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# RACE Act Prompts More Pediatric Clinical Trials for Oncology Drug Developers


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## Abstract

Many providers prescribe drugs off-label to pediatric patients, despite the fact that there have been few pediatric trials for many of these drugs. To meet this need, The Food and Drug Administration (FDA) is enacting the Research to Accelerate Cures & Equity (RACE) for Children Act, which amends and updates the Pediatric Research Equity Act (PREA). RACE Act will require new drugs intended for adult cancer treatment to also be studied in pediatric cancers when the molecular target of the drug is relevant to pediatric oncology. This paper discusses the need for and the importance of pediatric research, the RACE Act, and how it applies to precision medicine. It will also address pediatric dosing challenges, oral formulation considerations, involving pediatric patients into adult trials, study design, and master protocols. Finally, this paper claims the need for more knowledge sooner. This will broaden developments in pediatric cancer, and prioritize diagnoses with a need to improve overall survival rate and progression-free survival, with the goal to lessen long-term impact. It is by implementing RACE Act that the stage will be set for future development of novel therapies.


## Setting the Stage

Past and current legislation have tried to make a difference in the world of pediatric oncology. In the mid-1900s, without good, controlled studies, many drugs had negative effects on children. This ultimately led to regulation making it difficult to conduct clinical trials in pediatric patients.[1] With limited pediatric studies came inadequate pediatric labeling and lack of sound evidence on medication use and appropriate treatment for many pediatric conditions. Dr. Harry Shirkey, the first chairman of the American Academy of Pediatrics (AAP) committee on drugs, coined children as "therapeutic orphans" in response to pediatric warnings inserted into drug labeling.[2] Shirkey claimed that such warnings regarding drug use in the pediatric population deprived children of modern drugs, as they were studied very little in the pediatric population.

The 1997 Food and Drug Administration Modernization Act (FDAMA) rewarded pharmaceutical companies with patent extensions for running pediatric trials. In 2002, it was reauthorized through the Best Pharmaceutical for Children Act (BPCA) and provided a manufacturer with exclusivity in return for voluntarily conducting pediatric studies. The FDA issued the Pediatric Research Equity Act (PREA) in 2003, which requires pediatric studies be considered for all adult drug programs. However, PREA allows for pediatric waivers based on adult indications, and since many adult cancer types rarely occur in pediatrics, many manufacturers received waivers for their drugs to be studied in pediatric trials. In fact, the impact of BPCA on childhood cancer drug development has been modest, and the impact of PREA has been thus far minimal.[3] The National Pediatric Cancer Foundation reported that, since 1980, fewer than 10 drugs have been developed for use in children with cancer, as compared with hundreds of drugs that have been created exclusively for adults with cancer.[4]

Industry and oncologists often use "best guesses" from adult data regarding chemotherapy agents for use in children. This practice—though without any other options—leads to the off-label prescribing of highly toxic drugs in life-threatening conditions in pediatrics because the necessary information is not available for pediatric prescribers until several years after the initial approval in adults. On average, it takes 8 years from the time a drug product is approved for use in adults until the label is updated to include pediatric data.[5]

The need for improved pediatric cancer therapies continues as pediatric cancer has devastating impact. According to the Surveillance, Epidemiology, and End Results (SEER) Program, despite improvements in overall childhood cancer cure rates, the incidence continues to climb from 17/100,000 children in 2007 to 19/100,000 children in 2016.[6] Pediatric cancer is the largest cause of death by disease in children and young adults ages 1-19 years. While the average years of life lost by adult cancer patients are, for example, 10 years for prostate cancer and 18.8 years for breast cancer, pediatric oncology deaths rob, on average, 68.3 years of life per child death.[7] Curesearch data shows that the average age of death is 10.4 years.[17] We can do better.

## RACE Act

The FDA's Research to Accelerate Cures & Equity (RACE) for Children Act goes into effect on August 18, 2020. The act amends and updates PREA. It will require new drugs intended for adult cancer treatment to also be studied in pediatric cancers when the molecular target of the drug is relevant to pediatric oncology.

For example, the cancerous cells in an adult lung cancer may use the same process to grow as a cancer that manifests in a different part of a child's body. If a cancer drug affects the progression of that process in adults and is deemed by the FDA to also have a relevant target in pediatric cancer, then that drug will need to be studied in the pediatric indication as well as the planned adult indication, even if the prospective indications are different. This is largely due to our increasing understanding of precision medicine. According to the FDA, the extension of precision medicine into pediatrics has been both delayed and limited in part due to waivers as pediatric studies are presently based on indication. Often, the types of cancers in pediatric patients and adults differ in etiology, biology, organ of origin, and natural history which could result in pediatric trials not being required under PREA.[8] We know that the mechanism which drives the malignancy may be the same, and that is what precision medicine is targeting for adult cancer, and already some trials for pediatric cancer. We can do better by prioritizing this research in pediatrics.

## Precision Medicine

One of the first precision oncology clinical trials occurred in adults with progressive disease despite multiple therapies and was reported in 2010 by von Hoff and colleagues.[9] This study found that, not only could molecular targets be identified in patient tumors—that enough data could be generated to develop a treatment regimen based on that target—but it also showed that 27% of the patients demonstrated longer progression-free survival when compared to patients who received the clinician's best choice for therapy. This trial also highlighted that patients with refractory tumors may have simple targets which we already can treat.

In another precision trial, Drilon *et al* reported in 2018 that larotrectinib had significant antitumor activity in patients with TRK fusion-positive cancer regardless of the age of the patient or the manifestation of disease.[10] Participants in this study ranged in age from 4 months to 76 years and had one of 17 different types of unique TRK fusion-positive tumors.

We should also consider imatinib, the first personalized anticancer drug for chronic myeloid leukemia, which was known from early on to work for both adults and children.[11] That same drug's use for Philadelphia-positive acute lymphoblastic leukemia, when used along with standard therapy, improved the 3-year survival rate from 35% to 80%.[12] Many of these patients ultimately avoided hematopoietic cell transplantation which poses greater risks.[13]

On a very large scale, The National Cancer Institute and the Children's Oncology Group (COG) are conducting the pediatric Molecular Analysis for the Therapy Choice (MATCH) study. MATCH is a phase II basket trial in which patients aged 1-21 years with relapsed or refractory solid tumors or lymphomas receive drugs paired to their specific tumor molecular abnormalities. [14] Approximately 25% of patients with a tumor submitted for pediatric MATCH screening have been assigned to an investigational therapy facilitating the evaluation of molecularly targeted agents in biomarker-positive pediatric cohorts through a collaborative, nationwide study in an 18-month period. The study is still ongoing and expected to be completed in September 2027 with a goal of 1,500 participants.[15]

There are unique challenges and substantial considerations that need to be well thought-out before instituting pediatric trials. Children have unique growth and developmental characteristics that will be discussed in more detail in the next section. Cohen *et al* conducted a systematic review of 109 pediatric oncology phase I trials published from 2012-2017 describing the safety profile and response outcomes. They found that targeted therapy trials were associated with lower rates of dose limiting toxicity than cytotoxic therapy trials, while achieving comparable objective response rates when compared against historical literature, generated when targeted therapies were less prevalent.[16] Findings like these could also be interpreted to mean targeted therapies will reduce late effects, but more studies will need to be done to follow patients closely after receiving precision medicine-based treatment.

Surviving cancer is not where this ends. With conventional therapy, many survivors are left with significant impacts on endocrine, cardiovascular, hearing, urinary, immunological, mental, and psychological status for many years and still live with the fear of reoccurrence post-treatment. Survivors of pediatric cancer therapies are at risk for secondary cancers due to cytotoxic agents or radiation therapy. CureSearch data indicate that 60% of survivors develop late effects.[17] It will be important to maintain our high, long-term follow up standards for children being treated with precision therapies, as well as the more conventional cytotoxic therapies. Resources to enable such ongoing long-term follow ups are critical and should be highly stressed in all precision medicine trials.

## Pediatric Dosing Challenges

The challenges in pediatric oncology trials which result from the growth and development of pediatric patients are many, and as mentioned in the opening remarks, ultimately led to this population being ignored when it comes to searching for better therapies. Pediatric patients are not just little adults.[18] "A child is not just half an adult to be given half the adult dose".[19] Simple allometric dose adjustment is often inadequate, and calculating dosages is challenging, particularly at the stage of selecting appropriate starting doses in pediatrics. [20] There has been a view that drug use in pediatrics should not be started until long-term safety data is well known in the adult population. Waiting that long could certainly delay children's access to therapies. In a recent analysis of 25 molecularly targeted agents approved by the FDA or European Medicines Agency (EMA) for adult cancers and evaluated in pediatric cancers, the toxicities in children associated with 24 were similar to those observed in adult patients. The main pharmacokinetic (PK) parameters were comparable as well, except for drugs with a narrow therapeutic index.[21]

Although the practice for dose administration is commonly based on body surface area for many cytotoxic medications, this is seldom the case for targeted therapies. For these therapies, fixed dosing precludes the need for body size normalization and dosing errors, especially in the infant group where accurate metered dosing is particularly problematic.[22] The intent of early phase I trials is to establish the recommended dose and/or schedule for new drugs or drug combination for phase II trials. The guiding principle is to avoid exposing too many patients to subtherapeutic doses while preserving safety and maintaining rapid accrual.[23] Studies in pediatric subjects are typically conducted after a therapeutic dose has been determined in adult studies with similar disease characteristics. If the disease progression and PK/pharmacodynamic (PD) relationships can be expected to be similar between pediatric and adult subjects, then an initial cohort of subjects for PK characterization to select a dose that provides similar exposure to the adult therapeutic dose can be followed by larger expansion cohort, without evaluation of multiple doses. This is especially true for targeted therapies that do not have a narrow therapeutic index, and tend to have better safety profiles compared to cytotoxic drugs.[24] Given the rarity of pediatric cancer, and thus potential enrollment numbers, the approach of limiting the initial or dose-escalation cohort to a few doses allows enrollment of sufficient numbers of subjects across age ranges to provide a better understanding of PK comparability to the adult population. This approach also addresses the objective of including a wide variety of tumor types and age ranges.

When the safety profile or disease similarity cannot be ascertained, then a more extensive study for PK characterization and dose finding may be required. Models such as 3+3, rolling 6, or Bayesian designs like the continual reassessment method or adaptive logistic regression design are commonly used in dose escalation trials.[25] Paoletti *et al* reviewed pediatric dose-finding studies and concluded that for approximately 75% of the molecularly targeted agents studied, the pediatric recommended phase II dose was similar (90-130%) to the adult recommended phase II dose, and to the FDA-approved dose in adults.[26] For the dose expansion phase, an adaptive and Bayesian design could be used to ensure that a minimal number of subjects are exposed to a drug that does not show therapeutic benefit.[27] If a maximum tolerated dose has not been reached, it is reasonable to consider an expansion cohort of children to be dosed at the same recommended phase II dose as adults. If a maximum tolerated dose has been reached, then dosing children at 80% of the adult dose, or at the next lower tested dose level, followed by dose escalation, if tolerated and assuming the administered dose will provide exposure equivalent to target exposure in adults, is considered reasonable.[28]

Dose benchmarks such as these increase the likelihood that patients will benefit as they are near the adult dosage, while still recognizing that their bodies may not yet be fully equipped to handle full adult dosing. Incorporating known, similar data from adult trials to pediatrics trials, such as toxicity profile, exposure response data, and clinical profile of the drug, can help to ensure that given dosages to pediatric patients in trials will have benefit as well as be safe. The exceptions are, as always, those agents with narrow therapeutic index, and particularly drugs with suspected differences in the volume of distribution, where the more traditional escalation schedule with an emphasis on safety should be considered.

## Oral Formulation Considerations

Oral drug delivery is recognized as a benefit for many, especially for high portability, ease of administration, and as a less invasive and time-consuming form of treatment compared to intravenous administration. Some regulatory authorities may require age-appropriate formulations that do not restrict dosing flexibility or present palatability issues for long-term usage. Liquid formulations are often prescribed for the pediatric patient and offer many obvious benefits such as specific dosing, ease of swallowing for some pediatric patients compared to tablets, and allowing for administration through a gastric tube, which may be common in many pediatric populations with special needs. Liquid dosing volumes should be minimal to reduce exposure to the preservatives in the liquid and electrolytes that could cause serious imbalances, especially in neonates or very small children. Smaller amounts also help by reducing coating in the mouth, which may affect taste and therefore palatability.[29] With very small volumes, careful instruction needs to be provided to minimize the possibility of overdosing. Too small a volume may also be a concern for a child with doses administered via a nasogastric or surgically implanted gastric tube, due to the possibility of the entire dose not reaching the stomach when administered. Careful consideration of liquid formulations and their effect on absorption and bioavailability will also need to be undertaken. Sugar alcohols placed in liquid medications can have an effect on absorption and bioavailability by increasing gastrointestinal fluid volume, leading to reduced small intestinal transit time, possibly leading to lower efficacy in certain pediatric age groups, and thus affecting the proper dose needed.[30]

The ages at which alternative formulations are tolerated may be surprising. Oral dissolving tablets have been developed into mini dissolving tablets and are becoming widely accepted. Studies have shown that children as young as 6-12 months of age can swallow an oral dissolving mini tablet with a diameter of 1-2mm.[31] Van Reit Nales *et al* found in their trial which administered four oral placebos (small 4mm tablets, powder, suspension, and syrup) to children between the ages of 1-4 years that the tablets were the best accepted formulation, and that the tablets and syrup were the most preferred.[32]

Palatability is an overarching term encompassing not only taste but also whether the formulation is agreeable or acceptable to the taker. Palatability should always be considered in pediatrics, as children often reject medicines they dislike. Many younger children will automatically refuse, fight, or spit out a drug whose taste or texture is not pleasant. Garruti de Medeiros and Santa Garruti conducted a literature review and found that flavor is one of the main determinants for medication compliance in pediatrics. Palatability testing with children is the most reliable method for assessing formulations for this population and should be carried out before new formulations are introduced on the market and across a wide variety of ages and cultural contexts.[33] Even those that are considered acceptable at first may become a source of contention for a family over time, so acceptability needs to be monitored.

There are particular points in a pediatric patient's course of therapy that may make oral medicines problematic, leading to withdrawal from a clinical trial. Patients may have various physical declines, such as a brain tumor impacting neurological swallowing function, post-therapy mucositis, or an infection, which put a patient's resources and general abilities at a less than ideal level, and which may be unsafe for oral drug administration. Being thoughtful and having a variety of dosing options is ideal but sometimes impractical.

As always, attention should be paid to strict instructions to take the medication with or without food; pediatric patients may have a stronger will than that of their drug administrator. A drug's bioavailability that is impacted by food content in

the stomach may be especially problematic given a child's often variable intake or restricted diets due to therapy or family preference.

## Including Pediatric Patients in Adult Trials

There are challenges in executing pediatric oncology clinical trials. Simply by the nature of rare disease, pediatric oncology studies often lag behind adult studies. In the US, rare disease is defined in the 1983 Orphan Drug Act as <200,000 patients diagnosed. According to CureSearch, 15,300 children, adolescents, and young adults (ages 0-19 years) will be diagnosed with cancer each year. Approximately 25% of those diagnoses are leukemia, and 25% are central nervous system tumors. The other pediatric cancer diagnoses make up 2-6% each.[34] However, while the actual incidence is low, within the context of master trials, the patient data can be obtained while still utilizing precision medicine.

The FDA has published guidelines entitled "Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials," which state that drug development in children could be accelerated by reducing the lower age limit of adult trials and allowing adolescent patients access to those trials, as well as access to early first in human phase I studies.[35] The physiological maturation of the pediatric patient population needs to be studied and the ways in which the drug may impact the growing body must be considered. There are many physiologic similarities between adolescents and adults. For example, children 12 years of age and older have the same percentages of total body water, extracellular fluid, and intracellular fluid, and the same creatinine clearance as adults.[36] This suggests that the volume of distribution of drugs is likely to be similar. Certain enzymes in the liver and intestine mature as early as 2 years of age (cytochrome P450 CYP3A) to as late as 12 years (CYP2D6).[37] Thus, from a PK perspective, similarities could be expected between adolescents aged 12-17 and adults for certain drugs depending on enzymatic function. The fear of enrolling adolescents in adult trials probably stems, at least in part, from warnings based on reported toxicities in preterm newborns treated with antibiotics in the 1950s, which led to lawsuits in the US.[38]

Data from all pediatric patients were combined rather than looking at specific ages and the maturing body. Such an approach would be valid if children remained as vulnerable as premature newborns until their 17th birthday, but that is not the case.

Thus, potential strategies to support enrollment of adolescents include reducing adult trial inclusion criteria to 12 years of age for phase II trials and allowing adolescents to participate in phase I trials where there is scientific rationale and potential therapeutic benefit such as the presence of a drug target. These strategies are endorsed by the American Society of Clinical Oncology and Friends of Cancer Research[39], the Innovative Therapies for Children with Cancer[40], ACCELERATE[41], and more recently by the FDA.[42] Taking that further, and on the basis of scientific evidence where the disease, safety, PK, and dosages in adolescents were comparable to those in adults[43], some have recommended that adolescents be included in adult oncology clinical trials and/or first in patient studies to avoid the lag time that currently hinders pediatric drug development and access to useful therapies.

It is important to have investigators committed to the introduction and support of enrolling a patient in a clinic trial. Stagnant outcomes for adolescents and young adults (AYAs) 15-39 years of age with cancer are partly attributed to poor enrollment into clinical trials.[44] In other words, enroll in a clinical trial at onset, and you have already improved your chances. There are many complex needs of adolescents and young adults, such as changing body image, seeking independence, and life plans to name a few. Many hospitals and providers are not equipped to take on such unique challenges. Searching for pediatric institutions that accept young adults, but more importantly recognize that outcomes are better when enrolled in a trial, is of paramount importance. Allowing for a young adult recently diagnosed with medulloblastoma in his or her early 20s, a much more common diagnosis in the younger patient, to be enrolled into medulloblastoma trials, possibly at a pediatric institution, may be vital to that patient's prognosis. Equally important, and expected with the RACE Act, is to allow the adolescent to be included in adult trials for the reasons mentioned above. The study's inclusion criteria should reflect the biology of the cancer while making the age ranges wider.

## Study Design

Given the rarity of pediatric cancer, one can imagine the even smaller subset of specific molecular targets for each diagnosis. However, in 2018, Forrest *et al* undertook a review of the seven pediatric oncology clinical sequencing studies that had been published at that time. In that review, they reported that between 30-60% of those pediatric patients with relapsed, refractory, or high-risk solid tumors demonstrated potentially actionable alteration, but when reviewed, only 3-18% received targeted therapy matched to an identified actionable variant.[45] It is unrealistic to study specific genetic sub-populations by more traditional trial designs due not only to limited numbers, but also to cost.

Consider trials that study therapies based not on diagnosis, but on genetic make-up, allowing for a diverse population with the same molecular target. Over the previous decade, master protocols have been developed and used in response to the era of precision medicine. Master protocols include sub-studies to evaluate multiple hypotheses with a goal of improving efficiency in clinical research. Therefore, multiple studies can occur within one master trial rather than numerous separate studies. The ultimate benefit is obtaining the data efficiently and effectively, and analyzing the results correctly so that best practices can be established for appropriate patient populations.

It has, however, been well documented that a lack of standardization and inconsistency in wording occurs in master protocols.[46] An inherent challenge then is standardization of trial type so it can be well understood among the research community. A common understanding of these terms will be necessary to ensure that regulatory boards and potential trial participants know which questions to ask of trial administrators pertaining to patient safety and trial objectives.[47] Such understood commonality will also help strengthen collaboration and facilitate further research.[48] According to the FDA, a Master protocol is a protocol designed with multiple sub-studies, which may have different objectives and involve coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure.[49] At its very definition, there are inherent challenges and a collaborative effort will be needed across industry, reaching globally. Drugs included in sub studies may have different manufacturers, may be targeting different diseases and have a different molecular make up. Such studies are likely to require numerous trial sites, and quite possibly more than one clinical research organization (CRO) and/or consortia.[50] The FDA outlines 3 major challenges[51]:

1. Difficulty attributing adverse events to specific drug if multiple drugs are administered/studied within various arms if the trial lacks a single internal control
2. Assessing the safety profile of any given investigational drugs may be difficult if multiple drugs are being studied in the trial
3. Potential for overinterpretation of results when the trial contains multiple study groups

It is imperative to keep in focus the potential risks associated with the products, trial population(s), and the study's operational complexity. The Clinical Trials Facilitation and Coordination Group has a recommendation paper on the initiation and conduct of complex clinical trials which outlined 8 key mitigating strategies[52], including:

1. Clearly describe and justify design
2. Maintain scientific integrity
3. Ensure the quality of trial conduct and optimize clinical feasibility
4. Ensure the safety of trial subjects
5. Maintain data integrity
6. Reassess the benefit-risk balance at critical steps throughout clinical trial
7. Validate all companion diagnostics
8. Consider data transparency

## Master Protocols

The framework of master protocols promotes clinical research that is highly efficient, making the best use of trial infrastructures, resources, and time.[53] At the center of pediatric trials in the face of RACE Act is an unwavering need for commitment for collaboration across industry.

**A basket trial** is a master protocol designed to test a single investigational drug or drug combination in different populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristic. Each sub-study should include specific objectives, inclusion criteria, and its own analysis plan including sample size justification and stopping rules. In the era of precision medicine, it refers to a design in which a targeted therapy is evaluated on multiple diseases that have common molecular alterations.[54] *See Figure 1 below.*

**An umbrella trial** is a master trial designed to evaluate multiple investigational drugs administered alone or as drug combinations in a single disease population. Sub-studies in umbrella trials can include dose-finding. Umbrella trials can have randomized controlled designs to compare to a control arm, typically the standard of care for the target population which may change over time if new drugs replace previous standards of care. In the era of precision medicine, they are typically used to describe a trial to evaluate multiple targeted therapies for a single disease that is stratified into subgroups by molecular alteration.[55] *See Figure 1 below.*

**Platform trials** are used to evaluate several interventions against a common control group and can be perpetual. This design has pre-specified adaptation rules to allow dropping of ineffective intervention(s) and flexibility of adding new intervention(s) during the trial. *See Figure 1 below.*

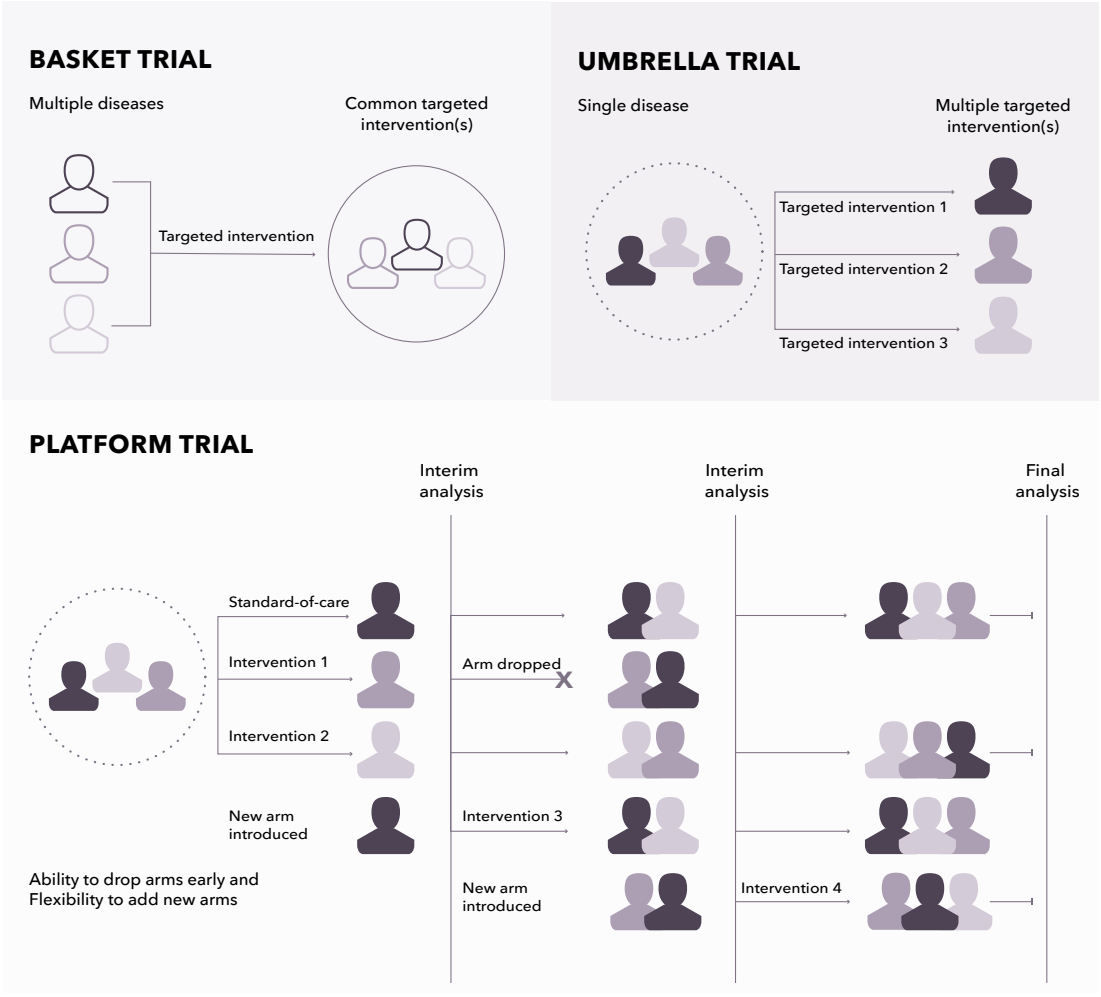


**Figure 1: Graphical representation of basket trials, umbrella trials, and platform trials. This figure illustrates a simple graphical representation of basket, umbrella, and platform trials. There may be other forms of mater protocols. The clip art in the figure was generated by the authors.**

## Conclusion

Various studies have concluded that nearly 50% of pediatric tumors could have a targetable molecular alteration.[56] This statistic cannot be ignored, and precision trials need to be considered for all pediatric oncology drugs going forward. Starting now, we need more knowledge sooner that will drive broader developments in pediatric cancer. Prioritization should lie with those diagnoses and the need to improve overall survival rate and progression-free survival, with the goal to lessen long term impact. For example, those with brain tumors have poorer outcomes. Even low-grade tumors, if incompletely resected, can lead to years of multiple therapies with substantial impact on quality of life and, though infrequent, a chance for mutation to a higher-grade tumor.[57] A diagnosis of diffuse intrinsic pontine glioma is generally considered incurable with life expectancy around 18 months. While outcomes for pediatric leukemia and lymphoma have improved substantially, due in part to combination chemotherapy, acute myeloid leukemia and relapsed disease in general remain difficult to cure.[58]

Society often feels more protective of the young, the innocent, and those who, through no fault of their own, succumb to such dreadful diagnosis. While lifestyle influences may play a role in adult cancer diagnosis, they are believed not to be a factor in pediatric cancer diagnosis. Most parents would be willing to take the place of a child embarking on therapies that cut short their naivety of youth, or of a young adult who would otherwise be embarking on their next great adventure. It is by implementing the RACE Act that the stage will be set for future development of novel therapies. Champions will put their time, energy, money, and focus on improving the lives of those that need it most by giving them options and hope.

Years ago, a very wise and experienced pediatric oncologist told us, “Someday, we will treat cancer by molecular make-up rather than diagnosis.” In our recent work, we have thought of him often and with gratitude. We are thankful on behalf of the patients and families we serve for him, and others like him, who have recognized we can do better and take action to help develop therapies and improve trials for our most valuable—our children.

And we will.

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