AMENDMENT TWO (2)

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PURPOSE OF SOLICITATION AMENDMENT

The purpose of this amendment is to respond to questions submitted by interested offerors.

The hour and date specified for receipt of Offers remains unchanged.

Except as provided herein, all terms and conditions of the solicitation remain unchanged and in full effect.

A recording of the pre-proposal conference and associated materials have been posted here:

https://sbir.nih.gov/engage/news#081817.

General Questions

Question 1: Is OMB clearance required if the project will involve the collection of information from 10 or more public respondents?

Answer 1: No, OMB clearance in accordance with the Paperwork Reduction Act (PRA) is no longer required for NIH-funded research, in accordance with the enactment of the 21st Century Cures Act. SBIR offerors no longer need to restrict the number of surveys, interviews, etc. proposed for a project due to this concern.

Question 2: How often - how many times a year - does NIH announce the contract opportunity? What is the next contract announcement?

Answer 2: The NIH and the CDC issue one consolidated SBIR contract solicitation per year, generally sometime between June and August of each year. Solicitation PHS 2018-1 is this year's consolidated SBIR contract solicitation – it was issued on July 18, 2017, and contracts will be awarded off of this solicitation in fiscal year 2018. These annual solicitations are for initial SBIR awards, and each awarding component independently manages the solicitation process for transitioning awardees from Phase I to potential Phase II.

Question 3: Will the next announcement have the same Topics as this announcement?

Answer 3: No, almost all Topics change from year to year. Occasionally, some Topics of great continuing interest will be repeated, although they may have revisions to the specifications. There is no guarantee that any Topic will be offered again.

Topics for each year are not released until a preliminary notice is issued, at least 15 days prior to the full solicitation being made available, on https://www.fbo.gov/ and on https://sbir.nih.gov/funding.

Question 4: How soon after completion of Phase I can an awardee begin work on a successful Phase II proposal?

Answer 4: *For Phase I only submissions, the gap between a Phase I award and a successful Phase II award varies, as each awarding component independently manages the solicitation process for transitioning awardees from Phase I to potential Phase II – however, for NIH, the gap may be up to 1 year or so, as the Phase II proposal will need to go through external peer review technical evaluation, which can be a lengthy process to coordinate.*

However, for Fast Track submissions at NIH that result in a contract award with a contractual option for Phase II, a successful Phase II project has the potential to begin immediately following the completion of Phase I, as the external peer review technical evaluation has already been satisfied during the Fast Track process.

Question 5: Can I propose collaboration with a specific NIH investigator in my proposal?

Answer 5: *Only if the NIH investigator obtains all approvals required by standard operating procedures for intramural scientist collaboration on extramural funded grants and contracts, and the opportunity to collaborate with the NIH investigator was offered to all offerors on comparable terms as those offered to any one offeror.*

Question 6: What is the difference between a contract and a grant?

Answer 6: *Please refer to* https://sbir.nih.gov/apply *for general information on this topic. For this contract solicitation, it is important that you adhere to all the requirements set forth in the solicitation document PHS 2018-1 and its amendments, which provide all the information necessary to submit a successful contract proposal.*

Question 7: If I am initiating an idea, which cannot "fit" into a solicitation topic, am I limited to a grant?

Answer 7: *For a contract solicitation, it is very important that the proposal address how the proposed technology would meet the goals, objectives, and deliverables set forth in the Topic description, as one of the evaluation criteria set forth in Section 6 addresses whether the approach has a reasonable chance of meeting the topic objective. If you feel like your project may not be reviewed favorably under this evaluation criterion, you may be in a better position to submit a grant application, which allows for more flexibility. You may review grant opportunities on the* https://sbir.nih.gov/funding *website.*

Question 8: Does the designated institutional official who will review financial disclosure statements from each Investigator have to be a CPA or other licensed finance professional? Can you further clarify the part of the objectivity clause that defines the PI's disclosure of Financial Interest in accordance to the 2011 vs. the 1995 standards?

Answer 8: *Institutional responsibilities regarding investigator financial conflicts of interest are only required for Phase II SBIR contracts funded by Public Health Service appropriations. If your Phase II SBIR proposal is being considered for funding, you may discuss specific compliance concerns with the particular contracting officer who is responsible for your individual proposal's negotiation and award, after reviewing the regulations found at 45 CFR Part 94 (available at* https://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=0af84ca649a74846f102aaf664da1623&rgn=div5&view=text&node=45:1.0.1.1.51&idno=45*) as well as HHS guidance (available at* https://www.hhs.gov/ohrp/regulations-and-policy/guidance/financial-conflict-of-interest/index.html*).*

Section 2.3 Fast Track Proposals (NIH Only)

Question 1: While acknowledging that the Government has complete discretion in making awards, does the statement 'Fast Track proposals will be accepted' for a particular Topic imply that funds are actually available to support a Fast Track if sufficiently meritorious?

Answer 1: *Upon award of a Phase I contract with an option for Phase II, through the Fast Track submission process, an awarding component is not necessarily setting aside funds specifically for that specific potential Phase II award; although, 3.2% of our agency's extramural Research/Research & Development budget will be set aside each year for all SBIR awards, in general. The decision to fund or not fund the Phase II component of a successful Fast Track submission is based on all the factors set forth in Section 6.4 Award Decisions, which involves other factors outside of technical merit and availability of funds.*

Section 2.5 I-Corps™ at NIH

Question 1: We have completed NSF I-Corps. Shall we be eligible for NIH ICorps?

Answer 1: Companies that have already completed a different I-Corps program are not necessarily ineligible for the I-Corps™ at NIH program, as I-Corps programs can differ. When submitting an application in the second step of the I-Corps process, as described in Section 2.5 of the contract solicitation, the company should discuss the outcomes achieved under the previous I-Corps program and discuss the unique outcomes that they hope to achieve through this additional I-Corps™ at NIH opportunity.

Question 2: Is I-Corps restricted to only Ph.D.'s or could management of SBC also attend?

Answer 2: To be selected for I-Corps participation, the company must propose a specific 3-person team, which includes both scientific/technical, business, and industry representation, in accordance with the description set forth in Section 2.5 of the contract solicitation.

Question 3: Does the $50K for I-Corps come out of the max budget for Phase I?

Answer 3: No, the potential I-Corps funding (not to exceed $50,000), would be in addition to the basic Phase I project funding (not to exceed the specific amount set forth in the Topic description in Section 12).

Section 4.2 Offeror Eligibility and Performance Requirements

Question 1: I have a collaborator who is willing to perform necessary animal studies in Phase I; however, the costs might amount to more than the 1/3rd of the proposed project budget that is allowed for collaborators. Would you have any suggestions?

Answer 1: One suggestion might be that the applicant company itself perform all the data analysis for the animal work, to reduce the cost of the subaward.

Question 2: If a proposed subcontract, such as a CMO for drug-scale up, does not do any 'research', does this work still count as part of the one-third effort that we are allowed to have completed by someone other than the applicant small company?

Also, if the applicant small company is doing software development, would this be included in the calculation of the applicant small company's own 'research or analytical effort' in regards to Section 4.2 performance requirements?

Answer 2: For this solicitation, we have stated that we will be measuring the 'two-thirds effort' requirement for a Phase I (and the 'one-half effort' requirement for a Phase II) by using the total contract dollars allocated in the budget. All dollars spent toward a subaward of any type will be counted towards the proportion of effort completed by someone other than the SBIR awardee itself. The Government will review the Appendix C budget and total all dollars that will be allocated to the small business applicant's own effort versus all dollars that will be allocated to subcontractor and/or consultant effort, regardless of the nature of that effort.

Question 3: Does the number of employees of a subcontractor count against the 500 employee limit for "Small Business Concern" if the Subcontractor IS NOT an Affiliate?

Answer 3: No, as long as the collaborating organization (performing a subaward) does not meet the definition of "Affiliate" (as established by federal regulation here: http://www.ecfr.gov/cgi-bin/text-idx?SID=b02d16dbfcddf646e5c0728d5e632a61&mc=true&node=se13.1.121_1103&rgn=div8*), the subaward's business size does not have any relevance.*

Question 4: Can a foreign entity be involved together with a US company?

Answer 4: The research or R&D project must be performed in its entirety in the United States. Whenever possible, work outside the United States which is necessary for the completion of the project should be supported by funding other than the SBIR contract. In those rare instances where the study design requires use of a foreign site (e.g., to conduct testing of specific patient populations), the investigator must provide compelling scientific justification in the application for the need and use of a foreign site. Similarly, in those rare instances where it may be necessary to purchase materials from other countries, investigators must thoroughly justify the request.

NIH will consider these instances on a case-by-case basis. If requesting a deviation, please clearly state this in your business/pricing proposal AND your technical proposal, along with the scientific justification, to ensure that all parties review the request appropriately. You must receive a written authorization for this deviation at the time of your contract award to be in compliance with SBIR requirements.

Question 5: Does the Principal Investigator on the offer need to be a medical researcher? Does the Principal Investigator need to have a Ph.D. or M.D.?

Answer 5: The Principal Investigator, and other significant team members, must demonstrate the training and experience necessary to carry out and lead the specific technical approach proposed. Technical personnel proposed will be evaluated for sufficiency to perform the technical approach proposed, and there is not a requirement for any one particular type of background or degree.

Section 4.19 Prior, Current, or Pending Support of Similar Proposals or Awards

Question 1: Can one company apply for two awards?

Answer 1: A company may submit only one SBIR/STTR application or proposal to a Department of Health and Human Services (HHS) component for each unique research project. Therefore, a company may submit more than one application/proposal for consideration as long as they are each for separate and distinct projects.

You may not submit an application/proposal for a project that is "essentially equivalent" to a project already submitted for consideration for any SBIR funding opportunity within the Department of Health and Human Services. See Section 4.19 of the solicitation document, as well as the definition of "Essentially Equivalent" in Section 3.1 of the solicitation document.

Question 2: If two contracts are awarded, can clinical studies overlap, as long as requirements of both contracts are met?

Answer 2: Two contracts or grants may not be awarded if the work would be essentially equivalent, as discussed above and in the solicitation document. If there is a component of work that could be leveraged for two different, successful research proposals, this should be communicated with Government staff during the pre-award negotiation phase for any affected proposal, so that the Government may incorporate safeguards into the award documents to avoid situations where services rendered could be charged under more than one award.

Question 3: If two contracts are awarded, are two PI's needed?

Answer 3: The PI on any SBIR proposal/application must be more than 50% employed by the small business applicant company; however, there is not necessarily a minimum percent effort that must be contributed by the PI on each project. During the evaluation process, technical reviewers will review whether the PI commitment to the individual project is found sufficient to successfully complete the work proposed. There is no rule prohibiting a PI 100% employed by the small business from applying 50% effort to one proposed, discrete project, and 50% effort to a separate project – however, each technical review panel will have the opportunity to evaluate whether the proposed effort is sufficient on each individual project, and weaknesses noted in technical evaluation will have an impact on the competitiveness of a proposal.

Note, as well: OFFERORS SHOULD ASSURE THAT THE PRINCIPAL INVESTIGATOR, AND ALL OTHER PERSONNEL PROPOSED, SHALL NOT BE COMMITTED ON FEDERAL GRANTS AND CONTRACTS FOR MORE THAN A TOTAL OF 100% OF THEIR TIME. IF THE SITUATION ARISES WHERE IT IS DETERMINED THAT A PROPOSED EMPLOYEE IS COMMITTED FOR MORE THAN 100% OF HIS OR HER TIME, THE GOVERNMENT WILL REQUIRE ACTION ON THE PART OF THE OFFEROR TO CORRECT THE TIME COMMITMENT.

Section 4.22 Payment

Question 1: What schedule is in place for distributing monies? What are the Disbursement terms - are they upfront, installments, or reimbursement?

Answer 1: For general information on how payments are processed for federal contracting, review Section 4.22 of the solicitation document.

Individual contracting officers may use their discretion in setting up appropriate payment schedules. If you are notified that your proposal is being considered for award, you may begin discussing the potential payment schedule with the specific contracting officer point of contact named in that notification.

Section 5 Contract Requirements

Question 1: Who owns the intellectual property/technology/capabilities/source code developed under SBIR contracts?

Answer 1: *Review Sections 5.5, 5.6, and 5.7 of the solicitation document in regards to Copyrights, Technical Data Rights, and Patent Rights. In general, the small business concern normally retains rights and ownership, while the Government is granted a royalty-free license.*

You may review specific terms and conditions that will be included in any resultant contracts here: https://www.law.cornell.edu/cfr/text/48/52.227-20 *and* https://www.law.cornell.edu/cfr/text/48/52.227-11.

The Government does typically require the delivery of source code and object code developed, modified, and/or enhanced under a Government contract; however, it will not be used in a way inconsistent with the rights discussed above.

Section 6 Method of Evaluation

Question 1: Can your proposal be technically acceptable and not awarded and if so, does that happen?

Answer 1: *Yes, as stated in Section 6.1 of the solicitation document. This occurs frequently, as there are often more proposals deemed technically acceptable than there are funds available. Therefore, the Government will consider all of the evaluation factors for award stated in Section 6.4 of the solicitation document to make funding decisions that are deemed to be in the best interest of the Government.*

Section 7.3 Limitation on the Length of the Technical Proposal (Item 1)

Question 1: Are links acceptable in the proposal?

Answer 1: *Technical proposals shall not include links to internet web site addresses (URLs) or otherwise direct readers to alternate sources of information. Augmentation of the page limit through use of hyperlinks, etc. is not permissible.*

Section 7.4 Submission, Modifications, Revision, and Withdrawal of Proposals

Question 1: Should registration in eCPS be done by a business leader or the research principal investigator?

Answer 1: *There is no requirement about which company personnel should register or submit within eCPS.*

Question 2: How do you get from eRA commons into eCPS?

Answer 2: *Companies should access eCPS directly, using the instructions set forth in Section 7.4 of the contract solicitation. A company should be able to use its existing eRA commons log-in information to access eCPS; however, no interaction or connection with eRA commons exists outside of this log-in capability.*

Question 3: Do you need to use the same file name with a revised submission?

Answer 3: *You may use the same file name if you revise your files uploaded to eCPS prior to the submission deadline; however, you may also make a revision notation on the end of the file name, if desired, to assist with version control. Lack of compliance with suggested file naming conventions will not prevent submissions from being accepted – compliance merely assists the Government with the organization of submitted files.*

Section 8 Proposal Preparation and Instructions

Question 1: Do all team members need to be identified by the end date of Oct. 20th or would members be added after the fact if their expenses are budgeted in the final financial worksheet? Do we need to submit anticipated costs for vacancies in the team during phase I? If our team is not complete, can we recruit after the submittal deadline for Phase I?

Answer 1: Team members can be added after the submission deadline, if their anticipated costs have been budgeted in the proposal submitted by the submission date. It is not required that all personnel be named at the time of proposal submission.

However, 20% of your technical evaluation score for a Phase I, and 15% of your technical evaluation score for a Phase II, will be based on "The qualifications of the proposed Principal Investigators, Project Directors, supporting staff and consultants." The evaluation panel may note a weakness of varying degrees on proposals that do not have all significant personnel in place, depending on how critical and integral the unfilled position is to the particular, specific project. The evaluation panel will make the final assessment, in accordance with the scoring matrix in Section 6 of the solicitation.

In lieu of having an exact person named, you may at least discuss your intention to add this position to the team, the type of qualifications you will be looking for in filling that position, and a plan for how/when you will bring that position into the team, etc., to provide as much information as possible to the evaluation panel at the time of proposal submission.

Question 2: Could you clarify the requirement for a Business Proposal. Is this a proposal for commercialization of the product? The Pricing Proposal Appendix C - appears to be a standard research budget outline.

Answer 2: It is important to distinguish between the Commercialization component of the Technical Proposal and the Business Proposal. A Phase I Technical Proposal must address potential commercial applications of the product being proposed, as set forth in Section 8.8(A)(6). Likewise, a Phase II Technical Proposal must include a more thorough discussion as part of a Commercialization Plan, as set forth in Section 8.8(B)(9).

How your technical proposal addresses potential commercialization of your product is important, because it comprises 20% of your Phase I technical evaluation score, as set forth in Section 6.2, and 25% of your Phase II technical evaluation, as set forth in Section 6.3. Any discussion of how you propose to commercialize your product must be discussed within your Technical Proposal, and within the appropriate page limit set forth for the Technical Proposal in Section 7.3.

The Business Proposal should not address how you will commercialize your product. Your Business Proposal addresses your business's eligibility to be considered for an SBIR award, and sets forth your requested budget to perform the work detailed in your Technical Proposal. The Business Proposal is not scored; however, it will be evaluated for compliance and cost/price reasonableness. The Business Proposal does not have a page limit, and for a Phase I SBIR award, it is not usually very long. The Business Proposal consists of a Pricing Proposal (Appendix C), a Venture Capital certification (if appropriate, see Section 4.6), Proof of Registration in the SBA Company Registry, and a Summary of Related Activities (Appendix F) form for each key personnel.

Please review Sections 8.3 and 8.4 for a high level outline of what is required for a Technical Proposal and a Business Proposal, in conjunction with Sections 8.5 and 8.6, which break down the details of the research plan (- the "Content of the Technical Element").

Section 8.2 Fast Track Proposal Instructions (NIH Only)

Question 1: Do we need to include our CVs for both Phase I and II, if we submit a Fast Track submission?

Answer 1: As stated in Section 8.2 of the solicitation, a Fast Track submission must include a <u>complete</u> Phase I proposal and a separate, <u>complete</u> Phase II proposal. These proposals will be evaluated and scored separately and independently of each other. Therefore, Senior/Key Personnel and Bibliography of Directly Related Work should be addressed in your Phase I proposal in accordance with Section 8.8(A)(7), and Personnel should be addressed in your Phase II proposal in accordance with Section 8.8(B)(3).

Section 8.8 Content of Technical Element (Item 1)

Question 1: Is there a standard sectional breakdown of the Technical Element required or recommended for all offerors to use when generating and compiling their proposals? What should be included in the Technical Element?

Answer 1: *For a Phase I proposal the Content of the Technical Element (or Research Plan) does not have any page limits for internal sections. For Phase II, the only such page limit is that the Commercialization Plan section must not exceed 12 pages. Companies may use their best judgement in addressing all content sent forth in Section 8.8 within the overall Technical Proposal page limit.*

All Technical Proposals should include the material discussed in Section 8.8 (and follow the organizational structure set forth in Section 8.8). Further details are also provided in Sections 8.9 through 8.15, as applicable, depending on the particular considerations appropriate for the type of research being proposed.

Question 1: Can you clarify when letters of support are requested?

Answer 1: *Letters of support are requested for proposals under all Topics in the following situations, as set forth in sections 8.8 A.9., 8.8 A.10., 8.8 B.3., 8.8 B.9.e., and 8.8 B.10: when a subcontractor or consultant collaborator is proposed, a letter must be included from each individual confirming his/her role in the project and extent of involvement; when facilities other than those of the applicant are proposed, a letter must be included stating that leasing/rental arrangements have been negotiated and will be available for the use of the SBIR applicant; and, for Phase II proposals under a Fast Track submission, letters should be included in the Finance Plan section of your Commercialization Plan.*

In addition, some of the specific Topic Descriptions in Section 12 refer to additional and/or more specialized letter requirements, so check your individual Topic of interest carefully.

All of these letters should be included in your Technical Proposal to ensure that they are reviewed by all reviewers.

In addition, costs associated with collaborators should be addressed in Appendix C of the Business Proposal, and letters that discuss or confirm financial information for collaborators can also be included in the Business Proposal to support the evaluation of the proposed project budget. For NIH Topics, please note that information submitted in the Business Proposal, however, will not be seen by all evaluators, some of whom will only review the Technical Proposal.

Section 8.10 Human Subjects Research and Protection from Risk

Question 1: If a proposed project is regarded as Human Subjects Research, do I need a certain certification beforehand in order to submit the proposal?

Answer 1: *Projects that will include Human Subjects Research must be compliant with relevant NIH/CDC policies prior to award, or in certain instances, prior to the conduct of the portions of the work involving human subjects research - not prior to the submission of the proposal. However, offerors are encouraged to address the human subjects research instructions set forth in Section 8.10 of the solicitation in as much detail as they are able to within their proposal, at the time the proposal is submitted, so that the proposal may be evaluated as comprehensively as possible, and any concerns noted may be resolved as efficiently as possible.*

Section 8.16 Content of the Pricing Proposal (Item Two)

Question 1: Is profit/fee included in the budget capped at 7% of total costs, like it is for SBIR grants?

Answer 1: *The SBIR Policy Directive states that SBIR awards are allowed reasonable fee or profit consistent with normal profit margins provided to profit-making firms for R/R&D work. Contract awards use a structured agency approach to determine reasonableness, in accordance with Federal Acquisition Regulation (FAR) 15.404-4 Profit, which can be viewed here: https://www.law.cornell.edu/cfr/text/48/15.404-4 . If contracting personnel are concerned about whether the fee/profit proposed is reasonable, this issue will be addressed in negotiations prior to award.*

Question 2: How do I know what is allowable as a direct cost for my SBIR contract proposal's budget?

Answer 2: *For SBIR contracts, costs that are reasonable to perform the work proposed and are 100% allocable to completing the SBIR project as set forth in the contract may be included as direct costs in the budget, as long as the same costs are not included in an indirect cost pool (for the creation/administration of G&A/F&A/Overhead rates), and are not expressly "unallowable" (prohibited) in accordance with the Federal Acquisition Regulation (FAR) Subpart 31.2 – Contracts with Commercial Organizations, which can be viewed here:* https://www.acquisition.gov/?q=browsefar .

Note that SBIR grants may have different policies on allowable direct costs, and this guidance applies only to SBIR contracts. Also, note that if your proposal is found to be competitive for award following initial evaluation, a contracting officer may discuss the appropriateness of certain costs with you in a pre-award negotiation phase, on a case-by-case basis, so budget concerns will have the opportunity to be resolved prior to a final award decision being made.

Question 3: Could the budget be used to provide lodging and subsistence allowance to bring together research team in one location?

Answer 3: *Yes, a portion of the budget may be used to cover travel costs for this purpose, if justified and related to the needs of the project. The reason for travel, location of travel, number of travelers, and number of nights of lodging must be described in Appendix C.*

Question 4: Is there a page limit for the Business Proposal?

Answer 4: *No, the business proposal does not have a page limit. Information placed in the business proposal will not be considered during technical evaluation, and will be used only to consider cost/price reasonableness and general compliance with the SBIR program eligibility requirements.*

Question 5: Can you give examples of how team members can be compensated for their efforts through an SBIR award?

Answer 5: *Compensation could include salary, stipends, hourly rate, etc. The type of compensation and amount is determined by the applicant company, but must be in accordance with the salary rate limitation set forth in Section 5.1 of the solicitation. See* https://www.hhs.gov/grants/contracts/contract-policies-regulations/hhsar/part-352-solicitation-provisions-contract-clauses/index.html#352.231-70 *for additional information on the Salary Rate Limitation.*

Section 12 Component Instructions and Technical Topic Descriptions

NATIONAL CANCER INSTITUTE (NCI)

National Cancer Institute (NCI), Topic 370: Targeted Therapy for Cancer- and Cancer Therapy-Related Cachexia

Question 1: The Topic descriptions states "Activities not supported by this topic: Proposals involving supplements and food products will not be considered." My intuition is that the intent of this was to prevent study of poorly-defined foods, herbs and preparations that are not drugs. If a project were to involve n-acetyl cysteine, which can be sold as a nutraceutical "supplement," to enhance the activity of beta alethine, would this project be excluded from consideration under this Topic?

Answer 1: *If the offeror can make a case that the drug/drug combination affects a target that is known to be involved in causing cancer- or cancer related-cachexia, it would be considered within the scope of what is appropriate for Topic 370.*

Question 2: Our project does not address Cachexia specifically, although it is definitely a targeted therapy for cancer. Can we still submit our proposal for this Topic?

Answer 2: *Topic 370 is restricted to proposed technologies that would prevent or treat cachexia that is related to cancer. Cancer therapies that are not proposed to affect a target that is known to be involved in causing cachexia will not be considered for funding under this SBIR Topic. You are encouraged to consider SBIR grant opportunities.*

Question 3: **Our company has invented a new technology of making novel bispecific antibodies for cancer therapy. In order to compare our technology with the current approved drug, we used the same drug targets (CD3xCD19) as Amgen's Blincyto. My understanding is that the target therapy includes all agents hitting targets, no matter the agent is BsAb, Ab or chemical. Please clarify for me?**

Answer 3: *Topic 370 is restricted to proposed technologies that would prevent or treat cachexia that is related to cancer. Cancer therapies that are not proposed to affect a target that is known to be involved in causing cachexia will not be considered for funding under this SBIR Topic. You are encouraged to consider SBIR grant opportunities.*

National Cancer Institute (NCI), Topic 371: Drugs to Exploit the Immune Response Generated by Radiation Therapy

Question 1: **We have engineered lymphocytes to target and eliminate cells specifically expressing a molecule induced after radiation therapy—hence this would be a combinatorial cellular therapy approach—to enhance radiotherapy. We see 'cellular therapies' listed within the broad range of agents although the title 'drugs' suggests more conventional approaches. Would this project be considered within the scope of this Topic?**

Answer 1: *The development of agents (including cell-based therapies) that can modulate responses (immune) induced by radiation, would be considered to fit within the scope of Topic 371. Regarding your specific aims, you are encouraged to look at the expected activities and deliverables set forth in the Topic description to get a sense for what sort of aims would be most appropriate, as aims that would match up with the expected activities and deliverables would be considered most competitive for award.*

Question 2: **Can we focus the Phase 1 activities on the use of non-ionizing energy- specifically ultrasound energy- as the immune modulating agent that is used in combination with Radiation Therapy? If so we suggest that the first sentence under the Project Goals heading be modified to address energy-based modalities.**

Answer 2: *NCI will not be revising the overall Topic description. However, the criteria for agents is quite broad. The two specific requirements for the topic are that: 1) The agents have to modulate the immune components; and 2) The agents have to be tested in combination with radiation.*

National Cancer Institute (NCI), Topic 372: Development and Validation of Non-Mouse Reagents to Enable Preclinical Development of Novel Therapeutics

Question 1: **Will the use of cell-based high-throughput/high content imaging assays be within the scope of this Topic? For example, we work on an angiogenesis assay incorporating human genetic variability aiming for an identification of novel anti-angiogennic drug candidates and/or toxicity assessment. Will the use of a zebrafish model be within the scope of this Topic? For example, for toxicity assessment of novel anti-angiogenic drugs using high-content imaging for zebrafish vascular system.**

Answer 1: *The goal of the Topic is to enable a variety of useful assays in non-mouse, non-human animal models such as rat, rabbit, and canine by funding the development of reagents optimized to the selected model system. While the type of assay and non-mouse, non-human animal models are not restricted, the offeror must justify both the need for the assay and selection of the model system (animal chosen). If the scenario you propose first is focused on human assays, then it would not meet the topic goals. The scenario you propose second could meet the topic goals, but the need and value for both the zebrafish model and reagents optimized to the zebrafish would need to be fully justified in the proposal.*

Question 2: **I have developed and patented a canine scFv phage display library which enables one to isolate scFv of canine origin to target tumor associated antigens of interest in vivo in canine cancer patients with spontaneous disease. Does this project sound like a good fit for Topic 372?**

Answer 2: *The project describes appears to fit within the overall scope of what is intended for Topic 372. It will be important to adhere to the expected activities and deliverables listed in the Topic description.*

Question 3: **The Topic description notes that "A commercial supplier of reagents resulting from this topic is advantageous…" I am a basic science researcher and a veterinarian, so my interest would be in developing the clones and validating the target. Would it be acceptable to state that once my antibodies were validated, I would license them to a commercial company and get a letter of support from that company? Or is a letter not necessary for a Phase I proposal?**

Answer 3: *Identification of a commercial supplier of reagents would be advantageous in a Phase I proposal – however, it is not a strict requirement and lack of this component would not exclude you from consideration.*

National Cancer Institute (NCI), Topic 373: Tools and Technologies for Monitoring RNA Modifications

Question 1: **Researchers investigating modified RNAs are interrogating structural effects resulting from the modification. The first step in determining whether a modification causes a structural perturbation is to determine the secondary structure. Would a software that enables a user to: (1) upload NMR and other biophysical data of a modified RNA, (2) upload NMR and other biophysical data of the control unmodified RNA, and (3) analyze both sets of data to accurately determine the secondary structure of the RNAs be of interest to the NCI under the SBIR Topic?**

Answer 1: *No - the focus of this SBIR topic is on the development of assays or tools to detect or monitor covalent modifications of eukaryotic RNAs. Determining the structural perturbations induced by RNA modifications is not within the scope of this Topic. You are encouraged to consider SBIR grant opportunities.*

National Cancer Institute (NCI), Topic 375: Diagnostic Imaging for Cancer Immunotherapies

Question 1: **We are unsure whether our project would be a better fit for Topic NIH/NCI 375 or Topic NIH/NCI 376.**

Answer 1: *If the specific aims of your proposed research focus on immunotherapy, Topic 375 would likely be more appropriate. If the specific aims of your proposed research focus on the tumor microenvironment, Topic 376 would likely be more appropriate. Also, it is recommended that you read through the Questions & Answers provided for both Topics to assist you in making this determination.*

Question 2: **We are considering submitting a proposal on development of imaging tracer for imaging PD-L1 on tumor cells. If successful, this tracer will be used for selection of patient for therapy with approved drugs for stimulating immune response. However, we are in doubt about whether to apply under Topic NIH/NCI 375 or under Topic NIH/NCI 376.**

Answer 2: *Based on the description you have provided, we believe Topic 375 would be the better fit for your potential proposal.*

Question 3: **Acceptable imaging modalities listed in the Topic description include but are not limited to: "optical imaging, PET, SPECT, or MRI." Will sample-driven histological imaging modalities (e.g. multiplex immunofluouresence or immunohistochemistry on tissue biopsies) be considered on equal footing as the non-invasive methods listed in the solicitation?**

Answer 3: *Innovative projects based on sample-driven histological imaging modalities will be considered as within the scope of this Topic if they can be used to identify patients who are likely to respond to cancer immunotherapies, evaluate the efficacy and potential toxicities of the treatment, and/or monitor cancer patients' prognosis.*

Question 4: **Would a proposal that used a mouse cancer model be appropriate for this topic?**

Answer 4: *Yes, using a mouse cancer model is appropriate for this Topic.*

Question 5: **Would a proposal to develop an optical microscopy solution for diagnostic and/or mapping tumor micro-environment in prostate cancer be appropriate for this Topic?**

Answer 5: *Topic 375 is focused on diagnostic imaging for cancer immunotherapy. The development of an optical microscopy solution for diagnostic and/or mapping tumor microenvironment in prostate cancer would not have enough of a focus on immunotherapy to be considered within the scope of this Topic, unless the focus on immunotherapy were increased.*

National Cancer Institute (NCI), Topic 376: Imaging-Based Tools for Longitudinal and Multi-Dimensional Mapping of the Tumor and its Microenvironment

Question 1: We are unsure whether our project would be a better fit for Topic NIH/NCI 375 or Topic NIH/NCI 376.

Answer 1: If the specific aims of your proposed research focus on immunotherapy, Topic 375 would likely be more appropriate. If the specific aims of your proposed research focus on the tumor microenvironment, Topic 376 would likely be more appropriate. Also, it is recommended that you read through the Questions & Answers provided for both Topics to assist you in making this determination.

Question 2: If we propose an imaging tool for mapping specific cancer, for example lung cancer, would it still fit the objectives of this Topic? Or you are looking for "platform" solutions that would work for every cancer?

Answer 2: This topic is not limited to platform development and proposals to map a specific cancer through an imaging tool would be considered within the scope of this Topic, provided the proposal meets the other goals and deliverables listed.

Question 3: Our measurement technique works on tissue biopsy samples (in-vitro). Is that a conflict with the goals of Topic 376?

Answer 3: Topic 376 solicits the development of in vivo assays so this proposed in vitro assay would not fit the Topic goals.

National Cancer Institute (NCI), Topic 377: Bridging the Guideline Implementation Gap: Clinical Decision-Support to Improve Cancer Symptom Management

Question 1: I would like clarification on the management of 8 common cancer-related symptoms that have associated national CPGs. Besides the 11 Clinical practice guidelines for cancer supportive care one of the guidelines cover 15 sub-categories that will have similar weight to the other 10 clinical practice guidelines if they were listed separately. Can more than one cancer related symptom be selected from the same clinical practice guideline?

Answer 1: The proposed project should focus on the management of symptoms caused by cancer and/or its treatment. While symptom management is a component of survivorship care, the decision support proposed for development is specifically for guideline-based symptom management, including the management of symptoms in cancer survivors, rather than decision-support to implement guideline-based survivorship care more broadly (e.g. screening, risk reduction, exercise, surveillance).

Question 2: Are the sponsors of this Topic interested in responses that focus on treatment identification and management in addition to or instead of symptom management?

Answer 2: No. The focus needs to be on translation of symptom management guidelines into computable algorithms <u>for decision support to improve management of cancer and treatment-related symptoms</u>.

National Cancer Institute (NCI), Topic 378: Mobile Application for Surveillance of Post-Radiation Therapy Health-Related Quality of Life

Question 1: It indicates that a biostatistician would need to be involved. Would you be able to explain their role in this project?

Answer 1: A biostatistician is explicitly mentioned in the context of statistical justification of the planned sample size for usability testing/validation in Phase II. However, in addition, a statistician may be of value throughout the project to help interpret usability testing and workshop results, especially in Phase II.

Question 2: The Topic Description specifies that a Phase I activity is to "perform small scale usability testing with at least 25 cancer patients." For the purposes of Phase I activities on this specific contract topic, does NCI consider this usability testing to be an activity requiring a Human Subject Protection plan? Or is the required usability testing exempt under one or more of the HHS exemption categories?

Answer 2: NCI does require IRB review for any project involving usability testing of software, which is required under Topic 378. The IRB may decide the project is exempt, or may opt for an expedited IRB review, and either one of these IRB outcomes is acceptable with NCI. For these reasons, NCI does feel it is appropriate to affirmatively

address Human Subjects Research through a section within your proposal, in accordance with the instructions set forth in the solicitation – however, in this section, you may address why you feel an exemption is appropriate, if applicable. If NCI feels your justification is not appropriate, you will have an opportunity to resolve any concerns prior to a final award decision being made.

Question 3: We are planning to get primitive data from a hospital's database without identifiable or private information on patients. Since this is a Phase I application, and data is not obtained through the interaction/intervention of patients nor any identifiable or private information on patients, would this be considered Human Subject Research?

Answer 3: See Answer 2, above. Also, note that whether or not a project involves human subjects research is not tied to whether the project is in Phase I or Phase II.

Question 4: Which medical record systems must the final app be able to interface with?

Answer 4: Topic 378 does not require compatibility with specific named medical record systems. However, compatibility with at least one of the major electronic medical record systems is encouraged, and would be a significant strength.

Question 5: Regarding the workshop required in Phase I to deliver a report of issue toxicities on the proposal: Is there an anticipated form for the workshop to take? Is there a deliverable for this workshop?

Answer 5: There is not a required format for the workshop, offerors may use their professional judgement, in accordance with the stated goals listed in the Phase I Activities and Deliverables description. The deliverable for the workshop would be to describe its outcome in the first quarterly technical progress report.

Question 6: Question regarding the use of the CTAE: Can we supplement the NCI instrument with follow up questions and perhaps even pictures or other recording devices?

Answer 6: It is fine to supplement PRO-CTCAE as you suggest. Topic 378 does not prohibit that.

National Cancer Institute (NCI), Topic 379: Software Enabling Data Integration from Wearable Sensors to Generate Novel Analytics for Cancer Patients

Question 1: Is there a particular sensor (e.g., fitbit or apple watch) or sensor signal (e.g., PPG, GSR, accelerometry, biochemical measures) on which you would prefer initial efforts (e.g., Phase I work) to focus, that could then be expanded on as the effort progresses?

Answer 1: NCI is interested in initial work with sensor signal(s) from bimodal wearables (HR+accelerometer, Apple, Fitbit, etc.) and any other wearable or implantable device currently used to measure biochemistry (e.g., Profusa, Dexcom, etc.).

Question 2: Is real-time information delivery to the patient desired?

Answer 2: Not initially, although ultimately this may be a desired target audience. For now, the focus should be on targeting clinicians and cancer researchers looking to implement their respective cohorts and/or solutions in a "bring your own device(s)" approach.

Question 3: What is the desired level of fidelity of information delivered to the patient, as this might have implications for FDA approval (e.g., your heart rate is high, which with your doctor vs. you may be having an adverse reaction to therapeutics, seek immediate help)?

Answer 3: The desired level of information to the patient should not be the focus of the initial prototype. It is desirable to have the ability to eventually open up more information to the patient, at the discretion of the clinical researcher or clinicians utilizing the platform.

Question 4: Is real-time availability of information to clinicians a goal?

Answer 4: Yes, or at a minimum, continuous, in a "fit-for-purpose" manner (e.g. measurement device 1 data per hour and measurement device 2 per 3.5 hours, etc.). The optimum goal will be to have a platform that can uptake data from multiple external/passive/wearable sources as they stream and integrate together relative to time (e.g., multiple data streams by which could be processed with novel predictive analytics). Subsequently generated

data streams and analytical predictions/assessment could then be used by 1) researchers to understand progression and the implications / deviations in patient behavior or other biological parameters that are not currently understood at the temporal granularity necessary to utilize in support of clinical decisions; or 2) by clinicians whom already have clear prognostic understanding of particular biological parameter(s) and need a convenient tool to monitor in aid of the current standard of care.

Question 5: The topic indicates that completely passive monitoring is the eventual goal. Is any interaction with the participant acceptable? If so, how much interaction with the patient is acceptable (e.g., cross-daily requests for symptom ratings vs. no interaction)?

Answer 5: Complete passive monitoring possibly, yet without removal of caregiver / patient interactions necessary for optimal delivery and patient outcomes (i.e., not for patient isolation solely because they are passively monitored by multiple metrics). As far as acceptability of patient interactions, yes, caregiver / patient interaction of symptoms through platform is encouraged.

Question 6: Would you like to see a user interface for clinicians to view single patients?

Answer 6: Yes, this is very important to have.

Question 7: Would you like to see a researcher interface through which researchers can view only de-identified population-level data?

Answer 7: Yes, this is very important to have.

Question 8: If all three functions (interaction with the patient, interaction with the clinician, and interaction with researchers) are desired, which is of highest importance during the initial Phase I effort?

Answer 8: For the initial prototype platform, NCI envisions use among clinical cancer researchers. Thus, the target should remain for research use, in order to bolster the eventual translation to wearables / passive monitoring for direct clinical applications and / or in support of clinical decisions, remotely.

Question 9: Do you envision more complex analytics (e.g., machine learning across large-scale data acquired across hours, days, or weeks) to occur on devices themselves or in the cloud?

Answer 9: The more complex predictive analytics would be optimal if cloud-based. Moreover, the optimal solution would be de-identified data prior to leaving patient-side with the cloud-side only seeing data+demographics.

Question 10: Is system output (e.g., estimates of response to therapeutics) supposed to be integrated into electronic medical records? Should this occur automatically through something like a user account linked to a patient record, or is this something the patient/clinician/researcher should oversee?

Answer 10: Ultimately, yes, integration into EMRs is a goal. Yet, much will need to occur before this can take place. It should be assumed as such though for this Topic that the ability to output data/estimates to EMR is desirable, and at that point, oversight should be left to clinician / researcher and the platform should have the ability to output in format(s) utilized for EMRs.

Question 11: Does NCI have specific sensors they would want included in the study proposal? (e.g. step monitors, heart rate, % muscle mass, % body fat, etc.)?

Answer 11: Sensors could include: steps, HR, %body fat, and continuous glucose monitor (Dexcom or other similar devices).

Question 12: What does the term "external monitoring of environment" in terms of sensors mean? Is it temperature, humidity, secondhand smoke? Do you have anything in mind specifically tailored for cancer patients or is this for general environmental conditions?

Answer 12: External monitoring could be any of the elements mentioned above, as well as MS Kinect, etc. These can be wearable or just local to the individual (connected home devices, etc.). This would be tailored for general environmental condition monitoring platforms.

Question 13: The Topic description specifies a role for an Epidemiologist. Please describe what role you foresee for them in this project?

Answer 13: For usability testing, an epidemiologist is recommended but is not required.

Question 14: Is there an expectation that such sensors will be used on actual human test subjects - usability testing on actual persons?

Answer 14: This would be ideal, to display usability of platform with humans in real world settings.

Question 15: Might software-related milestone evaluations include product demonstrations?

Answer 15: Yes, software demonstrations will be the best way of ensuring milestones are met and are highly encouraged.

Question 16: We may want to add other assessment tools that further monitor patient use of the product. How should we include this?

Answer 16: Securely and de-identified.

Question 17: For device monitoring, might this include devices that measure FDA protected metrics such as ECG?

Answer 17: Yes, ECG monitors (implantable, etc.) would be of interest to be able to incorporate into the delivered platform, when available to be used.

Question 18: What is a monitoring platform? Do you have a list in mind? Or is the goal just flexibility of monitoring devices?

Answer 18: Monitoring platform is defined as a wearable or external sensing device/platform that could enable remote monitoring of patient chemistry, vitals, or contextual information - all of which could be collectively analyzed with predictive analytics to enable clinical decision support and more. The goal is the flexibility of the topic deliverable(s) to be utilized in a device-agnostic manner – in essence, a platform which could be used by a researcher to understand patient/disease characteristics, out-of-clinic, with any monitoring platform (regardless of type, manufacturer, etc.). Ultimately, enabling a "bring-your-own-device" mantra to understanding disease characteristic X or patient cohort Y with a myriad of devices could enable a deeper, more precise understanding of each patient and respective disease/disease characteristic.

Question 19: The Phase II activity listed below for 'validation and scale-up between the offeror, NCI, and/or NCI-identified third party sources to access relevant input data types' is unclear to me. Is this meant to be a validation study using subjects that are part of an ongoing NCI study?

Answer 19: This language is intended to convey that NCI or an NCI-identified third party may provide input data for the offeror to test their system.

Question 20: Our primary question is regarding scope: Our project plan is to develop a system that integrates data collected from wearable sensors that passively and continuously track bodily movement in free living contexts with patient-report symptoms and physiologic variables to better understand patient responses to cancer treatment and potentially develop prognostic indicators of future adverse events, disease progression, etc. Our questions are: 1) since we are integrating other systems and information into the current wearable device platform do we still fit within the scope of this Topic, and relatedly, 2) is our plan sufficient in scope for this Topic, since it is acknowledged that multiple systems may be needed in order to capture all information to adequately care for patients?

Answer 20: Based on the description provided, this project would likely be considered within the scope of what is considered appropriate for this Topic.

Question 21: We have an app that allows you to see how intense the solar radiation is in your current location, notifies you when the sun's strength is above a preset limit, and reminds you when it's time to re-apply your sunscreen, helping you to stay protected and reducing your chances of developing or aggravating skin cancer. The technology directly targets decreasing skin cancer risk, but is not monitoring biological data (heart rate, respiration, etc.) for the patient. Also, it is not ascertaining reactions to treatments. Would this project be considered within the scope of Topic 379?

Answer 21: The project described does not sound like it would be considered within the scope of this Topic. You are encouraged to consider SBIR grant opportunities.

National Cancer Institute (NCI), Topic 380: Computer Aided Decision Support for Radiation Oncology

Question 1: Do you want to see any particular type of cancer investigated?

Answer 1: For Topic 380, the offeror should be certain to choose a well-defined patient population to focus on, but that choice is open to the offeror.

National Cancer Institute (NCI), Topic 381: Development of Artificial Intelligence (AI) Tools to Understand and Duplicate Experts' Radiation Therapy Planning for Prostate Cancer

Question 1: Can you elaborate further on what cross disciplinary expertise should be included on the project team?

Answer 1: The expertise required depends on the particular project plan put forth by the contractor and should have all of the necessary expertise to develop & commercialize the proposed product.

Question 2: Will NCI provide the "Standard 3D CT datasets," or is the contractor expected to provide this?

Answer 2: The contractor is expected to collaborate with clinical sites that can provide the data.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

National Heart, Lung, and Blood Institute (NHLBI) – Topic 103: Devices for Transcatheter Surgery and Topic 104: Tapered Guidewires for Transcatheter Electrosurgery

Question 1: Is there any additional information regarding the technical aspects of Topics 103 and 104?

Answer 1: For additional information on the subject matter of Topics 103 and 104, you should review the information located in PubMed Central: https://www.ncbi.nlm.nih.gov/pubmed/ .

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

National Institute of Allergy and Infectious Diseases (NIAID), Topic 051: Inhaled Delivery of Clofazimine (CFZ) – An Important Anti-tuberculosis Drug

Question 1: The solicitation states that while several attempts have been made to develop inhalation therapy for TB, so far none of them have been commercialized. What are the key reasons for this, in NIAID's view? For example, are these efficacy or safety issues, or lack of incentives?

Answer 1: NIAID believes the key reason to be lack of incentives.

Question 2: We understand that NIH previously funded Phase I programs to develop inhaled delivery of clofazimine. Could you provide reasons why NIH is seeking again applications for the development of such a product? What were the weaknesses of the previous programs that caused them not to be further supported by NIH or other bodies?

Answer 2: While proposals have been sought in this area of research before, they have not necessarily resulted in successful, funded awards, following the initial technical evaluation process. As NIAID believes that this is an important area of scientific exploration, because such a product would be a paradigm shift in the treatment and cure of tuberculosis, NIAID is again seeking proposals for the development of this product.

Question 3: Can Phase I be limited to the pharmaceutical development of the formulation and device, without any animal studies? Is *in vitro* efficacy essential in Phase I?

Answer 3: In accordance with the Topic Description, in vitro efficacy is required in Phase I, but animal studies are not required for Phase I. Animal studies are required for Phase II.

Question 4: The delivery platform to be developed is described as being inexpensive, hand-held, and self-contained. Is the inexpensive criterion based on the US market? Can a self-contained inhalation platform still involve the use of battery power and/or compressed air? Is a nebulized formulation acceptable (rather than an inhaled powder)?

Answer 4: The evaluation of whether the platform is inexpensive is not necessarily based on the US market. Battery is acceptable; however, compressed air is not self-contained. A nebulized formulation is acceptable if the formulation is administered via a self-contained unit.

Question 5: Is the drug product envisioned also meant for usage in low resource settings?

Answer 5: Yes.

Question 6: What type of quantitative studies would satisfy the criteria to assess toxicity and pharmacology *in vitro*?

Answer 6: It would be up to the offeror to propose quantitative studies that would satisfy the criteria based upon his/her expertise.

Question 7: Could *in vivo* studies be performed instead of *in vitro* ones in order to assess toxicity and pharmacology?

Answer 7: Yes.

National Institute of Allergy and Infectious Diseases (NIAID), Topic 055: Adjuvant Development for Vaccines and for Autoimmune and Allergic Diseases

Question 1: We have previously completed an NIH-funded grant for development of a vaccine with positive animal study results. The chosen adjuvant showed increased efficacy as compared to non-adjuvanted and we would now like to compare the in vivo effect of different adjuvants with our vaccine. Would adjuvant comparison be applicable under this topic? To our knowledge none of the adjuvants we would evaluate have yet been licensed for use with a vaccine.

Answer 1: The goal of each proposal must be the development of a single adjuvant (or single combination-adjuvant) for one or more human vaccines (licensed or investigational). During Phase I, this Topic will support the development of novel combinations of previously described individual adjuvants or the comparison of previously described individual adjuvants. The scope of such studies should include studies for selection of the final adjuvant formulation, and Phase II must focus on development of a vaccine containing one adjuvant or combination-adjuvant.

The goal is to support pre-IND studies and advance novel adjuvants towards licensure for human use. Each application must include documentation that the offeror has intellectual property protection and/or proprietary freedom to develop the adjuvant:vaccine and eventually move forward with clinical development so as to meet this goal.

Question 2: Can animal studies be supported during Phase I?

Answer 2: Animal studies may be supported during Phase I.

National Institute of Allergy and Infectious Diseases (NIAID), Topic 057: Development of Sample Sparing Assays

Question 1: What volume of clinical specimen (blood or plasma) would be considered "sample sparing" for the study of human immune responses? For example, would 100 uL of blood be considered sample sparing for the analysis of cytokines?

Answer 1: The amount of blood/plasma necessary for the sample sparing depends on the amount of cytokines to be analyzed and what the offeror is proposing to be statistically viable for the research.

National Institute of Allergy and Infectious Diseases (NIAID), Topic 058:
Bioinformatics tools to make data FAIR (Findable, Accessible, Interoperable, and Re-usable)

Question 1: Is NIAID looking for tools that can operate on data after a study is complete, but prior to submission into the data sharing repositories (Immport, ImmuneSpace, ITN TrialShare, etc.)?

Answer 1: The intent of this Topic is to perform a gap analysis on one or more of the five databases mentioned in the background paragraph to determine if any of the data is not FAIR and to develop new or improved methods or solutions to make the data FAIR. This would be done using data that is already publicly shared by the bioinformatics resource(s).

Question 2: Can tools be for any part of the data lifecycle of a research study - to support data quality during data generation? Support better data processing and metadata generation? Or for post-processing of data prior to submission to data repositories?

Answer 2: Please refer to the Answer 1, above.

Question 3: Would a proposal that leverages an existing product currently in-development by a startup and starting trials with NIAID be considered responsive and responsible, if the goal of the effort was to tailor that tool's output to meet the Project Goal of making data FAIR prior to submission to data repositories?

Answer 3: Please refer to the Answer 1, above. The gap analysis and any proposed methods or solutions would be leveraging publicly shared data from one or more of the five bioinformatics resources after data has already been submitted to the data repository(ies).

Question 4: Is NIAID interested in data preparation tools that can be used to make data FAIR and improve upon common tools used for data processing (e.g. Microsoft Excel)?

Answer 4: The goal of this Topic is to identify whether any of the data being publicly shared from one or more of the five databases mentioned in the background paragraph is not FAIR and to develop new or improved methods or solutions to make the data FAIR.

Question 5: What other data sharing sources or sites will be important to prepare data for?

Answer 5: The intent of this Topic is to identify any data that is not consistent with FAIR principles from one or more of the five bioinformatics resources mentioned in the background paragraph and to develop a method or solution to make the data FAIR. The FAIR data should facilitate data integration and indexing by popular search engines to provide more relevant search results or to complement specialized search, retrieval, and presentation tools such as those provided by the bioinformatic resources mentioned in the background paragraph.

Question 6: To what degree must the proposal address security requirements for development and hosting of potentially sensitive (e.g. PII and PHI) data for Phase I and Phase II? Can these requirements be elaborated and addressed during execution of the R&D effort?

Answer 6: The intent of this Topic is to perform a gap analysis one or more of the five bioinformatics resources mentioned in the background section to identify any publicly shared data that is not consistent with FAIR principles. As the data is already publicly shared, there should not be any security concerns regarding PII and PHI data.

Question 7: Would the customization of an existing tool or the development of "plug-ins" to data processing tools be considered within the scope of this Topic's project goals?

Answer 7: Customization of an existing tool or the development of "plug-ins" to data processing tools would be within scope provided it constitutes a new or improved solution for making the data identified in the gap analysis consistent with FAIR principles.

Question 8: Are there any universal standards that are expected to apply across data sources or repositories?

Answer 8: It is up to the offeror to determine which standards would address the needs and requirements to make any identified data from the gap analysis of one or more of the five bioinformatics resources consistent with FAIR principles.

Question 9: Can we start with just one of the databases for Phase I?

Answer 9: Starting with just one of the databases for Phase 1 would be within the scope of this Topic, provided it addresses the need for a gap analysis to identify which data in the database would be inconsistent with FAIR principles and proposes a new or improved method or solution for how to make the identified data FAIR.

Question 10: Does NIAID expect there to be any letters of support from Universities or NIH as part of the proposal for building these tools?

Answer 10: There are no letter of support requirements that are specific to only this Topic; however, review the entire contract solicitation for when letters of support may be desired, in general, for any proposal.

Question 11: What is the expectation of having a medical research Principal Investigator on the offer? Is this required for the proposal to be considered for award?

Answer 11: Having a medical research Principal Investigator is not a requirement – the technical personnel proposed will be evaluated for sufficiency to perform the technical approach proposed. The Principal Investigator, and other significant team members, must demonstrate the training and experience necessary to carry out and lead the specific technical approach proposed.

Question 12: Would NIAID consider offers that elaborate the technical tool requirements using iterative and incremental development (e.g. Agile software development)?

Answer 12: Please refer to the Technical Evaluation Criteria in Section 6 of the contract solicitation for how technical reviewers will assess the technical merit of the proposed approach.

Question 13: Do you want a separate database developed to store additional information or integrated into the pre-existing databases?

Answer 13: The proposed method or solution should reflect the approach that the offer since believes will best achieve the project goals, activities and deliverables, as considered against the criteria established in the Technical Evaluation Criteria set forth in Section 6 of the contract solicitation, including identification of clear milestones that have a reasonable chance of meeting the topic objective.

National Institute of Allergy and Infectious Diseases (NIAID), Topic 059: Diagnostics to Enable Malaria and Neglected Tropical Diseases (NTDs) Elimination

Question 1: Is malaria the main focus of this Topic? Therefore, the system has to detect malaria plus one or more other NTDs?

Answer 1: This Topic is focused on malaria or any Neglected Tropical Disease slated for elimination. Proposals do not need to address malaria.

Question 2: Is detection of Chagas disease considered responsive to this topic?

Answer 2: No, detection of Chagas disease is not considered to be within the scope of this Topic.

Question 3: Will the POC diagnostic device be placed in rural clinics (fixed) or will it be deployed so it has to be ultraportable with battery powered operation?

Answer 3: The proposed POC diagnostic device could be designed to either be placed in rural clinics (fixed) or be deployed, as long as its use supports disease elimination efforts.

Question 4: Is the use of a microwave spectroscope to analyze breath samples for malaria diagnosis acceptable?

Answer 4: Yes, as long as it is appropriate for use in a low- and middle-income countries setting in terms of cost.

Question 5: Are there size or cost requirements of the platform device and each subsequent test?

Answer 5: There are no specific size or cost requirements of the platform device, although see Answer 4, above.

Question 6: Any specifications/preference on turn-around-time and throughput per device?

Answer 6: There are no specifications/preferences on turn-around-time and throughput per device. The final product should demonstrate the necessary sensitivity and specificity to reliably detect asymptomatic infections that are outside the limits of detection of currently available diagnostics.

Question 7: Will DNA/RNA target amplification /detection technologies be considered responsive (multiplexed real-time PCR, isothermal amplification)?

Answer 7: Yes, DNA/RNA target amplification/detection technologies (multiplexed real-time PCR, isothermal amplification) are within the scope of this Topic.

National Institute of Allergy and Infectious Diseases (NIAID), Topic 061: Induction of Mucosal Immune Response to Parenterally Delivered Vaccines

Question 1: Can we propose a novel mucosal vaccine to a disease which has no vaccine at present (neither mucosal nor parenteral)?

Answer 1: Yes, this would be considered within the scope of Topic 061.

National Institute of Allergy and Infectious Diseases (NIAID), Topic 062: Novel Vaccine Technologies and Strategies to Promote Sustained Vaccine Efficacy

Question 1: Does the term 'sustained vaccine efficacy' refer to current vaccine efficacy in general (so that we can propose a new technology to any infectious disease of our choice) or should we target a disease which already has a vaccine, and propose technologies to improve the efficacy of that specific vaccine?

Answer 1: As noted within the Topic 062 description, the focus of this contract Topic is the development of novel vaccine technologies and strategies to promote sustained vaccine efficacy against malaria or pertussis. Thus, proposals should focus on malaria or pertussis to be considered for award.

NATIONAL INSTITUTE OF DRUG ABUSE (NIDA)

National Institute of Drug Abuse (NIDA), Topic 163: Digital Markers for Marijuana Intoxication

Question 1: Do you prefer to have administration of known doses of THC then repeated assessment of the individual such as a controlled study using NIDA-sourced substances? Or would you prefer a more pragmatic design with commercially available products that may be more representative of public use, but less controlled?

*Answer 1: Given that marijuana is a Controlled substance under the Federal Controlled Substances Act, no federal funds can be used to purchase or handle marijuana purchased from any organization other than those with a CI Manufacturers license. Therefore, we recommend that any studies using marijuana should use material obtained from the NIDA Drug Supply Program (*https://www.drugabuse.gov/researchers/research-resources/nida-drug-supply-program*). Alternatively, THC is also commercially available as dronabinol capsules or THC oral solution, both of which are CII. Such orally administered THC has the potential benefits of a more reproducible degree of bioavailability than smoked plant material, particularly when administered following a high fat meal (see Stott 2013 DOI 10.1007/s00228-012-1393-4, Oh 2017 Doi 10.2147/CPAA.S119676).*

Question 2: What is the size of the expected pilot clinical study scheduled to occur during the 6-month Phase I period?

Answer 2: The goal of the Phase I clinical trial is to evaluate feasibility and validity of the digital markers to detect marijuana intoxication. This study should be focused to determine the behavioral/psychological effects of various doses of THC/marijuana as determined by 1) conventional expert assessment tools and the degree to which they correlate with those recorded by the experimental digital assessment tool, and 2) the degree of variability of associated with the two systems and their reproducibility under relevant different conditions. The study participants should be healthy volunteers who use marijuana and have 24-hours marijuana abstinence prior the study. Participant enrollment with 10-15 subjects will be acceptable.

Question 3: Is there a preferred gold standard for cannabinoid intoxication for purposes of validating this biosensor?

Answer 3: *Currently there is the difficulty in establishing an absolute correlation between measured values in biological specimens (i.e. blood, urine or saliva concentration of THC) and intoxication of individuals due to the effects of tolerance and variable pharmacokinetics of marijuana between regular and occasional users. To validate digital biomarkers, psychomotor and behavioral tests performed by a trained observer would be preferred as standards. The use of the blood, urine or saliva levels of THC may supplement such observations.*

Question 4: Could you elaborate on what you mean by DSM V tests in this context? We are unaware of any DSM V tests for cannabis intoxication.

Answer 4: *Although many laboratory tests can be used to determine THC concentration, none has been found to be quantitative to determine magnitude of intoxication and specific for diagnosis of psychomotor impairment. In the context of this announcement, NIDA suggests the use of established and validated psychomotor/ behavioral endpoints such as those which examine impaired movement and/or motor coordination reaction times, anxiety, and impaired judgment.*

Question 5: What exactly is the "digital marker" that the Topic is looking for? Our biosensor generates real-time data of drug levels in the serum – is this considered a "digital marker"?

Answer 5: *Using this announcement NIDA is looking for the development of mHealth technologies that can measure the behavioral or other pharmacological changes in marijuana intoxicated individuals. Technologies that are not portable, or detect the THC or metabolite concentrations in biological specimens are out of the scope of this announcement.*

Question 6: Can you please expound on the requirement for coding the "digital marker" on Apple/Apple frameworks/software? We are confused about the software requirements of the Topic, whether it requires an app to be developed, etc. Our biosensor has an internal processor for the signals, and the generated data can be transmitted wirelessly.

Answer 6: *ResearchKit and ResearchStack are open-source software platforms designed specifically for medical and health research; it simplifies the creation of apps that can help physicians and scientists gather data from willing participants. The framework allows researchers to circumvent the development of custom code for common tasks such as sharing, storage, and syncing of research data. It helps to create apps to recruit human subjects in research, present informed-consent materials, create surveys and tasks, and monitor sensors interoperable with smartphone technology. ResearchKit and ResearchStack platforms have built-in sensors and also can seamlessly work with additional hardware extensions (add-apters) that are frequently developed and available.*

For instance, Apple's iPhones have a number of built-in sensors, including Touch ID, Barometer, Accelerometer, Gyroscope, Proximity Sensor, and Ambient Light Sensor. The Touch ID is a biometric technology that provides user identification through a finger scanner, the Barometer measures atmospheric pressure, the Accelerometer measure the tilting motion and orientation of the iPhone, and the Three-Axis Gyroscope enables 3-axis angular acceleration around the X, Y and Z axes, enabling precise calculation of yaw, pitch, and roll. The Proximity Sensor deactivates the display and touchscreen when the phone is brought near the face during a call and the Ambient Light Sensor adjusts the display brightness.

The currently available external hardware extensions (add-apters) can measure pulse rate, breathing pattern, blood pressure, blood oxygen saturation, heart rate variability, galvanic skin response, and glucose concentration, and can even help detect ear infections and track inhaler medication use. Some add-adapters can be directly purchased through iTunes or third-party vendors; others must be purchased through a physician.

NIDA is very interested in various approaches to develop "digital biomarkers" and correlate them with behavioral or psychological changes at marijuana intoxication. Either the existent built-in sensors, /external add-apters or new designed technologies can be proposed.

For more information about ResearchKit, ResearchStack and the developed apps visit https://www.apple.com/researchkit/ *and* http://researchstack.org/.

Question 7: What does the Topic mean by "embedded digital markers in an app" and subsequent clinical testing of the app?

Answer 7: The goal of this announcement is to develop a mobile application with digital assessment tools that can detect psychomotor and behavioral changes after marijuana use. This app must be created based on Apple Inc.'s ResearchKit or/and Android ResearchStack frameworks. "Digital markers for marijuana intoxication" may be proposed based on available built-in sensors, seamlessly working additional hardware extensions (add-apters) or new technologies. In the case of a new technology, it should be digitally compatible with the app platform. "Embedded digital markers in an app" means that a research app must work with built-in or wirelessly working sensors. The subsequent clinical testing is a pilot clinical study to test feasibility and capability of the proposed digital markers.

National Institute of Drug Abuse (NIDA), Topic 164: Development of Portable Neuromodulatory Devices for the Treatment of Substance Use Disorders

Question 1: The announcement specifically calls out non-invasive modalities such as transcranial magnetic stimulation and direct current stimulation. There is also a brief mention of vagal nerve stimulation. For this opportunity, would NIDA be interested in a minimally-invasive peripheral nerve stimulation therapy delivered using a percutaneous lead connected to a portable external pulse generator?

Answer 1: Yes, TMS and TDCS were often mentioned as exemplars, but NIDA is very interested in any neuromodulatory devices, including those that provide peripheral nerve stimulation therapy to treat substance use or pain (i.e., resulting in opioid sparing), with the requirement that they are portable. Be sure to note that Phase I activities include feasibility of the device showing bio-equivalency based on prototypic measure, and demonstrating device capability. The device must have a refractory period. Also, it must be clear the technology translates peer-reviewed academic research studies using prototypic neuromodulatory technologies.

Question 2: Are preliminary data recommended showing that the proposed therapy or device demonstrates bio-equivalency based on prototypic measures?

Answer 2: No, preliminary data are not needed to show the proposed device demonstrates bio-equivalency based on prototypic measures—this is a Phase I requirement. However, data that supports the feasibility of the device are recommended for inclusion in the proposal.

Question 3: For the prototypic measures, which biological signals or markers of substance use disorder (SUD) would be acceptable? Would pain-pressure thresholds be acceptable? In general, these measures would be acceptable?

Answer 3: Some examples of biological signals or markers of substance use disorder related endpoints, such as craving, dependence, relationship between changes in the circuit-based target and biomarkers/measures of brain function, domains of functions, and symptom/functional measures. Measures for pain should be standard, validated endpoints. However, the studies should ultimately be focused on opioid sparing, i.e., the reduction of opioid use.

Question 4: Is opioid abuse an acceptable SUD indication for this announcement? If so, would a therapy that reduces pain and facilitates opioid cessation (either directly or indirectly through a concomitant therapy) be of interest to NIDA? In this case, would a biological signal for pain or central sensitization be an acceptable prototypic measure for demonstrating bio-equivalency (e.g., pain-pressure thresholds)?

Answer 4: Yes, opioid use and abuse are acceptable SUD indications for this announcement. We also are interested in treatment of pain (i.e., resulting in opioid sparing). Based on empirical data, pain or central sensitization would be an acceptable prototypic measure for demonstrating bio-equivalency. However, the studies should ultimately be focused on opioid sparing, i.e., the reduction of opioid use.

Question 5: For the 1-week outpatient study required in Phase I, do the participants need to be SUD patients if the goals per the announcement are to evaluate 1) measures of acceptability including retention of the portable device, 2) measures of discomfort, 3) portability, and 4) durability?

Answer 5: Those measures are important as the Phase 1 trial is intended to evaluate the feasibility of the device. The participants do not need to be SUD patients. However, Phase I activities also include, for example, showing bio-equivalency based on prototypic measures and demonstrating device capability, for example, by comparing

the effects using imaging or other techniques (e.g., fMRI, EEG). Initial safety studies also are required in Phase I.

Question 6: Are we advised to present proof-of-concept/pilot data that are tailored to SUDs or could we instead present device data showing the treatment effects in other indications, while describing how the device by modulating the same brain circuitry, could positively affect SUDs?

Answer 6: The goal of this announcement is to develop new or convert existing neuromodulatory technologies used for other indications to treat SUDs or pain, in a manner that will facilitate wide application and enhance market penetration. Thus, pilot data need not be tailored to SUDs. Data are acceptable that show the treatment effects in other indications, as long as the circuitry that is modulated is relevant to SUDs or pain.

Question 7: One of the Phase I activities and deliverables is to conduct a 1-week outpatient study following determination of milestone acceptability by NIDA. Is the agency expecting applicants to describe this study as part of the Phase I proposal and include the expenses of this study in the Phase I budget of $225,000? If so, do you have any recommendations as how to fit the costs of both clinical studies (POC clinical trial with a minimum of 15 patients and the outpatient study with a minimum of 24 patients) in the Phase I budget?

Answer 7: There was an error in the guidelines regarding enrollment – a single study, to assess the feasibility and acceptability of the device, is required. Participant enrollment with a minimum of 15 subjects will be acceptable. Note that the Phase I POC study is not an efficacy study for SUDs. It is intended to be a feasibility study for the device, evaluating 1) measures of acceptability including retention of the portable device, 2) measures of discomfort, 3) portability, and 4) durability. In addition, however, the Phase I proposal should include studies addressing bio-equivalency for the device based on prototypic measures and to demonstrate device capability, for example, by comparing the effects using imaging or other techniques (e.g., fMRI, EEG). Applications should describe the 1-week outpatient study for Phase I within the budget parameters.

CENTER FOR GLOBAL HEALTH (CGH)

Center for Global Health (CGH), Topic 009: Improving Global Laboratory Diagnostic Capacity: Modular, End-user-assembled Biosafety Cabinets for Sustainable Biocontainment

Question 1: We would like to propose our ionization process as the module for eradicating communicable pathogens. Could you comment if it is responsive for the topic or not. Do we have to include a HEPA module?

Answer 1: The use of "HEPA" was a suggestion referring to one type of biological containment system. We are looking for one that allows the user to manipulate materials in a "safe" area, and in the case of the traditional biosafety cabinet with HEPA, the air flow acts as the safety barrier. A HEPA is not a necessary component of the containment system if the applicant can build a device that functions to adequately contain biological pathogens.

NATIONAL CENTER FOR CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION (NCCDPHP)

NCCDPHP, Topic 039: Finding Human Carriers of Taeniasis to Prevent Neurocysticercosis Associated Epilepsy

Question 1: Is the outcome of this topic to create a kit that can be used for detection or simply to find the monoclonal antibodies / Aptamers?

Answer 1: The outcome of this Topic is to find pairs of monoclonal antibodies/aptamers.

Question 2: Does the objective rely only on finding said antibodies in stool sample or would Serological or Direct procedures also be considered?

Answer 2: In accordance with the Topic description, Phase I activities should focus on use of stool samples.

Question 3: **Could you elaborate on what successful affinity to binding range would be? What Specificity range in % would be considered acceptable in Phase I? Should there also be a sensitivity factor to the test to displace the need for prior identification of infection, or will determination of infestation be made separately through a coprological examination prior to applying the coproantigen test?**

Answer 3: *The offeror should use their professional judgement in determining an acceptable specificity range for Phase I. Also, the Topic description does not address a coprological examination in association with the coproantigen test. The focus of the Topic is on the development of a human taeniasis coproantigen detection assay.*

Question 4: **Do the 5 Monoclonal antibodies/aptamers to be delivered need to be of the same disposition or should they be of different variety?**

Answer 4: *The offeror should use their professional judgement to propose the best approach to achieve the goals, activities, and deliverables set forth in the Topic description.*

Question 5: **Could the CDC or proposing component provide access to the research team access to previous studies or permission access to NCBI articles on the subject?**

Answer 5: Free access is available to NCBI articles about coproantigen tests for *T. solium* using PubMed. Here are two examples of available references: Detection of Taenia solium taeniasis coproantigen is an early indicator of treatment failure for taeniasis. Bustos JA, Rodriguez S, Jimenez JA, Moyano LM, Castillo Y, Ayvar V, Allan JC, Craig PS, Gonzalez AE, Gilman RH, Tsang VC, Garcia HH; Cysticercosis Working Group in Peru. Clin Vaccine Immunol. 2012 Apr;19(4):570-3. doi: 10.1128/CVI.05428-11. Epub 2012 Feb 15. PMID:22336287. Development of a species-specific coproantigen ELISA for human Taenia solium taeniasis. Guezala MC, Rodriguez S, Zamora H, Garcia HH, Gonzalez AE, Tembo A, Allan JC, Craig PS. Am J Trop Med Hyg. 2009 Sep;81(3):433-7. PMID:19706909.

Question 6: **Is there a possibility to obtain a compliance advisor from the requesting component to help us navigate legal protocol?**

Answer 6: *No. The CDC does not provide advisors to help SBIR awardees navigate legal protocol.*

NATIONAL CENTER FOR EMERGING ZOONOTIC AND INFECTIOUS DISEASES (NCEZID)

NCEZID, Topic 015: Antifungal-containing Solution for Corneal Tissue Storage and Transport

Question 1: **I am looking through the solicitation for the development of an antifungal-containing solution for corneal tissue storage and transport, and I was hoping for a bit of clarification of the problem. I identified a publication from JAMA Ophthalmology in July 2014 that appeared to perform a large portion of the research requested in the solicitation and identified the appropriate dosages of Amphotericin-B that successfully inhibit the growth for Candida species, and at which point the dosage of this drug begins to demonstrate toxicity to the corneal tissue.**

Are there holes in this published research that the solicitation is trying to fill in, perhaps with regards to stabilization of the antifungal agents, storage requirements and shelf-life, or the identification of alternative antifungals?

Is there any additional information you can provide on the goals of this solicitation outside further validation of the 2014 publication?

Answer 1: *Yes, the JAMA paper Layer et al 2014 establishes encouraging evidence that Amphotericin B supplementation in Optisol is effective against C. albicans and C. glabrata with no compromise in corneal cell density at several concentrations. This is a substantial existing step toward a commercializable product that reduces the risk of post-keratoplasty endophthalmitis in vivo.*

We encourage addressing the remaining steps needed to move from published basic scientific evidence to a clinically relevant and FDA-compliant commercialized product. This might include filling gaps in existing research relating to therapeutic use and corneal delivery of this new product, as well as establishing partnerships to assist in the transition from bench science discovery to a competitive product in the corneal storage solution market.

Question 2: Would the agency accept the use of compounds that are in the developmental process - such as our dHDPs or is the request limited to products that are already on the market? One of the advantages to the dHDPs is that the development of resistance to these peptides has not been demonstrated.

Answer 2: There is no requirement that an existing compound be used in a proposal responding to this Topic, and compounds in development would be equally considered. We encourage you to use amphotericin B and other clinically relevant antifungal drugs (e.g., voriconazole) as positive controls for any new compounds tested (JAMA paper by Layer et al 2014, Riddell 2011 Clin Infec Dis) and to address the product's efficacy and safety as well as the remaining steps needed to move from basic scientific evidence to a clinically relevant and FDA-compliant commercialized product. This might include filling gaps in existing research relating to therapeutic use and corneal delivery of this new product, as well as establishing partnerships to assist in the transition from bench science discovery to a competitive product in the corneal storage solution market.

NCEZID, Topic 017: Identification of Brucella canis Seroreactive Proteins and Serology Assay Development

Question 1: Would you be kind enough to clarify whether both B. canis and B. abortus RB51 proteomes are to be screened with sera from dogs and humans infected with B. canis to identify antigens that are common to both B. canis and B. abortus strain RB51?

Answer 1: Dog sera would be used to look for appropriate B. canis antigens but would not be appropriate for B. abortus RB51. CDC will make other sera available (primarily from vaccinated cattle) that could be used for B. abortus RB51.

Question 2: Will strains of B. canis and B. abortus be supplied from an established stock or must the research team take samples from infected populations and culture them themselves?

Answer 2: Type strains are available, if needed.

Question 3: Can you say why the spread of B. canis is of Economic Importance in the U.S.?

Answer 3: In the US more than 70 million dogs are kept as pets. Estimated spending on pets in the US in 2016 exceeded 60 billion USD. As an animal host for pathogens of the genus Brucella, specific and sensitive serological detection of Brucella infection in dogs is an economic factor for the pet industry but also, given the potential for human infection, highly relevant for human public health. For every dog identified as brucellosis positive, there are groups of people who may have been exposed to the pathogen.

Question 4: Is the goal of mapping the proteome of bovine vaccine strain B. abortus RB51 to create a way of diagnosing if cattle have already been vaccinated or to detect if a human has been infected?

Answer 4: The main objective of this Topic is the identification of optimal antigens for development of serodiagnostic tests detecting human antibodies against rough Brucella strains with high specificity and sensitivity.

Question 5: Since species of Brucella are considered a Biological Threat, will the working team need any special clearance or permits to handle and keep said organisms?

Answer 5: Established expertise working with human pathogens, clinical specimens, and familiarity with the relevant biosafety and regulatory requirements would be a plus. B. canis and B. abortus RB51 themselves are not select agents and to not require special permits. This may also vary according to the approach selected for the project.

Question 6: If the team lacks Biohazard training could the award be used to administer such training?

Answer 6: No.

Question 7: If new techniques are needed to culture these organisms or special equipment training is needed is it ok to use the award to pay for these?

Answer 7: No.

End of Amendment 2