

Frequently Asked Questions and Answers
Maximizing the Scientific Value of Existing Biospecimen Collections:
Scientific Opportunities for Exploratory Research (R21 Clinical Trial
Not Allowed)

Updated July 15, 2019

Eligibility for the R21

1. Are foreign investigators eligible to apply as Principal Investigators (PIs) for this Funding Opportunity Announcement (FOA)?
 - A. Foreign individuals are eligible to apply, but must demonstrate that the proposed research can directly contribute to the U.S. Food and Drug Administration's (FDA) regulatory authority over the manufacture, marketing, and distribution of tobacco products. Individuals must also demonstrate that they will be employed by an eligible institution for the full award period of the grant.

2. Are foreign institutions eligible to apply?
 - A. Yes. However, research proposed in applications from foreign institutions must be specific to the U.S. population and provide information that will be useful to U.S. regulations.

Budget

3. Is there a budget cap on R21 applications?
 - A. Yes. The combined budget for direct cost for the entire project period may not exceed \$275,000. No more than \$200,000 in direct cost may be requested in any single year.
Two years maximum.

Application Requirements/Submission

4. Where can the applicant find additional information regarding application submission?
 - A. The National Institutes of Health (NIH) provides multiple resources for applicants with submission questions. Below is a list of resources, depending on the type of question being asked:
 - For questions regarding Grants.gov registration and submission, as well as downloading forms and application packages, please contact Grants.gov Customer Support at support@grants.gov.
 - For questions regarding application instructions, process, and finding additional NIH grant resources, please contact GrantsInfo at GrantsInfo@nih.gov.
 - For questions regarding ASSIST, eRA Commons registration, submitting and tracking an application, documenting system problems that threaten submission by the due date, and postsubmission issues, please contact [Finding Help Online](#). Telephone: 301-402-7469 or 866-504-9552 (toll free).

- For peer review questions, contact Dr. Jonathan Ivins from the Center for Scientific Review at ivinsj@csr.nih.gov.
- For financial/budgetary questions, please contact the appropriate grants management contact listed in Section VII of the FOA.
- For scientific and responsiveness questions, please contact the appropriate scientific contact listed in Section VII of the FOA.

5. When are applications due?

A. October 8, 2019, August 7, 2020, and March 8, 2021.

6. Am I required to submit a letter of intent (LOI)?

A. An LOI is not required, and it does not enter into the review process. However, it allows NIH staff to estimate the potential review workload and plan the review. Investigators are encouraged to communicate with NIH scientific research contacts to discuss their research ideas and specific aims prior to submitting applications, as all proposed research must be within the scientific interest areas covered in this FOA. We suggest submitting an LOI 60 days before the application due date. Applications that are non-responsive will not move forward to the review process.

Suggested content of LOI:

- Descriptive title of proposed activity
- Name(s), address(es), and telephone number(s) of the Principal investigators/PI(s)
- Names of other key personnel
- Participating institution(s)
- Number and title of this funding opportunity
- Specific aims

7. Where do I send the LOI?

A. The letter may be sent by email to: TRSP@mail.nih.gov

Or by regular mail to:

Tobacco Regulatory Science Program
 Office of Disease Prevention
 6100 Executive Boulevard
 Room 3B01, MSC 7530
 Bethesda, MD 20892-7530 (Use Rockville, MD 20852 for Express Mail)
 Tel: 301-451-7464
 Fax: 301-480-2230

Responsiveness

8. How do I know if my application is responsive to this FOA?
 - A. This is a critical question, as **each of the specific aims** in the application must meet the following criteria to be considered responsive. The project must:
 - Address one or more of the scientific interest areas listed in the FOA, **and**
 - Fall within the scope of the FDA Center for Tobacco Products' (CTP) regulatory authority.

As such, applicants are strongly encouraged to contact the scientific research contacts listed in Section VII of this FOA for feedback about responsiveness prior to submitting an application.

Note that upon receipt, applications will be **evaluated for responsiveness** by the FDA CTP and participating NIH Institutes. **Only applications that are within the scope of the scientific research areas listed in the FOA and the FDA CTP's regulatory authority will be peer reviewed.** Your application title, abstract, and specific aims are used to make this determination, so it is important that you are clear about your proposed scientific aims and how they may potentially inform the FDA CTP's regulatory authority. Staff reviewing your application will refer to other parts of the application if responsiveness is unclear based on title, abstract, and specific aims. If your application is deemed responsive, it will undergo scientific peer review by experts convened specifically for this FOA (by the NIH Center for Scientific Review). If your application is deemed non-responsive, it will be withdrawn prior to evaluation of its scientific merit, i.e., peer review.

9. The FDA CTP has regulatory authority over the manufacture, marketing, and distribution of tobacco products. What are some examples of these authorities?
 - A. [The Family Smoking Prevention and Tobacco Control Act](#) gave the FDA responsibility and authority to, among other things:
 - Restrict cigarettes and smokeless tobacco retail sales to youth.
 - Restrict the sale and distribution of tobacco products, including advertising and promotion, as appropriate to protect public health.
 - Review modified risk tobacco products, such as those marketed for use to reduce harm, prior to their introduction to the market.
 - Adjust warning labels for cigarettes and smokeless tobacco products in order to promote greater public understanding of the risks of tobacco use.
 - Establish standards for tobacco products (for example, setting limits on harmful and potentially harmful constituents and nicotine levels), as appropriate to protect the public health.
 - Review new tobacco products prior to their introduction to the market.

For more information, see [The Family Smoking Prevention and Tobacco Control Act](#) – An Overview.

10. What research areas are not within FDA CTP regulatory authorities?

A. In general, CTP's regulatory authorities do not extend to:

- Setting tax rates for tobacco products
- Regulating therapeutic products, such as those marketed to treat tobacco dependence (regulated by other parts of FDA)
- Setting clean indoor air policies
- Regulating tobacco growing
- Requiring the reduction of nicotine yields to zero
- Providing cessation services
- Banning all cigarettes, smokeless tobacco products, little cigars, other cigars, pipe tobacco, or roll-your-own tobacco products
- Changing the minimum age to purchase tobacco products

11. What are the research interest areas for this [FOA](#)?

A. Applicants must conduct at **least one new lab measurement** from existing biospecimens but might also combine the new measurements with pre-existing biospecimen data. In addition, this FOA is interested in, but not limited to the scientific areas listed below which are examples and are not meant to be an exhaustive list:

- Compare biomarkers of tobacco exposure and potential harm related to use of non-cigarette tobacco products across surveys.
- Identify and develop biomarkers of harm and exposure unique to new and emerging non-cigarette tobacco products (both tobacco specific and flavor specific), including but not limited to e-cigarettes.
- Examine the effect of chronic exposure to waterpipe tobacco smoke/hookah on biomarkers of inflammation and other harm.
- Utilize urinary specimens to analyze biomarkers of tobacco exposure not currently measured by other national studies in urine, but on the [Harmful and Potentially Harmful Constituents](#) (e.g., aromatic amines, proxies for benzo[a]pyrene) list.
- Utilize blood specimens to analyze biomarkers of tobacco exposure not currently measured by other national studies, including those on the [Harmful and Potentially Harmful Constituents](#) (e.g., carboxyhemoglobin, lead, and other toxic metals) list.
- Examine alterations in genetic and epigenetic markers associated with exposure to tobacco products, including comparison of new products (e.g., e-cigarettes—including closed systems and tank systems—and heat-not-burn tobacco) to traditional cigarettes, cigarillo, cigar use, and smokeless tobacco products, and in combusted and non-combusted tobacco products.
- Examine the health effects of transitioning from combusted to non-combusted tobacco use, using biomarker outcomes.
- Prospectively compare biomarker expression profiles to self-reported tobacco products use and analyze measures associated with biomarkers of exposure that may inform risk associated with tobacco exposure for mortality/morbidity by age, sex, and race/ethnicity.
- Assess between-persons differences and within-person changes over time in

attitudes, behaviors, exposure to tobacco products, and related biomarkers among and within population sub-groups identified by such characteristics as race-ethnicity, gender, age, sexual orientation, and/or time in the United States or by risk factors, such as pregnancy or co-occurring substance use or mental health disorders or by disease status.

- Identify and examine biomarkers of harm and exposure between dual and poly-tobacco users, including but not limited to electronic nicotine delivery systems (ENDS) and combusted tobacco products.

12. Could researchers include biospecimens collected in other countries in their proposal?

- A. Foreign biospecimens may be included only if a dataset is relevant to the U.S. population and U.S. regulation of tobacco. Applications not using nationally representative biospecimens will need to provide justification why the dataset is unique, and why the research questions cannot be answered from biospecimens collected in the United States.

13. What are some examples of existing biospecimens applicants can use in their proposed research?

- A. Below are examples of biorepositories that are linked to their study data and contain biospecimens that may be relevant to this FOA.
- Descriptions and access to the Population Assessment of Tobacco and Health (PATH) Study biospecimen collections and associated datasets are at the National Addiction & HIV Data Archive Program (NAHDAP) website at: <https://www.icpsr.umich.edu/icpsrweb/content/NAHDAP/pathstudy-biospec-index.html>.
 - Descriptions and access to the National Health and Nutrition Examination Survey (NHANES) biospecimen collections and associated datasets are at the NHANES website at: <https://www.cdc.gov/nchs/nhanes/index.htm>.
 - Descriptions and access to the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial collections and associated datasets are at the PLCO website at: <https://biometry.nci.nih.gov/cdas/plco/>.
 - Descriptions and access to other publicly available biospecimen collections and associated datasets can be found at the National Heart, Lung, and Blood Institute (NHLBI) Biospecimen and Data Repository Information Coordinating Center (BioLINCC) website at: www.biolincc.nhlbi.nih.gov.

The above websites provide detailed information about the parent study, research use restrictions specified by the informed consent document of the parent study, and the number and material type of the biospecimens in the collection. Directions to requests to search for biospecimens with specific characteristics are provided in the respective websites. **The request to search for biospecimens from a specific collection(s) may be initiated at any time but must be initiated at least 30 days prior to the FOA Application Due Date that the applicant proposes to use.** Confirmation of this must be provided in the application. Given that the time to complete a search and provide a Letter of Availability varies due to the respective study protocols, complexity of a search and/or the necessity to perform additional searches, applicants should ensure they allow adequate time for a search to be performed and confirmed.

14. What topics are non-responsive to this FOA?

A. Although the following research topics may be within FDA CTP's regulatory authority to fund, they are not to be included in the FOA and will be deemed out of scope and not reviewed:

- Applications that do not use existing data/biospecimens.
- Applications focusing on non-tobacco products.
- Short-term studies of the acute effects of reduced nicotine content cigarettes.
- Studies of short-term health effects and/or acute topography/clinical pharmacology testing of early generation ENDS products.

15. What are some special considerations when preparing applications?

A. For Tobacco Industry Funding of Applicants: The FDA CTP has adopted the following guidance regarding tobacco industry funding of applicants responding to this FOA.

- The National Advisory Council on Drug Abuse (NACDA) has set forth points with regard to existing or prospective sponsored research agreements with tobacco companies or their related entities and the impact of acceptance of tobacco industry funding on National Institute of Drug Abuse's (NIDA) credibility and reputation within the scientific community. Please see [Points to Consider Regarding Tobacco Industry Funding of NIDA Applicants](#) for details. While this guidance was originally issued for NIDA applicants, it is relevant for all applications submitted under this FOA.

Review

16. Will more weight be assigned in the review for applications that address more than one of the scientific interest areas?

A. No. Reviewers will be looking to see if the research question is addressed adequately and appropriately. When approaching which research priorities to address, we recommend that investigators think about what scientific evidence the FDA would need to support a product review process or regulatory decision.

17. On what basis are applications selected for funding?

A. Applications will be selected for funding based on scientific merit, current availability of funds, and FDA CTP current research priorities.

18. What are some special review considerations for R21 applications?

A. The R21 exploratory/developmental grant supports investigation of novel scientific ideas or new model systems, tools, or technologies that have the potential for significant impact on biomedical or biobehavioral research. An R21 grant application need not have extensive background material or preliminary information. Accordingly, reviewers will emphasize the conceptual framework, the level of innovation, and the potential to significantly advance our knowledge or understanding. Appropriate justification for the proposed work can be provided through literature citations, data from other sources, or, when available, from investigator-generated data. Preliminary data are not required for R21 applications; however, they may be included if available.

19. What review criteria has been modified from the typical NIH review to fit this FOA?

A. Significance, Innovation, and Approach criteria have been modified for this FOA:

- Significance: Does the project address an important problem or critical barrier to progress in the field? Is the prior research that serves as the key support for the proposed project rigorous? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, and technologies related to the manufacture, distribution, and marketing of tobacco products?
- Innovation: Does the application challenge and seek to shift current research in the field of tobacco science as it relates to the manufacture, distribution, and marketing of tobacco products? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, or instrumentation proposed? Will the outcomes of the project provide new information to further develop the knowledge base that informs the manufacture, distribution, and marketing of tobacco products in order to protect public health?
- Approach: Are the variables selected to define participant groups appropriate for fulfilling the specific aims of the study? Are the types, numbers, and volumes of biospecimens justified? Have the proposed assays been validated for use with the specific types of biospecimens requested? Have sufficient preliminary data been presented to demonstrate accuracy and robustness of the proposed assays? Have the investigators provided assay validation data? If multiple assays are available for a proposed analyte, have the investigators justified their choice for using a particular assay? Have the investigators described the laboratory quality control plan and if so, is it adequate? Have the investigators provided effect sizes and used power calculations to determine the sample sizes needed to detect significant effects for each aim? Did they state the power levels they wished to achieve with the proposed sample sizes? Does the statistical analysis plan adequately describe the data that will be analyzed and the statistical methods that will be used? Does the plan address statistical issues germane to the research such as measurement error, multiple comparison testing, bias, interactions, and data adjustments? Are individuals with sufficient expertise and experience proposed to conduct the data analyses?

Post-Award Management and Reporting

20. Which NIH Institute/Center (IC) will manage my award?

- A. It depends on the nature and scope of the research projects proposed. Applicants may request assignment to a particular Institute in their cover letter, but the NIH will make the final determination regarding Institute assignment.

21. Are the reporting requirements for these awards the same as other NIH grants?

- A. No. A mid-period progress report will be due every 6 months following the project start date, as well as the annual progress report and all reports required by the NIH at the time of grant close-out.

22. Are policies and procedures different for these awards?
- A. Yes. This includes exclusion from [Streamlined Noncompeting Award Process \(SNAP\)](#) and all carryover requests requiring prior approval from both the NIH and the FDA CTP.
23. Some researchers are under limitations with respect to accepting funds from the tobacco industry. How will these FDA research awards be funded?
- A. As mandated in the Tobacco Control Act, the FDA is authorized to collect fees from tobacco product manufacturers and importers for its activities related to the regulation of the manufacture, distribution, and marketing of tobacco products. Although the tobacco user fees are specified in statute, Congress must actually appropriate the funds before the FDA can obligate them. The tobacco industry has no control over FDA CTP funding decisions. The FDA uses some of these funds to award research grants.

NIH Guide FOA:

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<https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-19-021.html>

NIH FDA Tobacco Regulatory Science Program website:

<https://prevention.nih.gov/tobacco-regulatory-research>