	222 (100%)	98 (100%)
PubMed ID	11 (40.7%)	26 (21.7%)	37 (16.7%)	6 (6.1%)
Study references	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Citation for study references	27 (100%)	120 (100%)	222 (100%)	98 (100%)

TABLE 2 Frequency and proportion of trials with a given variable completed within four periods

	Period for start date			
Variable	Before 21Nov1997 (n=27)	21Nov1997-31Aug2008 (n=120)	01Sep2008-17Apr2017 (n=222)	18Apr2017-01May2020 (n=98)
	I	II	III	IV
Results reported	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Yes	4 (14.8)	23 (19.2%)	30 (13.5%)	0 (0%)
No	23 (85.2%)	97 (80.8%)	192 (86.5%)	98 (100%)
Study has at least one facility in USA	27 (100%)	113 (94.2%)	190 (85.6%)	89 (90.8%)
Yes	15 (55.6%)	71 (59.2%)	89 (40.1%)	38 (38.8%)
No	12 (44.4%)	42 (35.0%)	101 (45.5%)	51 (52.0%)
Study has just one facility	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Yes	13 (48.1%)	38 (31.7%)	117 (52.7%)	62 (63.3%)
No	14 (51.9%)	82 (68.3%)	105 (47.3%)	36 (36.7%)
Type of arm	9 (33.3%)	57 (47.5%)	162 (73.0%)	73 (74.5%)
Active Comparator	1 (3.7%)	5 (4.2%)	18 (8.1%)	12 (12.2%)
Experimental	8 (29.6%)	45 (37.5%)	121 (54.5%)	55 (56.1%)
No Intervention	0 (0%)	3 (2.5%)	5 (2.3%)	1 (1.0%)
Placebo Comparator	0 (0%)	0 (0%)	3 (1.4%)	0 (0%)
Sham Comparator	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Other	0 (0%)	4 (3.3%)	14 (6.3%)	5 (5.1%)
Are results primary or secondary outcomes	15 (55.6%)	98 (81.7%)	220 (99.1%)	98 (100%)
Primary	15 (55.6%)	93 (77.5%)	216 (97.3%)	93 (94.9%)
Secondary	0 (0%)	5 (4.2%)	3 (1.4%)	5 (5.1%)
Other	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Type of allocation	8 (29.6%)	52 (43.3%)	100 (45.0%)	42 (42.9%)
Non-Randomized	1 (3.7%)	20 (16.7%)	25 (11.3%)	11 (11.2%)
Randomized	7 (25.9%)	32 (26.7 %)	75 (33.8%)	31 (31.6%)
Interventional model	10 (37.0%)	62 (51.7%)	164 (73.9%)	73 (74.5%)

Crossover Assignment	0 (0%)	1 (0.8%)	5 (2.3%)	4 (4.1%)
Factorial Assignment	0 (0%)	1 (0.8%)	0 (0%)	1 (1.0%)
Parallel Assignment	2 (7.4%)	33 (27.5%)	83 (37.4%)	34 (34.7%)
Sequential	0 (0%)	0 (0%)	0 (0%)	1 (1.0%)
Single Group Assignment	8 (29.6%)	27 (22.5%)	76 (34.2%)	33 (33.7%)
Observational model	2 (7.4%)	18 (15.0%)	52 (23.4%)	25 (25.5%)
Case Control	1 (3.7%)	1 (0.8%)	3 (1.4%)	0 (0%)
Case-Control	0 (0%)	1 (0.8%)	4 (1.8%)	7 (7.1%)
Case-Crossover	0 (0%)	0 (0%)	1 (0.5%)	1 (1.0%)
Case-Only	0 (0%)	4 (3.3%)	23 (10.4%)	1 (1.0%)
Cohort	1 (3.7%)	12 (10.0%)	17 (7.7%)	11 (11.2%)
Family-Based	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Other	0 (0%)	0 (0%)	3 (1.4%)	5 (5.1%)
Primary purpose	24 (88.9%)	93 (77.5%)	164 (73.9%)	73 (74.5%)
Basic Science	0 (0%)	0 (0%)	2 (0.9%)	1 (1.0%)
Device Feasibility	0 (0%)	0 (0%)	1 (0.5%)	1 (1.0%)
Diagnostic	0 (0%)	1 (0.8%)	4 (1.8%)	6 (6.1%)
Health Services Research	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Prevention	0 (0%)	12 (10.0%)	24 (10.8%)	10 (10.2%)
Supportive Care	0 (0%)	9 (7.5%)	25 (11.3%)	15 (15.3%)
Treatment	24 (88.9%)	71 (59.2%)	102 (45.9%)	33 (33.7%)
Other	0 (0%)	0 (0%)	5 (2.3%)	7 (7.1%)
Observational timing	2 (7.4%)	20 (16.7%)	55 (24.8%)	25 (25.5%)
Cross-Sectional	0 (0%)	2 (1.7%)	3 (1.4%)	7 (7.1%)
Retrospective	0 (0%)	6 (5.0%)	20 (9.0%)	3 (3.1%)
Prospective	2 (7.4%)	11 (9.2%)	30 (13.5%)	14 (14.3%)
Other	0 (0%)	1 (0.8%)	2 (0.9%)	1 (1.0%)
Type of masking	13 (48.1%)	47 (39.2%)	166 (74.8%)	73 (74.5%)
None (Open-Label)	12 (44.4%)	64 (53.3%)	125 (56.3%)	59 (60.2%)
Single	1 (3.7%)	2 (1.7%)	15 (6.8%)	4 (4.1%)
Double	0 (0%)	5 (4.2%)	12 (5.4%)	6 (6.1%)
Triple	0 (0%)	0 (0%)	3 (1.4%)	1 (1.0%)
Quadruple	0 (0%)	2 (1.7%)	11 (5.0%)	3 (3.1%)
Was subject masked?	-	6 (5.0%)	29 (13.1%)	9 (9.2%)
Yes	-	6 (5.0%)	29 (13.1)	9 (9.2%)
Was caregiver masked?	-	3 (2.5%)	13 (5.9%)	6 (6.1%)

Yes	-	3 (2.5%)	13 (5.9%)	6 (6.1%)
Was investigator masked?	-	4 (3.3%)	23 (10.4%)	8 (8.2%)
Yes	-	4 (3.3%)	23 (10.4%)	8 (8.2%)
Was outcome accessor masked?	-	5 (4.2%)	27 (12.2%)	8 (8.2%)
Yes	-	5 (4.2%)	27 (12.2%)	8 (8.2%)
Sampling method	2 (7.4%)	20 (16.7%)	53 (23.9%)	25 (25.5%)
Non-Probability Sample	2 (7.4%)	12 (10.0%)	46 (20.7%)	18 (18.4%)
Probability Sample	0 (0%)	8 (6.7%)	7 (3.2%)	7 (7.1%)
Gender	27 (100%)	120 (100%)	222 (100%)	98 (100%)
All	27 (100%)	119 (99.2%)	214 (96.4%)	96 (98.0%)
Female	0 (0%)	1 (0.8%)	6 (2.7%)	2 (2.0%)
Male	0 (0%)	0 (0%)	2 (0.9%)	0 (0%)
Were healthy volunteers eligible?	27 (100%)	120 (100%)	221 (99.5%)	95 (96.9%)
Yes	0 (0%)	9 (7.5%)	17 (7.7%)	21 (21.4%)
No	27 (100%)	111 (92.5%)	204 (91.9%)	74 (75.5%)
Study status	1 (3.7%)	11 (9.2%)	52 (23.4%)	58 (59.2%)
Active, not recruiting	0 (0%)	0 (0%)	2 (0.9%)	0 (0%)
Completed	0 (0%)	0 (0%)	0 (0%)	1 (1.0%)
Not yet recruiting	0 (0%)	0 (0%)	2 (0.9%)	3 (3.1%)
Recruiting	1 (3.7%)	11 (9.2%)	48 (21.6%)	54 (55.1%)
Intervention or exposure	25 (92.6%)	112 (93.3%)	202 (91.0%)	91 (92.9%)
Behavioral	0 (0%)	11 (9.2%)	35 (15.8%)	13 (13.3%)
Biological	7 (25.9%)	26 (21.7%)	13 (5.9%)	2 (2.0%)
Combination Product	0 (0%)	0 (0%)	0 (0%)	1 (1.0%)
Device	0 (0%)	0 (0%)	7 (3.2%)	7 (7.1%)
Diagnostic Test	0 (0%)	0 (0%)	1 (0.5%)	7 (7.1%)
Dietary Supplement	0 (0%)	0 (0%)	4 (1.8%)	0 (0%)
Drug	16 (59.3%)	57 (47.5%)	95 (42.8%)	31 (31.6%)
Genetic	0 (0%)	3 (2.5%)	13 (5.9%)	1 (1.0%)
Procedure	2 (7.4%)	8 (6.7%)	7 (3.2%)	6 (6.1%)
Radiation	0 (0%)	0 (0%)	5 (2.3%)	0 (0%)
Other	0 (0%)	7 (5.8%)	22 (9.9%)	23 (23.5%)
Type of non-inferiority	-	9 (7.5%)	11 (5.0%)	0 (0%)
Non-inferiority	-	0 (0%)	1 (0.5%)	0 (0%)
Non-inferiority or Equivalence	-	2 (1.7%)	2 (0.9%)	0 (0%)
Superiority	-	2 (1.7%)	1 (0.5%)	0 (0%)

Superiority or Other (legacy)	-	1 (0.8%)	4 (1.8%)	0 (0%)
Other	-	4 (3.3%)	3 (1.4%)	0 (0%)
One or two-sided confidence interval	-	6 (5.0%)	9 (4.1%)	0 (0%)
1-sided	-	2 (1.7%)	0 (0%)	0 (0%)
2-sided	-	4 (3.3%)	9 (4.1%)	0 (0%)
Outcome type	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (0%)
Primary	0 (0%)	6 (5.0%)	6 (2.7%)	0 (0%)
Secondary	4 (14.8%)	17 (14.2%)	23 (10.4%)	0 (0%)
Other-Prespecified	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Type of adverse event	4 (14.8%)	23 (19.2%)	222 (100%)	0 (0%)
Serious	4 (14.8%)	18 (15.0%)	29 (13.1%)	0 (0%)
Other	0 (0%)	5 (4.2%)	1 (0.5%)	0 (0%)
Type of adverse event assessment	4 (14.8%)	12 (10.0%)	20 (9.0%)	0 (0%)
Non-systematic Assessment	0 (0%)	3 (2.5%)	2 (0.9%)	0 (0%)
Systematic Assessment	4 (14.8%)	9 (7.5%)	18 (8.1%)	0 (0%)
Organ system affected by adverse event	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (0%)
General disorders	0 (0%)	3 (2.5%)	0 (0%)	0 (0%)
Infections and infestations	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Investigations	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Metabolism and Nutrition	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Musculoskeletal	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0%)	1 (0.8%)	1 (0.5%)	0 (0%)
Nervous	2 (7.4%)	0 (0%)	1 (0.5%)	0 (0%)
Pregnancy, puerperium and perinatal	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Product Issues	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Psychiatric	0 (0%)	2 (1.7%)	0 (0%)	0 (0%)
Renal and urinary	1 (3.7%)	0 (0%)	1 (0.5%)	0 (0%)
Respiratory, thoracic and mediastinal	0 (0%)	5 (4.2%)	3 (1.4%)	0 (0%)
Skin and subcutaneous tissue	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)

Surgical and medical procedures	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Total	0 (0%)	3 (2.5%)	10 (4.5%)	0 (0%)
Vascular	1 (3.7%)	6 (5.0%)	9 (4.1%)	0 (0%)
Type of result reported	4 (14.8%)	23 (19.2%)	30 (13.5%)	0 (0%)
Baseline	4 (14.8%)	21 (17.5%)	22 (9.9%)	0 (0%)
Outcome	0 (0%)	1 (0.8%)	6 (2.7%)	0 (0%)
Participant Flow	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Reported Event	0 (0%)	0 (0%)	2 (0.9%)	0 (0%)
Type of sponsor	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Industry	0 (0%)	14 (11.7%)	46 (20.7%)	18 (18.4%)
NIH	2 (7.4%)	4 (3.3%)	5 (2.3%)	0 (0%)
Other	25 (92.6%)	102 (85.0%)	171 (77.0%)	80 (81.6%)
Was sponsor the lead or collaborator?	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Collaborator	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Lead	27 (100%)	119 (99.2%)	222 (100%)	98 (100%)
Type of study	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Interventional	24 (88.9%)	96 (80.0%)	166 (74.8%)	73 (74.5%)
Observational	3 (11.1%)	24 (20.0%)	55 (24.8%)	25 (25.5%)
Observational (Patient Registry)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Overall status of study	27 (100%)	120 (100%)	222 (100%)	98 (100%)
Active, not recruiting	0 (0%)	8 (6.7%)	24 (10.8%)	7 (7.1%)
Completed	18 (66.7%)	77 (64.2%)	110 (49.5%)	9 (9.2%)
Enrolling by Invitation	0 (0%)	0 (0%)	1 (0.5%)	3 (3.1%)
Not yet recruiting	0 (0%)	0 (0%)	0 (0%)	16 (16.3%)
Recruiting	1 (3.7%)	2 (1.7%)	34 (15.3%)	57 (58.2%)
Suspended	0 (0%)	0 (0%)	0 (0%)	1 (1.0%)
Terminated	1 (3.7%)	7 (5.8%)	21 (9.5%)	1 (1.0%)
Withdrawn	0 (0%)	4 (3.3%)	11 (5.0%)	3 (3.1%)
Unknown Status	7 (25.9%)	22 (18.3%)	21 (9.5%)	1 (1.0%)
Last reported status of study	7 (25.9%)	22 (18.3%)	21 (9.5%)	1 (1.0%)
Active, Not Recruiting	7 (25.9%)	12 (10.0%)	1 (0.5%)	0 (0%)
Not yet recruiting	0 (0%)	1 (0.8%)	2 (0.9%)	0 (0%)
Recruiting	0 (0%)	9 (7.5%)	18 (8.1%)	1 (1.0%)
Phase of trial	24 (88.9%)	96 (80.0%)	166 (74.8%)	73 (74.5%)

Early Phase I	0 (0%)	1 (0.8%)	4 (1.8%)	3 (3.1%)
Phase 1	0 (0%)	13 (10.8%)	27 (12.2%)	11 (11.2%)
Phase 1/Phase 2	0 (0%)	2 (1.7%)	11 (5.0%)	7 (7.1%)
Phase 2	11 (40.7%)	32 (26.7%)	37 (16.7%)	6 (6.1%)
Phase 2/Phase 3	0 (0%)	0 (0%)	3 (1.4%)	0 (0%)
Phase 3	10 (37.0%)	27 (22.5%)	14 (6.3%)	7 (7.1%)
Phase 4	1 (3.7%)	5 (4.2%)	12 (5.4%)	5 (5.1%)
N/A	2 (7.4%)	16 (13.3%)	58 (26.1%)	34 (34.7%)
Number of arms	9 (33.3%)	57 (47.5%)	162 (73.0%)	73 (74.5%)
1	6 (22.2%)	19 (15.8%)	67 (30.2%)	31 (31.6%)
2	1 (3.7%)	28 (23.3%)	65 (29.3%)	35 (35.7%)
3	0 (0%)	3 (2.5%)	18 (8.1%)	2 (2.0%)
4	1 (3.7%)	3 (2.5%)	6 (2.7%)	3 (3.1%)
5	0 (0%)	1 (0.8%)	2 (0.9%)	1 (1.0%)
7	0 (0%)	2 (1.7%)	3 (1.4%)	0 (0%)
8	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
9	1 (3.7%)	0 (0%)	0 (0%)	0 (0%)
11	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
12	0 (0%)	0 (0%)	0 (0%)	1 (1.0%)
Number of groups	1 (3.7%)	14 (11.7%)	30 (13.5%)	13 (13.3%)
1	0 (0%)	6 (5.0%)	18 (8.1%)	2 (2.0%)
2	1 (3.7%)	6 (5.0%)	8 (3.6%)	8 (8.2%)
3	0 (0%)	2 (1.7)	3 (1.4%)	2 (2.0%)
4	0 (0%)	0 (0%)	1 (0.5%)	1 (1.0%)
Does study have expanded access	27 (100%)	118 (98.3%)	221 (99.5%)	97 (99.0%)
No	27 (100%)	118 (98.3%)	221 (99.5%)	97 (99.0%)
Does study have a data and safety monitoring committee	11 (40.7%)	75 (62.5%)	199 (89.6%)	84 (85.7%)
Yes	5 (18.5%)	40 (33.3%)	89 (40.1%)	32 (32.7%)
No	6 (22.2%)	35 (29.2%)	110 (49.5%)	52 (53.1%)
Does study involve a FDA-regulated drug	-	7 (5.8%)	38 (17.1%)	97 (99.0%)
Yes	-	3 (2.5%)	16 (7.2%)	21 (21.4%)
No	-	4 (3.3%)	22 (9.9%)	76 (77.6%)
Does study involve a FDA-regulated device	-	7 (5.8%)	38 (17.1%)	97 (99.0%)
Yes	-	0 (0%)	1 (0.5%)	1 (1.0%)
No	-	7 (5.8%)	37 (16.7%)	96 (98.0%)

Product manufactured in and exported from US	-	-	6 (2.7%)	90 (91.8%)
Yes	-	-	3 (1.4%)	4 (4.1%)
No	-	-	3 (1.4%)	4 (4.1%)
Is there a plan to share ipd	4 (14.8%)	3 (2.5%)	67 (30.2%)	98 (100%)
Yes	0 (0%)	0 (0%)	20 (9.0%)	8 (8.2%)
No	4 (14.8%)	2 (1.7%)	36 (16.2%)	40 (40.8%)
Undecided	0 (0%)	1 (0.8%)	11 (5.0%)	17 (17.3%)

TABLE 3 Characteristics [n (%)] of completed studies and studies terminated/withdrawn due to poor accrual (total N=105)

Variable	Study status (N=105)		Number of studies with data
	Completed n = 87	Terminated/withdrawn due to poor accrual n = 18	
Enrollment			95 (90.5)
1-100	64 (79.0)	13 (92.9)	77 (81.1)
101-1,000	13 (16.0)	1 (7.1)	14 (14.7)
>1,000	4 (4.9)	0 (0)	4 (4.2)
Primary Purpose			102 (97.1)
Basic science	0 (0)	0 (0)	0 (0)
Device feasibility	1 (1.2)	0 (0)	1 (1.0)
Diagnostic	3 (3.6)	0 (0)	3 (2.9)
Health services research	0 (0)	0 (0)	0 (0)
Prevention	15 (17.9)	3 (16.7)	18 (17.6)
Screening	0 (0)	0 (0)	0 (0)
Supportive care	12 (14.3)	4 (22.2)	16 (15.7)
Treatment	51 (60.7)	11 (61.1)	62 (60.8)
Other	2 (2.4)	0 (0)	2 (2.0)
Intervention type			105 (100)
Behavioral	18 (20.7)	3 (16.7)	21 (20.0)
Biological	18 (20.7)	4 (22.2)	22 (21.0)
Combination product	0 (0)	0 (0)	0 (0)
Device	3 (3.4)	0 (0)	3 (2.9)
Diagnostic test	0 (0)	0 (0)	0 (0)
Dietary supplement	0 (0)	0 (0)	0 (0)
Drug	38 (43.7)	10 (55.6)	48 (45.7)
Genetic	0 (0)	0 (0)	0 (0)
Procedure	3 (3.4)	1 (5.6)	4 (3.8)
Radiation	1 (1.1)	0 (0)	1 (1.0)
Other	6 (6.9)	0 (0)	6 (5.7)
Phase			105 (100)
Early phase I	2 (2.3)	1 (5.6)	3 (2.9)
Phase I	22 (25.3)	3 (16.7)	25 (23.8)
Phase I/Phase II	4 (4.6)	0 (0)	4 (3.8)
Phase II	20 (23.0)	7 (38.9)	27 (25.7)
Phase II/Phase III	0 (0)	0 (0)	0 (0)
Phase III	10 (11.5)	2 (11.1)	12 (11.4)

Phase IV	0 (0)	0 (0)	0 (0)
Not applicable	29 (33.3)	5 (27.8)	34 (32.4)
Interventional Study Model			90 (85.7)
Crossover assignment	2 (2.7)	2 (11.8)	4 (4.4)
Factorial assignment	0 (0)	0 (0)	0 (0)
Parallel assignment	29 (39.7)	8 (47.1)	37 (41.1)
Sequential assignment	0 (0)	0 (0)	0 (0)
Single group assignment	42 (57.5)	7 (41.2)	49 (54.4)
Allocation			53 (50.5)
Non-randomized	7 (16.7)	3 (27.3)	10 (18.9)
Randomized	35 (83.3)	8 (72.7)	43 (81.1)
Arm type			90 (85.7)
Active comparator	5 (6.8)	2 (12.5)	7 (7.8)
Experimental	60 (81.1)	13 (81.3)	73 (81.1)
No intervention	2 (2.7)	0 (0)	2 (2.2)
Placebo comparator	2 (2.7)	0 (0)	2 (2.2)
Sham comparator	0 (0)	1 (6.3)	1 (1.1)
Other	5 (6.8)	0 (0)	5 (5.6)
Number of arms			90 (85.7)
1	32 (43.2)	6 (37.5)	38 (42.2)
2	31 (41.9)	10 (62.5)	41 (45.6)
3	4 (5.4)	0 (0)	4 (4.4)
4 or more	7 (9.5)	0 (0)	7 (7.8)
Masking			93 (88.6)
None (Open label)	60 (80.0)	14 (77.8)	74 (79.6)
Single	6 (8.0)	1 (5.6)	7 (7.5)
Double	5 (6.7)	2 (11.1)	7 (7.5)
Triple	1 (1.3)	0 (0)	1 (1.1)
Quadruple	3 (4.0)	1 (5.6)	4 (4.3)
End point of study			22 (21.0)
Safety	0 (0)	1 (100.0)	1 (4.5)
Efficacy	1 (4.8)	0 (0)	1 (4.5)
Safety and efficacy	17 (81.0)	0 (0)	17 (77.3)
Other, includes bioavailability and bioequivalence studies	3 (14.3)	0 (0)	3 (13.6)
Number of primary outcomes			96 (91.4)
1	57 (73.1)	11 (61.1)	68(70.8)
>1	21 (26.9)	7 (38.9)	28(29.2)
Sponsor			105 (100)
Children's Oncology Group (COG)	18 (20.7)	2 (11.1)	20 (19.0)
Industry	23 (26.4)	6 (33.3)	29 (27.6)

Individual	0 (0)	1 (5.6)	1 (1.0)
Institution outside the US (other than universities and hospitals)	1 (1.1)	0 (0)	1 (1.0)
NIH	3 (3.4)	1 (5.6)	4 (3.8)
University/hospital	42 (48.3)	8 (44.4)	50 (47.6)
Number facilities participating in trial			105 (100)
1	40 (46.0)	9 (50.0)	49 (46.7)
>1	47 (54.0)	9 (50.0)	56 (53.3)
Primary disease			105 (100)
Leukemia	23 (26.4)	2 (11.1)	25 (23.8)
Brain and spinal cord	16 (18.4)	4 (22.2)	20 (19.0)
Neuroblastoma	4 (4.6)	1 (5.6)	5 (4.8)
Wilm's tumor	1 (1.1)	0 (0)	1 (1.0)
Lymphoma	1 (1.1)	0 (0)	1 (1.0)
Rhabdomyosarcoma	1 (1.1)	0 (0)	1 (1.0)
Retinoblastoma	5 (5.7)	3 (16.7)	8 (7.6)
Multiple types of cancer	30 (34.5)	4 (22.2)	34 (32.4)
Other	6 (6.9)	4 (22.2)	10 (9.5)
Data and safety monitoring committee			88 (83.8)
Yes	38 (52.8)	13 (81.3)	51 (58.0)
No	34 (47.2)	3 (18.8)	37 (42.0)

TABLE 4 Chi-square test of independence for completed and terminated/withdrawn study due to poor accrual

Variable	**Study status** (N = 105)							
	Completed (n = 87)	**Terminated or withdrawn due to poor accrual** (n = 18)	**# of studies with data**	X^2	**df**	***p-value***	**OR**	**95% CI for OR**
Enrollment	81	14	95					
1-100	64 (79.0)	13 (92.9)		-	1	.294*	.29	.04-2.37
>100	17 (21.0)	1 (7.1)						
Primary Purpose	87	18	105					
Treatment	51 (58.6)	11 (61.1)		.04	1	1.000	.90	.32-2.55
Other (basic science, device feasibility, diagnostic, health services research, prevention, screening, supportive care)	36 (41.4)	7 (38.9)						
Intervention type	87	18	105					
Drug	38 (43.7)	10 (55.6)		.85	1	.439	.62	.22-1.72
Other (behavioral, biological, combination product, device, diagnostic test, dietary supplement, genetic, procedure, radiation)	49 (56.3)	8 (44.4))						
Phase	87	18	105					
Early (early phase I, phases I, I/II, II)	48 (55.2)	11 (61.1)		-	2	.930*	**	**
Late (phases II/III, III, IV)	10 (11.5)	2 (11.1)						
Not applicable	29 (33.3)	5 (27.8)						
Interventional Model	73	17	90					

Parallel group	29 (39.7)	8 (47.1)		.31	1	.596	.74	.26-2.14
Not parallel	44 (60.3)	9 (52.9)						
Allocation**			53					
Arm type	74	16	90					
Experimental	60 (81.1)	13 (81.3)			1	1.000*	.99	.25-3.95
Other (active comparator, no intervention, placebo comparator, sham comparator, other)	14 (18.9)	3 (18.8)						
Number of arms	74	16	90					
1	32 (43.2)	6 (37.5)		.18	1	.784	1.27	.42-3.86
>1	42 (56.8)	10 (62.5)						
Masking	75	18	93					
No (open label)	60 (80.0)	14 (77.8)			1	1.00*	1.14	.33-3.98
Yes	15 (20.0)	4 (22.2)						
End point of study	87	18	105					
Safety	24 (27.6)	4 (22.2)			3	.825*	**	**
Safety and efficacy	24 (27.6)	7 (38.9)						
Efficacy	10 (11.5)	2 (11.1)						
Other (includes bioavailability and bioequivalence studies)	29 (33.3)	5 (27.8)						
Number of primary outcomes	78	18	96					
1	57 (73.1)	11 (61.1)		1.01	1	.390	1.73	.59-5.04
>1	21 (26.9)	7 (38.9)						
Sponsor	87	18	105					
Industry	23 (26.4)	6 (33.3)			2	.843*	**	**
University/hospital	42 (48.3)	8 (44.4)						
Other (COG, individual, institution outside US other than universities and hospitals, NIH)	22 (25.3)	4 (22.2)						

Number of participating facilities	87	18	105					
1	40 (46.0)	9 (50.0)	49	.10	1	.800	.85	.31-2.35
>1	47 (54.0)	9 (50.0)	56					
Primary disease	87	18	105					
Single most common types (leukemia, brain and spinal cord, neuroblastoma, Wilm's tumor, lymphoma, rhabdomyosarcoma, retinoblastoma)	51 (58.6)	10 (55.6)		.06	1	1.000	1.13	.41-3.15
Other cancers and multiple types	36 (41.4)	8 (44.4)						
Data and safety monitoring committee	72	16	88					
Yes	38 (52.8)	13 (81.3)	51	4.36	1	.050	3.88	1.02-14.78
No	34 (47.2)	3 (18.8)	37					

*Fisher's exact test performed because expected frequency < 5 in cells

** Risk Estimate statistics cannot be computed. They are only computed for a 2*2 table without empty cells.

TABLE 5 Multiple logistic regression for completed and terminated/withdrawn study due to poor accrual

Variables in the Equation

		B	S.E.	Wald	df	*p* value	OR	95% C.I. for OR	
								Lower	Upper
	Data and Safety Monitoring Committee	1.233	.709	3.019	1	.082	3.430	.854	13.779
	Enrollment	1.418	1.091	1.690	1	.194	4.129	.487	35.019

Summary

Cancer is the second-leading cause of death among children in the United States.[1] Clinical trials are the conduit to new effective therapies for children with cancer because they ascertain whether new drug discoveries are safe and effective.[2] However, inadequate accrual is a significant barrier to the completion of trials as only two-thirds of children with cancer are treated on clinical trials.[3] More children with cancer should be enrolled on clinical trials to enable successful completion of oncology trials, thus facilitating timely availability of new effective therapies. The purposes of this dissertation compendium underpin several gaps in the identification of 1) barriers to enrollment in pediatric oncology clinical trials and 2) trial-level predictors of early termination of pediatric oncology trials due to poor accrual. The synthesis of the findings from the scoping and systematic reviews suggests associations between trial-level factors and early trial termination of pediatric oncology trials due to poor accrual. The analysis of pediatric clinical trials data reported in ClinicalTrials.gov did not demonstrate trial-level predictors of early trial termination of pediatric oncology trials due to poor accrual, most likely due to not including important factors such as eligibility criteria and trial complexity. Further research is recommended to examine the discrepancies between findings of the literature reviews and exploratory analysis, with attention on the predictor variables with larger effect sizes in the exploratory analysis. Future trials should be designed considering trial-level factors such as eligibility criteria and interventional study model that may affect accrual and completion of pediatric oncology trials.

Theoretical Frameworks

Two frameworks guided the literature searches and organization of results/discussion in this dissertation compendium. The modified Socioecological Model (SEM) addresses influential factors of clinical trial accrual at the trial, individual/intrapersonal, interpersonal, organizational, community, and policy levels.[4] The first manuscript demonstrated that factors impacting accrual and completion of oncology clinical trials operate at multiple levels. Bennette et al.'s[5] conceptual model of trial-level factors associated with low trial accrual has the following four critical domains for assessing trial-level factors associated with low trial accrual: background, disease-related, treatment-related, and trial design. The second and third manuscripts identified trial-level factors within the four domains.

Manuscript #1: Scoping review: Barriers and facilitators to enrollment in pediatric oncology clinical trials

The first manuscript in this dissertation, *Barriers and Facilitators to Enrollment in Pediatric Oncology Clinical Trials*, investigated the literature to determine the currently known barriers and facilitators to enrollment in oncology clinical trials for children. Merely 60% of pediatric cancer patients receive therapy by participating in a clinical trial.[3] Clinical trials are the means by which new potential therapies for cancer and its symptoms are tested for their safety and efficacy before being marketed.[5] These clinical trials often face obstacles to enrollment and completion due to their increasing costs during a time when sponsors and participating sites have limited resources.[6,7] Also, clinical trial enrollment is challenging due to the uncertainty of a new intervention's effectiveness and potential side effects, both known and unknown.

Enrollment is important because a clinical trial's success is based upon having an adequate sample size to produce valid results.[8]

Accepted for publication in *Pediatric Nursing* journal, the scoping review was directed by Arksey and O'Malley's [9] methodological framework and ascertained barriers and facilitators to enrollment in pediatric oncology clinical trials. Findings from the review demonstrated trial-level barriers included lack of an available trial, trials closed to accrual, and eligibility criteria. Individual factors associated with enrollment included age, sex, race/ethnicity, insurance status, cancer characteristics, and motivation. Interpersonal factors included parents' desire for continuity of care by healthcare providers, physicians' discussions with parents and children about clinical trials, and physicians' attitudes about clinical trials. Organizational factors that influenced enrollment included local availability of a clinical trial and continuity of care. No studies of community or policy-level barriers and facilitators were found. The review's findings included a gap in theoretically based knowledge about trial-level barriers and facilitators to enrollment in pediatric oncology clinical trials.

Manuscript #2: Trial-level Factors Affecting Accrual and Completion of Oncology Clinical Trials: A Systematic Review

The second manuscript in this dissertation, *Trial-level Factors Affecting Accrual and Completion of Oncology Clinical Trials: A Systematic Review*, explores the literature to identify trial-level factors that affect accrual and/or completion of oncology clinical trials, gaps in the literature, and prospects for research in the future. Oncology clinical trials are known to terminate early or be extended due to inadequate accrual, negatively affecting the resources of trial sponsors and participating institutions.[6, 10, 11] Delayed

or early terminated trials hinder the marketing of new safe and effective cancer therapies for patients.

Guided by the PRISMA statement, a sample of the literature was systematically selected for the review.[12] Studies were included if they were: a) empirical studies that analyzed trial-level factors that influenced accrual and/or completion of oncology trials and b) studies that analyzed data from state, regional, national, or international clinical trial databases. The systematic review's findings indicated the following background factors were associated with oncology clinical trial accrual and/or completion: sponsor, number and location of participating institutions, competing trials, time of trial opening, and fast-track status. Disease-related factors included the annual incidence and type(s) of targeted cancer. Several types of treatment such as drugs, radiation and surgery were examined in the studies. Trial design factors included trial development time, eligibility criteria, randomization, sample size, trial phase, placebo use, and required protocol procedures and their timing. Future studies with a theoretical foundation could be conducted to assess the association between trial-level factors and accrual/trial completion. Researchers also could concurrently investigate background, disease-related, treatment-related, and trial design factors that affect accrual for specific cancers and populations.

Manuscript #3: Predictors of Early Termination of Pediatric Oncology Clinical Trials Due to Poor Accrual: An Exploratory Analysis

The third manuscript in this dissertation, *Predictors of Early Termination of Pediatric Oncology Clinical Trials Due to Poor Accrual: An Exploratory Analysis*, describes patterns in the presence of variables and completeness of data entry for

variables in the ClinicalTrials.gov database over the past 20 years for pediatric oncology clinical trials and investigates trial-related factors that may affect early termination of pediatric oncology clinical trials due to low accrual. Due to low patient participation, pediatric oncology clinical trials are often terminated early or extended. The Institute of Medicine (IOM) has urged for improvement in the selection, conduct and completion of oncology trials.[13]

The amount of available data in ClinicalTrials.gov differed among variables across different time periods that were based on the effective dates of regulations affecting ClinicalTrials.gov. Of the following trial-level factors, none were significantly associated ($p < 0.05$) with early termination of pediatric oncology trials: enrollment, primary purpose, intervention type, phase, interventional study model, allocation, arm type, number of arms, masking, primary end points, number of primary outcomes, sponsor, number of participating facilities, primary disease, and data monitoring committee. However, the use of a data and safety monitoring committee and number of primary outcomes warrant further investigation due to their odds ratios. None of the trial-level factors combined were predictive of early termination of pediatric oncology trials due to low accrual. Future research can build upon this study by including pediatric oncology clinical trials conducted throughout the world, rather than just those within the United States. In addition, researchers can examine additional variables in the ClinicalTrials.gov database that were not investigated in this study (e.g. eligibility criteria).

Contributions

The results of the individual manuscripts and the triangulation of their findings contribute to the science of clinical trials. The scoping review found a gap in theoretically based knowledge about trial-level barriers and facilitators to enrollment in pediatric oncology clinical trials. The gap in knowledge supported the conduct of manuscript #3, *Predictors of Early Termination of Pediatric Oncology Clinical Trials Due to Poor Accrual: An Exploratory Analysis*. Also, due to gap in knowledge about trial-level barriers and facilitators to enrollment in pediatric oncology clinical trials, currently known trial-level barriers and facilitators to enrollment in adult oncology clinical trials were investigated in the second manuscript, *Trial-level Factors Affecting Accrual and Completion of Oncology Clinical Trials: A Systematic Review.* Several trial-level barriers and facilitators to enrollment in adult oncology clinical trials were identified, such as enrollment, intervention type, phase, allocation, arm type, sponsor, number of participating facilities, primary disease. These trial-level barriers and facilitators were subsequently utilized as independent variables in the analysis reported in manuscript #3 to determine predictors of early termination of pediatric oncology clinical trials due to poor accrual. Other possible predictor variables were identified in ClinicalTrials.gov, which included primary purpose, number of primary outcomes, interventional study model, number of arms, and the use of a data and safety monitoring committee. As indicated in Manuscript #3, none of the examined independent variables were predictive of early termination of pediatric oncology trials due to low accrual. The basic information available in ClinicalTrials.gov may not be detailed enough to evaluate some important

factors, without having to code textual data on criteria factors and/or individually search for the trials in the literature to glean additional details.

The triangulation of the three manuscripts' findings contribute to the science of clinical trials by identifying possible predictors of early termination of pediatric oncology clinical trials due to poor accrual. National organizations, such as the Institute of Medicine (IOM), have called for improvements in clinical trials. The IOM has appealed for increased efficiency in clinical trials, higher rates of completion, and prioritization of the most feasible and needed trials.[14] Evidence from the literature reviews performed in this dissertation suggest that for pediatric oncology clinical trials to successfully complete in an efficient manner, knowledge of trial-level factors that affect accrual and completion of those trials is warranted.[5,15] In particular, knowledge of non-modifiable trial-level factors such as trial phase may also enable healthcare providers to educate patients, possibly increasing acceptance of and participation in trials.[6,15] Evidence from this dissertation also indicates knowledge of trial-level factors that affect accrual and completion of trials may also allow sponsors and institutions to accurately predict a trial's accrual and completion which, in turn, enables prioritization of the most feasible trials.[7]

This dissertation also contributes to the science of clinical trials by demonstrating additional research is needed to identify predictors of enrollment in pediatric oncology clinical trials. This is evidenced by trial-level barriers and facilitators identified in manuscripts #1 and #2 failing to align with the results of the exploratory analysis in manuscript #3 which did not identify any predictors of early termination of pediatric

oncology clinical trials due to poor accrual. Based on these findings, predictors of enrollment in pediatric oncology clinical trials may differ from those in adult oncology trials.

Limitations

This dissertation has limitations. The scoping and systematic reviews may not have included all available literature due to inadvertently omitted search terms. Since there was only one reviewer, studies included in the reviews could not be assessed for inter-rater reliability based on inclusion and exclusion criteria. A limitation of the third manuscript, an exploratory analysis of trial-related factors that may affect early termination of pediatric oncology clinical trials due to low accrual, was lack of inclusion of all clinical trials conducted worldwide. Some trials are not required to be registered on ClinicalTrials.gov.[16] No other clinical trial registries were utilized due to the technical difficulties in the identification and elimination of duplicate trials. Bias may also be present since only one database, which could contain inaccurate data, was utilized.[17]

Other limitations of this dissertation are related to changes in regulations over the last two decades which resulted in discrepancies in the type and completeness of data that investigators submitted into the database during that time frame.[18] The amount of available data differs among variables and across different time periods affected by new regulations. Other than variables pertaining to results, recent trials have more completeness of variables than those trials conducted in the more distant past, possibly skewing this study's results. Results could also differ based on the cut-off dates for time periods as it takes time for laws and policies to be fully implemented.[19] For example,

study design was not required to be entered on ClinicalTrials.gov until implementation in 2008 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). It is likely study design was entered for fewer trials in 2008 than 2010 due to the lag in sponsors' knowledge of and compliance to the Act. Therefore, there would be different percentages of completeness for the study design variable data for period 2 and period 3 if the cutoff for those periods was 2010 rather than 2008. If 2010 had been utilized as the cutoff date, the percentage of completeness for study design would likely have been higher for period 2 and period 3. Results could also differ based on the date of the dataset as sponsors/principal investigators can retrospectively update information on ClinicalTrials.gov.[20] Finally, some of the groups within variables were small. This increases the likelihood of type II errors, possibly resulting in missed identified predictors.

Lessons Learned

There were many lessons learned in the dissertation process. First, large databases such as ClinicalTrials.gov can be challenging to utilize as multiple strategies and much time may be required to successfully import data files into SPSS. Second, it is important to ensure the computer to be used for file import into SPSS and analyses has sufficient memory and processing capabilities. Third, after files are imported, additional variables need to be created and data correctly coded to facilitate analyses; this can be time-consuming. Labeling of variables is of the utmost importance for organization when many variables are present. Fourth, differences exist between missing data and data not present due to it not being required so both need to be coded and analyzed appropriately.

Fifth, many clinical trials cases are necessary when there are several variables and groups for chi-square analyses. The researcher was unable to perform all chi-square analyses that were originally planned due to this issue. Thus, groups were combined if appropriate and Fisher's exact test was performed.

Future Research

Future advancements in this area of scholarship specific to the program of trial-level research include an expansion of this dissertation's investigation of trial-related factors that may predict early termination of pediatric oncology clinical trials due to low accrual. Future analyses of ClinicalTrials.gov data will include clinical trials throughout the world, rather than merely those in the United States. Additional independent variables that were not included in the compendium's third manuscript due to time constraints will be investigated. For example, the specific types of eligibility criteria which will require manual review and coding as that variable is in free text format within the ClinicalTrials.gov dataset. This knowledge may further assist with the strategic design of pediatric oncology clinical trials to avoid inadequate accrual and early termination of the trials. The results from a future manuscript describing these analyses will drive subsequent studies evaluating strategies to offset the effects of trial-level factors that adversely impact accrual and trial completion.

Conclusion

The major findings from this body of scholarship suggest there may be trial-level factors that predict accrual and/or completion of pediatric oncology clinical trials. Additional studies examining trial-level factors should investigate pediatric oncology

trials that have been conducted worldwide and incorporate multiple trial databases such as ClinicalTrials.gov and European Union Drug Regulating Authorities Clinical Trials Database (EudraCT). The design of future oncology clinical trials should address approaches to minimize trial-level factors such as burdensome eligibility criteria and a single participating facility that are associated with or predictive of early trial termination or institute additional measures to offset the impact of the factors.

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Appendix A

Institutional Review Board for Human Research (IRB)
Office of Research Integrity (ORI)
Medical University of South Carolina

Harborview Office Tower
19 Hagood Ave., Suite 601, MSC857
Charleston, SC 29425-8570
Federal Wide Assurance # 1888

To: Cherie Hauck, Ph.D. Student

From: Amy Haynes, CIP
IRB Administrator II

Date: July 1, 2019

Re: Not Human Research Determination

This memo is in response to the submitted Not Human Research (NHR) application, ***Predictors of Early Termination of Pediatric Oncology Clinical Trials Due to Poor Accrual (Pro00087993)***. Based on your application, this project meets the Not Human Research criteria set forth by the Code of Federal Regulations (45CFR46) of:

a. the specimens and/or private information/data were not collected specifically for the currently proposed research project through an interaction/intervention with living individuals AND

b. the investigator(s) including collaborators on the proposed research cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

Therefore, this project has been deemed not to be human research and is not subject to oversight by the Medical University of South Carolina IRB. If there are any changes to the application you provided, please resubmit for a NHR determination.

Appendix B Glossary of Common Site Terms for ClinicalTrials.gov

Term	Definition
Accepts healthy volunteers	A type of eligibility criteria that indicates whether people who do not have the condition/disease being studied can participate in that clinical study.
Active comparator arm	An arm type in which a group of participants receives an intervention/treatment considered to be effective (or active) by health care providers.
Adverse event	An unfavorable change in the health of a participant, including abnormal laboratory findings, that happens during a clinical study or within a certain amount of time after the study has ended. This change may or may not be caused by the intervention/treatment being studied.
Age or age group	A type of eligibility criteria that indicates the age a person must be to participate in a clinical study. This may be indicated by a specific age or the following age groups: The age groups are: • Child (birth-17) • Adult (18-64) • Older Adult (65+)
All-cause mortality	A measure of all deaths, due to any cause, that occur during a clinical study.
Allocation	A method used to assign participants to an arm of a clinical study. The types of allocation are randomized allocation and nonrandomized.
Arm	A group or subgroup of participants in a clinical trial that receives a specific intervention/treatment, or no intervention, according to the trial's protocol.
Arm type	A general description of the clinical trial arm. It identifies the role of the intervention that participants receive. Types of arms include experimental arm, active

	comparator arm, placebo comparator arm, sham comparator arm, and no intervention arm.
Baseline characteristics	Data collected at the beginning of a clinical study for all participants and for each arm or comparison group. These data include demographics, such as age, sex/gender, race and ethnicity, and study-specific measures (for example, systolic blood pressure, prior antidepressant treatment).
Canceled submission	Indicates that the study sponsor or investigator recalled a submission of study results before quality control (QC) review took place. If the submission was canceled on or after May 8, 2018, the date is shown. After submission of study results, a study record cannot be modified until QC review is completed, unless the submission is canceled.
Certain agreements	Information required by the Food and Drug Administration Amendments Act of 2007. In general, this is a description of any agreement between the sponsor of a clinical study and the principal investigator (PI) that does not allow the PI to discuss the results of the study or publish the study results in a scientific or academic journal after the study is completed.
Certification	A sponsor or investigator may submit a certification to delay submission of results information if they are applying for FDA approval of a new drug or device, or new use of an already approved drug or device. A sponsor or investigator who submits a certification can delay results submission up to 2 years after the certification/extension first submitted date, unless certain events occur sooner.
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.

ClinicalTrials.gov identifier (NCT number)	The unique identification code given to each clinical study upon registration at ClinicalTrials.gov. The format is "NCT" followed by an 8-digit number (for example, NCT00000419).
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.
Contact	The name and contact information for the person who can answer enrollment questions for a clinical study. Each location where the study is being conducted may also have a specific contact, who may be better able to answer those questions.
Country	The Country field is used to find clinical studies with locations in a specific country.
Cross-over assignment	A type of intervention model describing a clinical trial in which groups of participants receive two or more interventions in a specific order. For example, two-by-two cross-over assignment involves two groups of participants. One group receives drug A during the initial phase of the trial, followed by drug B during a later phase. The other group receives drug B during the initial phase, followed by drug A. So during the trial, participants "cross over" to the other drug. All participants receive drug A and drug B at some point during the trial but in a different order, depending on the group to which they are assigned.
Data Monitoring Committee (DMC)	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.
Early Phase 1 (formerly listed as Phase 0)	A phase of research used to describe exploratory trials conducted before traditional phase 1 trials to investigate how or whether a drug affects the body. They involve very limited human exposure to the drug and have no therapeutic or diagnostic goals (for example, screening studies, microdose studies).
Eligibility criteria	The key requirements that people who want to participate in a clinical study must meet or the characteristics they must have. Eligibility criteria consist of both inclusion criteria (which are required for a person to participate in the study) and exclusion criteria (which prevent a person from participating). Types of eligibility criteria include whether a study accepts healthy volunteers, has age or age group requirements, or is limited by sex.
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.
Exclusion criteria	A type of eligibility criteria. These are reasons that a person is not allowed to participate in a clinical study.
Expanded access	A way for patients with serious diseases or conditions who cannot participate in a clinical trial to gain access to a medical product that has not been approved by the U.S. Food and Drug Administration (FDA). Also called compassionate use. There are different expanded access types.
Expanded access status	• Available: Expanded access is currently available for this investigational treatment, and patients who are not participants in the clinical study may be able to gain access to the drug, biologic, or medical device being studied. • No longer available: Expanded access was available for this intervention previously but is not currently available and will not be available in the future.

	• Temporarily not available: Expanded access is not currently available for this intervention but is expected to be available in the future. • Approved for marketing: The intervention has been approved by the U.S. Food and Drug Administration for use by the public.
Expanded access type	Describes the category of expanded access under U.S. Food and Drug Administration (FDA) regulations. There are three types of expanded access: • Individual Patients: Allows a single patient, with a serious disease or condition who cannot participate in a clinical trial, access to a drug or biological product that has not been approved by the FDA. This category also includes access in an emergency situation. • Intermediate-size Population: Allows more than one patient (but generally fewer patients than through a Treatment IND/Protocol) access to a drug or biological product that has not been approved by the FDA. This type of expanded access is used when multiple patients with the same disease or condition seek access to a specific drug or biological product that has not been approved by the FDA. • Treatment IND/Protocol: Allows a large, widespread population access to a drug or biological product that has not been approved by the FDA. This type of expanded access can only be provided if the product is already being developed for marketing for the same use as the expanded access use.
Experimental arm	An arm type in which a group of participants receives the intervention/treatment that is the focus of the clinical trial.
Extension request	In certain circumstances, a sponsor or investigator may request an extension to delay the standard results submission deadline (generally one year after

	the primary completion date). The request for an extension must demonstrate good cause (for example, the need to preserve the scientific integrity of an ongoing masked trial). All requests must be reviewed and granted by the National Institutes of Health. This process for review and granting of extension requests is being developed.
Factorial assignment	A type of intervention model describing a clinical trial in which groups of participants receive one of several combinations of interventions. For example, two-by-two factorial assignment involves four groups of participants. Each group receives one of the following pairs of interventions: (1) drug A and drug B, (2) drug A and a placebo, (3) a placebo and drug B, or (4) a placebo and a placebo. So during the trial, all possible combinations of the two drugs (A and B) and the placebos are given to different groups of participants.
First posted	The date on which the study record was first available on ClinicalTrials.gov. There is typically a delay of a few days between the date the study sponsor or investigator submitted the study record and the first posted date.
First submitted	The date on which the study sponsor or investigator first submitted a study record to ClinicalTrials.gov. There is typically a delay of a few days between the first submitted date and the record's availability on ClinicalTrials.gov (the first posted date).
First submitted that met QC criteria	The date on which the study sponsor or investigator first submits a study record that is consistent with National Library of Medicine (NLM) quality control (QC) review criteria. The sponsor or investigator may need to revise and submit a study record one or more times before NLM's QC review criteria are met. It is the responsibility of the sponsor or investigator to ensure that the study record is consistent with the NLM QC review criteria.
Food and Drug Administration	U.S. Public Law 110-85, which was enacted on September 27, 2007. Section 801 of FDAAA amends Section 402 of the U.S. Public Health Service Act to

Amendments Act of 2007, Section 801 (FDAAA 801)	expand ClinicalTrials.gov and create a clinical study results database.
Funder type	Describes the organization that provides funding or support for a clinical study. This support may include activities related to funding, design, implementation, data analysis, or reporting. Organizations listed as sponsors and collaborators for a study are considered the funders of the study. ClinicalTrials.gov refers to four types of funders: • U.S. National Institutes of Health • Other U.S. Federal agencies (for example, Food and Drug Administration, Centers for Disease Control and Prevention, or U.S. Department of Veterans Affairs) • Industry (for example: pharmaceutical and device companies) • All others (including individuals, universities, and community-based organizations)
Gender-based eligibility	A type of eligibility criteria that indicates whether eligibility to participate in a clinical study is based a person's self-representation of gender identity or gender (yes, no). Gender is distinct from sex.
Group/cohort	A group or subgroup of participants in an observational study that is assessed for biomedical or health outcomes.
Human subjects protection review board	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. Also called an institutional review board, or IRB, or an ethics committee.
Inclusion criteria	A type of eligibility criteria. These are the reasons that a person is allowed to participate in a clinical study.

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.
Informed consent form (ICF)	The document used in the informed consent or process.
Intervention model	The general design of the strategy for assigning interventions to participants in a clinical study. Types of intervention models include: single group assignment, parallel assignment, cross-over assignment, and factorial assignment.
Intervention/treatment	A process or action that is the focus of a clinical study. Interventions include drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available. Interventions can also include noninvasive approaches, such as education or modifying diet and exercise.
Interventional study (clinical trial)	A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study's protocol. Participants may receive diagnostic, therapeutic, or other types of interventions.
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.
Last update posted	The most recent date on which changes to a study record were made available on ClinicalTrials.gov. There may be a delay between when the changes were submitted to ClinicalTrials.gov by the study's sponsor or investigator (the last update submitted date) and the last update posted date.
Last update submitted	The most recent date on which the study sponsor or investigator submitted changes to a study record to ClinicalTrials.gov. There is typically a delay of a few

	days between the last update submitted date and when the date changes are posted on ClinicalTrials.gov (the last update posted date).
Last update submitted that met QC criteria	The most recent date on which the study sponsor or investigator submitted changes to a study record that are consistent with National Library of Medicine (NLM) quality control (QC) review criteria. It is the responsibility of the sponsor or investigator to ensure that the study record is consistent with the NLM QC review criteria.
Last verified	The most recent date on which the study sponsor or investigator confirmed the information about a clinical study on ClinicalTrials.gov as accurate and current. If a study with a recruitment status of recruiting; not yet recruiting; or active, not recruiting has not been confirmed within the past 2 years, the study's recruitment status is shown as unknown.
Listed location countries	Countries in which research facilities for a study are located. A country is listed only once, even if there is more than one facility in the country. The list includes all countries as of the last update submitted date; any country for which all facilities were removed from the study record are listed under removed location countries.
Location terms	In the search feature, the Location terms field is used to narrow a search by location-related terms other than Country, State, and City or distance. For example, you may enter a specific facility name (such as National Institutes of Health Clinical Center) or a part of a facility name (such as Veteran for studies listing Veterans Hospital or Veteran Affairs in the facility name). Note: Not all study records include this level of detail about locations.
Masking	A clinical trial design strategy in which one or more parties involved in the trial, such as the investigator or participants, do not know which participants have been assigned which interventions. Types of masking include: open label, single blind masking, and double-blind masking.

NCT number	A unique identification code given to each clinical study record registered on ClinicalTrials.gov. The format is "NCT" followed by an 8-digit number (for example, NCT00000419). Also called the ClinicalTrials.gov identifier.
No intervention arm	An arm type in which a group of participants does not receive any intervention/treatment during the clinical trial.
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. A patient registry is a type of observational study.
Observational study model	The general design of the strategy for identifying and following up with participants during an observational study. Types of observational study models include cohort, case-control, case-only, case-cross-over, ecologic or community studies, family-based, and other.
Other adverse event	An adverse event that is not a serious adverse event, meaning that it does not result in death, is not life-threatening, does not require inpatient hospitalization or extend a current hospital stay, does not result in an ongoing or significant incapacity or interfere substantially with normal life functions, and does not cause a congenital anomaly or birth defect; it also does not put the participant in danger and does not require medical or surgical intervention to prevent one of the results listed above.
Other study IDs	Identifiers or ID numbers other than the NCT number that are assigned to a clinical study by the study's sponsor, funders, or others. These numbers may include unique identifiers from other trial registries and National Institutes of Health grant numbers.

Other terms	In the search feature, the Other terms field is used to narrow a search. For example, you may enter the name of a drug or the NCT number of a clinical study to limit the search to study records that contain these words.
Outcome measure	For clinical trials, a planned measurement described in the protocol that is used to determine the effect of an intervention/treatment on participants. For observational studies, a measurement or observation that is used to describe patterns of diseases or traits, or associations with exposures, risk factors, or treatment. Types of outcome measures include primary outcome measure and secondary outcome measure.
Parallel assignment	A type of intervention model describing a clinical trial in which two or more groups of participants receive different interventions. For example, a two-arm parallel assignment involves two groups of participants. One group receives drug A, and the other group receives drug B. So during the trial, participants in one group receive drug A "in parallel" to participants in the other group, who receive drug B.
Participant flow	A summary of the progress of participants through each stage of a clinical study, by study arm or group/cohort. This includes the number of participants who started, completed, and dropped out of the study.
Patient registry	A type of observational study that collects information about patients' medical conditions and/or treatments to better understand how a condition or treatment affects patients in the real world.
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. -typically 20-80 participants[1]
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. -typically 100 – 300 participants[1]
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. -typically 1,000 – 3,000 participants[1]
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.
Phase Not Applicable	Describes trials without FDA-defined phases, including trials of devices or behavioral interventions.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Placebo comparator arm	An arm type in which a group of participants receives a placebo during a clinical trial.
Primary completion date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies

	with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures. The "estimated" primary completion date is the date that the researchers think will be the primary completion date for the study.
Primary outcome measure	In a clinical study's protocol, the planned outcome measure that is the most important for evaluating the effect of an intervention/treatment. Most clinical studies have one primary outcome measure, but some have more than one.
Primary purpose	The main reason for the clinical trial. The types of primary purpose are: treatment, prevention, diagnostic, supportive care, screening, health services research, basic science, and other.
Principal investigator (PI)	The person who is responsible for the scientific and technical direction of the entire clinical study.
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.
Quality control (QC) review	National Library of Medicine (NLM) staff perform a limited review of submitted study records for apparent errors, deficiencies, or inconsistencies. NLM staff identify potential major and advisory issues and provide comments directly to the study sponsor or investigator. Major issues identified in QC review must be addressed or corrected (see First submitted that met QC criteria and Results first submitted that met QC criteria). Advisory issues are suggestions to help improve the clarity of the record. NLM staff do not verify the scientific validity or relevance of the submitted information. The study sponsor or investigator is responsible for ensuring that the studies follow all applicable laws and regulations.
Randomized allocation	A type of allocation strategy in which participants are assigned to the arms of a clinical trial by chance.

Recruitment status	• Not yet recruiting: The study has not started recruiting participants. • Recruiting: The study is currently recruiting participants. • Enrolling by invitation: The study is selecting its participants from a population, or group of people, decided on by the researchers in advance. These studies are not open to everyone who meets the eligibility criteria but only to people in that particular population, who are specifically invited to participate. • Active, not recruiting: The study is ongoing, and participants are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled. • Suspended: The study has stopped early but may start again. • Terminated: The study has stopped early and will not start again. Participants are no longer being examined or treated. • Completed: The study has ended normally, and participants are no longer being examined or treated (that is, the last participant's last visit has occurred). • Withdrawn: The study stopped early, before enrolling its first participant. • Unknown: A study on ClinicalTrials.gov whose last known status was recruiting; not yet recruiting; or active, not recruiting but that has passed its completion date, and the status has not been last verified within the past 2 years.
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.
Removed location countries	Countries that appeared under listed location countries but were removed from the study record by the sponsor or investigator.

Reporting group	A grouping of participants in a clinical study that is used for summarizing the data collected during the study. This grouping may be the same as or different from a study arm or group.
Responsible party	The person responsible for submitting information about a clinical study to ClinicalTrials.gov and updating that information. Usually the study sponsor or investigator.
Results database	A structured online system, such as the ClinicalTrials.gov results database, that provides the public with access to registration and summary results information for completed or terminated clinical studies. A study with results available on ClinicalTrials.gov is described as having the results "posted." Note: The ClinicalTrials.gov results database became available in September 2008. Older studies are unlikely to have results available in the database.
Results delayed	Indicates that the sponsor or investigator submitted a certification or extension request.
Results first posted	The date on which summary results information was first available on ClinicalTrials.gov. There is typically a delay between the date the study sponsor or investigator first submits summary results information (the results first submitted date) and the results first posted date.
Results first submitted	The date on which the study sponsor or investigator first submits a study record with summary results information. There is typically a delay between the results first submitted date and when summary results information becomes available on ClinicalTrials.gov (the results first posted date).
Results first submitted that met QC criteria	The date on which the study sponsor or investigator first submits a study record with summary results information that is consistent with National Library of Medicine

	(NLM) quality control (QC) review criteria. The sponsor or investigator may need to revise and submit results information one or more times before NLM's QC review criteria are met. It is the responsibility of the sponsor or investigator to ensure that the study record is consistent with the NLM QC review criteria.
Results returned after quality control review	The date on which the National Library of Medicine provided quality control (QC) review comments to the study sponsor or investigator. The sponsor or investigator must address major issues identified in the review comments. If there is a date listed for results returned after quality control review, but there is not a subsequent date listed for results submitted to ClinicalTrials.gov, this means that the submission is pending changes by the sponsor or investigator.
Results submitted to ClinicalTrials.gov	Indicates that the study sponsor or investigator has submitted summary results information for a clinical study to ClinicalTrials.gov but the quality control (QC) review process has not concluded. The results submitted date indicates when the study sponsor or investigator first submitted summary results information or submitted changes to summary results information. Submissions with changes are typically in response to QC review comments from the National Library of Medicine (NLM). If there is a date listed for results submitted to ClinicalTrials.gov, but there is not a subsequent date listed for results returned after quality control review, this means that the submission is pending review by NLM.
Secondary outcome measure	In a clinical study's protocol, a planned outcome measure that is not as important as the primary outcome measure for evaluating the effect of an intervention but is still of interest. Most clinical studies have more than one secondary outcome measure.
Serious adverse event	An adverse event that results in death, is life-threatening, requires inpatient hospitalization or extends a current hospital stay, results in an ongoing or significant incapacity or interferes substantially with normal life functions, or causes a congenital anomaly or birth defect.

	Medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered serious adverse events if they put the participant in danger or require medical or surgical intervention to prevent one of the results listed above.
Sex	A type of eligibility criteria that indicates the sex of people who may participate in a clinical study (all, female, male). Sex is a person's classification as female or male based on biological distinctions. Sex is distinct from gender-based eligibility.
Sham comparator arm	An arm type in which a group of participants receives a procedure or device that appears to be the same as the actual procedure or device being studied but does not contain active processes or components.
Single group assignment	A type of intervention model describing a clinical trial in which all participants receive the same intervention/treatment.
Sponsor	The organization or person who initiates the study and who has authority and control over the study.
State	The State field is used to find clinical studies with locations in a specific state within the United States. If you choose United States in the Country field, you can search for studies with locations in a specific state.
Statistical analysis plan (SAP)	The written description of the statistical considerations and methods for analyzing the data collected in the clinical study.
Status	Indicates the current recruitment status or the expanded access status.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events (that is, the last participant's last visit). The "estimated" study completion date is the date that the researchers think will be the study completion date.

Study design	The investigative methods and strategies used in the clinical study.
Study documents	Refers to the type of documents that the study sponsor or principal investigator may add to their study record. These include a study protocol, statistical analysis plan, and informed consent form.
Study IDs	Identifiers that are assigned to a clinical study by the study's sponsor, funders, or others. They include unique identifiers from other trial study registries and National Institutes of Health grant numbers. Note: ClinicalTrials.gov assigns a unique identification code to each clinical study registered on ClinicalTrials.gov. Also called the NCT number, the format is "NCT" followed by an 8-digit number (for example, NCT00000419).
Study record	An entry on ClinicalTrials.gov that contains a summary of a clinical study's protocol information, including the recruitment status; eligibility criteria; contact information; and, in some cases, summary results. Each study record is assigned a ClinicalTrials.gov identifier, or NCT number.
Study registry	A structured online system, such as ClinicalTrials.gov, that provides the public with access to summary information about ongoing and completed clinical studies.
Study results	A study record that includes the summary results posted in the ClinicalTrials.gov results database. Summary results information includes participant flow, baseline characteristics, outcome measures, and adverse events (including serious adverse events).
Study start date	The actual date on which the first participant was enrolled in a clinical study. The "estimated" study start date is the date that the researchers think will be the study start date.
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.

Submitted date	The date on which the study sponsor or investigator submitted a study record that is consistent with National Library of Medicine (NLM) quality control (QC) review criteria.
Title	The official title of a protocol used to identify a clinical study or a short title written in language intended for the lay public.
Title acronym	The acronym or initials used to identify a clinical study (not all studies have one). For example, the title acronym for the Women's Health Initiative is "WHI."
U.S. Agency for Healthcare Research and Quality (AHRQ)	An agency within the U.S. Department of Health and Human Services. AHRQ's mission is to produce evidence to make health care safer, higher quality, more accessible, equitable, and affordable, and to work within the U.S. Department of Health and Human Services and with other partners to make sure that the evidence is understood and used.
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.
Unknown	A type of recruitment status. It identifies a study on ClinicalTrials.gov whose last known status was recruiting; not yet recruiting; or active, not recruiting but that has passed its completion date, and the status has not been verified within the past 2 years. Studies with an unknown status are considered closed studies.

ClinicalTrials.gov. Glossary of common site terms. [Internet]. [place unknown] [updated 2020 Jan; cited 2020 Oct 21]. Available from: https://clinicaltrials.gov/ct2/about-studies/glossary

[1]National Institutes of Health. The Basics. [Internet]. Bethesda [MD][updated 2017 Oct 20; cited 2020 Oct 21]. [Available from: https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics