Specific Aims

The **objective** of this proposal is to directly and more completely characterize the perceptual experience of tinnitus using the novel application of a primary method for uncovering latent perceptual representations: reverse correlation. Tinnitus is the perception of ringing, buzzing, or hissing in the ears, which can range from mild and transient to debilitating. In the U.S. alone, it affects 45 million people per year, 30% of which report their tinnitus to be moderate to severe. A primary form of treatment habituation therapy that retrains a patients nervous system by habituating it to external sounds that mimic the perceptual experience of the tinnitus sound. Habituation therapies require accurate estimates of patients tinnitus experience in order to promote patient outcomes. There is a pressing need for new approaches to uncovering individuals perceptual experience of tinnitus, because current estimation methods rely on strongly reductionist assumptions concerning the nature of tinnitus sounds, and produce results that are correspondingly biased and incomplete. Reverse correlation holds promise in this regard, as a primary method used to characterize neural tuning that is known to allow for unconstrained and unbiased estimation of latent neural representations (e.g., neural receptive fields [17]), as well as higher-level cognitive representations, including psychophysical kernels that drive the top-down processes of perception (e.g., face or phoneme recognition)[1,5,14,18], and even abstract psychological categories (e.g., male vs. female faces)[4,10,16], all on the basis of fairly simple stimulus-response data [11,15]. Despite its wide acceptance in other areas of inquiry, reverse correlation has not been brought to bear with respect to uncovering tinnitus experience.

Our **long-term goal** is to directly uncover and more completely characterize the perceptual experience of tinnitus using the demonstrated capabilities of the reverse correlation approach. Our guiding hypothesis is that reverse correlation will produce estimates of tinnitus percepts that are substantially more rich, individualized and unbiased than currently possible using existing approaches. The rationale is that high quality characterization of tinnitus percepts can promote detailed assessment of tinnitus, helping to explain individual variability in tinnitus experience, and ultimately informing individualized treatment through enhanced habituation therapies. The proposed work will simultaneously improve the efficiency of the reverse correlation method itself, further enhancing its potential for adoption in clinical settings. We will test our central hypothesis and attain our objective via the following specific aims:

Aim #1: Uncover and reconstruct cognitive representations of tinnitus

Participants will classify white noise stimuli as sounding like their tinnitus or not. We will use reverse correlation to infer an unbiased estimate of each participant's cognitive representation of their tinnitus percept.

Aim #2: Develop efficient reconstruction algorithm for cognitive representations using compressive sensing

The efficiency of this method can be optimized to require fewer samples using advanced signal processing techniques. We will develop an open-source compressive sensing data analysis pipeline to acquire convergent cognitive representations using fewer trials. Our pilot data demonstrates that compressive sensing affords a 90% decrease in number of trials for equivalent resulant latent representation. We will also develop and distribute an open-source software implementation the of the reverse correlation method for speech perception, including the proposed compressive sensing framework, for use by the research community.

Aim #3: Characterize and interpret cognitive representations of tinnitus

Our compressive sensing framework will allow for rapid data acquisition from participants. We will characterize cognitive representations of tinnitus between participants and over time. What is the space of tinnitus cognitive representations? Are there subtypes or clusters on a lower dimensional manifold? We will employ dimensionality reduction and clustering algorithms to represent and visualize the data, providing direct insight into commonalities and variability of tinnitus experience in and between subjects.

A. Significance

Tinnitus, the perception of ringing, buzzing, or hissing in the ears when no external sound is present, is a health condition estimated to affect 10-15% of adults worldwide [9]. The condition is highly heterogeneous and can range from mild and transient to debilitating and constant. In the U.S., tinnitus affects approximately one in ten Americans, with 7.2% of those rating their tinnitus as severe ([1]. Tinnitus can be perceived unilaterally or bilaterally and may differ over time, even within individuals. This heterogeneity in characterization has important implications for research and clinical practice. Identifying patterns in how tinnitus sounds and its relationship to hearing may aid in identifying different forms of tinnitus and revealing their underlying mechanisms. However, the subjective nature of characterizing tinnitus makes it difficult to reliably define and measure [18].

Current methods to determine cognitive representations of tinnitus are inefficient and introduce bias, resulting in a lack of standardization in tinnitus assessment [9]. Alternate forced-choice (AFC) paradigm tasks ask the patient to determine which of two sounds is closer to their tinnitus percept [5, 6, 8, 11]. Recent computer and methodological advances have made the test more portable and efficient, but the AFC paradigm still relies on assumptions about the subject's tinnitus percept. Tinnitus percepts are too heterogeneous to be represented by pure tones or small-envelope waveforms. Adequately sampling the psychoacoustic space of possible tinnitus percepts via an AFC task is unfeasible. Other approaches have attempted to capture the richness of tinnitus percepts using likeness measures, in which the subject rates whether a presented stimulus is part of their tinnitus percept or not [15]. While this method is able to capture more features of cognitive representations of tinnitus, it is time-consuming and limited by the aural skills of the subject [18]. Both these approaches involve the subject comparing an external stimulus to their cognitive representation of the tinnitus percept, however AFC tasks introduce biases by artificially limiting the stimulus space and likeness measures are time-consuming. *We believe that a novel reverse correlation-based approach will produce efficient and unbiased cognitive representations of tinnitus percepts* [4].

Reverse correlation allows for unconstrained and unbiased characterization of latent representations directly from stimulus-response data by eliciting responses to richly varying stimuli, such as white noise (Marmarelis & Marmarelis, 1978; Nishimoto et al., 2006). Rich stimuli, by virtue of the fact that they are inherently vague, force the top-down process to exert a clearly measurable influence on responses. Latent representations that drive the top-down process can then be estimated by regressing observed responses against the stimuli over many trials (Mineault et al., 2009). Reverse correlation, as a method, is powerful enough to characterize any aspect of neurological, cognitive or psychological function that can be modeled as a transductive process (Ringach, 2004). It has become a primary method used to characterize the latent representations encapsulated in neural tuning (e.g., receptive fields; Ringach, 2004), and is closely related to the widely-used white noise approach to characterizing physiological (Marmarelis & Marmarelis, 1978) and engineering (Ljung, 1999) systems.

Reverse correlation, in addition to its prominence as an important tool relative to lower-level neural mechanisms, has been increasingly used for inferring higher-level cognitive representations, including psychophysical kernels that drive the top-down processes of perception (Ahumada & Lovell, 1971; Gosselin & Schyns, 2003; Neri & Levi, 2006; Smith et al., 2012), and even abstract psychological categories (e.g., male vs. female faces; Brinkman et al., 2017; Mangini & Biederman, 2004; Ponsot et al., 2018). Recent work in vision (e.g., Gosselin & Schyns, 2003; Liu et al., 2014) has demonstrated that reverse correlation can effectively characterize cognitive representations underlying letter and face recognition (Fig 2A). One speech study has also estimated steady-state representations of vowels the /a/ and /i/ using a closely-related paradigm to the one proposed here (Fig 2B; Brimijoin et al., 2013). Our proposed use of reverse correlation in the domain of speech expands on classic efforts to understand top-down processing in speech with the presentation of rich, vague stimuli to elicit responses from listeners (Warren & Warren, 1970; Vokey & Read 1985). These studies provide clear evidence that rich stimuli, such as white noise, are sufficient to engage the top-down process, even if they do not attempt to characterize the latent representations.

Incomplete characterizations of cognitive representations impoverish our scientific understanding of tinnitus, weak causal explanations for its etiology, and hinder progress towards effective treatments. Reverse correlation shows promise to provide a more complete characterization of cognitive representations of tinnitus and is applicable to other psychophysical domains as well. Directly characterizing complex representations of tinnitus can enable more effective, targeted treatments, reveal insights about subtypes of the condition, and pave the way for new tinnitus-masking assistive devices. Fully characterizing a high-dimensional representation of tinnitus will improve causal explanations for currently unexplained variability in tinnitus experience both between subjects and within single subjects over time.

A.3. Rigor of the Prior Research

The premise of the proposed work is that reverse correlation will deliver unbiased estimates of cognitive representations of tinnitus. Furthermore, that compressive sensing will dramatically increase the efficiency of experiments, resulting in convergent cognitive representations in a fraction of the samples.

The evidence for this premise is first based on well-established studies using reverse correlation to derive cognitive representations of sounds and symbols. Reverse correlation has been applied to infer cognitive representations from letters [4], vowel sounds [2], and faces [3, 17]. More broadly, it has been applied to infer the shape of receptive fields in linear transducers and spiking neurons [16]. The reverse correlation paradigm makes minimal assumptions about the derived cognitive representation since the subject is presented with high-dimensional random input. A large number of stimulus-response samples are typically required for accurate reconstruction of cognitive representations using conventional techniques. To address this inefficiency, studies often limit the richness of stimuli, or impose strict constraints on the reconstructions, leading to estimates that are biased or incomplete. However, recent advances in signal processing, most notably a techniques known as compressive sensing, are leading to dramatic improvements the efficiency of traditional sampling.

We propose to develop an advanced signal processing pipeline that will enable us to overcome the inefficiencies of existing reverse correlation methods through the use of compressive sensing, a recent advance in signal processing which has led to dramatic improvements the efficiency of traditional sampling and signal estimation methods (Baraniuk, 2007). Compressive sensing has recently gained wide recognition in domains such as medical imaging (Graff & Sidky, 2015; Lustig et al., 2008), where considerations of efficiency and bias reduction are critical. Compressive sensing holds promise to similarly improve the efficiency of reverse correlation, without the drawback of biasing estimates. By dramatically decreasing the number of trials needed for signal reconstruction, this technique will extend the range of perceptual mechanisms that can be estimated. Moreover, compressive sensing can be directly substituted for conventional, regression-based estimation, with no other required changes to existing experimental protocols. Our ultimate objective is to develop and validate a compressive sensing data processing pipeline - culminating in an open-source software tool that will allow for efficient and accurate reconstruction of latent representations using data obtained via the reverse correlation method.

Table 1: Example Table

City	N[a]	%Silly
San Diego	289	41%
Seattle	262	32%
Galveston	261	15%
St Louis	269	7%
New York	271	4%
Baltimore	231	2%
Total	1,586	21%

[a] All participants clowns.

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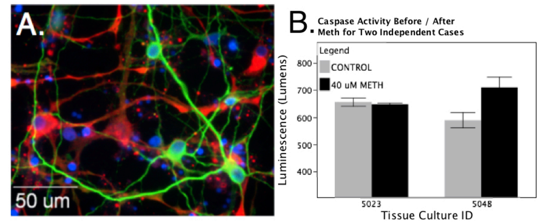

Figure 1: Example wrapped figure. (A) Impressive microscopy image. (B) Impressive data.

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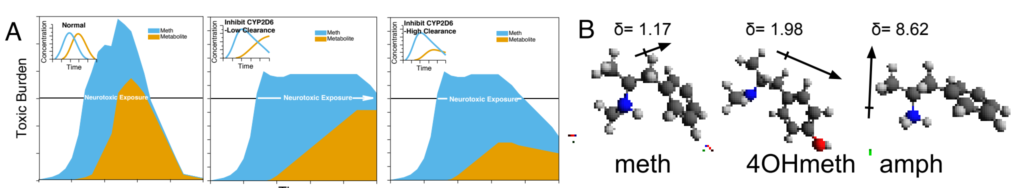

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B. Innovation

The proposed project is innovative for several reasons. First, we will leverage interdisciplinary collaboration between engineering (Lammert) and hearing science (Ben) to characterize tinnitus to inform clinical care. Second, we will apply reverse correlation to the tinnitus domain in a novel application, which promises to deliver unbiased, high-dimensional estimates of cognitive representations of tinnitus. Third, we will develop a signal processing pipeline to leverage compressive sensing to acquire accurate estimates of cognitive representations of tinnitus using significantly fewer samples. This pipeline will save experimenters and subjects time and will enable researchers to collect data from more subjects and from individual subjects over time. We will release our open-source software tool online with bindings to popular scientific computing languages.

C. Approach

In the proposed project, we will use reverse correlation to reveal unbiased high-dimensional representations of tinnitus and further characterize the condition using dimensionality-reduction and density-based clustering. In *Aim #1*, we will develop and run an experimental paradigm in which tinnitus patients listen to noisy stimuli and perform an alternate forced-choice task answering the question, "Does this sound like your tinnitus?" Reverse correlation frees us from the methodological constraint of imposing strong *a priori* assumptions about the tinnitus percept. In *Aim #2*, we will develop an open-source signal processing pipeline to reconstruct cognitive representations of tinnitus using compressive sensing. Compressive sensing holds promise to dramatically reduce the number of samples needed for accurate reconstruction, enabling us to run more experimental subjects for Aim #1, and retest subjects to examine the stability of cognitive representations of tinnitus over time. *Aim #3* contextualizes reconstructed cognitive representations of tinnitus by visualizing underlying subtypes or clusters on a lower dimensional manifold. We will employ dimensionality reduction and clustering algorithms to represent and visualize the data, providing direct insight into commonalities and variability of tinnitus experience in and between subjects.

C. Aim #1: Uncover and reconstruct cognitive representations of tinnitus

In this aim, we will identify high-dimensional cognitive representations of tinnitus using reverse correlation. Current methods for estimating cognitive representations of tinnitus fall broadly into three primary categories, each of which has limitations (Table 2). One approach is to use forced-choice selection tasks. In this experimental paradigm, the experimenter presents participants with multiple samples of auditory stimuli that vary in well-characterized and often highly-constrained ways, along specific dimensions (*e.g.*, pure tone frequency, width of spectral envelope) that are known to be, or are hypothesized to be, relevant to tinnitus representation or masking [18, 7]. The subject then makes a choice between stimuli. While new methodological advances in experiment design and technology have streamlined this approach [11, 6, 8], it is still constrained by *a priori* assumptions about the nature of tinnitus percepts. In contrast, likeness approaches use subjective judgment tasks, in which the subject rates how much (if at all) a presented stimulus is part of or masks their tinnitus percept [15]. While likeness measures provide more complete reconstructions of tinnitus cognitive representations, likeness tests are time-consuming and generally not used in clinical practice [18].

The highly-constrained nature of stimuli used in the forced selection approach necessarily results in recovered representations that are correspondingly constrained and typically low-dimensional. It has long been known, however, that representations limited to only a few dimensions are insufficient to account for the full richness of tinnitus experiences [18, 7]. Subjective judgment experiments yield more informative reconstructions but are time-consuming to employ. The nature of subjective judgment approach is such that it is best suited to uncover relations between perceptual categories, rather than characterizing cognitive representations directly, and thus provides limited information about how perceptual similarity comes about. While some of the recovered dimensions along which stimuli differ in these tasks correlate with frequently assumed dimensions of representation (*e.g.*, frequency and pitch to mask tinnitus percept), some recovered dimensions of contrast have no known characterization. Moreover, this approach is fundamentally limited by the precise stimuli presented to participants, and therefore may not systematically explore the entire space of perceptually-meaningful variables.

A third, more recent approach to uncovering cognitive representations is to employ neuroimaging (*e.g.*, fMRI) to identify neural activation patterns indicative of tinnitus. In investigations of functional connectivity in tinnitus patients, resting-state fMRI measures were found to be replicable and reliable, though no explicit representations have been proposed [10]. This approach is also limited, in that it can only uncover representations that have a definite, localized seat in the brain. Cognitive representations, by contrast, are commonly understood to be constructs that need not have such a localized neural seat by definition, and which can best be revealed through analyzing behavior.

Approach	**Stimulus**	**Measurements**	**Output**
Forced selection	Constructed stimuli, constrained variation	Subjective choice	Representation with defined acoustic properties
Likeness measures	Constructed stimuli, constrained variation	Subjective ratings	Frequency spectra
Neural monitoring	N/A	Neural signals (*e.g.*, fMRI)	Correlation maps in localized brain regions, functional connectivity maps
Reverse Correlation	Constructed stimuli, unconstrained variation	Response classification (*e.g.*, present/absent)	Representations best explaining classification behavior

Table 2: Comparison of approaches for estimating cognitive representations. Each approach has benefits and limitations regarding stimuli, measurements, and output. The proposed approach, featured in the final row, is the only approach that can directly uncover a time-frequency map of the cognitive representation that best explains tinnitus percepts.

In a set of two experiments described below, we propose to implement a reverse correlation approach for recovering cognitive representations of speech which allows for unconstrained, direct characterization of latent representations from yes-no responses to randomly-generated stimuli. Participants will be asked to classify random auditory stimuli as containing or not containing their tinnitus percept. Latent representations that drive the top-down process can then be estimated by regressing observed responses against the stimuli over many trials [13].

Reverse correlation has been applied across multiple fields to reveal underlying representations by application of unconstrained, noisy input. Reverse correlation has been used to characterize low-level latent representations encapsulated in neural tuning (*e.g.,* receptive fields) [16] and has been used to successfully recover cognitive representations underlying visual perception [4] Both existing experimental work (*cf.,* Fig 2B in [2]) and our preliminary simulation experiments (FIGURE CITATION) suggest that this method can be successfully translated into the auditory domain. Reverse correlation allows us (1) to uncover more complex, potentially higher-dimensional representations than would be possible using more focused, constrained stimuli, (2) to recover directly the nature of the representations themselves rather than the relation between the tinnitus percept and a masking sound, and (3) to recover cognitive representations of the tinnitus percept directly rather than a neural correlate. In short, reverse correlation will be able to provide deeper understanding of cognitive representations of tinnitus percepts than is possible with conventional methods.

C.1. Method

The proposed method for uncovering perceptual representations can be divided into a sequence of three main parts: (1) construction of vague, "random" stimuli for presentation to subjects, (2) experimental procedure and data collection, and (3) reconstruction of perceptual representations from subject responses.

C.1.1. Stimuli Construction

Stimuli will be generated randomly, in keeping with prior work in the visual domain [4]. The meaning of "random" with respect to the stimuli presented to subjects refers specifically to the shape of spectral envelope in the frequency domain. This shape will be determined randomly for all stimuli and will not be informed by prior knowledge or statistics over canonical examples of tinnitus. These random spectral envelopes will be used as the basis for building spectrograms that sound like tinnitus percepts.

Our preliminary testing suggests that truly random envelopes often result in the perception of colored noise. Minimal additional spectral-temporal constraints may need to be imposed on stimuli such that participants will interpret the stimuli as intending to be tinnitus percepts. This is similar to the approach taken in some visual domain experiments, where bandlimited random stimuli, or stimuli with partial superimposed templates, are presented [17] (CITE).

What are we doing to create the stimuli?

C.1.2. Experimental Procedure

Where are we getting our subjects?
How are we evaluating tinnitus in our subjects?
How do we phrase what we want the subjects to do?

C.1.3. Reconstructing Representations

To reconstruct cognitive representations from subject responses, we will generate a classification spectrogram by taking the difference between a spectrogram generated from the positive labels (the "yes" responses) and a spectrogram generated from the negative labels (the "no" responses) (FIGURE CITATION). Such reconstructed representations are the best least-squares fit to the behavioral data [4]. We theorize that the classification spectrogram is used as a template vector against which stimuli were compared in a linear matching model of response generation.

C.2. Aim #2: Develop an efficient reconstruction algorithm for cognitive representations using compressive sensing

In this aim, we employ advanced signal processing techniques to overcome critical inefficiencies in reverse correlation that limit its scope and impact.

Current attempts to characterize perceptual mechanisms using reverse correlation are limited in scope due to inefficiencies inherent to conventional methods. While reverse correlation allows for relatively unconstrained and unbiased estimation of latent representations using straightforward stimulus-response data [12, 14], the number of stimulus-response samples required for accurate estimation is typically very large [13]. This inefficiency limits the feasibility of applying reverse correlation more broadly, as subject participation must be maintained over long timelines.

5. Progress Report Publication List (Renewal Applications Only)

List the titles and complete references to all appropriate publications, manuscripts accepted for publication, patents, and other printed materials that have resulted from the project since it was last reviewed competitively. When citing articles that fall under the Public Access Policy, were authored or co-authored by the applicant and arose from NIH support, provide the NIH Manuscript Submission reference number (e.g., NIHMS97531) or the Pubmed Central (PMC) reference number (e.g., PMCID234567) for each article. If the PMCID is not yet available because the Journal submits articles directly to PMC on behalf of their authors, indicate "PMC Journal – In Process." A list of these journals is posted at: http://publicaccess.nih.gov/submit_process_journals.htm.

Citations that are not covered by the Public Access Policy, but are publicly available in a free, online format may include URLs or PMCID numbers along with the full reference (note that copies of these publications are not accepted as appendix material, see Part I Section 5.5.15 for more information).

6. Protection of Human Subjects

Refer to Part II, Supplemental Instructions for Preparing the Human Subjects Section of the Research Plan.

This section is required for applicants answering "yes" to the question "Are human subjects involved?" on the R&R Other Project Information form. If the answer is "No" to the question but the proposed research involves human specimens and/or data from subjects applicants must provide a justification in this section for the claim that no human subjects are involved.

Do not use the protection of human subjects section to circumvent the page limits of the Research Strategy.

7. Inclusion of Women and Minorities

Refer to Part II, Supplemental Instructions for Preparing the Human Subjects Section of the Research Plan. This section is required for applicants answering "yes" to the question "Are human subjects involved?" on the R&R Other Project Information form and the research does not fall under Exemption 4.

9. Inclusion of Children

Refer to Supplemental Instructions for Preparing the Human Subjects Section of the Research Plan, Sections 4.4 and 5.7. For applicants answering "Yes" to the question "Are human subjects involved" on the R&R Other Project Information Form and the research does not fall under Section 4, this section is required.

10. Vertebrate Animals

If Vertebrate Animals are involved in the project, address each of the five points below. This section should be a concise, complete description of the animals and proposed procedures. While additional details may be included in the Research Strategy, the responses to the five required points below must be cohesive and include sufficient detail to allow evaluation by peer reviewers and NIH staff. If all or part of the proposed research involving vertebrate animals will take place at alternate sites (such as project/performance or collaborating site(s)), identify those sites and describe the activities at those locations. Although no specific page limitation applies to this section of the application, be succinct. Failure to address the following five points will result in the application being designated as incomplete and will be grounds for the PHS to defer the application from the peer review round. Alternatively, the applications impact/priority score may be negatively affected.

If the involvement of animals is indefinite, provide an explanation and indicate when it is anticipated that animals will be used. If an award is made, prior to the involvement of animals the grantee must submit to the NIH awarding office detailed information as required in points 1-5 above and verification of IACUC approval. If the grantee does not have an Animal Welfare Assurance then an appropriate Assurance will be required (See Part III, Section 2.2 Vertebrate Animals for more information). The five points are as follows:

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Strategy section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.

2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.

3. Provide information on the veterinary care of the animals involved.

4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.

5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the American Veterinary Medical Association (AVMA) Guidelines on Euthanasia. If not, include a scientific justification for not following the recommendations.

Do not use the vertebrate animal section to circumvent the page limits of the Research Strategy.

11. Select Agent Research

Select Agents are hazardous biological agents and toxins that have been identified by DHHS or USDA as having the potential to pose a severe threat to public health and safety, to animal and plant health, or to animal and plant products. CDC maintains a list of these agents. See http://www.cdc.gov/od/sap/docs/salist.pdf.

12. Multiple PD/PI Leadership Plan

For applications designating multiple PD/PIs, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PD/PIs and other collaborators.

If budget allocation is planned, the distribution of resources to specific components of the project or the individual PD/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote on the Notice of Grant Award.

13. Consortium/Contractual Arrangements

Explain the programmatic, fiscal, and administrative arrangements to be made between the applicant organization and the consortium organization(s). If consortium/contractual activities represent a significant portion of the overall project, explain why the applicant organization, rather than the ultimate performer of the activities, should be the grantee. The signature of the Authorized Organization Representative on the SF424 (R&R) cover component (Item 17) signifies that the applicant and all proposed consortium participants understand and agree to the following statement:

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.

15. Resource Sharing

NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of the research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. See Part III, 1.5 Sharing Research Resources.

1. Data Sharing Plan: Investigators seeking $500,000 or more in direct costs (exclusive of consortium F&A) in any year are expected to include a brief 1-paragraph description of how final research data will be shared, or explain why data-sharing is not possible. Specific Funding Opportunity Announcements may require that all applications include this information regardless of the dollar level. Applicants are encouraged to read the specific opportunity carefully and discuss their data-sharing plan with their program contact at the time they negotiate an agreement with the Institute/Center (IC) staff to accept assignment of their application. See Data-Sharing Policy or http://grants.nih.gov/grants/guide/notice- files/NOT-OD-03-032.html.

2. Sharing Model Organisms: Regardless of the amount requested, all applications where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms or state why such sharing is restricted or not possible. See Sharing Model Organisms Policy, and NIH Guide NOT-OD-04-042.

3. Genome Wide Association Studies (GWAS): Applicants seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or an appropriate explanation why submission to the repository is not possible. GWAS is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, NIH Guide NOT-OD-07-088, and http://grants.nih.gov/grants/gwas/.

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