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The world's childhood cancer experts

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October 28, 2022

Martha Kruhm, M.S., RAC
Protocol and Information Office (PIO) Head
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

RE: Request for Amendments with FDA requested language for Pediatric MATCH consents

Dear Ms. Kruhm,

The study committee thanks CTEP for forwarding the Amendment Request dated October 17, 2022. In response to the request, please see attached Amendment #5 to APEC1621SC. The complete list of changes can be found below.

Please contact us if you have any further questions.

Sincerely,

Lee Baker, MPH, Protocol Coordinator (for)
Donald Parsons, M.D., PhD, **APEC1621SC** Study Chair, and
Douglas S. Hawkins, M.D., Group Chair, Children's Oncology Group

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I. Changes made to the protocol by the Principal Investigator:

#	Section	Comments
1.	General	The version date has been updated throughout the protocol.
2.	Study Committee	Study committee members have been updated.

II. Changes made to the informed consent document by the Principal Investigator:

#	Section	Comments
3.	General	The version date has been updated throughout the informed consent document.
4.	Why is this study being done?	The following phrase has been added: • **Please know that your eligibility for this trial may have been determined in part on the basis of a laboratory-developed test that has not been reviewed or approved by the FDA.**

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Activated: 07/24/2017
Closed:

Version Date: 10/28/2022
Amendment #: 5

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APEC1621SC

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE) SCREENING PROTOCOL

A COG Groupwide Screening Study

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OVERVIEW

The Pediatric MATCH (Molecular Analysis for Therapy Choice) study, (referred to as Pediatric MATCH in the remainder of this document), will match targeted agents with specific molecular changes identified using genomic sequencing technologies in refractory/recurrent tumors from children and adolescents with cancer. Pediatric MATCH will build upon experience from the adult NCI MATCH clinical trial. Pediatric MATCH will be a national trial under a single IND and will be led by NCI and the Children's Oncology Group (COG), a member of the NCI National Clinical Trial Network (NCTN).

Pediatric MATCH will employ an analytically validated next-generation sequencing targeted assay of more than 4,000 different mutations (SNVs, indels, copy number alterations, and gene fusions) across more than 140 genes. This assay will be coupled to a computer algorithm that uses pre-existing definitions and prioritization of target-agent pairs to assign patients by actionable mutation results to a targeted treatment.

As of Amendment #4: Starting in 2022, Pediatric MATCH will move to a new screening model, called Stage 2, in which tumor molecular profiling reports from CLIA-certified clinical laboratories are reviewed to determine molecular eligibility to Pediatric MATCH treatment protocols. Centralized tumor testing will no longer be performed as part of the study. The Stage 2 review process will utilize the same definitions for clinical actionability of tumor mutations as used throughout Pediatric MATCH.

The primary endpoint for Pediatric MATCH will be objective response rate. The study will use a trial design with the flexibility to open and close arms. The study drugs included in this trial will include agents that have at least an adult recommended phase 2 dose and that have shown some activity against tumors

with a particular genetic alteration(s). Patients with recurrent or refractory tumors enrolled on study will have tumor molecular profiling reports that are believed (in the opinion of the treating clinician) to confer eligibility to a Pediatric MATCH treatment arm. If confirmed by Pediatric MATCH review, the patient will be offered treatment on Pediatric MATCH.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To utilize clinical and biological data to screen for eligibility to phase 2 pathway-targeting specific subprotocols of pathway-targeting agents in pediatric patients with advanced solid tumors, non-Hodgkin lymphomas, and histiocytic disorders.

1.1.2 To determine the proportion of pediatric patients whose advanced tumors have pathway alterations that can be targeted by select anti-cancer drugs. ***(Completed as of Amendment #4. patients enrolled on or after Amendment 4 will not be included in this analysis as screening of unselected patients will no longer be conducted.)***

1.1.3 To determine the objective response rates (ORR; complete response + partial response) in pediatric patients with advanced solid tumors, non-Hodgkin lymphomas, and histiocytic disorders harboring *a priori* specified genomic alterations treated with pathway-targeting agents.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients receiving targeted therapies for advanced solid tumors, non-Hodgkin lymphomas, and histiocytic disorders.

1.2.2 To obtain preliminary or additional information about the tolerability of targeted therapies in children with advanced cancers.

1.2.3 To provide preliminary estimates of the pharmacokinetics of targeted therapies in children with advanced cancers.

1.2.4 To obtain preliminary information on the response rate to targeted therapy in

patients whose tumors lack actionable alterations as defined for the MATCH study, for selected agents for which efficacy is observed in the primary matched cohort.

1.3 Exploratory Aims

1.3.1 To increase knowledge of the genomic landscape of advanced pediatric solid tumors, non-Hodgkin lymphomas, and histiocytic disorders.

1.3.2 To describe the genomic changes that occur in advanced pediatric cancers between the time of initial diagnosis and relapse, in cases for which paired tumor specimens are available.

1.3.3 To explore approaches to diagnosing and profiling genomics of advanced pediatric cancers through evaluation of circulating tumor DNA

1.3.4 To determine the frequency and spectrum of germline cancer susceptibility mutations in children with relapsed solid tumors and non-Hodgkin lymphomas and assess the feasibility of return of those results in the NCTN group setting

Note: patients enrolled on or after Amendment 4 will not be included in return of results analysis as clinical germline testing will no longer be conducted.

2.0 BACKGROUND

The current approach to treatment of recurrent pediatric tumors is histology based, with patients directed to on- or off-protocol therapy depending on: 1) available clinical evidence for activity of a particular agent or regimen; 2) in the absence of clinical evidence, preclinical rationale supporting use of an agent/regimen; and 3) the availability of clinical trials for which the patient would be eligible. For some relatively common tumor types, phase 2 studies based on histologic diagnosis would commonly be used at recurrence. However, only a minority of pediatric phase 2 studies include rare tumor diagnoses. Phase 1 studies, which are generally not histologically driven, are recommended when there is no curative option with acceptable quality of life. It is uncommon for studies of recurrent pediatric tumors to be based on mutation status or other non-histologic criteria, although there are occasional exceptions such as studies with crizotinib in ALK-positive tumors. Although there are effective treatments for a few tumor types at relapse, such as Wilms tumor, the outcome following recurrence is generally poor. In addition, objective response rates in early phase trials of new agents remain unsatisfyingly low, generally <10%. Thus there is a strong rationale for considering new clinical trial designs that maximize the chance of benefit for patients enrolled onto early-phase studies by improving our ability to direct patients to the trials of the agents to which their tumors are most likely to respond.

One potential strategy is the use of molecular profiling to detect tumor mutations that may be predictive of response to "molecularly targeted" agents. Knowledge of the spectrum of mutations found in different tumor types has improved significantly over the past decade,[1] with a corresponding increase in the subsequent development of agents targeting those mutations. To date, however, only a relatively small number of targeted agents have been approved, and experience with many of these drugs for pediatric patients is limited, emphasizing the need for clinical trials to evaluate both the efficacy of specific agents as well as the benefit of molecular profiling for this purpose.

The number of genomic tests that can be used to molecularly profile tumors has continued to increase with advances in sequencing technologies. The spectrum of tests that are being utilized in the clinic for tumor analyses include: (1) targeted analyses of genetic alterations in individual genes (e.g. *BRAF*), (2) mutation panels evaluating a set of cancer genes of interest or members of specific biologic groups or genetic pathways (e.g. MAPK signaling pathway genes), and (3) unbiased genome-scale tests (e.g. whole exome or genome sequencing, RNA-sequencing). As for other types of clinical tests, the determination of the best methods for genomic characterization of tumors and assignment of molecularly-targeted therapies will require consideration of test cost, turnaround time, reproducibility, information yield, and other factors affecting feasibility in the clinical setting.

Previous studies have attempted to quantify the number of potentially targetable mutations in a variety of tumor types in order to inform the design of clinical trials involving molecular profiling. Preliminary results from clinical genomic analyses of pediatric solid tumor patients have been reported to show mutations of potential clinical relevance in a fraction of patients using either tumor whole exome sequencing of newly-diagnosed patients (as part of the Baylor College of Medicine BASIC3 study) or mutation panel-based testing of relapsed/refractory tumors (in the Dana-Farber Cancer Institute iCAT study).[2,3] Of note, only perhaps 10-20% of these alterations appear "targetable" ("druggable") by current FDA-approved or investigational targeted agents. Importantly, a recent genomic analysis of relapsed neuroblastoma has revealed the presence of clonal evolution of targetable mutations in MAPK pathway genes in the relapsed tumors (not present in the pre-therapy tumor), providing further rationale for testing relapsed tumor samples as opposed to diagnostic (pre-therapy) tumor specimens to maximize diagnostic yield in prospective clinical trials utilizing molecular profiling.[4]

Although they served to demonstrate the feasibility of genomic testing in the context of clinical trials, early studies evaluating the clinical benefit of molecular profiling were limited by the lack of availability of molecularly targeted agents. A common conclusion of early feasibility studies of clinical molecular profiling for relapsed/refractory cancers has been the small proportion of patients who go on to receive molecularly-targeted therapies (either on or off study) based upon those results. In the example of the SAFIR01/UNICANCER study of patients with metastatic breast cancer, for example, targeted therapy could be recommended in only 55 of 423 patients (13%), and only 43 patients actually received targeted therapy. Of these, 4 (9%) had an objective response, and 9 others (21%) had stable disease for more than 16 weeks.[5] These studies emphasize the need for clinical trials in which a selection of targeted investigational agents are available corresponding to the spectrum of targetable mutations that can be detected in the patient population being enrolled.

Several such studies are being conducted under National Cancer Institute (NCI)-sponsored protocols. The "Molecular Profiling-Based Assignment of Cancer Therapy for Patients With Advanced Solid Tumors (NCI-MPACT)" trial is a pilot study designed to test whether patients whose tumors contain gene mutations or amplifications in one of three genetic pathways (DNA repair, PI3K, or RAS/RAF) are more likely to benefit if treated with agents targeting that pathway than if treated with agents that do not.[6] Only patients with such mutations are entered onto the study; patients are then randomized to receive either the study drug identified to work on their tumor's pathway, or a study drug targeting one of the other pathways. Of note, the investigators plan to enroll approximately 800 subjects in order to be able to randomize 180. A different approach is being taken in the "Molecular Analysis for Therapy Choice" (NCI-MATCH) study, which utilizes a basic strategy of testing patient tumors for molecular targets under a screening protocol,

then directing patients to one of many separate phase 2 studies that have molecular eligibility criteria. These studies involve many thousands of patients. For example, NCI-MATCH proposed to screen 3000 patients and enter 1000 on clinical trials studying 15-30 different drugs.[7]

The adult NCI-MATCH study mutation panel underwent extensive validation testing prior to the opening of the study in August 2015. This testing revealed an observed sensitivity of 97% and specificity of >99% for the assay. Over the first 3 months of the adult NCI-MATCH 795 patients enrolled for screening, 739 biopsies were submitted, and sequencing was completed for 645 specimens (87%). Approximately 9% of patients had an actionable mutation as defined for the study, with 5% meeting molecular eligibility for assignment to one of the 10 treatment arms. This rate will likely increase as additional study arms are opened, with recent match rates reported as ~20 to 25%. The reported median turnaround time (TAT) was 27 days but increased from 14 days in the first month to 36 days in the last month, corresponding to a marked increase in study accrual. More recently (for subjects enrolled after May 30, 2016) the estimated median TAT has decreased to 15 days (Barb Conley, personal communication) despite an increase in study accrual to 100-120 subjects per week. This improved TAT reflects several modifications of the adult MATCH pipeline, including additional staffing and moving to a more high-throughput sequencing instrument. A third sequencing laboratory has also been selected.[10]

As of Amendment #4, NCI-MATCH study screening update prior to Stage 2 of Pediatric MATCH: In 2020, the feasibility of the centralized molecular screening approach utilized for the adult NCI-MATCH study was further confirmed with testing results reported for nearly 6000 patients. Of note, in the later stages of NCI-MATCH, the study protocol was modified to move from a centralized testing model to allow the use of clinical molecular testing results from approved clinical laboratories.[8]

Given the relatively small number of pediatric patients with recurrent solid or central nervous system tumors, and the relative infrequency of targetable mutations in those tumors, multi-institutional efforts will be required to determine whether molecular profiling and target-directed therapy will lead to improvements in patient outcomes. We propose a pediatric version of the NCI Molecular Analysis for Therapy Choice protocol, (Pediatric MATCH), as an initial step.

2.1 **Tumor Biopsy in Children with Cancer (Stage 1 Only. As of Amendment #4, tumor samples will no longer be submitted for centralized clinical testing.)**

Tumor biopsies are a fundamental component of the management of childhood cancer patients. A variety of procedures are utilized to obtain tumor tissue for diagnosis and risk-based therapy stratification, including open biopsies and resections, "minimally-invasive" surgeries (e.g. laparoscopy and thoracoscopy), and percutaneous biopsies.[9] Increasingly, molecular characterization of tumor tissue obtained by biopsy is being performed as part of the pathologic tumor evaluation, focusing specifically on histology-specific biomarkers or more broadly on potentially-targetable alterations (particularly in the context of relapsed and refractory tumors).

Although the majority of the reports in the medical literature on complication rates of specific biopsy procedures describe adult oncology patients, ample pediatric data do exist to support the general safety of tumor biopsy as well as that of specific biopsy procedures. In a recent report describing 1025 biopsy procedures (43% open, 6% minimally invasive, 50% percutaneous; median age 12.7 years, age range 0-33 years) targeting diverse non-CNS anatomic locations performed over a decade at a single pediatric institution, NCI CTCAE v.4.0 grade 3 or 4 adverse events were reported in 32 of 1025 (3.1%) patients.[10] Twenty-four of these 32 events were post-operative transfusions; the majority of these patients were anemic before the biopsy procedure and only 8 of 24 had clearly documented blood loss post-procedure. It was judged that the biopsy procedure may have contributed to two deaths noted within 30 days of the procedure; the first a child with progressive NHL and pre-operative sepsis and multiorgan system failure and the second a patient who had a presumed intratumoral hemorrhage after open biopsy of a hepatoblastoma. CTCAE grade 3 or 4 adverse events believed to be related to anesthesia were reported in 2 of 1025 (0.2%) cases; of note, nearly 94% of children underwent general anesthesia for their biopsy procedure in this series. In total, Serious Adverse Events related to biopsy procedures, including anesthesia, were reported in < 2% of children. Data for endoscopic and skin/subcutaneous biopsies were not reported, based on the authors' assessment that those procedures are "likely to be associated with an even lower rate of adverse events". Complication rates similar to those described by Interiano et al. (SAE rate < 2%) have also been reported in the context of specific disease indications, such as biopsy of localized neuroblastoma (2%; age < 20 years).[11]

Numerous studies have reported data regarding the safety of percutaneous biopsies of non-

CNS tumors in pediatric patients.[12-16] In these cohorts (n >1100 patients), CTCAE grade 3 or 4 adverse events were observed in 0 to 3.4% of procedures, with SAEs in < 2% (. The percutaneous biopsies were performed on the spectrum of anatomical sites that are routinely sampled in pediatric oncology patients: renal[13,17] (n=177, age < 21 years), lung[12] (n=64, mean age 10 years, range <1 to 20 years, assorted abdominal[16] (n=105, median age 3.9 years, range <1 to 14 years).and soft-tissue sites[18] (n=205, mean 11 years, range 4-18 years), and multiple sites including musculoskeletal and lymph nodes in addition to thoracic/abdominal tumors (n=415, median 9-10 years, range <1 to 33 years).[14,15]

Minimally-invasive surgical (MIS) procedures have also become increasingly utilized for tumor biopsy in pediatric patients.[19,20] The majority of pediatric data on MIS complication rates reported to date focus on thoracoscopy[21], a common method of sampling pediatric lung tumors: SAEs have been reported in <1% of procedures, with conversion to open biopsy performed in 3% of cases, n=333 patients (Guye et al. n=139, mean 9.2 years, range <1 to 17 years; Rothenberg et al. n=194, range < 1 to 18 years). [22,23] Laparoscopic procedures are also routinely used to biopsy or resect abdominal tumors in children[24,25], including adrenal tumors (e.g. neuroblastoma) and renal tumors, with reported rates of SAEs < 2% and conversion to open procedures in ~5% of laparoscopic adrenalectomy cases[26-29] (Al-Shanafey et al[27]. n=29, median age 3 years; range < 1 to 13 years; Leclair et al[28]. n=145, median age 6.8 months, range < 1 to 9 years; Nerli et al[29]. n=18, mean age 5.8 years, range 1 to 15 years; Skarsgard et al[30]. n=20, mean age 6.4 years, range 1-18 years) and similar reported risks for nephrectomy.[30,31] Of note, these data are for more extensive laparosopic procedures (resections) than biopsies.

Several types of surgical procedures are routinely performed to biopsy CNS tumors in pediatric patients. Although data regarding major adverse events are available for such procedures in children, they have been limited to smaller cohorts and have not generally reported following CTCAE grading criteria. A recent review of SEER data (n=5533 cases) reported a 30-day mortality rate of <2% after craniotomy in patients from 1 to 21 years of age (median age 10 years).[32] Neuroendoscopic biopsies are frequently utilized for intraventricular or periventricular tumors[33], often in conjunction with procedures to relieve symptomatic hydrocephalus (e.g. endoscopic third ventriculostomy or septostomy). A study of neuroendoscopic biopsies (with or without or without a CSF diversion procedure) in 49 pediatric patients (mean age 12 years, range <1 to 21 years) reported major adverse events in 3/49 procedures (6%).[34] A recent larger multi-institutional nationwide study of pediatric neuroendoscopic biopsies in Japan (n=206, age < 15 years) has described a similar frequency of major adverse events of 5-6% and also noted no difference in complication

rates between the pediatric cohort and a larger cohort of adult patients.[35] Stereotactic biopsy is another method of CNS tumor sampling for pediatric patients. In one series of 99 children (< 7 years of age), a complication rate of 5% was reported using a frame-based approach.[36] Stereotactic techniques are often used for cases in which deep or brainstem lesions are biopsied.[37] Although a majority of the publications describing this procedure provide only a broad view of the complication rate (e.g. "no mortality or permanent morbidity" in 106 children with brainstem masses (< 18 years of age) [38], more recent data have provided additional detail into the feasibility of these procedures. In the largest series reported to date (n=130, mean age 6 years, range 1 to 16 years), stereotactic biopsy of pediatric pontine gliomas resulted in transient worsening of neurologic deficit in 5 patients (3.9%) but no permanent deficits, major complications, or deaths.[39] In total, it is estimated that SAEs occur in between 2 and 5% of CNS biopsies performed in children.

In summary, a variety of procedures are currently in routine use to obtain tumor biopsies in pediatric patients. Such procedures are increasingly being used in the clinical care of children with relapsed and refractory tumors in order to facilitate clinical molecular testing. Published case series have revealed an estimated overall major complication rate of SAEs of < 2% for biopsy of non-CNS tumors and slightly higher for CNS tumors, with some variability depending on the specific procedure and tumor site. For children with relapsed or refractory cancer, this level of risk appears commensurate with the potential for direct benefit in the context of the precision oncology Pediatric MATCH study. The risk of complications from the procedure is significantly lower than what has been observed for children of similar clinical status participating on phase I trials, for whom dose-limiting (severe, life threatening or fatal) toxicities in the range of 15 to 25% have been reported.[40,41] Moreover, although additional data will be required to further evaluate the overall response rates for novel molecularly-targeted therapeutics in biomarker positive patients, data such as that reported for the pediatric phase I crizotinib study (in which responses were observed in 12/27 (44%) patients with known activating ALK aberrations)[42] suggest that utilizing a genotypically-driven approach may result in higher response rates than the historical rate of 5 to 10% for pediatric phase I trials.[40,41] In this context, utilization of the proposed range of biopsy procedures in order to make Pediatric MATCH broadly accessible to children with relapsed or refractory solid tumors and non-Hodgkin lymphomas appears justified. In particular, we believe that it is critically important to include children with CNS tumors, given both the clinical need for these patients and the observed rate of potentially actionable mutations in their tumors. For example, no effective chemotherapy options exist for children with high grade gliomas- extremely poor prognosis tumors known to harbor recurrent genetic alterations that are theoretically targetable by agents being prioritized for

Pediatric MATCH[43], including mutations in MAPK pathway mutations as well as fusions involving BRAF, NTRK and FGFR genes.

2.2 Germline Testing in Children with Cancer

The Pediatric MATCH study proposes to sequence tumor DNA obtained from patients with relapsed or refractory solid tumors and non-Hodgkin lymphomas using a panel of selected genes in order to assign targeted therapies based on the actionable mutations detected in each patient's tumor. The genetic alterations identified by such tumor sequencing can represent either somatic (tumor-specific) mutations or germline (constitutional) variants.[44-47] Although bioinformatic methods can be used to attempt to distinguish between these two possibilities, current methods are not adequate for this purpose.[45] Hence, the determination of whether a variant is somatic or germline requires the analysis of a patient-matched non-malignant tissue sample, most frequently blood, in addition to a tumor specimen.

Specific tumor types are known to be associated with underlying germline cancer susceptibility genes (e.g. retinoblastoma and *RB1*; adrenocortical carcinoma and *TP53*; atypical teratoid-rhabdoid tumor and *SMARCB1/SMARCA4*).[9] Recently, next-generation sequencing studies (including whole exome sequencing) of diverse cohorts of childhood cancer patients have revealed that approximately 10% of unselected patients harbor a pathogenic or likely pathogenic germline variant, as defined by the American College of Medical Genetics,[48] in a cancer susceptibility gene.[3,45,49,50] Importantly, many of the germline cancer gene variants revealed by this testing were not previously associated with the specific tumor type diagnosed in the patient, as has also been observed in adult cancer patients.[47] Although most germline cancer variants are not considered targetable (with some exceptions, such as the use of PARP inhibitors in patients with germline *BRCA1*/*BRCA2* variants) and thus not the primary focus in precision oncology trials, their identification can offer potential clinical benefit by guiding genetic counseling and preventive care of both the patient and their family.[51-53]

Rationale for germline testing approach for Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21):

A number of the genes that are included on the current version of the Oncomine Cancer Panel (ThermoFisher/Life Technologies) are known to be germline cancer susceptibility genes (see list of examples below), in addition to being targeted by somatic mutations. Additional germline cancer susceptibility genes are being added to the revised version of the panel that we will utilize for the Pediatric MATCH study.

A. Genes with full coding sequence analyzed: *APC, ATM, BAP1, BRCA1, BRCA2, CDKN2A, CDH1, MSH2, NF1, NF2, PTCH1, PTEN, RB1, SMAD4, SMARCB1, STK11, TP53, TSC1, TSC2, VHL, WT1*

B. Genes with hotspots analyzed: *ALK, CDK4, CHEK2, EGFR, EZH2, GATA2, HNF1A, HRAS, KIT, MET, MLH1, PDGFRA, RET*

The value of the Pediatric MATCH study – to patients and families as well as the scientific community – will be maximized by parallel sequencing of germline (blood) DNA using the same panel as for the tumor sequencing. This will allow determination of which mutations of interest (MOIs) and actionable mutations of interest (aMOIs) may represent germline variants in cancer susceptibility genes so that the patient and family can receive appropriate counseling and follow-up care. Equally important, it will clarify which variants detected in tumor DNA are NOT present in the germline, thereby relieving patients, families and oncologists of concern about germline risk and avoiding unnecessary workups. We believe that this germline testing is indicated, given: (i) the frequency of pathogenic and likely pathogenic germline cancer susceptibility variants in childhood cancer patients, (ii) the probability of detecting such variants (if present) using the selected study mutation panel, (iii) the clinical relevance of reporting those variants for the care of both childhood cancer patients and families, (iv) the ability of the COG to devise an efficient and responsible plan for return of these results to patients/families and their oncologists, (v) the reduction in recommendations for follow-up genetic evaluation for the majority of subjects with tumor only results, and (vi) the need to develop best clinical practice for responding to germline variants given the likelihood that systematic evaluation for inherited cancer susceptibility will likely become a routine part of pediatric oncology practice in the near future. Finally, we anticipate that this germline testing will provide rich scientific information about inherited predisposition to childhood cancer, including among children who are not found to have targets for therapy by tumor-focused sequencing.

The purpose of Pediatric MATCH study germline testing is to determine which of the variants that are being identified by tumor sequencing may actually be germline in nature and not to provide a comprehensive cancer susceptibility evaluation. This will be emphasized to the oncologists and within the informed consent document, which will also describe the potential risks of germline sequencing, namely: (i) anxiety related to the performance of genetic testing or the identification of a germline cancer susceptibility variant, and (ii) the risk of loss of privacy of genetic information resulting from such testing. Recent data suggest that the vast majority of parents of childhood cancer patients

believe that the potential benefits of clinical genomic testing (including both somatic and germline results of clinical relevance) outweigh these risks. As one example, the parents of only ~10% of newly-diagnosed childhood cancer patients eligible for the BASIC3 clinical and tumor germline exome sequencing study (which, unlike the Pediatric MATCH study, does not offer the potential benefit of availability of investigational molecularly-targeted agents) have reported declining study enrollment due to concerns about either anxiety from genetic testing results or privacy risks[54] [and DW Parsons, personal communication]. Interviews of parents of BASIC3 study subjects have provided further evidence for this positive risk-benefit calculation in the context of a childhood cancer diagnosis. [55]

In summary, current evidence and experience with the identification and reporting of germline cancer susceptibility variants for childhood cancer patients provide strong support for a Pediatric MATCH study approach in which blood samples are also analyzed in order to provide information about the somatic or germline nature of the variants identified through tumor sequencing. This approach simplifies the follow-up evaluation by the oncologist for the majority of subjects with tumor only findings and offers potential clinical benefit to study subjects and their families, including those patients who will not qualify to receive study therapy due to lack of a targetable mutation.

As of Amendment #4: **Germline testing in Stage 2 of Pediatric MATCH (for patients enrolled starting in 2022):**

In Stage 2 of Pediatric MATCH no centralized tumor testing will be performed as the study will rely exclusively on review of tumor molecular profiling results from outside clinical laboratories. Accordingly, no tumor mutations will be reported by Pediatric MATCH laboratories that could represent germline cancer susceptibility variants, eliminating the need for parallel (centralized) clinical testing of patient blood samples to determine the somatic or germline nature of variants included in tumor reports. Patient blood samples will be collected for research studies only.

2.3 Circulating Tumor DNA (ctDNA)

One appealing alternative approach to tumor sequencing for identifying gene variants includes sequencing circulating tumor (ct) DNA found in patient plasma, also known as liquid biopsy studies. This approach also allows for quantification and serial tracking of ctDNA, which could be used to assess disease burden and treatment response. Liquid biopsy technologies have demonstrated superior detection and quantification rates

compared to assays for circulating tumor cells.[56] Furthermore, ctDNA can be reliably extracted from plasma using commercially available kits making it feasible for any clinical or research laboratory to draw and ship appropriate samples for ctDNA studies. The integrity of ctDNA can be further enhanced by the use of specialized blood tubes, such as Streck Cell-Free DNA BCT tubes, widely employed for circulating fetal DNA studies and increasingly utilized in ctDNA assays. Many reports have now demonstrated the clinical utility of detecting and quantifying circulating tumor DNA from patients with solid tumors.[56,57] These assays have been used to assess disease burden, track disease response to therapy, identify clonal evolution, and predict relapse after remission. However, the application of cell free DNA technologies has yet to be applied systematically in pediatric solid tumors. In this study, we propose to collect plasma samples from patients prior to therapy to aid in ongoing studies to develop and assess ctDNA analysis strategies in solid tumors.

2.4 Overview of Proposed Pediatric MATCH Study

The Pediatric MATCH study will consist of a screening protocol to screen for eligibility to pathway-targeting specific subprotocols. This screening protocol will specify subject eligibility; details and logistics of tumor acquisition and molecular analysis as well as of reporting; response and adverse event evaluation criteria and stopping rules; the schedule of required observations; and the overall statistical plan. Consent for participation in the screening protocol will include consent and assent for:

- tumor genetic analysis and return of tumor sequencing results in Stage 1 of the trial
- ***As of Amendment #4: review of submitted tumor molecular profiling results from outside laboratories in Stage 2 of the trial***
- concept of molecularly targeted therapy, if match is identified
- possibility of assignment of patients with non-target-bearing tumors to selected agents that have demonstrated activity in target-bearing tumors
- optional research studies including further genomic characterization of tumor and blood samples and analysis of an archived specimen obtained prior to treatment (and prior to relapse/progression), if available

Individual agent-specific subprotocols will be developed for each treatment agent/regimen. Some subprotocols may include more than one primary cohort (each with different molecular eligibility criteria). The subprotocols will contain any additional treatment-specific eligibility criteria and the treatment plan including monitoring for adverse events, as well as pharmaceutical information, etc. There will be an agent-specific consent for each

subprotocol that details the specific risks of the agent.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. For CTEP and Division of Cancer Prevention (DCP) studies open to the National

Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form

FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements
Additional requirements to obtain an approved site registration status include:
- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review.

3.1.3 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DLT) is required for the study, the registrars must hold the OPEN Registrar task on the DLT for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.2 Procedures for Eligibility to Screening Protocol

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through the study-specific protocol. Documentation of the informed consent will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.3 Genetic Screening Procedures for Eligibility to Subprotocols

3.3.1 Screening approach for Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21):

Tumor and blood samples will be obtained from patients who enroll in the study through December 31, 2021. The results of the evaluation of the tumor specimens will determine if the patient's tumor has an actionable Mutation of Interest (aMOI) for which a MATCH treatment subprotocol is available.

- A tumor sample for screening is obtained from enrolled patients (see Section 5.2, Biopsy Methods, for additional information).
- A blood sample is obtained for germline testing.
- Tumor and blood samples are submitted to the COG Biopathology Center (BPC) at Nationwide Children's Hospital in Columbus, Ohio for pre-analytic processing, including DNA and RNA extraction, and quality control.
- FFPE specimens for immunohistochemistry (IHC) testing will be forwarded from the Biopathology Center to the MDACC clinical laboratory.
- The nucleic acid analytes (DNA/RNA) will be forwarded from the Biopathology Center to one of the CLIA-certified laboratories in the MATCH study-specific network for molecular profiling (MDACC, the NCI Molecular Characterization Laboratory (Frederick, MD) and Dartmouth) to assess for the presence of specific, pre-defined actionable mutations, amplifications or translocations of interest

(aMOIs).

- The laboratories will report whether or not an aMOI for patient assignment to one of the clinical trial subprotocols has been detected to the NCI informatics pipeline (MATCHbox).
- The automated rules engine in MATCHbox will generate a list of potential treatment assignments (TA) and the highest priority TA will be determined.
- The highest priority TA (or notification if no match was available) will be sent to the COG Operations Office. This will then be made available to the registering site via CTSU OPEN/Medidata Rave, with an email sent as notification of available TA (or if no match was available) approximately 14 days after receipt of the patient's tumor sample at the BPC. **The BPC does not provide testing results: any inquiries about treatment assignments or results should be directed to the COG study chair and COG research coordinator.**
- Patient is assessed for subprotocol eligibility and patient/family consents to treatment with the indicated agent in the trial subprotocol.
- If the patient is ineligible for the highest priority TA, the treatment assignment process is repeated, in order of priority, until either all TAs are exhausted or the patient is confirmed eligible and is registered to a treatment subprotocol.
- In cases where insufficient tumor is obtained for biomarker analysis, the enrolling site will be notified by the BPC and given the option of providing an additional tumor sample for screening.
- When each new treatment subprotocol is added, the informatics process will review previous test results for subjects who have been enrolled on the screening protocol within the past two years and report if there is a new treatment assignments (i.e. if there are any patients with a mutation that is an aMOI for the new subprotocol).

3.3.2 As of Amendment #4: Screening approach for Stage 2 of Pediatric MATCH (for patients enrolled starting 2022):

A clinical tumor molecular profiling report from a CAP/CLIA-approved laboratory will be submitted for patients who enroll in the study. The treating

COG site will indicate which molecular alteration in the submitted report they believe to be actionable and the open Pediatric MATCH study arm for which the patient is thought to be eligible.

NOTE: patients should only be enrolled in APEC1621SC if the treating clinician/site believes that the tumor molecular profiling report submitted for review contains an actionable mutation for an open Pediatric MATCH treatment subprotocol.

The results of the evaluation of this report by the Pediatric MATCH Molecular Review Committee (MRC) will determine if the patient's tumor has an actionable Mutation of Interest (aMOI) for which a MATCH treatment subprotocol is available. The levels of evidence used to define mutation actionability will remain as defined from the start of the study (Appendix III). The MRC will be composed of oncologists and molecular pathologists with specific expertise in interpretation of genomic testing results, including the screening protocol COG study chair, vice chair, and pathologists.

- The MRC will generate a list of potential treatment assignments (TA) and the highest priority TA will be determined.
- The highest priority TA (or notification if no match was available) will be sent to the COG Operations Office. This will then be made available to the registering site via CTSU OPEN/Medidata Rave, with an email sent to the treating institution as notification of available TA (or if no match was available) within one week after submission of the patient's tumor molecular testing report.
- Patient is assessed for subprotocol eligibility and patient/family consents to treatment with the indicated agent in the trial subprotocol.
- If the patient is ineligible for the highest priority TA, the treatment assignment process is repeated, in order of priority, until either all TAs are exhausted or the patient is confirmed eligible and is registered to a treatment subprotocol.

3.4 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternatives will be

carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

3.5 Eligibility Checklist

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist, documenting that the patient meets the criteria in Section 4.1 for study enrollment. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

NOTE: For enrollment onto the APEC1621SC screening protocol, patients do not need to meet all criteria described in Section 4.2 for subprotocol eligibility. However, patients will need to meet all criteria prior to enrollment on any assigned treatment subprotocol. Investigators are encouraged to consider these criteria when determining appropriateness and timing of enrollment onto the screening protocol.

3.6 Institutional Pathology Report

3.6.1 Pathology report submission procedure for Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21):

Immediately following enrollment, the institutional pathology report from the tumor specimen to be submitted for sequencing must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission. The surgical pathology ID (SPID) from the report will be used by the BPC to link the report to the tumor specimen.

3.6.2 *As of Amendment #4:* Pathology report submission procedure for Stage 2 of Pediatric MATCH (for patients enrolled starting 2022):

Immediately following enrollment, the institutional pathology report for the same tumor specimen analyzed in the submitted molecular profiling report (Section 3.3)

must be uploaded into RAVE using the same procedures as described for Stage 1 (Section 3.6.1).

3.7 ***As of Amendment #4:*** **Institutional Tumor Molecular Profiling Report (Stage 2 of Pediatric MATCH only)**

Immediately following enrollment, the clinical tumor molecular profiling report which will be used to evaluate the tumor specimen treatment assignment must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional molecular report prior to submission.

If a patient enrolled on APEC1621SC has clinical molecular tumor profiling performed on a sample obtained at a later date (i.e. not the tumor report initially reviewed for Pediatric MATCH) this report can be submitted for review by the Molecular Review Committee as described above. An institutional pathology report must also be submitted as described in Section 3.6 above that corresponds to the same sample as the new molecular profiling report.

At the time of APEC1621SC enrollment, the treating COG site must indicate which molecular alteration in the submitted report they believe to be actionable and the open Pediatric MATCH study arm for which the patient is thought to be eligible. This will be indicated in the CRFs in Medidata Rave.

The tumor profiling test submitted must be capable of identifying actionable mutations as defined in the relevant treatment subprotocol. It is anticipated that these will most often be next-generation sequencing tests of DNA (to identify single nucleotide variants, insertions, deletions, and gene amplifications) and/or RNA (to identify gene fusions). Examples of such tests would be FoundationOne Heme, TempusxT, CARIS DNA sequencing and CARIS RNA sequencing.

Examples of report types that cannot be submitted for review and cannot be used to determine eligibility for Pediatric MATCH treatment subprotocols include:

- Immunohistochemistry (IHC) reports
- Cytogenetics reports
- Fluorescence in situ hybridization (FISH) reports

Any questions about whether a specific report is acceptable or mutation is actionable can

be referred to the COG study chair and vice chair (Drs. Parsons and Janeway) who will consult with the Molecular Review Committee (MRC) as required.

3.8 Study Enrollment Instructions for Subprotocols

Patients may be enrolled on the APEC1621SC screening protocol if they meet the eligibility criteria in Section 4.1. Patients who give informed consent for the protocol in order to eligibility assessments are not considered enrolled and should not be enrolled until the eligibility assessments are completed and they are determined to meet all eligibility criteria.

Patients must be enrolled onto a therapeutic subprotocol within 2 weeks (14 days) of treatment assignment. Subprotocol therapy must start no later than 7 calendar days after the date of enrollment to the subprotocol.

Note: Drug orders should be placed with CTEP with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy onto a subprotocol. No starter supplies will be provided and agents can be ordered only after the patient is registered to a subprotocol.

3.8.1 Reassignment Request (if unable to enroll within 2 week timeframe):

The treating team may email PedsMATCHOps@childrensoncologygroup.org and the APEC1621SC study co-chairs (dwparson@texaschildrens.org, seibelnl@mail.nih.gov) with a request for a single treatment re-assignment for any patient who was previously matched to a therapeutic subprotocol arm, but were unable to enroll during the original specified reservations window. The request can be made within a year of the 'Pediatric MATCH-Reservation expiration date' stipulated in the original treatment assignment email when the patient was assigned. The treatment re-assignment request is subject to slot availability on the therapeutic subprotocol at the time of the request.

4.0 PATIENT ELIGIBILITY FOR TARGET SCREENING

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the

time of audit.

4.1 Eligibility Criteria for Enrollment onto APEC1621SC

4.1.1 Age: Patients must be ≥ 12 months and ≤ 21 years of age at the time of study enrollment.

4.1.2 Diagnosis: Patients with recurrent or refractory solid tumors, including non-Hodgkin lymphomas, histiocytoses (e.g. LCH, JXG, histiocytic sarcoma), and CNS tumors are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-HCG. In cases where patient enrolls prior to histologic confirmation of recurrent disease, patient is ineligible and should be withdrawn from study if histology fails to confirm recurrence. **Please Note: Patients with Hodgkin lymphoma and plexiform neurofibroma are not eligible.**

4.1.3 Tumor Testing Requirement: Tumor sample availability requirement for Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21) :
Patients must have an FFPE tumor sample available for MATCH study testing from a biopsy or surgery that was performed at any point after initial tumor recurrence/progression, or be planned to have a procedure to obtain such a sample that is considered to be of potential benefit by the treating clinicians including but not limited to the procedures listed in Section 5.2 below. A tumor sample from a clinically performed diagnostic (pre-treatment) biopsy will be acceptable for enrollment onto Pediatric MATCH only for children with high-grade gliomas of the brainstem (diffuse intrinsic pontine gliomas) or thalamus.

Please note: **Samples that have been decalcified using standardly utilized acid-based decalcification methods are not generally suitable for MATCH study testing; the nucleic acids will have been degraded in the decalcification process.**

4.1.4 Tumor molecular profiling report availability requirement for Stage 2 of Pediatric MATCH (patients enrolled starting 2022):

In Stage 2 of the study, no tumor samples will be submitted for centralized clinical tumor profiling. Instead, a tumor molecular profiling report from a CAP/CLIA-approved testing laboratory must be submitted for review by the Molecular Review Committee (MRC) as described in Section 3.8.

This molecular profiling must have been performed on a tumor sample that was obtained at any point after initial tumor recurrence/progression and must be accompanied by a pathology report for the same tumor specimen as specified in Section 3.7. A molecular profiling report for a diagnostic (pre-treatment) tumor sample will be acceptable for enrollment onto Pediatric MATCH only for children with high-grade gliomas of the brainstem (diffuse intrinsic pontine gliomas) or thalamus. In the event that molecular profiling reports are available from multiple timepoints, the most recent report should be prioritized for study submission.

4.1.5 Performance Status: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age). Note: Neurologic deficits in patients with CNS tumors must have been stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

4.1.6 Disease Status: **Patients must have radiographically measurable disease** (Refer to Section 12). **Measurable disease based on imaging obtained less than or equal to 56 days prior to enrollment.** Patients with neuroblastoma who do not have measurable disease but have MIBG+ evaluable disease are eligible. Measurable disease in patients with CNS involvement is defined as any lesion that is at minimum 10 mm in one dimension on standard MRI or CT.

Note: The following do not qualify as measurable disease:

- malignant fluid collections (e.g., ascites, pleural effusions)
- bone marrow infiltration except that detected by MIBG scan for neuroblastoma
- lesions only detected by nuclear medicine studies (e.g., bone, gallium or PET scans) except as noted for neuroblastoma
- elevated tumor markers in plasma or CSF
- previously radiated lesions that have not demonstrated clear progression post radiation

- leptomeningeal lesions that do not meet the measurement requirements for RECIST 1.1.

4.2 **General Inclusion Criteria for Subprotocols**

NOTE: patient does not need to meet all subprotocol criteria at time of enrollment onto the APEC1621SC screening protocol, but will need to meet all criteria prior to enrollment on any assigned treatment subprotocol. Patients must be enrolled onto a subprotocol within 2 weeks (14 days) of treatment assignment.

4.2.1 Performance Status: (See Section 4.1.4)

4.2.2 Disease Status: **At the time of treatment with subprotocol specified therapy, the patients must have radiographically measurable disease.** (See Section 12). Patients with neuroblastoma who do not have measurable disease but have MIBG+ evaluable are eligible. Measurable disease in patients with CNS involvement is defined as any lesion that is at minimum 10 mm in one dimension on standard MRI or CT.

Note: The following do not qualify as measurable disease:
- malignant fluid collections (e.g., ascites, pleural effusions)
- bone marrow infiltration except that detected by MIBG scan for neuroblastoma
- lesions only detected by nuclear medicine studies (e.g., bone, gallium or PET scans) except as noted for neuroblastoma
- elevated tumor markers in plasma or CSF
- previously radiated lesions that have not demonstrated clear progression post radiation
- leptomeningeal lesions that do not meet the measurement requirements for RECIST 1.1.

4.2.3 Prior Therapy: At the time of enrollment onto a subprotocol, the following general criteria for initiation of therapy will be required:

4.2.3.1 Patients must have fully recovered from the acute toxic effects of all prior anticancer therapy and must meet the following minimum duration from prior anticancer directed therapy prior to enrollment to the subprotocol. If after the required timeframe, the numerical eligibility criteria are met, e.g.

blood count criteria, the patient is considered to have recovered adequately.

a. Cytotoxic chemotherapy or other anticancer agents known to be myelosuppressive.
   See https://www.cogmembers.org/site/disc/devtherapeutics/default.aspx for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.≥ 21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).

b. Anticancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent.
   See https://www.cogmembers.org/site/disc/devtherapeutics/default.aspx for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.

c. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.

d. Corticosteroids: If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

e. Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g. Neulasta) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator.

f. Interleukins, Interferons and Cytokines (other than Hematopoietic Growth Factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than Hematopoietic Growth Factors)

g. Stem cell Infusions (with or without TBI):
- Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion: ≥ 84 days after infusion and no evidence of GVHD.
- Autologous stem cell infusion including boost infusion: ≥ 42 days.

h. Cellular Therapy: ≥ 42 days after the completion of any type of cellular therapy (e.g. modified T cells, NK cells, dendritic cells, etc.)

i. XRT/External Beam Irradiation including Protons: ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation. Note: Radiation may not be delivered to "measurable disease" tumor site(s) being used to follow response to subprotocol treatment.

j. Radiopharmaceutical therapy (e.g., radiolabeled antibody, 131I-MIBG): ≥ 42 days after systemically administered radiopharmaceutical therapy.

4.2.4 Organ Function Requirements

4.2.4.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

b. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.2.4.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity.

4.2.4.2 Adequate Renal Function Defined as:

- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.[58]

4.2.4.3 Adequate Liver Function Defined as:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 135 U/L. (For the purpose of this study, the ULN for SGPT is 45 U/L.)

4.2.5 Patients must be able to swallow intact capsules/tablets, unless otherwise specified in the subprotocol to which they are assigned.

4.2.6 Agent specific limitations on prior therapy will be included with specific treatment subprotocols.

4.3 General Exclusion Criteria for Subprotocols

4.3.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies, or because there is currently no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in females who are post-menarcheal. Males or females of reproductive potential may not participate unless they have

agreed to use an effective contraceptive method.

4.3.2 Concomitant Medications

4.3.2.1 Corticosteroids: At the time of consent and enrollment to regimen specific subprotocols, patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment to the subprotocol will not be eligible. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

4.3.2.2 Investigational Drugs: Patients must meet criteria for prior therapy (Section 4.2.3) at the time of consent and enrollment to a subprotocol. Other investigational agents may not be administered to patients while they are receiving study drug as part of a subprotocol (See Section 8).

4.3.2.3 Anticancer Agents: Patients must meet criteria for prior therapy (Section 4.2.3) at the time of consent and enrollment to a subprotocol. Other investigational agents may not be administered to patients while they are receiving study drug as part of a subprotocol (See Section 8).

4.3.2.4 Anti-GVHD agents post-transplant: Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible.

4.3.3 Infection: Patients who have an uncontrolled infection are not eligible.

4.3.4 Patients who have had a prior solid organ transplant are not eligible.

4.3.5 Additional agent specific criteria will be included with specific treatment subprotocols.

5.0 SUBMISSION OF EVALUATIONS/MATERIAL AND DATA FOR TARGET SCREENING

5.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility (see Section 4.0) must be

performed within 7 days prior to enrollment unless otherwise indicated. Platelet count should be obtained within 48 hours prior to biopsy. For treatment subprotocols, imaging studies and other required testing must be obtained as required by the subprotocol.

The following studies are required pre-study and then until the patient is enrolled onto a subprotocol or until the patient is off study as defined in Section 10.1.

STUDIES TO BE OBTAINED	Pre-Study/ Enrollment
History	X
Physical exam with vital signs	X
Performance Status	X
Blood sample (K2 EDTA tube) for genomics research, if available	X
Relapsed tumor sample for genomics research, if available	X
Blood sample (Streck tube) for ctDNA research, if available	X
Diagnostic (pre-relapse) tumor sample for additional genomics research, if available	X

Note: All Follow-up data, which includes all anti-cancer therapies received after enrollment must be submitted in accordance with the Case Report Forms (CRFs) schedule.

5.2 Biopsy Methods and Complication Monitoring

Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21)

5.2.1 Examples of biopsy procedures.

No biopsies performed exclusively for research purposes will be utilized to obtain tumor samples for the Pediatric MATCH study. Procedures such as those listed below are routinely used to obtain tumor tissue in patients for whom the procedure is deemed to offer potential clinical benefit. Decision about the indication for biopsy in an individual patient will be made by the treating clinicians.

- Percutaneous biopsy, including image-guided studies
- Excisional biopsy of readily accessible lesions (e.g. cutaneous or subcutaneous lesions, superficial lymph nodes)
- Laparoscopic or thoracoscopic biopsy
- Needle biopsy, including stereotactic biopsy, of CNS tumors

- Endoscopic biopsy of CNS tumors
- Other minimally-invasive biopsy procedures

5.2.2 Biopsies of patients with high-grade gliomas of the brainstem and thalamus.
As children with diffuse intrinsic pontine gliomas (DIPG, brainstem gliomas) generally progress following initial standard radiation therapy, tumor samples from clinically performed diagnostic (pre-treatment) biopsies will be acceptable for enrollment onto Pediatric MATCH for children with such tumors.

5.2.3 In the event that multiple post-recurrence/progression tumor samples are available, the sample from the most recent procedure should be prioritized for study testing.

5.2.4 Any complications associated with tumor samples for Pediatric MATCH: biopsy or biopsy-related anesthesia or imaging procedures performed after consent to this study will be reported and tracked as outlined in Section 6.3.

As of Amendment #4: **Stage 2 of Pediatric MATCH (patients enrolled starting 1/01/22):** Starting in Stage 2 of Pediatric MATCH, no tumor samples are being submitted for central clinical testing as part of the study and no biopsy-related complications will be reported or tracked.

5.3 Pathology Guidelines and Specimen Requirements

Before entering patients on this trial, clinicians should discuss this protocol with their pathologist and provide them with the protocol and list of the required materials that will need to be submitted.

It is the responsibility of the Principal Investigator at the institution to ensure that the pathologist is informed and to request that all patient specimens be forwarded to the COG Biopathology Center (BPC), as required. The BPC will NOT request materials.

5.4 Imaging Procedures

The use of imaging to facilitate biopsies will be decided by the clinical site and may include the following baseline imaging: FDG-PET, CT scan, or MRI which will be used for tumor disease evaluation. Should CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy.

5.5 Genomic Platform and Reporting

Genomic platform and reporting for Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21)

The Pediatric MATCH study will employ an analytically validated next-generation sequencing targeted assay of more than 4,000 different mutations of interest (MOIs; SNVs, indels, copy number alterations, gene fusions) across more than 140 genes (see Appendix I for gene list). This assay will be coupled to a computer algorithm (MATCHbox), that was initially developed for the adult NCI MATCH study and will be further optimized for the pediatric study, that uses pre-existing definitions of actionable mutations of interest (aMOIs) and prioritization of target-agent pairs, combined with clinical criteria specific to each subprotocol, to assign patients by actionable mutation results to a targeted treatment. The aMOIs (a subset of MOIs) and subprotocol-specific clinical criteria for use in the MATCHbox algorithm will be defined for each agent/subprotocol at the time of subprotocol development. The sequencing assays will be performed in one of the NCI MATCH CLIA-approved laboratories that are performing tumor sequencing for the adult MATCH study.

A Platform and Sequencing Committee was formed to evaluate and recommend a plan for the testing to be performed on Pediatric MATCH. The committee reviewed available options for sequencing platforms and determined that an adaptation of the ThermoFisher Oncomine panel developed for the adult MATCH study would be preferred. The committee then reviewed the contents of the current version of the panel being used for adult MATCH at both the gene and variant level, reviewed the pediatric literature for specific genes/variants (including CNVs, SNVs, indels, and fusions) relevant to high-priority Pediatric MATCH agents that would need to be included, and have provided these recommendations as the next version of the platform is currently being developed (e.g. the version of the platform that will be utilized for Pediatric MATCH). For example, the committee provided specific information about the spectrum of ALK and FGFR4 mutations observed in pediatric cancers and recommended inclusion of the full coding sequences of SMARCA4 and SMARCB1 (INI1) in anticipation of a potential EZH2 inhibitor arm of the study. The lead investigator for each subprotocol developed will work with the Target and Agent Prioritization committee and Platform Sequencing and Analysis committee in order to define the relevant genes and aMOIs within those genes for that subprotocol at the time of protocol development.

An extensive validation of the mutation panel being used for the adult NCI MATCH study has previously been performed to establish the performance of this test, including treatment assignment using MATCHbox. In addition, analytic performance plans have now been developed in order to further confirm the performance of the mutation panel using (1) pediatric tumor samples harboring genetic alterations that have previously been identified by testing in clinical laboratories and (2) blood samples harboring germline genetic alterations that have previously been identified by testing in clinical laboratories. These plans include a full assay system fit-for-purpose experiment in which clinical blood and tumor specimens will be obtained from either core needle biopsies, tumor resections, or archived FFPE specimens collected according to study protocols. This effort will test the entire MATCH specimen workflow system from sample collection, clinical database tracking, specimen shipment, central pre-analytic processing, nucleic acid extraction and quantity/quality checks, IHC testing, nucleic acid shipment, NGS testing in the laboratory network, NGS assay verification and reporting, MATCHbox treatment selection and reporting.

Sequencing of matched patient blood samples using the same cancer gene mutation panel will be performed in parallel with tumor sequencing in order to allow the somatic (tumor-specific) or germline nature of mutations detected by the panel to be determined. A germline results report, separate from the tumor report, will be generated by a clinical genomics lab with the appropriate expertise and experience to interpret a hereditary cancer panel and returned to treating physicians as soon as possible after the tumor reports are provided. Note: study treatment assignment will be based exclusively on results of tumor sequencing. Results obtained from sequencing of blood samples will not impact the process of tumor analysis or be separately used to determine study treatment assignment.

The treatment assignment algorithm (MATCHbox) will identify the first priority study for each patient based on the predefined set of genetic and clinical criteria for each subprotocol. If more than one molecular abnormality is identified as actionable for treatment on a Pediatric MATCH subprotocol, the one with the greater level of evidence that tumors harboring the variant will respond will be used to assign treatment (see Appendix III for variant level of evidence definitions). For SNV/indels, if more than one actionable mutation of interest (aMOI) is present with equivalent level of evidence, then the abnormality with the higher allele frequency (must be > 15% higher than the next lower allele frequency) will be used to assign treatment. If two variants are equivalent using these 2 parameters, the patient will be assigned to the subprotocol with fewer patients, or

randomized between subprotocols if numbers of patients on the relevant subprotocols are equal. If a subject is not able to receive that therapy, based for example on subprotocol-specific exclusion criteria, then they will be assigned to the second priority agent (if applicable), and so on in an iterative manner.

The mutation panel is anticipated to be updated approximately every 12 months over the course of the study, to include additional genes/variants as needed based on new data in the literature and novel agents of interest. This will be performed in conjunction with the adult NCI MATCH study team and include input on priority genes and variants to be included to serve the pediatric MATCH study.

As of Amendment #4: **Genomic platform and reporting for Stage 2 of Pediatric MATCH (patients enrolled starting 1/01/22):**

In Stage 2 of Pediatric MATCH centralized tumor and blood testing will not be performed and the MATCHbox informatics platform will not be used as part of the treatment assignment process. Patient assignment to treatment subprotocols will be made after confirmation (by the Pediatric MATCH Molecular Review Committee, MRC) of the presence of an actionable mutation (aMOI) in a submitted tumor molecular profiling report from a CLIA-certified laboratory. Levels of evidence for mutation actionability will remain as defined from the start of the study. Prioritization of treatment assignments (in the event that the patient is eligible for more than one treatment subprotocol based upon their outside molecular testing results) will follow the same procedures described above for Stage 1 of the study.

5.5.1 Tumor and Germline Mutation Reporting

Tumor and germline mutation reporting for Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21):

- A blood sample is drawn for germline sequencing from each child who participates in Pediatric MATCH, contingent upon parental permission/child assent/young adult participant consent, and sent from the COG study site to the COG Biopathology Center (BPC) for DNA extraction.
- The informed consent form includes specific language explaining that the germline sequencing results are not utilized for determination of subprotocol

eligibility and are not intended to replace a comprehensive genetic evaluation (if clinically indicated) but are being used for the sole purpose of determining which somatic mutations are present in the germline and which are not present in the germline, thereby permitting further evaluation of clinically relevant germline mutations and alleviating concerns about somatic mutations that are not present in the germline.

- Germline DNA is sent from the BPC to one of the designated CLIA/CAP-certified laboratories that is conducting tumor sequencing for the study. DNA/RNA extracted from the patient's tumor sample is also sequenced in the same laboratory as per study procedures.
- The sequencing laboratory analyzes the germline DNA using the same mutation panel that is being used to sequence tumor samples.
- The sequencing laboratory sends the resulting germline and tumor sequence data, including the tumor mutation report (listing both aMOIs and MOIs), to a COG-designated certified clinical genomics laboratory with the appropriate expertise and experience to interpret a hereditary cancer panel. The Baylor College of Medicine (BCM) and Children's Hospital of Los Angeles (CHLA) genetics laboratories have been selected to perform this interpretation.
- The tumor (somatic) sequencing results are used to determine potential eligibility for Pediatric MATCH study subprotocols as per study procedures (if an aMOI is identified). This notification of a potential match (or lack of a match) is sent to the site from COG as described above in (Section 3.3)
- A tumor sequencing report (including both aMOIs and MOIs) and a tumor immunohistochemistry report are separately provided to the treating clinician by the tumor testing laboratories as soon as they are available, without any delay related to germline sequence analysis or reporting. This is currently done by fax.
- The germline sequencing results are not utilized for determination of subprotocol eligibility.
- The clinical genomics laboratory then generates a germline report for the specific purpose of determining if any of the aMOIs and MOIs included in the tumor sequencing report may represent pathogenic or likely pathogenic germline variants in cancer susceptibility genes based on ACMG/AMP variant guidelines, and for informing oncologists which variants included in the tumor report are not

present in the germline.

- If a pathogenic or likely pathogenic germline aMOI or MOI is identified in the blood sample but was not reported in the tumor analysis (due to tumor sequencing failure or more focal tumor sequencing coverage issues) it will be included in the germline report.
- No confirmatory mutation testing (using an orthogonal platform) of germline variants identified will be performed (note this is not required by ACMG next-generation sequencing guidelines).
- If insufficient tumor DNA is available for sequencing (and therefore no tumor DNA sample is sent from the BPC to the sequencing laboratory) no germline DNA will be sent from the BPC to the sequencing laboratory and no germline analysis will be performed.
- The germline report will be provided to the treating institution by the clinical genomics laboratory, with a goal of return within one month of processing the blood sample for analysis. This is currently accomplished by placing a copy of the report in a shared secure location (Sharefile) to which the institutional PI has access. An email will be sent to the institutional PI automatically when a new germline report is available.
- The germline report will include language stating that further genetic evaluation, including confirmatory or additional genetic testing as clinically indicated, should be guided by the patient's oncologist in consultation with appropriate specialists.
- Examples of tumor and germline reports will be provided on the protocol webpage.
- The clinical genomics laboratories doing the germline reporting (BCM and CHLA) will have the capacity to do targeted mutation testing of variants identified in Pediatric MATCH, so that this can be performed (outside of the MATCH protocol) for family members desiring clinical follow-up as part of routine medical care if that is requested. Contact information for the BCM and CHLA laboratories will be provided to participating oncologists and included in the germline reports.
- The Germline Reporting committee is committed to developing education materials and central genetics expertise to support the oncologists receiving germline reports and provide information about local genetics resources for

families desiring further evaluation.

- Contact information for a Pediatric MATCH study resource to answer questions about both tumor and germline study testing and provide additional referral information (as indicated) will be posted on the COG protocol homepage.

As of Amendment #4: **Tumor and germline mutation reporting for Stage 2 of Pediatric MATCH (patients enrolled starting 1/01/22):**

- In Stage 2 of Pediatric MATCH centralized tumor and blood testing will not be performed and no clinical testing reports will be issued.
- Any questions about whether a specific report is acceptable or mutation is actionable can be referred to the COG study chair and vice chair (Drs. Parsons and Janeway) who will consult with the Molecular Review Committee (MRC) as required.

5.6 APEC1621SC Specimen Studies

5.6.1 Blood Sample for Genomic Research (required if available):

5.6.1.1 Sample collection and handling instructions

4 mL blood in EDTA will be collected after enrollment. If blood in an EDTA tube is collected over the weekend or on the day before a holiday, the sample should be stored in a **refrigerator** until shipped on the next business day.

5.6.1.2 Labeling

Label each blood collection tube with the patient's name, date of birth, COG patient ID, specimen type (blood) and the date and time the sample was drawn.

Record the exact date and time each sample is drawn on the CRF.

5.6.1.3 Shipping

Refer to Section 5.7 for shipping details.

5.6.2 **Relapsed Tumor for Genomic Research (required if available):**

5.6.2.1 Sample collection and handling instructions

Block or 20-30 (5 μm) unstained slides from tumor collected after relapse/recurrence. If slides are submitted in place of a block, the slides should be cut sequentially from one block and include the following:

- 1 unstained charged slide (the first) for H&E
- 6 unstained charged slides for IHC
- 15-25 unstained, air-dried (preferably uncharged) slides for macrodissection and nucleic acid extraction

Note: If relapsed tumor sample is available but quantity does not meet the criteria above, the available tumor may still be submitted for research.

Note: Send a block or slides from the most recent procedure if multiple post-recurrence/progression tumor samples are available. If a patient relapses after enrollment and another biopsy occurs for clinical reasons, this tissue may also be submitted for genomic research.

5.6.2.2 Labeling

Label blocks and slides with the COG patient ID, specimen type (P for primary or M for metastatic), surgical pathology ID and block number from the corresponding pathology report, and section number of the sequentially cut section (slides). In addition, the patient's name, date of birth, and the collection date **must** be labeled on the specimen.

Note: Stage 2 samples will not require patient's name and DOB.

The corresponding unredacted pathology report must be labeled with the patient's name, date of birth and BPC number.

Complete the APEC1621SC MATCH Genomic Research Tumor Specimen Transmittal Form and the site contact information form. The site contact information form must be included with each shipment of

specimens for genetic research Include the transmittal form, the pathology report, and the site contact information form with the shipment

New York State Institutions must complete the Non-Permitted Laboratory Test Request Approval Form. The Non-Permitted Laboratory Test Request Approval Form must be submitted with the MATCH Genomic Research Tumor Specimen Transmittal Form. The Non-Permitted Laboratory Test Request Approval Form can be found on the protocol page.

Note: Stage 2 will no longer require the Non-Permitted Laboratory Test Request Approval Form to be submitted.

5.6.2.3 Shipping
Refer to Section 5.7 for shipping details.

5.6.3 **Circulating Tumor (ctDNA) DNA Study (required if available):**

5.6.3.1 Sample collection and handling instructions
One blood sample for ctDNA extraction will be collected from all patients after enrollment onto APEC1621SC, into Streck Cell-Free DNA BCT tubes. Please note that this sample must be collected prior to start of subprotocol therapy. Streck Cell-Free DNA BCT tubes may be ordered via the BPC Kit Management application. (https://kits.bpc-apps.nchri.org/).

Peripheral blood samples for circulating tumor DNA should be obtained as follows:

- For patients ≥ 10 kg collect 20 mLs (10 mL per tube x 2 tubes)
- For patients ≥ 5 kg but < 10 kg collect 10 mL (one tube)
- For patients < 5 kg research samples will not be collected

Record the exact date and time each sample is drawn on the CRF.

In all cases, blood draw volumes should strictly adhere to institutional limitations, taking other blood draws into consideration. However, if a reduction in volume is required, samples should be collected in 10 mL increments (i.e. 0, 10, or 20 mL should be collected such that each Streck

Cell-Free DNA BCT is completely filled).

Established institutional guidelines should be followed for blood collection via vascular access devices. Heparin should be avoided in pre-collection flush procedures. If therapeutic heparin dosing contamination is a possibility, venipuncture is recommended as a first choice collection method. If a Streck Cell-Free DNA BCT tube immediately follows a heparin tube in the draw order, we recommend collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT.

For patients who do not have indwelling catheters, blood should be collected via venipuncture. To guard against backflow, observe the following precautions:

- Keep patient's arm in the downward position during the collection procedure.
- Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection.
- Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application.
- Fill tube completely.
- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results.
- Store blood in Streck tube at **room temperature** until shipment, completion of the case report form must occur before shipment.

5.6.3.2 Labeling

Label each blood collection tube with the patient's name, date of birth, COG patient ID, specimen type (blood) and the date and time the sample was drawn.

Complete the APEC1621SC ctDNA specimen transmittal form and include the transmittal form and corresponding unredacted pathology

report with the shipment.

Note: Stage 2 samples will not require patient's name or DOB.

5.6.3.3 Shipping
Refer to Section 5.7 for shipping details.

5.6.4 **Diagnostic (Pre-Therapy) Tumor Sample for Additional Genomics Research (required, if available):**

5.6.4.1 Sample collection and handling instructions
After enrollment, one block or 10-20 (5 µm) unstained slides from a tumor sample obtained at the time of original diagnosis (pre-therapy), will be collected if available. If slides are submitted in place of a block, the slides must be cut sequentially from one block with the first slide an unstained charged slide for H&E.

5.6.4.2 Labeling
Label blocks and slides with the COG patient ID, specimen type (P for primary or M for metastatic), surgical pathology ID and block number from the corresponding pathology report, and section number of the sequentially cut section (slides). In addition, the patient's name, date of birth, and the collection date **must** be labeled on the specimen.

Complete the APEC1621SC Diagnostic Tumor specimen transmittal form and include the transmittal form and corresponding unredacted pathology report with the shipment.

5.6.4.3 Shipping
Refer to Section 5.7 for shipping details.

5.7 APEC1621SC Specimen Shipment

Stage 1 ONLY: **Blood samples should be shipped the same day as collection.** Ship both EDTA and Streck tubes at room temperature on Monday through Friday for Tuesday through Saturday delivery.

Ship blood by FedEx Priority Overnight using the COG FedEx account. Ship blood for Saturday delivery if shipped on Friday.

- If blood for genomics research (EDTA) is collected over the weekend or on the day before a holiday, the sample should be stored in a refrigerator until shipped on the next business day.
- Blood sample for ctDNA (Streck tube) must remain at room temperature if it cannot be shipped the day of collection.

Ship blocks or slides on Monday through Thursday by FedEx Priority Overnight using the COG FedEx account; do not send blocks or slides for Saturday delivery.

Include the specimen transmittal form, site contact information form and a copy of the corresponding pathology report (when sending tissue). The copy of the **unredacted** pathology report sent to the BPC must include the patient's name, and date of birth, and BPC number.

As of Amendment #4 and after Stage 2 accrual begins: **pathology report must be redacted and uploaded to RAVE. The redacted report must include the COG patient ID and the patient BPC number. The site contact information form must be completed in RAVE and sent with all specimens. Please send a copy of the redacted report to the BPC with any tissue submitted.**

Shipping Address:

COG Biopathology Center
APEC1621SC-Peds MATCH*
Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

Ship samples by FedEx Priority Overnight using a FedEx shipping label obtained through the COG FedEx account.

*Labeling is extremely important for this project. Packages **must** be labeled "APEC1621SC-Peds MATCH" in order to ensure appropriate processing at the BPC.

5.8 Agent selection

Rationale for agent selection approach for Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21):

The study Target and Agent Prioritization (TAP) committee will review target and agent pairs for inclusion in the Pediatric MATCH Trial. TAP committee membership includes pediatric oncologists with expertise in cancer genomics, with representation from the COG disease committees relevant to the trial patient population, in addition to NCI/CTEP, FDA, and adult NCI MATCH study leadership. In preparation for the study, the TAP committee compiled a comprehensive list of targeted agent classes that could be considered for inclusion, then conducted a formal review process (with two primary reviewers for each target/agent pair) that culminated in a written review that was presented to the committee with a recommended priority score that was then voted on by the committee. Based on this ranking, the committee leadership determined the top priority target-agent pairs by assessing factors including (1) the level of evidence linking the biomarker to response to the agent (see Appendix III), (2) the ability of the proposed MATCH assay to detect the biomarker, (3) the frequency of the relevant genetic alterations in pediatric cancers, and (4) the suitability of each target-agent pair for the planned trial design and endpoints. Appendix I details the initial list of prioritized agent classes, the genes and types of alterations relevant to each drug, the estimated frequency of actionable alterations for each drug, and the tumor types known to be most frequently mutated.

As part of their process the TAP committee also evaluates the available data regarding blood brain barrier penetration for each potential study agent. In cases in which it is known from previous clinical studies that adequate levels of the agent cannot be achieved in the CNS to induce tumor responses, the TAP committee may recommend that children with CNS tumors not receive that agent. In general, however, given the known extent of disruption of the blood brain barrier in CNS tumors, the goal will be to treat children with both CNS and non-CNS tumors with each study agent (presuming that they have a defined targetable agent).

A subset of TAP committee members have participated (and continue to participate) in a

series of calls led by CTEP with numerous pharmaceutical companies whose portfolios include the prioritized classes of agents. The company representatives formally present the relevant agent or class of agents and engage in discussion with the TAP committee members. Based upon this review process (including additional preclinical and clinical information from each company) the TAP committee then recommends specific agents for inclusion for the study. Refer to the 'APEC1621-Master Version Control protocol' for agents that have been recommended for inclusion. The rationale for the selection of each agent will be described in detail in each subprotocol.

Over the course of the study, the TAP committee will continue to meet on a quarterly basis to evaluate whether additional target-agent pairs should be discussed and reviewed by the committee in order to determine suitability for inclusion in the study. If a high priority agent is nominated by a TAP committee member then ad hoc reviews will also be conducted as required.

As of Amendment #4: **Rationale for agent selection approach for Stage 2 of Pediatric MATCH (for patients enrolled starting 1/01/22):**

No additional agents will be selected for study in Stage 2.

5.9 Patients with non-target bearing (biomarker negative) tumors

It is anticipated that a minority of children with relapsed or refractory cancer will have an actionable mutation of interest (aMOI) for which a study agent is available. An important question to address for select agents, should a significant signal of activity be observed in pediatric patients, is whether the signal is truly confined to biomarker positive patients. In order to provide data relevant to this question of agent specificity, for select agents that have demonstrated preliminary signs of activity (defined as ≥ 3 CR/PRs) in biomarker positive patents, patients with non-target bearing (biomarker negative) tumors may be enrolled on an independent stratum. These biomarker negative cohorts may either be histology-specific (if ≥ 3 responses are observed in a specific histology, see Section 11.2.3 for additional details) or histology-agnostic (if ≥ 3 responses are observed, but not in any one histology), and will preferentially enroll patients to the earliest opened cohort when possible within slot availability/cohort suspension constraints. Patients in the biomarker negative cohorts will not be counted for purposes of determining the primary objective (response rate to targeted agents in patients whose tumors bear the target).

A recommendation regarding whether each particular agent is appropriate for potential

inclusion of biomarker negative subjects (presuming the bar for observed responses in biomarker positive subjects has been met) will be made in the corresponding subprotocol based on the recommendation of the TAP committee. This decision will be based upon a number of factors, including (1) specific mechanism of action of the agent, (2) potential promiscuity of the targeted molecular pathway, (3) degree of permissiveness of the agent-target interaction, (4) available preclinical data in non-target-bearing tumor models, and (5) available clinical data for patients with non-target-bearing tumors. The same factors utilized in assessing evidence to support a link between a biomarker and response to the agent (see Appendix III) will be applied to assess evidence for response in a biomarker negative population. The concept for each individual subprotocol in which a biomarker negative population is proposed will describe the evidence supporting potential activity of that agent in a biomarker negative population.

6.0 TREATMENT PROGRAM

6.1 Overview of Treatment Plan

Refer to subprotocol.

6.2 Grading of Adverse Events

Adverse events (toxicities) will be graded according to version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). All appropriate treatment areas should have access to a copy of version 5.0 of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP website (http://ctep.cancer.gov). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair dose -limiting toxicity attributable to subprotocol therapy should be reported as defined in the subprotocol.

6.3 Definition of Biopsy-Related Target Toxicity (TT)

Tracking of biopsy-related target toxicity in Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21):

Biopsy related target toxicity (TT) will be defined as:

- Any Grade 4 or Grade 5 toxicity or complication associated with tumor samples for pediatric MATCH, that is probably or definitely attributable to any biopsy or

biopsy-related anesthesia or imaging procedure that occurs within 14 days of a biopsy performed after enrollment on this study

- Any Grade 3 toxicity or complication associated with tumor samples for pediatric MATCH, that is probably or definitely attributable to any biopsy or biopsy-related anesthesia or imaging procedure that occurs within 14 days of a biopsy performed after enrollment on this study and which in addition meets any of the following criteria:
    - An adverse event that results in any inpatient hospitalization in which an unplanned intervention is administered (i.e. any hospitalization for other than planned observation) or prolongation of existing hospitalization for ≥ 48 hours
    - Permanent adverse sequelae
    - A life-threatening adverse event
    - Other important medical events (IMEs) that may not result in death, be life threatening, or require hospitalization but may be considered a serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

These target toxicities will require expedited reporting via CTEP-AERS as outlined in Table A of Section 13.

As of Amendment #4: **Tracking of biopsy-related target toxicity in Stage 2 of Pediatric MATCH (for patients enrolled starting 1/01/22):**

Starting in Stage 2 of Pediatric MATCH, no tumor samples are being submitted for clinical testing as part of the study and no biopsy-related complications will be reported.

6.4 Definition of Dose-Limiting Toxicity (DLT)

Dose-limiting hematological and non-hematological toxicities will be defined any of the following events that are at least possibly related to subprotocol therapy, as specified in each subprotocol. The DLT observation period for the purposes of determining safety and feasibility of the protocol directed therapy will be the first cycle of therapy as defined in the subprotocol.

Unless otherwise specified in the subprotocol, the standard definition of DLT will be:

Non-Hematological DLT:

- Any ≥ Grade 3 non-hematological toxicity attributable to protocol therapy. Specific exclusions and additional non-hematologic DLTs will be outlined in each subprotocol.

7.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

Dose modifications for dose-limiting toxicity will be detailed in the subprotocols.

8.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

8.1 Concurrent Anticancer Therapy

Patients may receive concurrent cancer therapy while enrolled on the screening portion of APEC1621SC, but must meet criteria for prior therapy (Section 4.2.3) at the time of consent and enrollment to a subprotocol. Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients while they are receiving study drug as part of a subprotocol. If these treatments are administered the patient will be removed from protocol therapy.

8.2 Investigational Agents

Patients may receive investigational agents while enrolled on the screening portion of APEC1621SC, but must meet criteria for prior therapy (Section 4.2.3) at time of consent and enrollment to a subprotocol. No other investigational agents may be given while the patient is enrolled on an APEC1621 subprotocol and receiving protocol directed therapy.

9.0 AGENT INFORMATION: GENERAL OVERVIEW

9.1 Refer to Subprotocol for agent information.

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Off Study Criteria from APEC1621SC Screening Protocol

a) Two years from the date of patient enrollment onto APEC1621SC if not enrolled onto a subprotocol.
b) Two years from the date of technical failure resulting in inability to yield sequencing results and no further plan to obtain additional tumor sample [STAGE 1 ONLY, does not apply after Amendment #4]
c) The fifth anniversary of the most recent date of patient enrollment onto a subprotocol.
d) Death
e) Lost to follow-up
f) Withdrawal of consent for any further required observations or data submission.
g) Physician determines it is not in the patient's best interest.
h) Histologic diagnosis of recurrent malignancy not confirmed within one month of enrollment.

10.2 Criteria for Removal from Subprotocol Therapy

a) Each subprotocol will outline specific criteria for removal from subprotocol therapy. Removal from subprotocol therapy does not constitute removal from the APEC1621SC screening protocol.

Patients who are removed from protocol therapy during cycle 1 should continue to have the required observations until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

Patients who are off subprotocol therapy will continue to be followed on the APEC1621SC screening protocol. Follow-up data submission will occur until one of the Off Study criteria outlined in Section 10.1 is met. Ongoing adverse events, or adverse events that emerge after the patient is removed from subprotocol therapy, but within 30 days of the last dose of subprotocol investigational agent, must be followed and reported in the subprotocol via RAVE and CTEP-AERS (if applicable). Serious adverse events that occur during the follow-up period (more than 30 days after the last administration of investigational agent) and have an attribution of possible, probable, or definite require reporting per Footnote 1 of Table A. Follow-up data will be required unless consent is withdrawn.

10.3 APEC1621SC Re-screening upon removal from subprotocol therapy

Patients who are removed from subprotocol therapy may be assigned to another MATCH treatment subprotocol if the Molecular Review Committee (MRC) identified an actionable mutation for that subprotocol in the tumor profiling report(s) reviewed for that patient. If a tumor profiling report is available from a later date or becomes available while the patient is enrolled on APEC1621SC that report can be submitted for review by the MRC. The treatment assignment process is repeated, in order of priority, until all potential treatment assignments are exhausted.

The treating team will need to complete a re-screen step in OPEN, to indicate that they would like the patient to be considered for assignment to a new MATCH treatment subprotocol (if available).

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

Sample size and study duration for Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21):

The expected accrual rate is 200-300 patients per year, of which 10% or 30 patients/year are expected to have an actionable mutation of interest (aMOI) for which a study agent is available. A total of 1500 enrollments is planned during Stage 1.

As of Amendment #4: **Sample size and study duration for Stage 2 of Pediatric MATCH (patients enrolled starting 2022):**

It is anticipated that 50 patients per year will enroll on the screening protocol, of whom 50% (25 patients per year) will be eligible for enrollment on the primary cohorts of a treatment subprotocol.

It is noted that as of Amendment #4, there are no sample size goals associated with the screening study. APEC1621SC serves to support subprotocols. The ceiling in the table below is calculated based on a rate of 50% would enroll to subprotocols and the maximum of enrollments from subprotocols.

DOMESTIC PLANNED ENROLLMENT REPORT					
Race Categories	**Ethnicity Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	5	5	5	6	**21**
Asian	36	61	0	0	**97**
Native Hawaiian or Other Pacific Islander	4	0	0	0	**4**
Black or African American	156	165	0	0	**321**
White	613	911	131	125	**1780**
More Than One Race	11	0	0	0	**11**
Total	**825**	**1142**	**136**	**131**	**2234**

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Race Categories	**Ethnicity Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	**0**

Asian	1	2	0	0	**3**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	6	6	0	0	**12**
White	23	34	5	5	**67**
More Than One Race	0	0	0	0	**0**
Total	**30**	**42**	**5**	**5**	**82**

11.2 Dosing Considerations

If a pediatric RP2D dose has been established, the patient will be treated at that dose.

11.2.1 Pediatric MATCH Sub-arm Dosing in the Absence of Pediatric Phase 1 Data

If there is no prior pediatric phase 1 data, study investigators will review relevant data with the pharmaceutical partner to identify a drug specific dosing plan for testing in children with recurrent/refractory cancer, and trial participants will be closely monitored to ensure tolerability of the selected dose. Limited pharmacokinetic sampling may be done for patients enrolled on these arms. In general, the dosing for the Pediatric MATCH subprotocols will follow the guidelines below:

- For agents where the adult RP2D is below the adult MTD, the adult RP2D (normalized to body surface area or body weight) will be used for evaluation in the Pediatric MATCH, understanding that further dose optimization may be required in a future pediatric study.
- For drugs for which the adult RP2D is at the adult MTD, the pediatric subprotocol will evaluate an initial cohort of patients at a dose level approximately 30% below the adult MTD and then complete the study using the adult RP2D, assuming that both dose levels are tolerated. Rules for determining tolerability of these dose levels are described in Section 11.2.2.

11.2.2 **Determination of Recommended Phase 2 Dose (RP2D)/Tolerable Dose**

For drugs for which the adult RP2D is the adult MTD, the pediatric subprotocol will evaluate an initial cohort of patients using a modified rolling 6 design starting at a dose level approximately 30% below the adult MTD and then completing the study using the adult RP2D, assuming that both dose levels are tolerated. The DLT evaluation period for the purpose of dose escalation will be cycle 1 of therapy. Accrual will be suspended to assess tolerability when a cohort of six has enrolled at the starting dose level.

The rolling six phase 1 trial design will be used for the conduct of this study. [59] Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	*Decision*
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the recommended dose has been defined.

**If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then dose escalation will be stopped.

In addition to determination of the RP2D, a descriptive summary of all toxicities will be reported.

11.3 Subprotocol Study Design

The primary cohort(s) and any biomarker negative expansion cohorts defined below will employ single stage A'Hern designs of N=20 and N=10 respectively. The agent will be deemed worthy of further study in the relevant subset of patients (i.e. biomarker positive in any histology, biomarker positive in a particular histology, etc) if the decision rule is met. Operating characteristics are shown below.

Cohort	N	Decision Rule	Alpha	Power
Primary biomarker positive	20	≥ 3 responses	10%	90%
Any biomarker negative	10	≥ 2 responses	9%	74%

Histology-specific biomarker positive expansion cohorts will, by definition, be deemed worthy of further study, since they will have at least 3 responses. The table below shows 90% confidence intervals (Wilson method) for a range of observable response rates.

Cohort Size	Observed Response Rate	90% Confidence Interval
10	30%	13% - 56%
10	40%	19% - 65%
10	50%	27% - 73%

11.3.1 Primary Cohort:

Each subprotocol will evaluate at least one primary cohort of 20 mutation-matched ("biomarker positive") evaluable patients of any histology for the primary study aim of determining the objective response rate (CR/PR according to the response criteria in Section 12.3) to the agent, given the molecular eligibility criteria for that cohort. Some subprotocols may include several primary cohorts each with different non-overlapping molecular eligibility criteria (for example: subjects with *TSC1* and *TSC2* mutations in cohort A, subjects with *PIK3CA* mutations in cohort B). Using an A'Hern design[60] with alpha=10%, a sample of N=20 will provide 90% power to detect an improvement in response rate from 5%, if the treatment is ineffective, to 25% if the targeted therapy is sufficiently effective to warrant further study. If there are at least 3 responses out of 20 in the primary cohort, the biomarker/therapy match will be deemed a success.

11.3.2 **Histology-Specific Biomarker Positive Expansion Cohorts:**

If ≥ 3 patients with the same histology in the primary cohort show signs of objective response (CR/PR according to the response criteria in Section 12.3), a histology-specific biomarker positive expansion cohort will open after the primary cohort is completed to up to 7 evaluable patients, for a total sample size of 10 evaluable biomarker positive patients with that histology. This will allow us to estimate more precisely the activity in biomarker positive patients of that histology. See Appendix II for a list of target tumor histologies. We will open up to 3 such expansion cohorts for biomarker positive patients (i.e., if 3 histologies have ≥ 3 responses, we will open a total of 3 expansion cohorts as described above). Note that this can only happen if the response rate in the primary cohort is at least 45% (9/20) and there cannot be more than 21 additional evaluable patients in total for these expansion cohorts.

11.3.3 **Biomarker Negative cohorts:**

If the TAP committee has determined that it is appropriate to enroll biomarker negative patients in the study based on the characteristics of the particular agent (See Section 5.8) and the pharmaceutical provider of the agent agrees with that conclusion, then the following expansion cohorts may open and will preferentially enroll patients to the earliest opened cohort when possible within slot availability/cohort suspension constraints.

11.3.3.1 **Histology-Agnostic Biomarker Negative Cohort:**

If at any time ≥ 3 patients in the primary cohort show signs of objective response, but there are < 3 responses of the same histology, then a single cohort of 10 biomarker negative patients of any histology will be opened. If in the course of the study the primary cohort continues to have responses such that ≥ 3 responses are observed in the same histology, then biomarker negative cohorts will be opened as described in Section 11.3.3.2 and biomarker negative patients with that histology will be reallocated to the histology-specific cohort. If 2 or more responses are seen in the non-histology-specific biomarker negative cohort, the regimen will be declared active for biomarker negative patients. This will provide a low probability (9%) of carrying forward agents with response rates less than 5% and a moderately high probability (74%) of identifying agents with response rates ≥ 25%.

11.3.3.2 **Histology-Specific Biomarker Negative Cohorts**:
If at any time ≥ 3 patients in the primary cohort with the same histology show signs of objective response, then 10 patients with the same histology but without the biomarker will be enrolled. If 2 or more responses are seen in a histology-specific biomarker negative cohort, the regimen will be declared active for biomarker negative patients of that histology. Using this A'Hern single stage design will assure a low probability (9%) of carrying forward agents with response rates less than 5% and provide a moderately high probability (74%) of identifying agents with response rates ≥ 25%. Up to a total of 3 such biomarker negative cohorts can be opened, for a total of 30 biomarker negative patients.

For biomarker negative cohorts: If more than one histology-specific cohort is opened alongside a histology-agnostic cohort, accrual to the histology-agnostic cohort will stop if no activity is observed in the histology-specific cohorts and activity has not yet been observed in the histology-agnostic cohort.

11.3.4 **Subprotocol Sample Size:**
Each subprotocol will require a minimum of 20 evaluable patients (or 4 evaluable patients if criteria in Section 11.2.2 is met), and a maximum of 96 patients can be enrolled, allowing for 15% inevaluability. This maximum could only occur if the primary cohort has ≥ 12 responses, with 9 evenly split among 3 histologies and 3 responses spread amongst other histologies, and the TAP committee has determined that it is reasonable to enroll biomarker negative patients. If biomarker negative enrollment is not allowed on the subprotocol, the maximum sample would be 49 patients, allowing for 15% inevaluability.

11.4 Match Rate Feasibility Analysis

Stage 1 of MATCH: The match rates will initially be assessed after accrual to 200 patients or one year after study activation, whichever occurs first, then on a quarterly basis.

As of Amendment #4: **Stage 2 of MATCH:** The match rates will be assessed in 2023 after one year of Stage 2 operations.

11.5 **Methods of Analysis**

Response criteria are described in Section 12. A responder is defined as a patient who achieves a best response of PR or CR on the study. Response rates will be calculated as the percent of evaluable patients who are responders, and confidence intervals will be constructed using the Wilson score interval method.[61] Decision making for A'Hern design cohorts will follow rules described above.

Toxicity tables will be constructed to summarize the observed incidence by type of toxicity and grade. A patient will be counted only once for a given toxicity for the worst grade of that toxicity reported for that patient. Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen.

11.6 **Evaluability for Response**

Any eligible patient who is enrolled and receives at least one dose of protocol therapy on any APEC1621 sub-protocol will be considered evaluable for response. Any patient who receives non-protocol anti-cancer therapy during the response evaluation period will be considered a non-responder for the purposes of the statistical rule, unless they show an objective response prior to receiving the non-protocol anti-cancer therapy (in which case they will be considered a responder.). Patients who are not evaluable for response evaluation may be replaced for the purposes of the statistical rule. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. Preliminary assessment of activity using institutionally provided tumor measurements will be entered into CDUS quarterly. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

11.7 **Evaluability for Toxicity**

All eligible patients who receive at least one dose of protocol therapy (according to subprotocol guidelines) on any APEC1621 subprotocol will be considered in the evaluation of toxicity.

11.8 **Monitoring of Biopsy Related Adverse Events**

Monitoring of biopsy related adverse events in Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21):

Patients who undergo a biopsy after enrolling on APEC1621SC will be monitored to determine whether they experience a biopsy related target toxicity (TT) as defined in Section 6.3. Biopsy related target toxicity will be monitored separately for subjects with CNS tumors and non-CNS tumors who receive a biopsy for the purpose of obtaining a tumor sample for MATCH using the following monitoring rule: If 3 or more of the first 33 patients who undergo a biopsy after enrolling on MATCH experience a biopsy related target toxicity, the data for the relevant cohort of the study (CNS or non-CNS tumors) will be sent to the study committee and DSMC for review to determine whether actions are required. Otherwise additional monitoring will continue, up to 88 patients who undergo a biopsy after enrolling on MATCH. A similar review will be conducted if 5 or more biopsy-related target toxicities are observed in that cohort. If the true biopsy related target toxicity rate is 2%, then the monitoring rule will be tripped with 0.05 probability. If the true research-biopsy related target toxicity rate is 10%, then the rule will be tripped with 0.95 probability. In order to avoid delays and logistical problems due to pausing accrual while each accrued patient's toxicity data are evaluated, this study will continue to concurrently enroll patients without waiting for target toxicity outcomes to be determined for evaluable patients. Re-evaluation will occur at 30 days post-biopsy of any biopsy-related target toxicities that have been reported in the CNS tumor cohort.

As of Amendment #4: **Monitoring of biopsy-related adverse events in Stage 2 of Pediatric MATCH (for patients enrolled starting 1/01/22):**

Starting in Stage 2 of Pediatric MATCH, no tumor samples are being submitted for clinical testing as part of the study and no biopsy-related complications will be captured.

11.9 Progression free survival (PFS)

Progression free survival will be defined as time from the initiation of subprotocol treatment to the occurrence of any of the following events: disease progression or disease recurrence or death from any cause. All patients surviving at the time of analyses without events will be censored at their last follow-up date.

PFS along with the confidence intervals will be estimated using the Kaplan-Meier method. Patients with local calls of disease progression (i.e. calls made by the treating institution), will be counted as having had an event, even if the central review does not declare progression. We will also report PFS based on central radiology review as a secondary analysis, if adequate number of disagreements in progressions exist between the treating institutions and the central radiology review to make such an analysis meaningful. Duration

of PFS response will be summarized for responders.

11.10 Correlative Studies

A descriptive analysis of pharmacokinetic (PK) parameters will be performed in specific subprotocols to define systemic exposure, drug clearance, and other pharmacokinetic parameters. Refer to specific subprotocols for more information on the pharmacokinetic (PK) parameters being performed.

Approaches to diagnosing and profiling genomics of tumors through the evaluation of Circulating Tumor DNA will also be explored. A next-generation sequencing based assay will be utilized to quantify the DNA present in the plasma.

A descriptive analysis of the exploratory aims described in Section 1.3 will be performed and will be summarized with simple summary statistics. All of these analyses will be descriptive in nature.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in version 5.0 of the NCI Common Terminology Criteria for Adverse Events v5.0 (CTCAE) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

- Toxicity and Adverse events probably or definitely attributable to tumor biopsy on this protocol will be tabulated as part of APEC1621SC Screening Protocol.
- Toxicity and Adverse events related to administration of APEC1621 subprotocol directed protocol therapy will be tabulated according to the subprotocol.
- Toxicity and Adverse events that occur related to therapy prior to administration of APEC1621 subprotocol directed therapy or in participants who do not enroll on a subprotocol will not be collected.

12.2 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of subprotocol treatment to time of progression or death, whichever occurs first.

Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence.

12.3 Response Criteria for Patients with Solid Tumors

All APEC1621 sub-protocols will use the same response criteria and interval of response assessment. Tumor disease evaluations will be performed at the end of every other cycle x 3, then every 3 cycles. In addition to the scheduled scans, a confirmatory scan should be obtained the cycle following initial documentation of objective response.

As outlined, patients will be assigned to one of the following categories for assessment of response: a) solid tumor (non-CNS) and measurable disease (Section 12.4); b) neuroblastoma with MIBG positive lesions (Section 12.5); c) CNS tumor (Section 12.7); and d) non-Hodgkin lymphoma/histiocytosis (Section 12.8). Note: Neuroblastoma patients who do not have MIBG positive lesions should be assessed for response as solid tumor patients with measurable disease.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[62] Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

12.3.1 Definitions

12.3.1.1 Evaluable for objective response:
Eligible patients who receive at least one dose of protocol therapy will be considered evaluable for response. Evaluable patients who demonstrate a complete or partial response confirmed by central review before receiving non-protocol anti-cancer therapy will be considered a responder. All other evaluable patients will be considered non-responders.

12.3.1.2 Evaluable Non-Target Disease Response:
Eligible patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease and have received at least one dose of protocol therapy will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or

unequivocal progression of the lesions.

12.3.2 **Disease Parameters**

12.3.2.1 Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

12.3.2.2 Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

12.3.2.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

12.3.2.4 Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved

organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

12.3.2.5 Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3.3 **Methods for Evaluation of Measurable Disease**

All measurements should be taken and recorded in metric notation using a ruler or calipers.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

12.3.3.1 Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

12.3.3.2 Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung.

However, CT is preferable.

12.3.3.3 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

12.3.3.4 PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST or International Pediatric non-Hodgkin Lymphoma Response Criteria measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

12.3.3.5 Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

12.3.3.6 Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

12.3.3.7 FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A 'positive' FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

For patients with a positive PET scan at diagnosis, PET can be used to follow response in addition to a CT scan using the International Pediatric non-Hodgkin Lymphoma Response Criteria.[63]

12.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target and non-target

lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

12.4.2 **Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm

short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Overall Best Response Assessment
Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.9 from a sequence of overall response assessments.

12.5 Response Criteria for Neuroblastoma Patients

Please refer to specific subprotocols for response criteria used to assess neuroblastoma patients. Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of ^{123}I for MIBG imaging is recommended for all scans.

12.6 Response Criteria for Patients with CNS Tumors

12.6.1 Measurable Disease

Any lesion that is at minimum 10 mm in one dimension on standard MRI, for CNS tumors.

12.6.2 Evaluable Disease

Evaluable disease is defined as at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by

nuclear medicine techniques, immunocytochemistry techniques, tumor markers, CSF cytology, or other reliable measures.

12.6.3 Selection of Target and Non-Target Lesions

For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response. If multiple measurable lesions are present, up to 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g., 8 mm lesion for a 4 mm slice).

Any change in size of non-target lesions should be noted, though does not need to be measured.

12.6.4 Response Criteria for Target Lesions

Response criteria are assessed based on the product of the longest diameter and its longest perpendicular diameter. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence. Response Criteria for target lesions:

- **Complete Response (CR):** Disappearance of all target lesions. Off all steroids with stable or improving neurologic examination.

- **Partial response (PR):**≥ 50% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements; on a stable or decreasing dose of steroids with a stable or improving neurologic examination.

- **Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR, nor sufficient increase in a single target lesion to qualify for PD; on a stable or decreasing dose of steroids with a stable or improving neurologic examination..

- **Progressive Disease (PD):** 25% or more increase in the sum of the products of the perpendicular diameters of the target lesions, taking as reference the smallest sum of the products observed since the start of treatment, or the appearance of one or more new lesions.

  Increasing doses of corticosteroids required to maintain stable neurological status should be strongly considered as a sign of clinical progression unless in the context of recent wean or transient neurologic change due e.g. to radiation effects.

12.6.5 Response Criteria for Non-Target Lesions:

- **Complete Response (CR):** Disappearance of all non-target lesions.

- **Incomplete Response/Stable Disease (IR/SD):** The persistence of one or more non-target lesions.

- **Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

12.6.6 Response criteria for tumor markers (if available):
Tumor markers will be classified simply as being at normal levels or at abnormally high levels.

12.6.7 Overall Response Assessment
The overall response assessment takes into account response in both target and non-target lesions, the appearance of new lesions and normalization of markers (where applicable), according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, marker and new lesions in the preceding columns.

Target Lesions	**Non-target Lesions**	**Markers**	**New Lesions**	**Overall Response**
CR	CR	Normal	No	**CR**
CR	IR/SD	Normal	No	**PR**

CR	CR, IR/SD	Abnormal	No	**PR**
PR	CR, IR/SD	Any	No	**PR**
SD	CR, IR/SD	Any	No	**SD**
PD	Any	Any	Yes or No	**PD**
Any	PD	Any	Yes or No	**PD**
Any	Any	Any	Yes	**PD**

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.9 from a sequence of overall response assessments.

12.7 Response Criteria for Patients with non-Hodgkin Lymphoma/Histiocytosis

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric non-Hodgkin Lymphoma Criteria[63], with modification from the Lugano classification.[64]

12.7.1 Evaluation of Measurable Disease

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric non-Hodgkin Lymphoma Criteria[63], with modification from the Lugano classification. [64]

Disease Parameters

1. Measurable disease: A measurable node must have an LDi (longest diameter) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

2. Non-measured disease: All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (e.g., cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

3. Target lesions: For patients staged with CT, up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include

mediastinal and retroperitoneal disease, if involved.

12.7.2 Evaluation of Measurable Disease

Complete Response (CR)
Disappearance of all disease. CT or MRI should be free of residual mass or evidence of new disease. FDG-PET should be negative.

Complete Response Unconfirmed (CRu)
Residual mass is negative by FDG-PET; no new lesions by imaging examination; no new and/or progressive disease elsewhere.

Partial Response (PR)
50% decrease in SPD (the sum of the products of the largest diameter and the perpendicular diameter for a tumor mass) on CT or MRI; FDG-PET may be positive (Deauville score or 4 or 5 with reduced lesional uptake compared with baseline); no new and/or PD; morphologic evidence of disease may be present in BM if present at diagnosis; however, there should be 50% reduction in percentage of lymphoma cells.

No Response (Stable Disease)
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Progressive disease
For those with > 25% increase in SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with increase in lesional uptake from baseline, or development of new morphologic evidence of disease in BM.

Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[64]

Complete Response (CR): Absent non-measured lesions.

Partial response (PR): Absent/normal, regressed, lesions, but no increase.

Stable Disease (SD): No increase consistent with progression

Progressive Disease (PD): New or clear progression of preexisting

non-measured lesions.

12.7.3 Evaluation of organ enlargement[64]

Complete Response (CR): Regress to normal

Partial response (PR): Spleen must have regressed by >50% in length beyond normal

Stable Disease (SD): No increase consistent with progression

Progressive Disease (PD): In the setting of splenomegaly, the splenic length must increase by 50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline.

New or recurrent splenomegaly

12.8 **Best Response**

Two objective status determinations of disease status, obtained on two consecutive determinations, separated by at least a 3 week time period, are required to determine the patient's overall best response. Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluations (the first evaluation is the first radiographic evaluation after treatment has been administered) will have a best response of progressive disease. Best response is unknown if the patient does not qualify for a best response of progressive disease and if all objective statuses after the first determination and before progression are unknown.

12.8.1 **Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both

measurement and confirmation criteria.

Table 1: For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 28 days Confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 28 days Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥ 28 days from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 2. Sequences of overall response assessments with corresponding best response.

1st Assessment	2nd Assessment	Best Response
Progression		Progressive disease
Stable, PR, CR	Progression	Progressive disease
Stable	Stable	Stable
Stable	PR, CR	Stable
Stable	Not done	Not RECIST classifiable

PR	PR	PR
PR	CR	PR
PR, CR	Not done	Not RECIST classifiable
CR	CR	CR

Table 3: Overall Response for Patients with Neuroblastoma and Measurable Disease

CT/MRI	MIBG	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	PD	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	CR/PR/SD	Non-PD	Non-PD	Any	SD
PR	CR/PR	Non-PD	Non-PD	Any	PR
CR/PR	PR	Non-PD	Non-PD	Any	PR
CR	CR	Non-PD	Non-PD	Elevated	PR
CR	CR	CR	CR	Normal	CR

Table 4: Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only
If patients are enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered progressive disease.

MIBG	CT/MRI	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	New Lesion	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	No New Lesion	Non-PD	Non-PD	Any	SD
PR	No New Lesion	Non-PD	Non-PD	Any	PR
CR	No New Lesion	Non-PD	Non-PD	Elevated	PR
CR	No New Lesion	CR	CR	Normal	CR

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded)

until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the data collection packet for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting of biopsy-related adverse events in Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21):

Reporting requirements may include the following considerations if related to biopsy related target toxicity: 1) whether the adverse event is considered serious; 2) the grade (severity); and 3) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any Complications associated with tumor samples for pediatric MATCH: **biopsy, biopsy-related anesthesia, biopsy related target toxicity or imaging procedures performed after consent to this study will be reported and tracked as protocol-related adverse events and graded according to NCI CTCAE v5. Any grade complication will be considered a Serious Adverse Event if it meets the criteria outlined in Table A.**

Biopsy related target toxicities (TT) as defined in Section 6.3 will require expedited reporting via CTEP-AERS as outlined in Table A.

Reporting of biopsy-related adverse events in Stage 2 of Pediatric MATCH (for patients enrolled starting 1/01/22):

Starting in Stage 2 of Pediatric MATCH, no tumor samples are being submitted for clinical testing as part of the study and no biopsy-related complications will be reported.

13.1 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

Expedited reporting requirements for SAEs in Stage 1 of Pediatric MATCH (patients enrolled from start of study in July 2017 through 12/31/21):

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with biopsy related target toxicities. A Serious Adverse Event (SAE) is any adverse event (experience) occurring in ANY of the following outcomes **only** related to biopsy related target toxicities:

1) Death

2) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.

3 A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

4) A congenital anomaly/birth defect.

5) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.1.1 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and

assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

13.1.2 CTEP-AERS Expedited Reporting Methods

Expedited AE reporting for this study must only use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page https://ctepcore.nci.nih.gov/ctepaers/pages/task.

Send supporting documentation to the NCI by fax (fax# 301-897-7404) and by email to the APEC1621SC COG Study Assigned Research Coordinator. **ALWAYS include the ticket number on all faxed and emailed documents**.

Expedited reporting requirements for SAEs in in Stage 2 of Pediatric MATCH (for patients enrolled starting 1/01/22):

Starting in Stage 2 of Pediatric MATCH, no tumor samples are being submitted for clinical testing as part of the study and no biopsy-related SAEs will be reported.

13.2 Steps to Determine if an Adverse Event is to be reported in an Expedited Manner

Step 1: Identify the type of adverse event using version 5.0 of the NCI CTCAE. The descriptions and grading scales found in version 5.0 of the CTCAE will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE v5.0. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the adverse event using the NCI CTCAE v5.0.

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or

- there are any protocol-specific exceptions to the reporting requirements.

- Any biopsy related target toxicity equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any biopsy related target toxicity results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
- As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.
- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at http://ctep.cancer.gov (telephone CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable). Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.
- When the adverse event requires expedited reporting, submit the report within 5 or 7 calendar days of learning of the event (refer to Table A).

Table A: Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)*
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death
2) A life-threatening adverse event

3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

* **Only biopsy related target toxicities should be reported via CTEP AERs refer to section 13.6.**

13.3 **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements:**

- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased
BLOOD/LYMPHATICS DISORDERS	Anemia

13.4 **Definition of Onset and Resolution of Adverse Events**

Note: These guidelines below are for reporting adverse events on the COG case report forms and do not alter the guidelines for CTEP-AERS reporting.

13.4.1 If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

13.4.2 If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

13.4.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.4.4 The resolution date of the AE is defined as the date at which the AE returns to baseline or less than or equal to Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

13.4.5 An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.5 Other Recipients of Adverse Event Reports

13.5.1 Events that do not meet the criteria for CTEP-AERS reporting (Section 13.2) should be reported at the end of each cycle using the forms provided in the CRF packet (See Section 14.1).

13.5.2 Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

13.6 Specific Examples for Expedited Reporting of Biopsy-Related Target toxicities

13.6.1 Reportable Categories of Biopsy-Related Target toxicity relating to Death for Screening Protocol

- Any death that occurs due to biopsy-related target toxicity should be reported, refer to Section 6.3 and Section 11.8 for more information. All other occurrences of death (**unrelated** to biopsy) should be reported in RAVE but **should not be reported as an SAE.**

13.6.2 Reporting of Biopsy-Related Target toxicity relating to Secondary Malignancy

Secondary Malignancy:
A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

1) Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
2) Myelodysplastic syndrome (MDS)
3) Treatment-related secondary malignancy.

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each

protocol.

Second Malignancy:
A *second malignancy* is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

13.6.3 Reporting of Biopsy-Related Target toxicities relating to Pregnancy, Pregnancy Loss, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Death Neonatal", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 897-7404. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

Pregnancy
Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

Pregnancy needs to be followed **until the outcome of the pregnancy is known** at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all necessary follow-ups. This form is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

Any pregnancy loss needs to be reported expeditiously, as **Grade 4 "*Pregnancy loss"*** *under the "**Pregnancy, puerperium and perinatal conditions" SOC***. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

Death Neonatal

Neonatal death, defined in CTCAE v5.0 as "***Newborn deaths occurring during the first 28 days after birth***" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously, as **Grade 4 "*Death Neonatal*"** under the system organ class (SOC) of "General disorders and administration site conditions", **when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

13.6.4 Unanticipated Events

In accordance with OHRP guidelines, Unanticipated Events are defined as any event that includes an incident, experience, or outcome that meets the following criteria:

- Unexpected, related to or possibly related to participation in research, and anything that suggests that the research places subjects or others at a greater risk of harm

For more information please refer to the guidelines on the OHRP website (https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/)

Unanticipated problems warrant consideration of substantive changes in the screening protocol or informed consent document in order to protect the safety, welfare, or rights of subjects. In addition, unanticipated problems may present unanticipated risks to others (e.g., parents of the subjects) in addition to the subjects. While these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly provided to the IRB and DSMC in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

1. Non-computerized Information: *e.g.*, Roadmaps, Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.
2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.
3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the data form packet.

See separate Data Form Packet, which includes submission schedule.

14.2 Access to RAVE for Data Submission/ Data Reporting

Data collection for this study will be done through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam/index.jsp), appropriate RCR registration and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the COG or COGC roster at the enrolling site. Please refer to Appendix VII for more detailed information on the necessary registration procedures.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com, or by email to the COG Study Assigned Data Manager.

14.3 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

14.4 CRADA/CTA/CSA

Refer to individual subprotocols.

14.5 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the COG Data and Safety Monitoring Committee.

14.5.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the developmental therapy scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, including adverse events related to biopsies and any unanticipated problems, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional

review boards can be prepared using the public data monitoring report as posted on the COG Web site.

14.5.2 Monitoring by the Study Chair

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed at regular intervals.

15.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

15.1 Computed Tomography (CT) with Contrast

Most, if not all, COG institutions will be using multi-detector helical CT scanners. This is preferred in order to decrease scanning time compared to conventional CT, allow image acquisition at the time of peak contrast enhancement, reduce/eliminate the need for sedation, and reduce image degradation from motion artifact. The volumetric acquisition of helical/spiral CT and the reconstruction of overlapping images increases the conspicuity of small lesions and facilitates multi-planar reconstruction for better depiction of certain lesions. Sagittal and coronal reconstructed images, as well as images reconstructed using a lung algorithm should be submitted where feasible, along with the axial imaging data. CT imaging should be performed with intravenous and oral contrast using age and weight-based adjustments to kVp and mA, in accordance with institutional practice and ALARA/Image Gently guidelines. Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

MRI may be used as an alternative modality for assessment of non-pulmonary disease sites (e.g. abdominal/pelvic disease), provided the institution is able to acquire images using phased array surface coils, cardiac gating and respiratory triggering, in order to minimize artifacts from cardiac motion, diaphragmatic motion and bowel peristalsis. Pulse sequences should include at a minimum axial and coronal T1, axial and coronal fat-saturated FRFSE-T2 and multi-planar post-gadolinium fat-saturated T1 weighted imaging. If MRI is used for imaging of the thorax, abdomen and/or pelvis, an unenhanced CT of the chest should still be obtained to evaluate the lungs.

15.2 **CT during PET/CT**

Nearly all PET scanners in use today are integrated PET/CT scanners. However, low dose CT scans performed on integrated PET/CT scanners for the purpose of attenuation correction are of non-diagnostic quality, are usually performed without intravenous contrast, and will not be acceptable for staging or response assessment. As noted above, staging CT scans should include intravenous and oral contrast. In some instances – particularly for staging – a diagnostic quality CT will have been performed prior to the PET/CT. In these cases an additional low-dose CT will still be required for attenuation correction of the PET images. Provided that the diagnostic quality CT scan has been performed within 14 days of the PET/CT, a repeat diagnostic CT examination is not necessary at the time of PET/CT. For post-therapy follow-up scans limited to the neck and/or thorax the use of IV contrast alone is sufficient, provided the scanning parameters are optimized to achieve diagnostic quality images. Some institutions perform the low dose attenuation correction CT with intravenous contrast. Please refer to Section 12.3.3.4 for the requirements.

15.3 **[18F] Fluorodeoxyglucose (FDG) PET**

The use of PET scans is optional but highly recommended. If there is positive disease by PET scan at diagnosis, PET scans have to be performed at repeat evaluation time points until the patient has achieved a CR.

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APPENDIX I: EXAMPLES OF PEDIATRIC MATCH AGENT CLASSES AND LINKED GENETIC ALTERATIONS.

Agent class	aMOI Frequency	Most frequent tumor types	Gene	Mutation by panel	Fusion by panel	CNV (amp) by panel	CNV (del) by IHC
TRK inhibitor	2-3%	LGG, HGG, infantile fibrosarcoma, sarcoma	*NTRK1*		Yes		
			NTRK2		Yes		
			NTRK3		Yes		
FGFR inhibitor	2-3%	NB, RMS, HGG	*FGFR1*	Yes	Yes		
			FGFR2	Yes	Yes		
			FGFR3	Yes	Yes		
			FGFR4	Yes			
EZH2 inhibitor	2-3%	NHL	*EZH2*	Yes			
			SMARCB1	Yes			Yes
			SMARCA4	Yes			Yes
PI3K/mTOR inhibitor	5-10%	OS, RMS, HGG	*PIK3CA*	Yes			
			PIK3R1	Yes			
			MTOR	Yes			

			PTEN	**Yes**			**Yes**
			TSC1	**Yes**			
			TSC2	**Yes**			
MEK inhibitor	**10-20%**	**NHL, LCH, RMS, LGG, HGG, NB,**	***ARAF***	**Yes**			
			BRAF	**Yes**	**Yes**		
			KRAS	**Yes**			
			NRAS	**Yes**			
			HRAS	**Yes**			
			NF1	**Yes**			
			GNAQ	**Yes**			
			GNA11	**Yes**			
			MAP2K1	**Yes**			
ALK inhibitor	**2-3%**	**NB, IMT, ALCL**	***ALK***	**Yes**	**Yes**		
			ROS1		**Yes**		
BRAF inhibitor	**5%**	**HGG, LGG, LCH, PTC, CP, glioneuronal**	***BRAF***	**Yes**			
PARP inhibitor	**1-3%**		***BRAC1***	**Yes**			

			BRAC2	**Yes**			
			ATM	**Yes**			
			RAD51C	**Yes**			
			RAD51D	**Yes**			
CDK 4/6 inhibitor	**2-23%**		***CDK4***			**Yes**	
			CDK6			**Yes**	
			CCND1			**Yes**	
			CCND2			**Yes**	
			CCND3			**Yes**	

Abbreviations: NHL, non-Hodgkin lymphoma; LCH, Langerhans cell histiocytosis; RMS, rhabdomyosarcoma; LGG, low grade glioma; HGG, high grade glioma; NB, neuroblastoma; OS, osteosarcoma; IMT, inflammatory myofibroblastic tumor; DFP, dermatofibrosarcoma protuberans; PTC, papillary thyroid carcinoma.

APPENDIX II: APEC1621SC TARGET HISTOLOGIES FOR EXPANSION COHORTS

Target tumor types considered for biomarker-positive expansion cohorts and biomarker-negative cohorts in the event of agent activity in a specific tumor type.

Tumor type
1. Ependymoma
2. Ewing Sarcoma/Peripheral PNET
3. Hepatoblastoma
4. Glioma, high grade
5. Glioma, low grade
6. Langerhans Cell Histiocytosis
7. Malignant Germ Cell Tumor
8. Medulloblastoma
9. Neuroblastoma
10. Non-Hodgkin Lymphoma
11. Non-RMS Soft Tissue Sarcoma
12. Osteosarcoma
13. Rhabdoid Malignancy
14. Rhabdomyosarcoma
15. Wilms Tumor
16. Other Histology (based on COG/NCI-CTEP approval)

APPENDIX III: LEVELS OF EVIDENCE FOR SUBPROTOCOL AGENTS AND GENE VARIANTS AS AMOI

Levels of Evidence for Pediatric MATCH trial arms (subprotocols)

Level 1	The drug is FDA approved for a malignant indication and there is a molecular abnormality that can serve as a valid predictive marker. The sub-protocol will not enroll patients with conditions for which the drug is approved, or patients with conditions for which the drug has been shown not to have benefit.
Level 2	The drug is investigational, but met a clinical endpoint (PFS, response) in any malignancy, has evidence of target inhibition and has evidence of a predictive molecular marker.
Level 3	The drug is investigational, but has demonstrated clinical activity in any malignancy and evidence of target inhibition, and has evidence of a predictive molecular marker.

Levels of Evidence for Gene Variants as aMOI.

Level 1	Gene variant credentialed for selection of an approved drug (e.g. BRAF V600E and vermurafenib)
Level 2a	Gene variant is an eligibility criterion for an ongoing clinical trial
Level 2b	Gene variant has been identified in an N of 1 response (e.g. TSC1 and everolimus)
Level 3a	Preclinical inferential data (in vivo and in vitro models) that provide biological evidence sufficient to support the use of a variant for treatment selection, e.g.: • Models with variants respond to treatment and models without variant do not respond to treatment • Gain of function mutations demonstrated in pre-clinical model, e.g. D769H variant of ERBB2 results in increased tyrosine kinase-specific activity and up regulates pathway signaling (clinical evidence not required) • Loss of function genes, tumor suppressor or pathway inhibitor (e.g. NF1) any variant that produces a stop codon including frameshift or demonstrated loss of function in pre-clinical model (does not require treatment evidence)

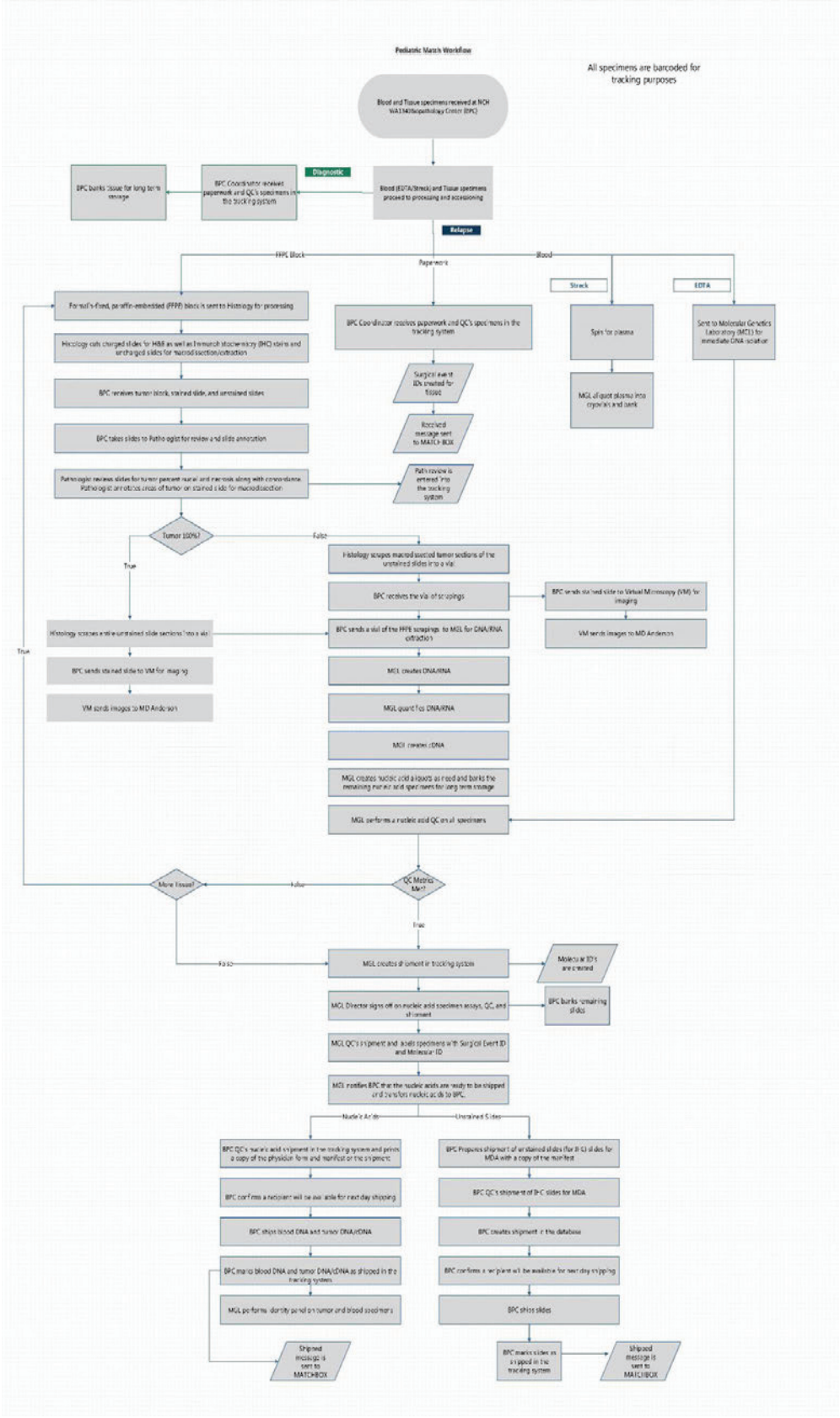
Level 3b Any known fusion transcript for a targeted gene (e.g. any reported ALK translocation)

Level 3c Any copy number amplification for a targeted gene.

APPENDIX IV: PERFORMANCE STATUS SCALES/SCORES

Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX V: BIOSPECIMEN FLOW DIAGRAM USED FOR STAGE 1 OF PEDIATRIC MATCH TRIAL AT NATIONWIDE CHILDREN'S HOSPITAL



APPENDIX VI: APEC1621SC YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621SC
(for children from 7 through 13 years of age)

We want to tell you all about this study. You and your family can decide if you want to be in it. Ask questions if you don't understand.

1. What is the name of the study? **A study of Molecular Analysis for Therapy Choice (MATCH) in children with a cancer that has come back after treatment or is difficult to treat**

2. Who is in charge of the study? The study is being done by Children's Oncology Group and is being done at other hospitals.

3. What is the study about? We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have.

4. What will happen to me on the Study? Children who take part in this study will be screened to see if your cancer has any specific changes that could help us decide what medicine might "match" best to your cancer. If we find a medicine that could "match" your tumor then we would talk to you about that medicine and what we know about it. If you decide to be treated with that medicine you will have some tests and check-ups done more often than if you weren't part of this study. We will follow your health after you finish the study treatment.

   Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that a medicine you receive may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.

   Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from a medicine used as part of this study. There may be risks that we don't know about.

5. Do I have to be in the study? You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. If you have any questions or don't like what is happening, please tell your parent, the doctor or nurse.

6. We are asking your permission to collect additional blood and tumor tissue. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken on tumor and blood samples we already have, so there would be no extra procedures. This would not change what medicines we would use to treat your tumor and would not provide any "benefits" to you. We hope that it might help us learn how to better treat other children's cancers in the future.

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621SC
(for teens from 14 through 17 years of age)

1. What is the name of the study? **A study of Molecular Analysis for Therapy Choice (MATCH) in children with a cancer that has come back after treatment or is difficult to treat**

2. Who is in charge of the study? The study is being done by Children's Oncology Group and is being done at other hospitals.

3. What is the study about? We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have.

4. What will happen to me on the Study? Patients who take part in this study will be screened to see if your cancer has any specific changes that could help us decide what medicine might "match" best to your cancer. If we find a medicine that could "match" your tumor then we would talk to you about that medicine and what we know about it. If you decide to be treated with that medicine you will have some tests and check-ups done more often than if you weren't part of this study. We will collect information about your health after you finish the study treatment.

   Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that a medicine you receive may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.

   Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from a medicine used as part of this study. There may be risks that we don't know about.

5. Will I be paid to be in this study? You will not be paid for being in this study.

6. Do I have to be in the study? You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. If you have any questions or don't like what is happening, please tell your parent, the doctor or nurse.

7. We are asking your permission to collect additional blood and tumor tissue. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken on tumor and blood samples we already have, so there would be no extra procedures. This would not change what medicines we would use to treat your tumor and would not provide any "benefits" to you. We hope that it might help us learn how to better treat other children's cancers in the future.

APPENDIX VII: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP:

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five-person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *COG*, and protocol number (*insert study number*).
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Protocol-Specific Requirements For Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Data Submission / Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.