Pre-Application Webinar: NCI Pediatric in Vivo Testing Program FOAs: RFA-CA-034 and RFA-CA-041

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September 8, 2020

Outline

1) **Overview** of the NCI in Vivo Testing Program and its relationship with planned related programs
2) **RFA-CA-20-034**: NCI Pediatric In Vivo Testing Program (U01 Clinical Trial Not Allowed): Research teams for in vivo testing to evaluate the activity of pediatric anticancer drug candidates
3) **RFA-CA-20-041**: NCI Pediatric In Vivo Testing Program Coordinating Center (U24 Clinical Trial Not Allowed)
4) **Questions:** Use Chat function to ask questions during the presentation and they will be answered at the end of the session

NCI Pediatric in Vivo Testing Program

- NCI commitment to pediatric preclinical in vivo testing is being strengthened to help address the RACE for Children Act provisions of the FDA Reauthorization Act of 2017 (FDARA)
  - Includes new molecularly targeted pediatric investigation requirement for certain oncology medicine applications
  - Applies if drug is “intended for the treatment of an adult cancer” and “directed at a molecular target that [FDA] determines to be substantially relevant to the growth or progression of a pediatric cancer
- The FDA’s initial list of potentially relevant molecular pediatric targets includes over 230 distinct molecular entities, indicating the need for higher throughput for pediatric preclinical testing

NCI Pediatric in Vivo Testing Program - Overview

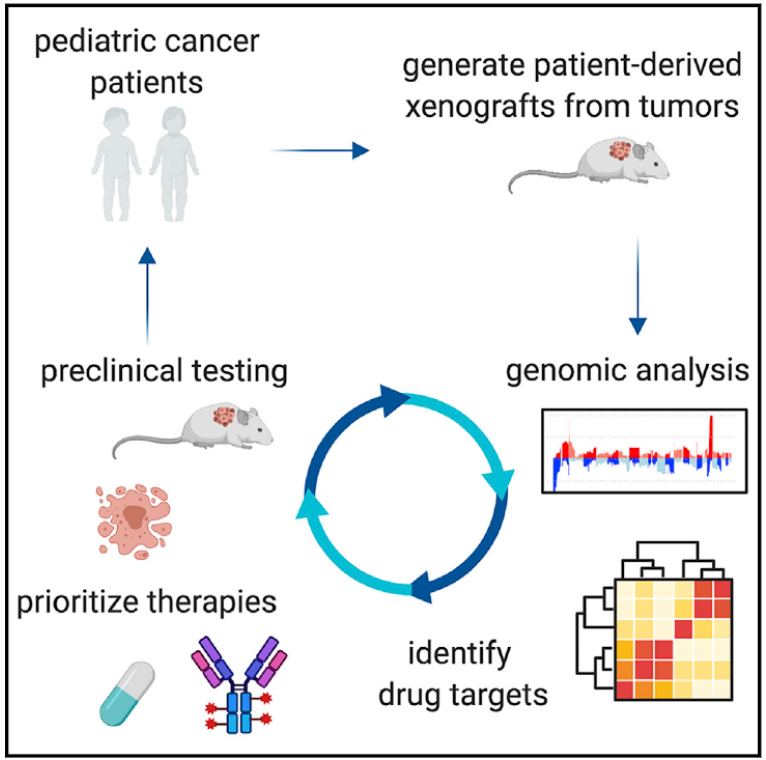
- Plan for 8 awards (3 more than current PPTC) for research programs for in vivo testing and 1 award for a Coordinating Center
- Open competition for in vivo testing sites and for the Coordinating Center applications from new research teams encouraged
- Agnostic in terms of models (e.g., PDX in immunodeficient mice, murine genetic models engineered to reflect the characteristics of specific pediatric cancers, and murine syngeneic models)
- Each team anticipated to test 8-10 agents per year
- Testing results become available to the research community

Coordinating Center – Selected responsibilities include:

- Administrative Coordination and Logistical Support, including:
  - Managing Steering Committee activities
  - Establishment and maintenance of a web-based collaboration system for effective communication across the program
- Data Management, Statistical, and Bioinformatics Support, including:
  - Procedures for ensuring the quality of data generated by Research Teams
  - Statistical analysis of data collected from the Research Teams and storage of data and analyses
- Scientific Coordination, including:
  - Scientific Project Management
  - Collaboration with and provision of support to Research Teams in the preparation of technical study reports and manuscripts

General Approach to Pediatric in Vivo Testing

- Large panels of genomically characterized models
- Genomic characterization available to research community (e.g., PPTC data available through PedcBioPortal https://pedcbioportal.org/study?id=pptc#summary
- Identification of agents for testing based on targets identified in models and clinical specimens
- Selection of models based on their molecular characteristics



Rokita JL, et. al; Cell Reports 2019

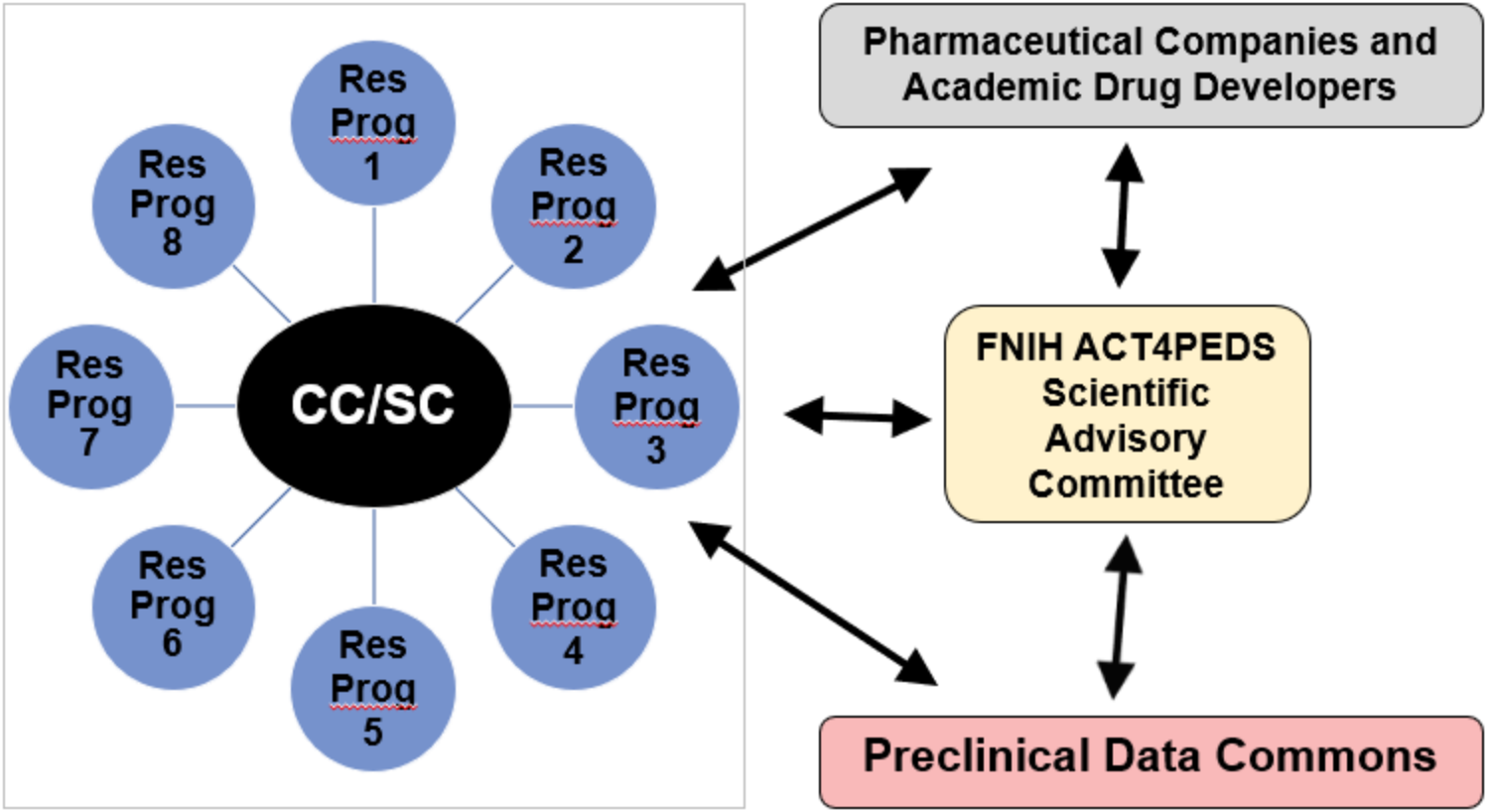
Interactions with FNIH Public-Private Partnership ACT4PEDS

- PIs of NCI in Vivo Testing Program Research teams and PI of Coordinating Center will serve on the FNIH ACT4PEDS Scientific Advisory Committee
- Data generated by NCI in Vivo Testing Program Research teams and analyzed through the Program's Coordinating Center will be submitted to the ACT4PEDS Data Commons.
- For more information about ACT4PEDS, including the white paper describing the public-private partnership, contact FNIH (Stacey Adam, sadam@fnih.org or Tanya Murza, tmurza@fnih.org)

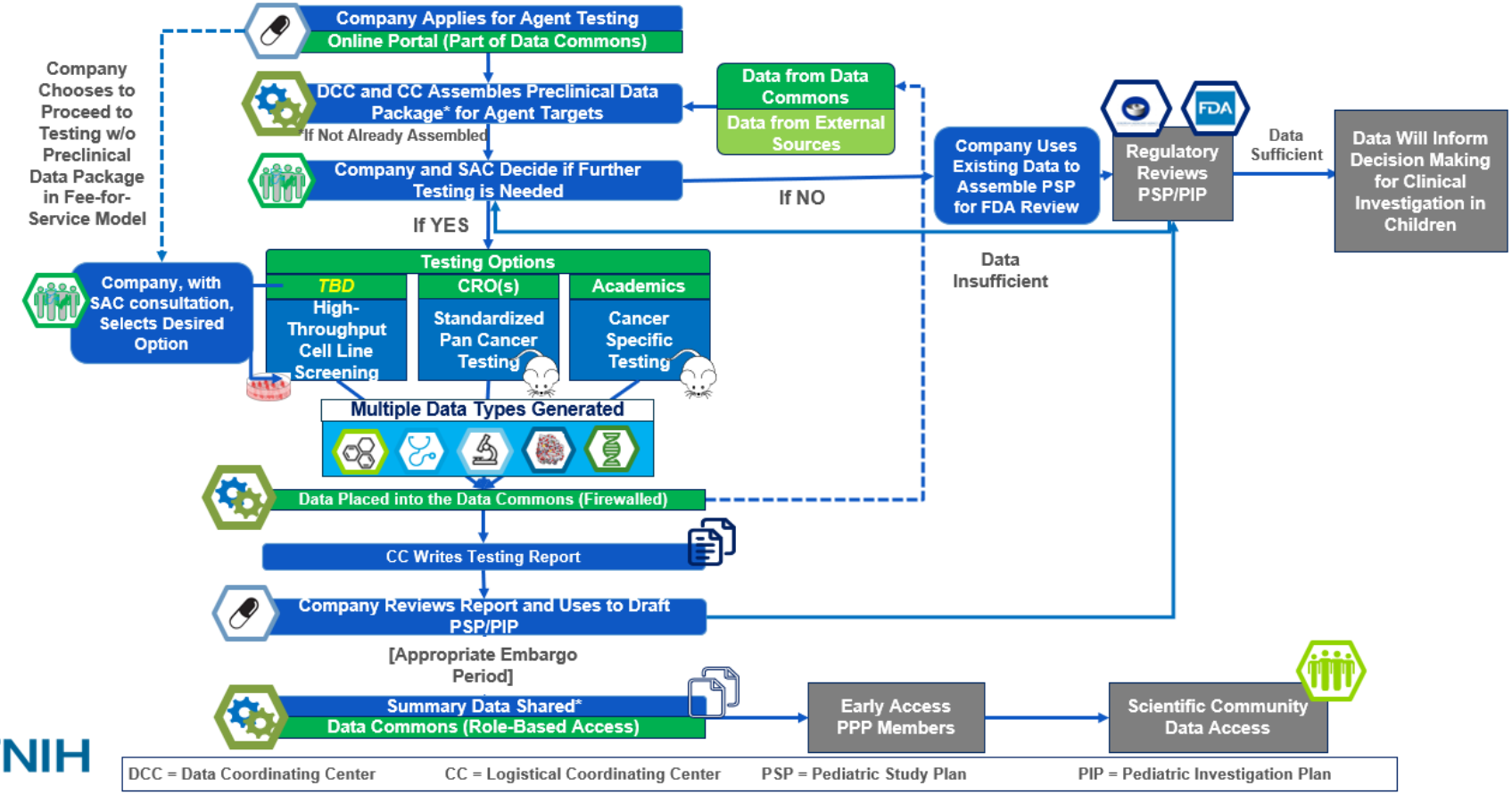
Preclinical Data Commons (planned)

- To aggregate/federate molecular characterization data for cell lines and PDX models from NCI-supported research teams and from external research teams
- To aggregate/federate molecular characterization data for clinical specimens to establish as comprehensive a dataset as possible to facilitate robust comparisons to preclinical data
- To aggregate, store, and compare existing and new testing data both from NCI-supported research teams and from external research teams
- Provide analyses of genomic, proteomic and epigenomic data to support decision-making for preclinical evaluations and for clinical development plans
- Make data available in ways that are easily accessible by the research community

Schema for NCI Pediatric in Vivo Testing Program



Operating Model – Current Potential Design



FNIH

Budget

Component	Direct Costs per Award	Total Costs Year 1
Research Teams for in Vivo Testing (n=8)	$0.45 million	$5.1 million
Coordinating Center	$0.5 million	$0.80 million
Total Combined	$3.65 million	$5.9 million

- RFA-CA-20-034: The application budget is limited to $450,000 in direct costs per year and should reflect the actual needs of the project
- RFA-CA-20-041: The application budget is limited to $500,000 in direct costs per year and should reflect the actual needs of the project
- Overall funding represents substantial increase in NCI support for pediatric preclinical in vivo testing

Timeline for NCI Pediatric in Vivo Testing Program

- August 25, 2020 – Publication of RFA in NIH Guide
- September 8, 2020 – Pre-application webinar
- October 9, 2020 – Letter of Intent (optional)
- November 9, 2020 – Application receipt data
- 1st Quarter 2021 – Peer review
- July 1, 2021 – Award

Letter of Intent

- Not required and does not enter into the review of a subsequent application
- Allows IC staff to estimate the potential review workload and plan the review.
- See RFAs for 5 items requested in LOI response
- Send to Malcolm.Smith@nih.gov
- October 9, 2020

Additional Molecular Characterization Opportunities

- NCI is planning through the Childhood Cancer Data Initiative to support genomic characterization of pediatric preclinical models (PDX and cancer cell lines)
- Information is planned to be available through a Guide Notice and also to be posted at the NCI CTEP website: https://ctep.cancer.gov/MajorInitiatives/Pediatric_Preclinical_Testing_Consortium.htm
- Characterization will include WES, RNA-seq, and DNA methylation array

RFA CA-20-034

NCI Pediatric In Vivo Testing Program

Section III - Eligibility for Pediatric In Vivo Testing Programs RFA-CA-20-034

- Wide range of institutions eligible, including: higher education institutions, nonprofits other than institutions of higher education, for-profit organizations, etc.
- Foreign institutions are eligible to apply
- Applicant organizations may submit more than one application
- Note: A letter from an institutional official indicating that the terms that are included in the Model MTA used by the Pediatric Preclinical Testing Consortium are acceptable to the applicant's institution. (see “Other Project Information”)
  - Contact Malcolm.Smith@nih.gov for questions/clarification re Model MTA

Section IV - Other Project Information for Research Teams for the Pediatric in Vivo Testing Program (1)

1. Relevant laboratory standard operating procedures for maintaining and testing preclinical models, including quality assurance/quality control procedures employed (use file name "SOPs").
2. A document with a table providing information on the clinical/demographic characteristics of the models proposed for testing and information on model creation and quality assurance (use file name "Models Demographic Characteristics"). The PDX models Minimal Information standard (PDX-MI) data elements should be followed to the extent possible.

Section IV - Other Project Information for Research Teams for the Pediatric in Vivo Testing Program (2)

3. A letter from an institutional official indicating that the terms that are included in the Model MTA used by the Pediatric Preclinical Testing Consortium are acceptable to the applicant's institution. Similar terms will apply for testing of agents through the Pediatric in Vivo Testing Program.

- How MTA process will work for NCI Pediatric in Vivo Testing Program:
  - At the beginning of the funding period NCI signs an MTA with each institution with a Research Program or Coordinating Center award. MTA will be based on the Model MTA template.
  - Then for each pharmaceutical company collaborating with the Pediatric in Vivo Testing Program, NCI negotiates an MTA with the company that has terms that match those of the institution MTAs.

Section IV – Application and Submission Information for Pediatric In Vivo Testing Programs RFA-CA-20-034 (1)

- **Research Strategy:** Specific Sub-Sections A-D must be included in Research Strategy
- **Sub-section A**. Investigators Capabilities and Experience
- **Sub-section B**. Preliminary Studies for New Applications / Progress Report for Renewal Applications
  - For new applications, describe preliminary studies that document experience and accomplishments in preclinical testing that are relevant to participation as a member of the Pediatric in Vivo Testing Program
  - For renewal applications from prior members of the NCI Pediatric Preclinical Testing Consortium, follow PHS 398 instructions for inclusion of a Progress Report

Section IV – Application and Submission Information for Pediatric In Vivo Testing Programs RFA-CA-20-034 (2)

- **Sub-section C**. Preclinical Models Proposed
  - Describe the preclinical models proposed for testing (e.g., xenografts, genetic models, murine syngeneic models)
  - Provide an overview of how they were established and an overview of their molecular characteristics.
  - Refer to the information provided in the "Other Attachments" documents ("Models Demographic Characteristics" and "Models Molecular Characteristics") for details of models' characteristics

Section IV – Application and Submission Information for Pediatric In Vivo Testing Programs RFA-CA-20-034 (3)

- **Sub-section C**. Preclinical Models Proposed
  - Provide an explanation for how the molecular characteristics of the models relate to key biological and genomic characteristics of the clinical disease that the models are intended to represent.
  - For syngeneic models that are to be used to evaluate immuno-oncology agents, provide data to support that the immune response observed using the models is relevant to that which might occur in children with cancer.
  - Describe the extent to which the models (or a subset of the models) reflect cancers with poor prognosis (e.g., as a result on intrinsic characteristics of the disease or as a result of documented refractoriness to treatment for the patient from which the model was established).

Section IV – Application and Submission Information for Pediatric In Vivo Testing Programs RFA-CA-20-034 (4)

- **Sub-section D**. Approach to Preclinical Testing
  - Provide an overview of the therapeutic opportunities that appear most compelling for the cancer type(s) intended for study by your Research Program based on current understanding of the biological and genomic characteristics of the disease. Illustrate these opportunities by providing examples of specific agents/targets that are high priorities for in vivo testing for the relevant cancer type(s). Explain how the proposed preclinical models are well-suited for addressing these opportunities.
  - Describe the overall strategy, methodology, and analyses proposed to accomplish the in vivo testing research objectives. Conventional testing, single mouse trial (SMT) design testing, and combination testing designs are all relevant.

Section IV – Application and Submission Information for Pediatric In Vivo Testing Programs RFA-CA-20-034 (5)

- **Sub-section D**. Approach to Preclinical Testing
  - Describe the ability to quantitatively assess for both tumor regression based on serial measurements of tumor volume and for time to event (e.g., based on a specified increase in tumor/leukemia burden) in models proposed for in vivo testing. This applies for models tested by subcutaneous placement as well as orthotopic placement.
  - Note for leukemia models, the expectation is that the testing methods will mimic systemic disease conditions (e.g., through initial tail vein inoculation).
  - Provide evidence of the ability to meet the required throughput of testing for the proposed disease panel(s). Testing of 8-10 agents per year is targeted, although for technically challenging models (e.g., orthotopic CNS tumors) a lower number may be justifiable.

Section IV – Application and Submission Information for Pediatric In Vivo Testing Programs RFA-CA-20-034 (6)

- **Note**. All applications, should address a Data Sharing Plan

Section V. Application Review Information (1)

- Standard NIH Review Criteria apply
- Review criteria specific to RFA-CA-20-034 apply in the following:
  - Significance
  - Investigators
  - Approach
  - Environment

Section V. Application Review Information (2)

- Significance: Review Criteria specific to this FOA:
  - What is the likelihood that the proposed research team will be able to implement an in vivo testing program for its intended disease(s) with appropriately molecularly characterized models that can make substantial contributions to the overall NCI Pediatric in Vivo Testing Program?

- Investigators: Review Criteria specific to this FOA:
  - Based on past performance, how strong are the qualities of the PI(s) and the entire team in terms of appropriate expertise, training, demonstrated experience, and an ongoing record of accomplishments in conducting pediatric preclinical testing?

Section V. Application Review Information (3)

- Approach: Review Criteria specific to this FOA:
  - To what extent does the proposed approach indicate a thorough understanding of the biology of the cancer(s) on which the applicant is focusing and an understanding of how the biology of the cancer(s) can serve as the basis for therapeutic opportunities?
  - How adequate are the preclinical models proposed for testing (e.g., xenografts, genetic models, cell lines) in terms of having the requisite level of molecular characterization (e.g., gene expression, copy number alteration, and exome sequencing or equivalent) and does molecular characterization confirm the likely relevance of the models to the clinical setting?
  - To what extent are models included within the proposed panel that reflect cancers with poor prognosis?

Section V. Application Review Information (4)

- Approach: Review Criteria specific to this FOA:
  - How strong is the understanding of the applicant of appropriate study design and testing methodologies that will allow development of robust datasets to accomplish in vivo testing research objectives?
  - Does the applicant provide an appropriate approach to preclinical testing study endpoints that allows quantitative assessment of both tumor regression and time to event? If not, to what extent is an acceptable alternative provided?
  - To what extent does the approach proposed by the applicant support the ability to complete testing of 8 to 10 agents per year in appropriately designed testing experiments? If a lower number is proposed due to the technical complexity of the model, is adequate justification provided?

Section V. Application Review Information (5)

- Environment: Review Criteria specific to this FOA:
  - Are the applicant's facilities to house and maintain a rodent colony sufficient for the type and quantity of rodents proposed?

Cooperative Agreement Terms and Conditions of Award – Research Team PD/PI Responsibilities

- Participation in the Program's Steering Committee
- Performance of the testing of agents in compliance with Program's Standard Operating Procedures (SOP) for in vivo testing and data submission, analysis, and reporting that are developed and maintained by the NCI Pediatric in Vivo Testing Program Coordinating Center.
- Participation with the Coordinating Center in the interpretation of testing results, in preparing study reports, in proposing additional testing based on results from initial testing, and in co-authoring manuscripts.
- Meeting at least once per year with other Program members (in addition to regular conference calls, videoconferencing, and electronic communications).

Cooperative Agreement Terms and Conditions of Award – Joint Responsibilities with NCI

- The Steering Committee will serve as the body for prioritizing agents for study by the Program, for defining the overall scope of research plans for agents selected for testing, and for approving the general SOPs under which the Program operates. The SC will include: the PI(s) of the Coordinating Center and the PI(s) of each of the Research Teams, the NCI Project Scientist, and others as appropriate.
- The PI(s) of the Coordinating Center and the PI(s) of each of the Research Teams will be expected to serve on the Scientific Advisory Committee (SAC) of the FNIH PPP for pediatric preclinical testing. The Program's Steering Committee may accept recommendations from the PPP SAC for agents to prioritize for testing within the Program.

RFA CA-20-041

NCI Pediatric In Vivo Testing Program Coordinating Center

Section III - Eligibility for Coordinating Center RFA-CA-20-041

- Wide range of institutions eligible, including: higher education institutions, nonprofits other than institutions of higher education, for-profit organizations, etc.
- Foreign institutions are not eligible to apply, but foreign components are allowed
- Applicant organizations may submit more than one application
- Note: A letter from an institutional official indicating that the terms that are included in the Model MTA used by the Pediatric Preclinical Testing Consortium are acceptable to the applicant's institution. (see “Other Project Information”)
  - Contact Malcolm.Smith@nih.gov for questions/clarification re Model MTA

Section IV - Other Project Information for Coordinating Center Applications RFA-CA-20-041

1. A template for a technical study report to be used in preparing a report of testing results for pharmaceutical collaborators. Use file name: "Technical Study Report".
2. Details of the analytical methods proposed to analyze *in vivo* data to be generated by the Research Teams. Include examples of standard graphical representations used to present in vivo testing results. Use file name: "Analytical Methods".
3. A letter from an institutional official indicating that the terms that are included in the Model MTA used by the PPTC are acceptable to the applicant's institution. Similar terms will apply for testing of agents through the NCI Pediatric in Vivo Testing Program.

Section IV – Application and Submission Information for Coordinating Center Applications RFA-CA-20-041 (1)

- **Research Strategy:** Specific Sub-Sections A-D must be included in Research Strategy
- **Sub-section A**. Comparable Experience Description (for New Applications) / Progress Report (for Renewal Applications)
  - For new applications, describe experience serving in a Coordinating Center role for an activity of comparable size and scope as the proposed NCI Pediatric in Vivo Testing Program.
  - For renewal applications, follow PHS 398 instructions for inclusion of a Progress Report

Section IV – Application and Submission Information for Coordinating Center Applications RFA-CA-20-041 (2)

- **Sub-section B**. Administrative Coordination and Logistical Support
  - Describe the proposed approach to specific administrative and logistical responsibilities
- **Sub-section C**. Data Management, Statistical, and Bioinformatics Support
  - Describe the proposed approach to specific data management, statistical, and bioinformatics responsibilities
- **Sub-section D**. Scientific Coordination
  - Describe the proposed approach to specific scientific coordination responsibilities

Section IV – Application and Submission Information for Coordinating Center Applications RFA-CA-20-041 (3)

- **Note**: There is an option for Subsections B-D for providing an approach to issues not specified in the FOA.
- **Note**: All applications should address a Data Sharing Plan.

Section V. Application Review Information for Coordinating Center Applications RFA-CA-20-041 (1)

- Standard NIH Review Criteria apply
- Review criteria specific to RFA-CA-20-034 apply for “Approach”:
- What is the likelihood that the applicant will be able to implement a Coordinating Center that can appropriately manage the administrative, data management and statistical, and scientific coordination requirements of the NCI Pediatric in Vivo Testing Program?
- To what extent does the application indicate a thorough understanding of the administrative coordination responsibilities of the Coordinating Center of a robust in vivo testing program and propose ways of addressing these responsibilities in a workable and efficient manner?

Section V. Application Review Information for Coordinating Center Applications RFA-CA-20-041 (2)

- How adequate is the approach to data management, statistical analysis, and bioinformatics that are workable and that will meet the needs of the NCI Pediatric in Vivo Testing Program for high quality data and reliable analyses?
- How well do provisions for data storage and data security, backup, and disaster recovery meet the needs of the NCI Pediatric in Vivo Testing Program and protect it from data loss and data breaches?
- To what extent does the approach proposed for scientific coordination support the ability of the applicant to provide appropriate scientific support in the preparation of research plans, technical study reports, and manuscripts?

Section V. Application Review Information for Coordinating Center Applications RFA-CA-20-041 (3)

- How well is the proposed plan for scientific project management designed to meet the needs of the NCI Pediatric in Vivo Testing Program in tracking multiple testing projects and ensuring that timelines are being met?

Cooperative Agreement Terms and Conditions of Award – Coordinating Center Responsibilities RFA-CA-20-041

- Specific responsibilities of the Coordinating Center awardee listed related to the following areas:
  - Administrative/logistical;
  - Data Management, Statistical, and Bioinformatics; and
  - Scientific Coordination

Cooperative Agreement Terms and Conditions of Award – Joint Responsibilities with NCI

- The Steering Committee will serve as the body for prioritizing agents for study by the Program, for defining the overall scope of research plans for agents selected for testing, and for approving the general SOPs under which the Program operates. The SC will include: the PI(s) of the Coordinating Center and the PI(s) of each of the Research Teams, the NCI Project Scientist, and others as appropriate.
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- Testing results become available to the research community
- Presentation and FAQs will be posted at CTEP/NCI website:
- https://ctep.cancer.gov/MajorInitiatives/Pediatric_Preclinical_Testing_Consortium.htm

QUESTIONS?

NATIONAL CANCER INSTITUTE

www.cancer.gov **www.cancer.gov/espanol**

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