Funding anesthesia research to ensure pediatric safety

2022 SmartTots Research Grant Request for Applications

Award Guidelines and Application Instructions

Application Deadline: February 28, 2022

International Anesthesia Research Society (IARS)
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IARS
Improving Health through Discovery and Education

REQUEST FOR APPLICATIONS

SmartTots, a Public-Private Partnership between the International Anesthesia Research Society (IARS) and the U.S. Food and Drug Administration (FDA), is a multi-year collaborative effort to increase the safety of anesthetic drugs for the millions of infants and children who undergo anesthesia each year.

Background

Laboratory animals exposed to most anesthetic and sedative drugs early in life show changes to the brain and nervous system that can interfere with memory, learning, and behavior. Accumulating clinical data in young children suggest alterations in behavior but not cognition in single and multiple exposures. All of the human studies to date have had significant limitations that make it impossible to conclusively determine whether anesthesia, surgery, hospitalization, or pre-existing conditions caused the neurobehavioral problems. Additional research, including long-term studies in neonates and young children, is needed to assess the effects of anesthetics and sedatives on the developing human brain.

Applicant Eligibility Criteria

- Applicants must hold a MD or PhD degree from an accredited institution.
- The official ProposalCentral online application must be used.
- All information and attachments requested in the application must be supplied. Failure to do so will disqualify the application.
- A maximum of $250,000 will be awarded. SmartTots may select a single application or multiple applications to be funded.
- Matching support from the applicant's institution is encouraged.
- Applications will be reviewed by a multidisciplinary team of experts assigned by the SmartTots Steering Committee to maintain the scientific merit of all SmartTots funded research projects.
- Grants will be awarded at the sole discretion of the SmartTots Steering Committee based on their relevance and probability of success.

Research Project Guidelines

SmartTots is accepting applications aimed at continuing the ongoing work to advance the knowledge and understanding of the effects of anesthetics on the developing brain and address current unknowns. Both clinical and preclinical projects are welcome. New projects continuing the work of an earlier study are encouraged. Pilot projects will be considered.

- The involvement of human subjects and/or vertebrate animals, as well as IRB and/or IACUC approval status, must be indicated in the application. Submitting the grant application with pending approvals is acceptable, however, approval must be obtained prior to award funds being allocated and documentation of approval and patient informed consent forms (if applicable) must be submitted upon request.
- Institutional indirect expenses will not be funded. Funds should be used only for research support and direct costs. Budget should not be used solely for salary support (NIH salary cap should be followed).
- Proposals should include a project schedule.
- Appropriate collaboration is encouraged, however, collaboration requires a biosketch from key personnel (the NIH definition of senior/key personnel should be followed).

Specific Questions of Interest

- What additional nonclinical data are necessary to more clearly define the potential window of vulnerability in humans given the diversity of possible endpoints and models available (e.g., significance of alterations in neuronal architecture vs apoptosis, additional functional behavioral endpoints such as social interaction data that may be more predictive of human outcome measures).
- What are the histological and functional endpoints and outcome measures to determine drug dose-duration relationships in rats and non-human primates?
- What is the impact of anesthetic and sedative agents on brain development in animal models of long-term sedation in the ICU, or repeated subanesthetic exposures for procedural sedation or pain control?
- What additional nonclinical data can more fully inform what durations of exposure to these agents may not result in adverse effects beyond neuroapoptosis?

- What is the threshold dose-duration for a single exposure and for multiple exposures needed to cause: (a) abnormal cell death; (b) changes in synaptic connectivity/spine formation; (c) functional deficits?
- Are these effects variable by brain region?
- What is the exact period of sensitivity to these effects?
- How does this period of sensitivity relate to human development?
- Are there differences among anesthetic agents?
- Are there differences when agents are combined?
- Are there differences between males and females?
- What are the effects on brain development of opioids and other drug combination regimens commonly used in pediatric clinical practice?
- Are there "safe" anesthetic agents?
- Are there agents that prevent or mitigate the adverse effects associated with general anesthesia? At what dose and under what conditions?
- Can the adverse effects of anesthesia be mitigated by behavioral means, such as environmental enrichment? Which human populations are at greatest risk?
- Are the effects greater in more vulnerable subgroups (e.g. in utero, premature infants and those with serious comorbidities)?
- Can the effects of anesthesia be separated from the effects of surgery or the underlying condition?
- Are there biomarkers of exposure to anesthetic agents, e.g. imaging studies, that can serve as intermediate outcomes that could be associated with longer term neurobehavioral outcomes?

Application Process

- The official ProposalCentral online application must be used.
- All information and attachments requested in the application must be supplied. Failure to do so will disqualify the application.

Application Review and Recipient Selection

- All applications will be reviewed by a multidisciplinary team of experts assigned by the SmartTots Steering Committee to maintain the scientific merit of all SmartTots-funded research projects.
- Grants will be awarded at the sole discretion of the SmartTots Steering Committee based on their relevance and probability of success.
- A maximum of $250,000 will be awarded. SmartTots may select a single application or multiple applications to be funded.
- The grant recipient(s) will be announced by June 2022.

Award Details

- SmartTots may select a single application or multiple applications to be funded. The maximum award amount for any selected project is $250,000. Applications must include a project budget and timeline.
- A final progress report and budget reconciliation must be submitted to IARS at the conclusion of the project.
- Any and all publications and/or presentations resulting from research that has utilized funds from a SmartTots grant must indicate the following: "Supported (or 'Supported in part') by a grant from SmartTots."

APPLICATION INSTRUCTIONS

Applicants must submit an online application using the ProposalCentral website (https://proposalcentral.com).

Deadline to submit an application is 11:59 PM EST on February 28, 2022.

Getting started in ProposalCentral

▪ If you are a new user of ProposalCentral, click the orange 'Need an account!' button to register as a new user in the system. After you register, complete your Professional Profile (4th tab from the left) before starting an application.
▪ If you are already registered with ProposalCentral, login with your username and password.
▪ To start an application, select the "Grant Opportunities" tab (tab furthest to the right). A list of applications will be displayed. Find the Grant Maker "International Anesthesia Research Society" and "SmartTots." Click the "Apply Now" link to create an application.

If you have difficulties registering, logging in, or creating your application, contact ProposalCentral Customer Support:
Toll-free U.S. and Canada: (800) 875-2562
Direct Dial International: (703) 964-5840
Email: pcsupport@altum.com

Application Format

The following information is required to submit a complete application. The numbers correspond to the application sections that appear on the left side of the online application.

1. **Title Page**. Enter the title of the research project. The title is limited to 75 characters in length (including spaces). Enter total amount requested in U.S. dollars.

2. **Download Templates & Instructions**. The Program Guidelines and Application Instructions document and all required templates to be completed and submitted within the application can be downloaded from this section. Click the "Download" icon to save each of the templates to your computer. Complete each template and convert completed templates to PDF format. You will upload these completed templates in PDF format, along with additional required attachments, in Section 11 of the application. Please see below in Section 11 for more instructions on how to complete and upload templates and attachments.

3. **Enable Other Users to Access this Proposal**. Optional. This section allows you to give other users access to your grant application, with varying levels of permissions.

4. **Applicant/PI.** Enter information for the applicant.

5. **Institution & Contacts**. Enter information regarding the lead institution, Signing Official, Financial Officer, and Department Chair.

6. **Collaborators**. Enter information regarding senior/key personnel on the project. Please follow the NIH definition of "key personnel." (According to http://grants.nih.gov/grants/glossary.htm#S8A: "The PD/PI and other individuals who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant." Typically these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level may be considered senior/key personnel if their involvement meets this definition. Consultants and those with a postdoctoral role also may be considered senior/key personnel if they meet this definition. "Zero percent" effort or "as needed" is not an acceptable level of involvement for senior/key personnel.")

7. **Project Summary.** Enter a brief description of the proposed project, including the aim and relevance to SmartTots, directly into the space provided. Please note that your answer is limited to 2,000 characters (including spaces) and any additional characters beyond the limit will be truncated. To ensure that you comply with the character limits, it is advised to draft your answers in Microsoft Word or a similar program, before entering them into ProposalCentral.

8. **Budget Period Detail.** Enter direct research expenses per your budget schedule. Note: Award funds may NOT be used for indirect costs or institutional overhead. These are not allowable expenses. Funds should be used only for research support and direct costs. The budget should not be used solely for salary support (NIH salary cap should be followed).

9. **Budget Summary**. A summary of the proposed budget appears here (fields are auto-populated per the data entered in Section #8). If applicable, provide a detailed budget justification in the space provided (explain and justify major equipment purchases, unusual supply requests, and patient care costs). Enter "N/A" if not applicable. Please note that your answer is limited to 3,000 characters (including spaces) and any additional characters beyond the limit will be truncated. To ensure that you comply with the character limits, it is advised to draft your answers in Microsoft Word or a similar program before entering them into ProposalCentral.

10. **Organization Assurances**. Indicate if the proposed project involves Human Subjects and/or Vertebrate Animals. If your study involves Human Subjects, please complete the Protections for Human Subjects checklist, the Data and Safety Monitoring Plan, and indicate the status of IRB approval and the date of approval (if approval is pending, enter date the request was submitted). If your study involves Vertebrate Animals, please complete and upload the Vertebrate Animals Section checklist and indicate the status of IACUC approval and the date of approval (if approval is pending, enter date the request was submitted). The assurances/certifications are made and verified by the signature of the institutional official signing the E-Signature page. If a grant is awarded, documentation of IRB and/or IACUC approval (if applicable) must be submitted upon request. NOTE: submitting the SmartTots application with pending IRB and/or IACUC approval is acceptable; however, approval must be obtained prior to the allocation of award funds.

11. **Attachments**. Prepare and upload the following documents into your application in portable document format (PDF). Use templates where provided. [conform spacing between numbered elements]
    1) ***NIH Biosketch – Applicant/Principal Investigator***
       - Upload this document as a PDF. Not to exceed 5 pages.
    2) ***NIH Biosketch – Collaborator/Key Personnel***
       - For each individual listed in Section 6 of the application, upload a biosketch in PDF format. Not to exceed 5 pages per collaborator.
    3) ***Letter of Recommendation – from Department Head***
       - A letter of recommendation written by the Department Chairman is required. The letter should include a statement of departmental commitment to the investigator and proposed project.
       - The letter should be composed on institution or department letterhead, signed, and given to the applicant to be uploaded to the application in PDF format.
    4) ***Proposal Narrative (template)***
       - Download the template, complete, save as PDF, and upload.
       - Follow the detailed instructions below. Proposal Narrative is limited to 7 pages, including figures and tables, excluding references.
    5) ***Facilities (template)***
       - Download the template, complete, save as PDF, and upload.
       - Provide a description of the research facilities, resources, and equipment that are available to the applicant and that will allow successful implementation of the proposed research program.
    6) ***Data and Safety Monitoring Plan – include for NIH-defined clinical trials: see https://grants.nih.gov/ct-decision for definition (template)***
       - Download the template, complete, save as PDF, and upload.
       - Provide a general description of a monitoring plan that you intend to establish as the overall framework for data and safety monitoring for your clinical trial.
    7) ***Other Support (form within ProposalCentral)***
       - Per the instructions within Proposal Central, provide active, applied for, and pending support for the principal applicant and any co-investigators.

8) ***E-Signatures - certification and acceptance of terms (form within ProposalCentral)***
- This page requires three signatures (Applicant, Department Chair and Designated Institutional Signing Official). All required signatures must be complete prior to the due date of the application in order to submit.

Other documents:

- ***NIH Biosketch – Co-Investigator (Optional; Upload as PDF. Not to exceed 5 pages per co-investigator.)***
- ***Human Subjects Checklist*** [required if the study involves human subjects]
- ***Data and Safety Monitoring Plan.*** [required if the study involves human subjects]
- ***Vertebrate Animals Checklist*** [required if the study involves vertebrate animals]

12. **Validate.** Validate the application within ProposalCentral. This is an essential step and checks for required data and attachments. You will not be able to submit your application unless all the required information has been provided. An application that has not been validated cannot be submitted.

13. **Application Preview.** After successfully validating your application, you may click "Download Signature Pages and Attached PDF Files" to preview your application and retain a copy. NOTE: The Signature Pages are NOT required. You do not need to do anything with these pages. Required signatures are obtained on the E-Signature/Certification and Acceptance of Terms form.

14. **Submit.** Once you have clicked the "Submit" button, an email will be sent to you confirming your submission.

Proposal Narrative Content and Guidelines

This section is adapted from the U.S. Department of Health and Human Services Public Health Service Grant Application Instructions (PHS 398).

Begin each section of the Proposal Narrative with a section header (e.g., Introduction, Specific Aims, Research Strategy, etc.).

- **Introduction and Specific Aims** (Limit: 1 page)
  - State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved.
  - List succinctly the specific objectives of the research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop a new technology.
- **Research Strategy (Limit: 6 pages)**
  - ***Significance***
    - Explain the importance of the problem or critical barrier to progress in the field that the proposed project addresses.
    - Explain how the proposed project will improve SmartTots-related scientific knowledge, technical capability, and/or clinical practice.
    - Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.
  - ***Approach***
    - Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Indicate how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.
    - Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.
    - If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high-risk aspects of the proposed work.
    - May include preliminary studies.
      - Discuss the PI's preliminary studies, data, and/or experience pertinent to this application.

- **Bibliography and References Cited** (No page limit)
  - Provide a bibliography of any references cited in the Proposal Narrative.
  - Each reference must include names of all authors (in the same sequence in which they appear in the publication), the article and journal title, book title, volume number, page numbers, and year of publication.
  - Follow scholarly practices in providing citations for source materials relied upon in preparing any section of the application.
  - References should be limited to relevant and current literature that is pertinent to the proposed research.

- **Rigor and Transparency Requirements**
  - In the planning process, investigators will need to consider how to address the basic principles of rigor and transparency and include how the following four areas of focus apply to their proposed research.
    - Scientific Premise: Applicants must ensure that there are key data to justify the premise for the project.
    - Scientific Rigor: The applicant must provide a rigorous experimental design, including strategies that ensure robust and unbiased results.
    - Consideration of Relevant Biological Variables: Applicant must address relevant critical biological variables, such as sex, age, source, weight, genetic strain.
    - Authentication of Key Biological and/or Chemical Resources (not score-able): Applicants should include a brief description of resources that are integral for the proposed project, for example cell lines, specialty chemicals, antibodies, and other biologics.

Formatting Guidelines for Attachments

- **Font**: Use an Arial, Helvetica, Palatino Linotype or Georgia typeface, a black font color, and a font size of 11 point or larger.
- **Margins**: Page margins should be no less than 0.5 inch on each side for all pages. Template margins may be altered within these specifications
- **Spacing**: Single-spaced text is acceptable. Space between paragraphs is recommended.
- **Page numbering:** The Proposal Narrative must be numbered consecutively. Do not use suffixes (e.g., 5a, 5b)
- **Figures, Graphs, Diagrams, Charts, Tables, Figures Legends, and Footnotes:** Text must be readily legible. Font size of 9 point of larger is recommended.
- **Grantsmanship:** Use English and avoid jargon. If terms are not universally known, spell out the term the first time it is used and note the appropriate abbreviation in parenthesis; the abbreviation may be used thereafter.

Inquiries

Inquiries or technical issues regarding ProposalCentral and the online application process should be directed to customer support at (703) 964-5840 or toll free at (800) 875-2562, or by email at pcsupport@altum.com.

Inquiries about the program guidelines, eligibility requirements, and application materials can be directed to IARS. Please contact the IARS Research Programs Director at (415) 296-6905, or by email at tbrazil@iars.org.