
# Broad Agency Announcement

# Safe Genes

# BIOLOGICAL TECHNOLOGIES OFFICE

# DARPA-BAA-16-59

**September 15, 2016**

**TABLE OF CONTENTS**

# PART I: OVERVIEW INFORMATION

- **Federal Agency Name** – Defense Advanced Research Projects Agency (DARPA), Biological Technologies Office
- **Funding Opportunity Title –** Safe Genes
- **Announcement Type –** initial announcement
- **Funding Opportunity Number –** DARPA-BAA-16-59
- **Catalog of Federal Domestic Assistance Numbers (CFDA) – "12.910 Research and Technology Development"**
- **Dates**
  - Posting Date **September 15, 2016**
  - Proposal Abstract Due Date, **October 6, 2016**
  - Proposal Due Date, **November 17, 2016**
  - Any other relevant date(s) - **Proposers Day, September 30, 2016** https://fbo.gov/spg/ODA/DARPA/CMO/DARPA-SN-16-67/listing.html

- **Concise description of the funding opportunity:** The Safe Genes program will create biological capabilities that enable the safe pursuit of advanced genome editing applications and protect against potential engineered genetic threats.
- **Anticipated individual awards** - Multiple awards are anticipated.
- **Types of instruments that may be awarded** - Procurement contract, cooperative agreement, or other transaction.
- **Agency contact**
  - Points of Contact
    The BAA Coordinator for this effort may be reached at:
    SafeGenes@darpa.mil
    DARPA/BTO
    ATTN: DARPA-BAA-16-59
    675 North Randolph Street
    Arlington, VA 22203-2114

# PART II: FULL TEXT OF ANNOUNCEMENT

## 1. Funding Opportunity Description

The Defense Advanced Research Projects Agency often selects its research efforts through the Broad Agency Announcement (BAA) process. This BAA is being issued, and any resultant selection will be made, using procedures under Federal Acquisition Regulation (FAR) 35.016 and the Department of Defense Grant and Agreement Regulatory System (DoDGARS) Part 22 for Cooperative Agreements. Any negotiations and/or awards will use procedures under FAR 15.4, Contract Pricing, as specified in the BAA (including DoDGARS Part 22 for Cooperative Agreements). Proposals received as a result of this BAA shall be evaluated in accordance with evaluation criteria specified herein through a scientific review process.

DARPA BAAs are posted on the Federal Business Opportunities (FedBizOpps) website at https://www.fbo.gov and, as applicable, the Grants.gov website at http://www.grants.gov. The following information is for those wishing to respond to the BAA.

DARPA is soliciting innovative research proposals to generate and evaluate novel biological tools and countermeasures that facilitate the safe pursuit of advanced genome editing applications, while reducing the risk of, and providing new protections against potential engineered genetic threats. Proposed research should investigate radically different approaches to integrate biosafety and biosecurity features into new genome editing biotechnologies and their derivative applications (e.g., gene drives) at their inception. Implementation of a "safety first" approach to the development of gene editors and derivative tools will foster, and even accelerate, responsible innovation while mitigating the risk of unintended consequences.

### 1.1. PROGRAM OVERVIEW

DARPA's Safe Genes program will address the underlying need for transformative innovation in biosafety and biosecurity in the context of emergent genome editing tools and their derivative technologies, including gene drives (self-perpetuating gene editing systems that bias inheritance in populations through sexual reproduction). The program will deliver novel biological capabilities to facilitate the safe and expedient pursuit of advanced genome editing applications while also providing the tools and methodologies to mitigate the risk of unintentional consequences or intentional misuse of these technologies. The Safe Genes program will support the development of the tools, methodologies, and foundational knowledge that are prerequisite for the safe application of advanced gene editing technologies beyond a research and laboratory setting.

The emergence of advanced genome editing tools has created the ability to modify genetic material in a manner that is precise, rapid, cost-effective, and broadly accessible. CRISPR-Cas represents the newest and most widely adopted tool in the genome engineering toolkit, which already consists of a diverse set of molecules including mega nucleases, transposons, recombinases, protein nucleic acids, zinc-finger nucleases, and TAL (transcription activator-like) effector nucleases. These editing tools have not only enabled significant advancements in genetic

research, including manipulation of previously inaccessible genomes, but have also set the groundwork for transformative applications.

In order to realize the full potential of genome editing and derivative technologies, new tools and methodologies to safely control activities, limit off-target effects, and reverse unwanted outcomes of these technologies is desirable. In the case of nuclease-based tools, the efficiency of target site modification and the resulting "edited" sequences can vary significantly based on target sequence, location in the genome, and how the intrinsic cellular repair processes resolve the consequent DNA breaks for a given editing event. In addition, the introduction of DNA breaks elsewhere in the genome beyond the intended target site (off-target activity) can exceed on-target modifications[1], posing a significant threat to safety and health of the host organism. New strategies to improve the efficiency, specificity, and overall predictability of gene editing systems have been encouraging[2,3,4]; however, significant gaps remain before these tools can be applied for practical use.

The need for advancement in the safe application of gene drive technologies is particularly urgent given their potential for significant and immediate impact in the field of biological technology. Standard approaches and best practices to prevent release of genetically engineered organisms from the laboratory[5,6] may not be sufficient for the investigation of gene drive organisms. Strategies that include stringent physical biocontainment and ecological confinement have been proposed to move forward with responsible innovation and experimental investigation of these tools. As the adoption of current genome editing tools expands to more scientists with varying levels of technical expertise, infrastructural resources, legal and ethical oversight, and intentions, the risks of genetic threats stemming from potential misuse, either accidental or intentional, of these technologies increase. To date, the state of the art in biosecurity and biosafety cannot sufficiently protect against these potential threats.

To bridge the gap between the current technological landscape and the future transformative applications of genome editing tools and engineered organisms, the Safe Genes program seeks research proposals that will lay the foundation for a set of layered, modular, and adaptable solutions to address the broadest range of emergent opportunities and future biodefense capabilities. First, proposers will be asked to design and develop the genetic circuitry and genome editing machinery for robust spatial, temporal, and reversible control of genome editing activity in living systems. Second, small molecules and/or strategies to provide prophylactic and treatment solutions that prevent or limit genome editing activity and protect the genome integrity of organisms and populations will be developed. Finally, proposers should develop "genetic

---

[1] Tsai *et al*., GUIDE-seq enables genome-wide profiling of off-target cleavage by CRISPR-Cas nucleases. *Nat. Biotechnol.* 2015 Feb;33(2):187-97.

[2] Ran *et al*., Double nicking by RNA-guided CRISPR Cas9 for enhanced genome editing specificity. *Cell*. 2013 Sep 12;154(6):1380-9.

[3] Shen *et al*., Efficient genome modification by CRISPR-Cas9 nickase with minimal off-target effects. *Nat Methods*. 2014 Apr;11(4):399-402.

[4] Komor *et al*., Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature*. 2016 Apr 20;533(7603):420-4.

[5] National Institutes of Health. *NIH Guidelines on Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*. Bethesda, MD; 2016.

[6] ASTMH (American Society of Tropical Medicine and Hygiene). Arthropod Containment Levels (ACLs). *Vector-borne and Zoonotic Diseases*. Vol. 3. 2 Nov 2003.

remediation" strategies that eliminate unwanted engineered genes from a broad range of complex population and environmental contexts to restore systems to functional and genetic baseline state. Overall success in these endeavors will create a foundation for translational applications of genome editing technologies while protecting against intentional or accidental misuse of these tools.

## 1.2. TECHNICAL OBJECTIVES AND PROGRAM STRUCTURE

Safe Genes will encompass a four year effort organized in two phases of two years duration each. During Phase I, performer teams will establish the fundamental tools and *in vitro* and *in vivo* proofs-of-concept for their selected Technical Area(s). The Phase II period will focus on *in vivo* and *in situ* demonstration of efficacy, safety, specificity, and stability of the selected tools and methodologies. Intermediate and end-of-phase milestones, outlined in this BAA, will be required in each phase to evaluate progress throughout the program. Quantitative metrics to assess technical performance towards milestones will be established by the proposer and agreed upon by DARPA (see Section 1.4 for details). In addition, all proposers are expected to implement and adhere to strict biosafety and biocontainment measures, described below (see Section 1.5 General Requirements).

The program consists of three Technical Areas (TAs) to be addressed concurrently:

- TA1: control of genome editing activity
- TA2: countermeasures and prophylaxis
- TA3: genetic remediation

The objective of TA1, control of genome editing activity, is to design and develop the genetic circuitry and genome editing machinery that will provide robust spatial, temporal, and reversible control of genome editing activity in living systems. The objective of TA2, countermeasures and prophylaxis, is to develop new small molecule and molecular strategies that provide prophylaxis and treatment solutions to prevent or limit genome editing activity and protect the genome integrity of organisms and populations of organisms. The objective of TA3, genetic remediation, is to create a capability to eliminate unwanted engineered genes from a broad range of complex populations of organisms and environmental contexts to restore systems to a functional and genetic baseline state.

Proposers may address one, two, or three TAs (see exception for gene drives below) and must meet key milestone decision points throughout the period of performance. In order to facilitate the potential for a layered safeguard approach, proposers that choose to address multiple TAs should select a single DARPA-relevant application that remains consistent throughout their proposal to ensure the most cohesive and impactful program outcome. Examples of DARPA-relevant applications may include, but are not limited to, vector control strategies to mitigate infectious disease, strategies to maintain and protect ecosystem biodiversity, or novel cellular therapeutics to promote host defenses or combat disease.

Proposers that pursue gene drive technologies (or any other self-perpetuating gene editing technology that may bias the outcome of reproductive inheritance) must address TA1 and at least one additional TA:

*Proposers *not* pursuing gene drive technologies:*

- Any Technical Area(s): TA1, TA2, and/or TA3

*Proposers pursuing gene drive technologies:*

- TA1 and either TA2 or TA3
  *or*
- All Technical Areas: TA1, TA2, and TA3

The deliverables from TA2 and/or TA3 must provide novel solutions to counter the gene drive technology and associated gene editor(s) and/or outcomes that result from the gene drive tool developed under TA1. Gene drive proposals that do not address TA1 and at least one additional TA (TA2 and/or TA3) will not be considered for funding.

### 1.3. TECHNICAL AREAS

### TA1: CONTROL OF GENOME EDITING ACTIVITY

Proposals to TA1 should focus on the development of high-fidelity gene editing systems that are spatially, temporally, and reversibly controllable. Genome editing activity here and throughout the Safe Genes program is defined broadly, extending beyond nuclease activities (e.g., may also include epigenetic modifiers, non-DNA-cutting repression and activation approaches, etc.) and beyond a single editor type (e.g., CRISPR-Cas). Depending on the proposer-defined end application selected, temporal and spatial control may also be broadly defined. For example, temporal and spatial control for a cellular therapeutic application may be defined on the timescale of seconds to minutes and in the spatial context of cell or tissue type, whereas temporal and spatial control for a gene drive vector control application may be defined as number of generations and geographic isolation. Proposers must clearly articulate the target temporal and spatial control parameters and quantitative performance metrics they aim to achieve that is consistent with the DARPA-relevant application of their choosing and represents a significant improvement over the state of the art.

Proposers must focus on a DARPA-relevant application of their choosing (see examples above in Section 1.2). Proposers should justify their choice of application, gene editor(s), and target organisms using data, models, and appropriate technical rationale based on:

1. likelihood for successful *in vivo* and/or *in situ* implementation of genome editing controller systems
2. ability to function in a variety of cellular and genetic contexts without interfering with endogenous host cellular processes and genetic circuitry
3. utility as a platform capability/generalizability
4. ability to test and evaluate in a suitable *in vitro*/*in vivo*/*in situ* model
5. assessment and mitigation of risk for intended *in vivo* and/or *in situ* use

6. likelihood for adoption and potential for disruptive impact in a given field
7. definition of quantitative performance metrics for efficacy, specificity, safety, and stability to support significant advancement beyond the state of the art and support successful demonstration of selected DARPA-relevant application

**Phase I (24 months): Identification and initial testing of controllers of genome editing activity**

Phase I should yield high-fidelity, temporally- and spatially-controllable genome editing systems that function reliably *in vivo*. Proposers may address control at the level of the genetic and molecular circuitry, at the level of gene editor design, or both (collectively termed "genome editing controllers" or "controllers" henceforth).

Proposers should first generate and test genome editing controllers that enable temporal and spatial control of editing activity *in vitro* (e.g., in cell culture) or at a small scale *in vivo*, if appropriate. Controllers should enable a genome editing construct to be activated as desired, inactivated following genome editing, and, as appropriate, removed from the system (e.g., self-limiting and/or self-extracting systems) to prevent further genome editing and eliminate the potential for unwanted persistence of the engineered construct in a given clinical or environmental context. Proposers should then perform *in vivo* or small cage trial in proof-of-concept experiments with relevant model organisms to generate initial data on controller function.

It is anticipated that proposers will utilize mathematical models and high throughput screening techniques to identify, design, and optimize functional genetic and molecular control circuitry and genome editors in an iterative manner. Design and optimization strategies must maximize editing efficiency, specificity, stability, safety, and reversibility to support eventual use *in vivo* and, if applicable, in contained environmental testing. Proposers may develop new methodologies and assays in support of characterizing genome editing controller efficacy and failure modes. Potential failure modes should be identified with proposer-defined characterization and mitigation plans. Some examples of potential failure modes may include, but are not limited to: off-target editing; unsuccessful activation, inactivation, or removal of a construct; lack of temporal or spatial control; etc. *In silico* models should support the genome editing controller design, build, and test process and help optimize *in vitro/in vivo/in situ* performance. Modeling and simulation results should complement experimental investigation that quantifies the genome editing system efficacy and characterizes both on-target and off-target system activities.

By the end of Phase I performers are expected to:

- Identify, test, and achieve basic demonstration (e.g., *in vitro* or small organism population cage testing) of candidate genome editing controllers that enable temporal and spatial control of genome editing activity that are:
    - Effective – e.g., meet user-defined on/off target kinetics for temporal control

  - Specific – e.g., exhibit user-defined activities only in target cells and tissues and only at target genetic loci; off-target activity below level of detection
  - Stable – e.g., perform effectively without deterioration over time or through generations
  - Safe – e g., reduce risk to a reasonable level that minimizes toxicity, immunogenicity; construct is reversible, self-limiting/self-extracting when no longer needed
- Achieve *in vivo* or small population demonstration of genome editing controllers that enable temporal and spatial control of genome editing activity (to include activation, editing of target locus or loci, and inactivation and/or removal) that is effective, specific, stable, and safe in the context of a proposer-defined DARPA-relevant application
- Demonstrate understanding of genome editing controller mechanisms, and failure modes (e.g., off-target activity, repair mechanisms, fitness deficits, mutation, etc), and establish plan to mitigate identified risks

**Phase II (24 months): Safety and efficacy testing of genome editing controllers**

Phase II efforts should pursue testing and characterization of genome editing controllers that were developed during Phase I in order to demonstrate effective, specific, and stable control in increasingly more complex and larger scale systems *in vivo* and/or *in situ* ((i.e. in populations of organisms and/or contained simulated natural environments). Function in these contexts should meet user-defined quantitative performance goals for on/off target effects and tunable spatial (e.g., tissue or cell specificity) and temporal control of a genome editing system that are relevant to the proposed end application. Proposers should characterize undesired outcomes or "failure modes" of genome editing controllers. For example, for *in situ* testing of a gene drive, failure mode characterization may include, but not be limited to, measurement of gene flow to other species in a contained environment, measurement of mutations at the target site that are recalcitrant to further genome editing, and assessment of stability of the genome editing controllers through multiple generations in a simulated natural environment.

In this phase, proposers should also assess the long-term stability of the genome editing controllers *in vivo* and/or *in situ*. Proposers must investigate whether (and how) genome editing controller performance deteriorates over time and determine the number of generations for which target editing efficiency of one or more specific loci can be maintained, while minimizing performance-limiting off-target activity. Proposers should identify any toxicological, immunological, or unintended effects on non-target cells, organs, tissues, or organisms. Any inefficiencies or deviations from optimal performance should also be used to inform and improve *in silico* models, iteratively optimize the design of the genome editing system, and limit detrimental impact to host system and environment, as appropriate. Proposers should utilize all efficacy, specificity, stability, and safety data obtained in TA1 to assess the risk associated with potential downstream applications of genome editing controllers either *in vivo* or *in situ* and develop appropriate risk mitigation strategies and/or novel risk assessment models.

By the end of Phase II performers are expected to:

- Achieve *in vivo* (or contained population) demonstration of candidate genome editing controllers that enable temporal and spatial control of genome editing activity that meet rigorous proposer-defined quantitative performance metrics for efficacy, specificity, stability, and safety (see examples for Phase I above)
- Identify, characterize, and mitigate, where possible, any failure modes when the genome editing system is utilized *in vivo* or *in situ*.
- Demonstrate the long-term stability and maintenance of high level of efficacy of the genome editing system after multiple generations
- Identify, characterize, and mitigate where possible, any toxicological, immunological, or unintended effects in utilizing the genome editing system
- Demonstrate that the genome editing system can be broadly applicable or generalizable through a demonstration of activity in at least one additional cell type, tissue, organ, or species, and/or control of at least one additional genome editing system

**TA2: COUNTERMEASURES AND PROPHYLAXIS**

Proposals to TA2 should focus on the development of small molecules and/or molecular strategies to provide prophylactic and treatment solutions to prevent or limit genome editing activity and protect the genome integrity of organisms and populations in a proposer-defined DARPA-relevant application. Phase I (24 months) will focus on discovery, identification and initial testing of countermeasures and prophylaxes against genome editing activity. Phase II (24 months) will focus on selecting top candidates and thoroughly characterizing *in vivo* safety and efficacy in a model organism consistent with the end application. Proposals must specify intermediate and final technical milestones and quantitative performance metrics (at a minimum every six (6) months) that demonstrate progress towards the overall goals of each phase. Proposals must provide detailed descriptions of their scientific and technical approaches in achieving technical milestones.

Proposers will focus on a DARPA-relevant application of their choosing (see Section 1.2) and must justify their countermeasure development strategy using data, models, and appropriate technical rationale, based on:

1. likelihood for successful prophylactic and therapeutic *in vivo* applications
2. ability to specifically inhibit genome editing activity
3. efficacy against more than one class of genome editor through common mechanism of action
4. efficacy of countermeasure in more than one species
5. assessment and mitigation of risk for intended *in vivo* or potential *in situ* use
6. definition of quantitative performance metrics for efficacy, specificity, safety, and stability to support significant advancement beyond the state of the art and support successful demonstration of selected DARPA-relevant application

**Phase I (24 months): Discovery and initial testing of genome editor countermeasures**

Phase I efforts should establish small molecule or molecular strategies capable of inhibiting genome editing activity *in vitro* and *in vivo* in a relevant model organism (e.g., mouse or insect). Proposers will identify inhibitors of genome editing activity *in vitro*. Proposers are encouraged to consider varying types of potential inhibitors (e.g., small molecules, antibodies, interfering RNAs, etc.). Each inhibitor, regardless of type, should exhibit key characteristics introduced in a proposer-defined DARPA-relevant application, including: specific inhibitory efficacy, generalizability, stability, and efficiency of delivery to targets for for downstream *in vivo* and/or *in situ* applications (e.g., population- or environmental-level genome editing activity inhibition). Generalizable inhibitors are defined as those that are capable of inhibiting multiple classes of gene editors in multiple species. Proposers should provide clearly articulated parameters and performance metrics to address each characteristic in order to meet the primary Phase I goal of demonstrating inhibition of genome editing activity.

Each inhibitor must be able to function either prophylactically to prevent and/or therapeutically to halt genome editing activity. Inhibitors should be characterized for their on-target specificity as well as off-target effects. In addition to considering multiple types of inhibitors that meet these criteria, proposers are encouraged to consider optimizations or modifications to inhibitors for improvements in characteristics including, but not limited to, inhibitory function, generalizability, and stability for downstream *in vivo* and/or *in situ* applications.

Top candidates must then be transitioned from *in vitro* testing systems to *in vivo* (e.g., animal or insect models) and/or *in situ* proof-of-concept experiments. Proposers must challenge a minimum of two classes of genome editing systems, with each top candidate *in vivo* to demonstrate the ability to serve as a prophylactic, therapeutic, or both. Inhibitors should be delivered to *in vivo* systems via a proposer-defined delivery system including, but not limited to, exogenous application, systemic or oral delivery, or nucleic acid based methodology. However, proposers are also encouraged to consider improving or developing novel *in vivo* delivery methods to optimize overall inhibitor efficacy. Proposer-defined parameters and performance metrics for prophylactic/therapeutic inhibitor delivery and efficacy should address and characterize the preliminary pharmacokinetic and pharmacodynamics (PK/PD) profiles of the selected inhibitors.

By the end of Phase I performers are expected to:

- Demonstrate inhibitors of genome editing activity *in vitro* that are:
    - Effective – e.g., enable the suppression of genome editing activity
    - Specific – e.g., does not interfere with normal cellular processes
    - Safe – e.g., non-toxic, non-immunogenic
- Achieve *in vivo* proof of concept that candidate inhibitors can inhibit genome editing activity in model systems
- Characterize the preliminary PK/PD profiles of *in vivo* inhibitors

**Phase II (24 months): *In vivo* safety and efficacy testing of genome editor countermeasures**

Phase II efforts must pursue *in vivo* validation and characterization of genome editing activity inhibitors in systems with increasing scale and complexity in order to establish top candidate inhibitors as first-in-class countermeasures against genome editing able to be used prophylactically or therapeutically with maximal efficacy in a proposer-defined DARPA-relevant model. In this phase, proposers will determine the suitability of *in vivo* and/or *in situ* application of inhibitors by thoroughly characterizing the safety and efficacy of genome editor activity suppression *in vivo* and *in situ*.

Proposers must select top candidate *in vivo* inhibitors from Phase I model organism studies that demonstrate specific inhibition of genome editing activity, specificity to target, generalizability, and optimal PK/PD profiles. Proposers must then characterize the safety of inhibitors when applied *in vivo*. Inhibitor function must remain effective *in vivo*, therefore proposers should validate the delivery of inhibitors to target cells, tissues, organs, or organisms with minimal off-target effects. Inhibitors should exhibit minimal toxicity and immune reactivity, should not cause permanent alterations to the host, or display other adverse effects in the proposer-defined models.

By the end of Phase II performers are expected to:

- Demonstrate *in vivo* that top candidate inhibitors of genome editing activity are:
    - Effective - e.g., enable suppression of genome editing activity *in vivo* both prophylactically and therapeutically in a proposer-defined DARPA-relevant model organism/system
    - Safe - e.g., no toxicity or adverse response in the proposer-defined model organism/system at efficacious doses/modes of delivery
    - Specific - e.g., targets proposer-defined genome editors and cell type with minimal off-target effects
    - Efficiently delivered - e.g., ensure inhibitors exhibit optimal PK/PD profiles and are able to achieve appropriate localization/concentration for optimal prophylactic and/or therapeutic efficacy
    - Generalizable - e.g., inhibit more than one class of genome editor in more than one species

**TA3: GENETIC REMEDIATION**

Proposals to TA3 should focus on the development of "genetic remediation" strategies that eliminate unwanted engineered genes from a broad range of complex population and environmental contexts to restore systems to functional and genetic baseline state. DARPA recognizes that the capability to remediate genes from environments is a platform capability that can address both engineered and natural genes; however, for this program proposers should only focus on engineered genes. In both phases of TA3, proposers will characterize how genetic remediation strategies affect a target organism population of a proposer-defined DARPA relevant model organism, including population structure of the target organism, gene flow from

targeted organism to non-target organisms or related species, etc. Proposers may develop new methodologies and assays in support of establishing baseline measurements for the systems that will be investigated. Investigations conducted under TA3 are intended to provide foundational data, knowledge and tools for genetic remediation. As such, strategies proposed for TA3 may strictly only consider genetic remediation in a contained environment. Proposals must specify intermediate and final technical milestones and metrics that demonstrate progress towards the overall goals of each phase. Proposals must provide detailed descriptions of their scientific and technical approaches in achieving technical milestones.

Proposers will focus on a DARPA-relevant genetic remediation application of their choosing and must justify their choice using data, models, and appropriate technical rationale based on:

1. likelihood for successful *in vivo* and/or *in situ* application at an organism population or environment level
2. stability of genetic remediation strategy for multiple generations
3. specificity of tool to target engineered genes and organisms
4. effective elimination of target gene activity
5. assessment and mitigation of risk for intended *in vivo* or *in situ* use
6. ability to restore baseline (non-engineered) phenotype and genotype
7. robustness of tool in a contained simulated *in situ* demonstration

**Phase I (24 months): Discovery and initial testing of genetic remediation strategies**

Phase I efforts should establish and validate molecular constructs and strategies are capable of genetic remediation, as defined above. Depending on the proposer-defined DARPA-relevant application, the removal or replacement of engineered genes in a population may be defined broadly. For example, unwanted engineered genes (e.g., gene drives, engineered antibiotic resistance genes) in a population of organisms may be functionally removed from the environment through excision or permanently repressed through long-lasting chromatin-based silencing. Remediation tools that are self-limiting or self-extracting and dependent on a proposer-defined duration of time, molecular stimulus, or other trigger are encouraged. Alternatively, engineered genes may be targeted for removal or replacement through mating with engineered organisms, viral delivery, or other means. Genetic remediation should ultimately result in a return to a proposer-defined baseline state, which should include the permanent reconstitution of a phenotypic (required), and genotypic (aspirational), wild-type state Proposers must clearly articulate the parameters they aim to achieve through genetic remediation that are consistent with the DARPA-relevant application of their choosing and represent a substantial improvement over the state of the art.

Proposers must first design and build systems for high-efficiency genetic remediation through discovery of strategies and components that enable efficient, targeted genetic remediation. Top candidate genetic remediation systems obtained from the testing should be transitioned to small scale experiments (i.e. benchtop or small cage) for characterization of population dynamics, gene flow, efficacy, failure modes (as defined in TA1), control, etc. Small scale experiments should aim to recapitulate environmental conditions as reasonably feasible (e.g. temperature, humidity,

mating patterns). Proposers should establish mathematical models to simulate the behavior of top candidates in genetically remediating populations of engineered organisms. *In silico* modeling and simulation results should complement experimental data from small scale experiments. It is anticipated that proposers will iteratively improve and optimize the efficacy of top candidate genetic remediation strategies. *In silico* models should support the prediction of genetic remediation efficacy, failure modes, and stability in increasingly large scale experiments. For each strategy, proposers should consider the risks associated with implementing genetic remediation in open field trials and determine possible methods for mitigation.

By the end of Phase I performers will have been expected to:

- Identify and test candidate genetic remediation strategies that enable the removal or replacement of an engineered gene from a population of organisms, such that the strategies are:
    - Effective – e.g., removes or replaces engineered genes in a target organism population and outpaces target gene spread.
    - Specific – e.g., acts only on target organism and avoids related species or strains
    - Safe – e.g., reduction of risk to the environment and other organisms to a reasonable level that minimizes toxicity, immunogenicity; construct is reversible, self-limiting/self-extracting when no longer needed
    - Stable – e.g., able to persist for a prosper-defined number of generations without reduction in efficacy or increase in failure modes
- Achieve small population-scale demonstration of genetic remediation that exhibit the efficacy, specificity, safety, and stability of the strategies
- Demonstrate understanding of genetic remediation mechanisms, failure modes, population dynamics, and potential risks
- Demonstrate ability of optimized in silico models to predict efficacy of genetic remediation strategies developed

**Phase II (24 months): Large scale and stability testing of genetic remediation strategies**

Phase II efforts should focus on scaling genetic remediation strategies to large, fully-contained cage and simulated environment trials, thoroughly characterizing the outcomes of genetic remediation, and further optimizing *in silico* models of genetic remediation in populations. In scaling genetic remediation experiments to large, fully-contained trials, proposers should aim to determine the efficacy and effects of larger population numbers and variables. For example, larger, fully-contained cages of engineered gene drive *Anopheles gambiae* may allow for co-habitation and crossbreeding with related species or strains in order to determine whether gene drives and constituent engineered genes can be inherited by hybrid progeny and whether genetic remediation can retain efficacy in this context. This increase in experimental complexity should allow for proposers to provide a more thorough characterization of a given genetic remediation strategy. Proposers should aim to expand on data generated in Phase I including: efficiency,

failure modes, and population dynamics. If applicable, the effects on co-habiting organisms should also be characterized.

In addition to increasing scale of population numbers and environmental variables, proposers must determine the pace of spread and the stability of genetic remediation strategies over time. Proposers should determine the temporal parameters within which effective target remediation can be maintained. Proposers must demonstrate stable remediation strategies that are robust, can persist to effectively act on a target organism population to achieve a desired effect, and subsequently remove or otherwise inactivate genetic remediation tools when no longer required. Experimental characterization should be utilized to further optimize *in silico* models developed in Phase I. Inclusion of data obtained with the introduction of additional environmental variables and increase in population sizes should result in *in silico* models which would more accurately predict the performance of genetic remediation strategies in open field trials.

By the end of Phase II performers are expected to:

- Demonstrate genetic remediation strategies can be utilized in increasingly complex environments while remaining:
    - Effective – e.g., removes or replaces a user-defined proportion of engineered genes in a population of engineered organisms in a large, fully contained cage trial or simulated natural environment
    - Specific – e.g., acts only on target organism and avoids related species or strains
    - Safe – e.g., reduction of risk to the environment and other organisms to a reasonable level that minimizes toxicity, immunogenicity; construct is reversible, self-limiting/self-extracting when no longer needed
    - Stable – e.g., efficacy is maintained over multiple generations

- Identify and characterize all the outcomes of genetic remediation, including failure modes, divergences from expected population dynamics, risks, etc
- Demonstrate any toxological, immunological, or other unintended effects can be mitigated
- Demonstrate the utility of *in silico* models for the prediction of performance of genetic remediation tools in fully-contained cage trials and simulated natural environments

### 1.4. PROGRAM METRICS AND MILESTONES

In order for the Government to evaluate the effectiveness of a proposed solution in achieving the stated program objectives, proposers are required to define specific and quantitative performance metrics for each task and subtask in support of the selected technical approach. Anticipated program milestones are specified below, however, proposers should note that the Government has identified these milestones with the intention of bounding the scope of effort, while affording the maximum flexibility, creativity, and innovation in proposing solutions to the stated problem.

Quantitative performance metrics will vary for each proposer-selected application and system. Proposers to the Safe Genes program are required to define ambitious, specific, and quantitative

metrics in support of program goals, including intermediate metrics (e.g., every 6 months, or sooner) to help further evaluate progress. Some exemplary milestones are included below for proposers to consider, but are not meant to be prescriptive. Final metrics are to be determined at time of award negotiation and are subject to DARPA approval. Proposers should note that program metrics that may serve as the basis for determining whether satisfactory progress is being made to warrant continued funding of the program.

<table>
<tr><th colspan="3">TA1: Control of genome editing activity</th></tr>
<tr><th>Phase</th><th>Milestones and Deliverables</th><th>Program Metrics</th></tr>
<tr><td>I</td><td>• Establish candidate genome editing controllers<br>• Test genome editing controllers for activity control using functional in vitro or benchtop assays<br>• Down-select top designs to assess for in vivo and/or small population proof-of-concept<br>• Demonstrate genome editing controllers that exhibit the following characteristics, in vivo and/or in populations of organisms (e.g., small cage):<br>  • high targeting efficiency<br>  • temporal and spatial control<br>  • limited off-target effects and failure modes<br>  • stability over time<br>  • safety during application<br>  • reversibility<br>• Characterize and quantify system failure modes in vivo and establish methods and tools to mitigate failure risk</td><td>• Initial in vitro and in vivo measures of :<br>o Efficacy – proposer-defined level of genome editor spatial/temporal control and target editing efficiency supportive of end application (e.g., ≥98% target editing efficiency only upon gene editor activation in cell of choice)<br>o Specificity – quantitative performance metrics will vary for each selected application. For example, off-target mutations should not exceed natural mutation rate (e.g., $1\times10^{-9}$ mutations/bp/generation for insects and $2\times10^{-8}$ for mammalian cells)<br>o Stability – genome editing controller does not degrade over time (e.g., N generations, where N is the duration of continuous propagation)<br>o Safety – genome editing controller exhibits no toxicity or immunogenicity and is reversible (e.g., genome editing controller is self-limiting/self-extracting (e.g., ≥98% of genome editor coding sequences removed following induced extraction))</td></tr>
<tr><td>II</td><td>• Initiate in vivo and/or in situ (simulated natural environment) testing to include characterization of spatial and temporal control, off-target effects, failure modes, target editing efficiency, and stability<br>• Establish baseline system measurements<br>• Demonstrate genome editing controllers that exhibit the following characteristics, in vivo and/or in large populations of organisms and complex environments (i.e., simulated natural environments):<br>  • high targeting efficiency<br>  • temporal and spatial control<br>  • limited off-target effects and failure modes<br>  • stability over time<br>  • safety during application</td><td>• Quantitative measures of in vivo and/or in situ genome editor controller efficacy, specificity, stability, and safety as defined above</td></tr>
</table>

| | | |
|---|---|---|
| | • reversibility<br>• Demonstrate genome editing controllers that are broadly applicable or generalizable in at least one additional cell type, tissue, organ, or species, and/or control of at least one additional genome editing system | |

| **TA2: Countermeasures and prophylaxis** | | |
|---|---|---|
| **Phase** | **Milestones and Deliverables** | **Program Metrics** |
| I | • Initiate discovery and testing of molecules and *in vitro* assays to test genome editor inhibition<br>• Demonstrate inhibitors of genome editing activity *in vitro* that are:<br>  • effective<br>  • specific<br>  • safe<br>• Select top candidates that inhibit genome editor activity for *in vivo* testing<br>• Demonstrate proof of concept that candidate inhibitors can inhibit genome editing activity *in vivo* in model systems<br>• Characterize the preliminary PK/PD profiles of *in vivo* inhibitors | • Initial *in vitro* and *in vivo* quantitative measures of efficacy, specificity, and safety<br>• Initial quantitative measures of PK/PD *in vivo* (e.g., concentrations of inhibitor isolated in non-target organs such as the spleen) |
| II | • Determine safety and efficacy of candidates *in vivo*.<br>• Characterize off-target effects.<br>• Select final, optimized candidates that exhibit effective suppression of genome editor activity *in vivo*. | • Quantitative measures of *in vivo*:<br>  o **Efficacy** – proposer-defined level of inhibition of genome editing activity (e.g., ≥98% inhibition of genome editor in cell line of choice)<br>  o **Specificity** – inhibition of only proposer-defined genome editors (e.g., transcriptomic analysis showing no fold difference in cellular processes in response to presence of therapeutic or prophylactic concentrations of inhibitors)<br>  o **Safety** – inhibitors exhibit no toxicity or immunogenicity (e.g., do not illicit a host immune response)<br>  o **Efficient delivery** – optimal PK/PD profile for ensuring target cell localization of inhibitors<br>  o **Generalizability** – proposer-defined level of inhibition of more than one genome editor in more than one species<br>• Identification, characterization, and quantitative measure *in vivo* or *in situ* of off-target effects and failure modes |

| **TA3: Genetic remediation** | | |
|---|---|---|
| **Phase** | **Milestones and Deliverables** | **Program Metrics** |
| I | • Identify and test candidate genetic remediation strategies that enable the removal or replacement of an engineered gene from a population of organisms<br>• Establish preliminary *in silico* models simulating genetic remediation efficacy and demonstrate ability to predict efficacy of genetic remediation strategies developed<br>• Demonstrate understanding of genetic remediation mechanisms, failure modes, population dynamics, and potential risks<br>• Demonstrate ability to revert or eliminate target engineered genes in small contained populations using transgenic or molecular strategies | • Initial benchtop or small cage quantitative measures of:<br>o **Efficacy** – removes or replaces engineered gened in a population and outpaces target gene spread (e.g., ≥98% target gene removal or replacement in a benchtop experiment)<br>o **Specificity** – acts only on target organism and avoids gene flow to non-target species (e.g., does not spread to related species via mating, horizontal gene transfer, etc.)<br>o **Stability** – genetic remediation strategy does not reduce efficacy over duration of time (e.g., *N* generations, where *N* is the duration of continuous propagation)<br>o **Safety** – genetic remediation strategy exhibits no toxicity or immunogenicity or is self-limiting (e.g., molecular constructs enabling remediation excises from ≥98% of organisms following function)<br>• Identification, characterization, and quantitative measure of off-target effects and failure modes |
| II | • Demonstrate ability to revert or eliminate target genes in a large, contained, simulated natural environment<br>• Characterize population dynamics, population structure, gene flow, fitness, generational stability, and failure modes Establish *in silico* models to predict the ability to remediate engineered genes in a simulated natural environment | • Quantitative measures of genetic remediation strategyefficacy, specificity, stability, and satety *in vivo* or in a simulated natural environment as above<br>• Identification, characterization, and quantitative measure of failure modes, population dynamics, population structure, gene flow, fitness, and generational stability |

## 1.5. GENERAL REQUIREMENTS

Regardless of the specific approach, application, and Technical Area(s) pursued, proposers to the Safe Genes program must address each of the following:

### Data Sharing

DARPA anticipates that a large amount of data will be generated under this program by each performer and that data analysis will be strengthened by compiling and integrating information across all performers. Therefore, proposals must include the description of a plan to share data with teams both internally to the Safe Genes performer group and externally with the broader research community, including approximate timelines for release of data. Data sharing plans to facilitate sharing and exchange of data will then be formalized in an Associate Contractor Agreement (ACA), to be included in the contract or agreement awarded.

**Biocontainment and Biosafety**

DARPA anticipates that large, physically contained cage trials of engineered organisms may be appropriate for some of the experimental demonstrations of Safe Genes capabilities. Such trials should only be undertaken when they are necessary to demonstrate the efficacy and stability of gene editing and gene drive tools and countermeasures and after laboratory and computer modeling experiments have shown promising results, but are no longer adequate to advance the science. However, this program will not support any proposals that include uncontained environmental release of such organisms.

Proposers must ensure and demonstrate throughout the program that all methods and demonstrations of capability comply with national guidance for manipulation of genes and organisms and follow all guidance for biological safety and biosecurity, including compliance with the NIH Guidelines, Arthropod Containment Guidelines (if applicable), and the Biological Weapons Convention. Proposers may also consider, if applicable, recent guidance and recommendations for the responsible development of gene drive technologies [7,8,9]. Proposals should address any potential biosafety, biosecurity, and/or biocontainment issues that the development of the proposed tools/capabilities might pose and include a discussion of approaches and strategies to manage, mitigate and monitor these risks during technology development. In addition, all proposed efforts must meet any applicable regulations designed to protect human health and the environment promulgated by the Environmental Protection Agency, the Food and Drug Administration, the Department of Agriculture, and any other agencies within the federal government. Proposers must also comply with any state or municipal regulations or ordinances governing biotechnology practices.

The Safe Genes program encourages research involving gene drives. As described above, gene drive proposals must encompass at minimum two TAs and meet the criteria and milestones of each. Proposals must include a detailed description of how engineered gene drive organisms will be prevented from unintended release from the laboratory. These measures may include physical (i.e. appropriate biosafety equipment) and/or ecological barriers (i.e. inability to thrive in local environment), molecular-based strategies (i.e. small-molecule dependent growth), relevant training of lab personnel, and/or any other means of biocontainment. Proposers are encouraged to utilize multiple layers of biocontainment, and should provide corresponding technical rationale to support their proposed plan. Proposers should also consider mechanisms that allow easier tracking and surveillance of gene drive organisms, such as genotypic (e.g. barcodes) or phenotypic (e.g. fluorescent) markers.

If large cage trials are proposed for a gene drive organism, proposals should include a detailed biocontainment strategy that is multilayered (i.e. depends on more than just physical containment). Proposals should also include monitoring and appropriate mitigation measures for any unintended release or outcome. In addition, proposers are encouraged to consider outreach

[7] Akbari *et al*., Safeguarding gene drive experiments in the laboratory. *Science*. 2015 Aug 28;349(6251):927-9.
[8] National Academies of Sciences, Engineering, and Medicine. *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values.* Washington, DC: National Academies Press (US); 2016.
[9] Carter and Friedman. *Policy and Regulatory Issues for Gene Drives in Insects: Workshop Report*. San Diego, CA: J. Craig Venter Institute; 2016.

and engagement activities for community stakeholders, as appropriate, and include communications and other types of expertise in their teams, as needed.

**Ethical, Legal, and Societal Implications (ELSI)**

DARPA maintains its commitment to ensuring that efforts funded under this BAA adhere to ethical and legal regulations currently in place for Federally and DoD-funded research. Program developments will be discussed with a panel of expert external advisors with expertise in bioethical issues that may emerge as a consequence of advances in biomedical science and technology. Proposers to this BAA should address potential ethical, legal, and societal implications of the proposed technology.

**Other requirements**

Performers are expected to participate in program reviews twice per year to provide scientific and technical updates to the entire Safe Genes performer community on progress towards their milestones and scientific goals, and to summarize outstanding challenges and limitations that must be overcome to achieve the overarching goals of the program. Performers are also expected to present a plan for early and continued engagement with regulators (e.g., EPA, FDA, etc.) throughout the program to discuss developing technologies and challenges to facilitate the eventual translation of the tools generated for practical use.

## 2. Award Information

Multiple awards are possible. The amount of resources made available under this BAA will depend on the quality of the proposals received and the availability of funds.

The Government reserves the right to select for negotiation all, some, one, or none of the proposals received in response to this solicitation, and to make awards without discussions with proposers. The Government also reserves the right to conduct discussions if it is later determined to be necessary. If warranted, portions of resulting awards may be segregated into pre-priced options. Additionally, DARPA reserves the right to accept proposals in their entirety or to select only portions of proposals for award. In the event that DARPA desires to award only portions of a proposal, negotiations may be opened with that proposer. The Government reserves the right to fund proposals in phases with options for continued work at the end of one or more of the phases.

Awards under this BAA will be made to proposers on the basis of the evaluation criteria listed below (see section labeled "Application Review Information," Section 5), and program balance to provide overall value to the Government. The Government reserves the right to request any additional, necessary documentation once it makes the award instrument determination. Such additional information may include but is not limited to Representations and Certifications. The Government reserves the right to remove proposers from award consideration should the parties fail to reach agreement on award terms, conditions and cost/price within a reasonable time or the proposer fails to timely provide requested additional information. Proposals identified for negotiation may result in a procurement contract, cooperative agreement, or other transaction

depending upon the nature of the work proposed, the required degree of interaction between parties, whether or not the research is classified as Fundamental Research, and other factors.

In all cases, the Government contracting officer shall have sole discretion to select award instrument type and to negotiate all instrument terms and conditions with selectees. Proposers are advised that regardless of the instrument type proposed, DARPA personnel, in consultation with the Government contracting officer, may select other award instruments, as they deem appropriate. DARPA will apply publication or other restrictions, as necessary, if it determines that the research resulting from the proposed effort will present a high likelihood of disclosing performance characteristics of military systems or manufacturing technologies that are unique and critical to defense. Any award resulting from such a determination will include a requirement for DARPA permission before publishing any information or results on the program. For more information on publication restrictions, see the section below on Fundamental Research.

**Fundamental Research**

It is DoD policy that the publication of products of fundamental research will remain unrestricted to the maximum extent possible. National Security Decision Directive (NSDD) 189 established the national policy for controlling the flow of scientific, technical, and engineering information produced in federally funded fundamental research at colleges, universities, and laboratories. The Directive defines fundamental research as follows:

> 'Fundamental research' means basic and applied research in science and engineering, the results of which ordinarily are published and shared broadly within the scientific community, as distinguished from proprietary research and from industrial development, design, production, and product utilization, the results of which ordinarily are restricted for proprietary or national security reasons.

As of the date of publication of this BAA, the Government expects that program goals as described herein either cannot be met by proposers intending to perform fundamental research or the proposed research is anticipated to present a high likelihood of disclosing performance characteristics of military systems or manufacturing technologies that are unique and critical to defense. Therefore, the Government anticipates restrictions on the resultant research that will require the contractor to seek DARPA permission before publishing any information or results relative to the program.

Proposers should indicate in their proposal whether they believe the scope of the research included in their proposal is fundamental or not. While proposers should clearly explain the intended results of their research, the Government shall have sole discretion to select award instrument type and to negotiate all instrument terms and conditions with selectees. Appropriate clauses will be included in resultant awards for non-fundamental research to prescribe publication requirements and other restrictions, as appropriate.

For certain research projects, it may be possible that although the research being performed by the prime contractor is restricted research, a subawardee may be conducting fundamental

research. In those cases, it is the prime contractor's responsibility to explain in its proposal why its subawardee's effort is fundamental research.

The following statement or similar provision will be incorporated into any resultant non-fundamental research procurement contract or other transaction:

> There shall be no dissemination or publication, except within and between the contractor and any subawardees, of information developed under this contract or contained in the reports to be furnished pursuant to this contract without prior written approval of DARPA's Public Release Center (DARPA/PRC). All technical reports will be given proper review by appropriate authority to determine which Distribution Statement is to be applied prior to the initial distribution of these reports by the contractor. With regard to subawardee proposals for Fundamental Research, papers resulting from unclassified fundamental research are exempt from prepublication controls and this review requirement, pursuant to DoD Instruction 5230.27 dated October 6, 1987.
>
> When submitting material for written approval for open publication, the contractor/awardee must submit a request for public release to the DARPA/PRC and include the following information: (1) Document Information: document title, document author, short plain-language description of technology discussed in the material (approx. 30 words), number of pages (or minutes of video) and document type (e.g., briefing, report, abstract, article, or paper); (2) Event Information: event type (conference, principal investigator meeting, article or paper), event date, desired date for DARPA's approval; (3) DARPA Sponsor: DARPA Program Manager, DARPA office, and contract number; and (4) Contractor/Awardee's Information: POC name, email and phone. Allow four weeks for processing; due dates under four weeks require a justification. Unusual electronic file formats may require additional processing time. Requests may be sent either via email to public_release_center@darpa.mil or by mail at 675 North Randolph Street, Arlington VA 22203-2114, telephone (571) 218-4235. Refer to the following for link for information about DARPA's public release process: http://www.darpa.mil/work-with-us/contract-management/public-release."

## 3. Eligibility Information

All responsible sources capable of satisfying the Government's needs may submit a proposal that shall be considered by DARPA.

### 3.1. ELIGIBLE APPLICANTS

#### 3.1.1. Federally Funded Research and Development Centers (FFRDCs) and Government Entities

Federally Funded Research and Development Centers (FFRDCs) and Government entities (e.g., Government/National laboratories, military educational institutions, etc.) are subject to applicable direct competition limitations and cannot propose to this BAA in any capacity unless they meet the following conditions: (1) FFRDCs must clearly demonstrate that the proposed

work is not otherwise available from the private sector; and (2) FFRDCs must provide a letter on official letterhead from their sponsoring organization citing the specific authority establishing their eligibility to propose to Government solicitations and compete with industry, and their compliance with the associated FFRDC sponsor agreement's terms and conditions. This information is required for FFRDCs proposing to be prime contractors or subawardees. Government entities must clearly demonstrate that the work is not otherwise available from the private sector and provide written documentation citing the specific statutory authority and contractual authority, if relevant, establishing their ability to propose to Government solicitations. At the present time, DARPA does not consider 15 U.S.C. § 3710a to be sufficient legal authority to show eligibility. While 10 U.S.C.§ 2539b may be the appropriate statutory starting point for some entities, specific supporting regulatory guidance, together with evidence of agency approval, will still be required to fully establish eligibility. DARPA will consider FFRDC and Government entity eligibility submissions on a case-by-case basis; however, the burden to prove eligibility for all team members rests solely with the proposer.

### 3.1.2. Non-U.S. Organizations

Non-U.S. organizations are/or individuals may participate to the extent that such participants comply with any necessary nondisclosure agreements, security regulations, export control laws, and other governing statutes applicable under the circumstances. See Section 4.2 "Security and Proprietary Issues" regarding the proposers capabilities to perform research and development at the classification level they propose.

### 3.1.3. Procurement Integrity, Standards of Conduct, Ethical Considerations, and Organizational Conflicts of Interest

Current federal employees are prohibited from participating in particular matters involving conflicting financial, employment, and representational interests (18 U.S.C. §§ 203, 205, and 208). Once the proposals have been received, and prior to the start of proposal evaluations, the Government will assess potential conflicts of interest and will promptly notify the proposer if any appear to exist. The Government assessment does NOT affect, offset, or mitigate the proposer's responsibility to give full notice and planned mitigation for all potential organizational conflicts, as discussed below.

Without prior approval or a waiver from the DARPA Director, in accordance with FAR 9.503, a contractor cannot simultaneously provide scientific, engineering, technical assistance (SETA) or similar support and also be a technical performer. As part of the proposal submission, all members of the proposed team (prime proposers, proposed subawardees, and consultants) must affirm whether they (their organizations and individual team members) are providing SETA or similar support to any DARPA technical office(s) through an active contract or subcontract. All affirmations must state which office(s) the proposer, subawardees, consultant, or individual supports and identify the prime contract number(s). All facts relevant to the existence or potential existence of organizational conflicts of interest (FAR 9.5) must be disclosed. The disclosure must include a description of the action the proposer has taken or proposes to take to avoid, neutralize, or mitigate such conflict. If in the sole opinion of the Government after full consideration of the circumstances, a proposal fails to fully disclose potential conflicts of interest

and/or any identified conflict situation cannot be effectively mitigated, the proposal will be rejected without technical evaluation and withdrawn from further consideration for award.

If a prospective proposer believes a conflict of interest exists or may exist (whether organizational or otherwise) or has questions on what constitutes a conflict of interest, the proposer should send his/her contact information and a summary of the potential conflict via email to the BAA email address before time and effort are expended in preparing a proposal and mitigation plan.

### 3.2. COST SHARING/MATCHING

Cost sharing is not required; however, it will be carefully considered where there is an applicable statutory condition relating to the selected funding instrument (e.g., for any Other Transactions under the authority of 10 U.S.C. § 2371). Cost sharing is encouraged where there is a reasonable probability of a potential commercial application related to the proposed research and development effort.

### 3.3. OTHER ELIGIBILITY REQUIREMENTS – COLLABORATIVE EFFORTS

While teaming is not required, teaming is *strongly encouraged* to meet the program goals across all Phases and TAs. It is expected that successful teams will require expertise in both theoretical and experimental science and technology, for example, in fields of biology relevant to the proposed organism, testing and evaluation systems, modeling, and control engineering.

DARPA will facilitate a Proposers Day (see Section 8.2 below) to encourage the formation of teams with the expertise necessary to meet the goals of the program and enable sharing of information among interested proposers through fbo.gov and the Proposers Day registration website.

DARPA requires that all teaming arrangements be resolved before proposal submission. Specific content, communications, networking, and team formation are the sole responsibility of the proposers. Teams/collaborative efforts must submit a single, integrated proposal led by a single Principal Investigator (PI) or prime contractor, even if addressing more than one Technical Area.

Proposers may join any number of teams as a subcontractor and still submit a separate proposal as the PI (with or without subcontractors). In all cases, collaborating team members must submit a unified proposal.

## 4. Application and Submission Information

### 4.1. ADDRESS TO REQUEST APPLICATION PACKAGE

This solicitation contains all information required to submit a proposal. No additional forms, kits, or other materials are needed. This notice, with the classified addendum, constitutes the total solicitation. No additional information is available, except as provided at FBO.gov or Grants.gov, nor will a formal Request for Proposal (RFP) or additional solicitation regarding this announcement be issued. Requests for the same will be disregarded.

## 4.2. CONTENT AND FORM OF APPLICATION SUBMISSION

### 4.2.1. Proprietary and Security Information

DARPA policy is to treat all submissions as source selection information (see FAR 2.101 and 3.104), and to disclose their contents only for the purpose of evaluation. Restrictive notices notwithstanding, during the evaluation process, submissions may be handled by support contractors for administrative purposes and/or to assist with technical evaluation. All DARPA support contractors performing this role are expressly prohibited from performing DARPA-sponsored technical research and are bound by appropriate nondisclosure agreements.

Submissions will not be returned. The original of each submission received will be retained at DARPA and all other non-required copies destroyed. A certification of destruction may be requested, provided the formal request is received at this office within 5 days after notification that a proposal was not selected.

#### 4.2.1.1 Proprietary Information

Proposers are responsible for clearly identifying proprietary information. Submissions containing proprietary information must have the cover page and each page containing such information clearly marked with a label such as "Proprietary" or "Company Proprietary." Note, "Confidential" is a classification marking used to control the dissemination of U.S. Government National Security Information as dictated in Executive Order 13526 and should not be used to identify proprietary business information.

#### 4.2.1.2 Security Information

DARPA anticipates that submissions received under this BAA will be unclassified. However, should a proposer wish to submit classified information, an *unclassified* email must be sent to the BAA mailbox requesting submission instructions from the Technical Office PSO.

Security classification guidance and direction via a Security Classification Guide (SCG) and/or DD Form 254, "DoD Contract Security Classification Specification," will not be provided at this time, since DARPA is soliciting ideas only. If a determination is made that the award instrument may result in access to classified information, a SCG and/or DD Form 254 will be issued by DARPA and attached as part of the award.

### 4.2.2. Submission Information

Proposers are strongly encouraged to submit a proposal abstract in advance of a proposal. This procedure is intended to minimize unnecessary effort in proposal preparation and review. DARPA will acknowledge receipt of the submission and assign a control number that should be used in all further correspondence regarding the proposal abstract.

DARPA will respond to abstracts with a statement as to whether DARPA is interested in the idea. If DARPA does not recommend the proposer submit a full proposal, DARPA will provide feedback to the proposer regarding the rationale for this decision. Regardless of DARPA's response to an abstract, proposers may submit a full proposal. DARPA will review all full proposals submitted using the published evaluation criteria and without regard to any comments resulting from the review of an abstract.

The typical proposal should express a consolidated effort in support of one or more related technical concepts or ideas. Disjointed efforts should not be included into a single proposal.

Restrictive notices notwithstanding, proposals may be handled, for administrative purposes only, by a support contractor. This support contractor is prohibited from competition in DARPA technical research and is bound by appropriate nondisclosure requirements. Proposals and/or proposed abstracts may not be submitted by fax or e-mail; any so sent will be disregarded.

Proposals not meeting the format described in the BAA may not be reviewed.

**For Proposers Submitting Proposal Abstracts or Full Proposals as Hard Copies/On CD-ROM:**

Proposers must submit an original hardcopy and one (1) electronic copy of the abstract or proposal in PDF (preferred) on a CD-ROM to the mailing address listed in Part I. Each copy must be clearly labeled with **DARPA-BAA-16-59**, proposer organization, technical point of contact, and proposal title (short title recommended).

Please note that submitters via hardcopy/CD-ROM will still need to visit https://baa.darpa.mil to register their organization concurrently to ensure the BAA office can verify and finalize their submission.

**For Proposers Submitting Proposal Abstracts or Full Proposals through DARPA's BAA Submission Portal:**

Abstracts and Full Proposals sent in response to DARPA-BAA-16-59 may be submitted via DARPA's BAA Website (https://baa.darpa.mil). Visit the website to complete the two-step registration process. Submitters will need to register for an Extranet account (via the form at the URL listed above) and wait for two separate e-mails containing a username and temporary password. After accessing the Extranet, submitters may then create an account for the DARPA BAA website (via the "Register your Organization" link along the left side of the homepage), view submission instructions, and upload/finalize the abstract. Proposers using the DARPA BAA Website may encounter heavy traffic on the submission deadline date; it is highly advised that submission process be started as early as possible.

All unclassified concepts submitted electronically through DARPA's BAA Website must be uploaded as zip files (.zip or .zipx extension). The final zip file should be no greater than 50 MB in size. Only one zip file will be accepted per submission. Classified submissions and proposals

requesting assistance instruments (cooperative agreements) should NOT be submitted through DARPA's BAA Website (https://baa.darpa.mil), though proposers will likely still need to visit https://baa.darpa.mil to register their organization (or verify an existing registration) to ensure the BAA office can verify and finalize their submission.

Technical support for BAA Website may be reached at BAAT_Support@darpa.mil, and is typically available during regular business hours, (9:00 AM- 5:00 PM EST Monday – Friday).

Proposers using the DARPA BAA Website may encounter heavy traffic on the submission deadline date; it is highly advised that submission process be started as early as possible.

**For Proposers Requesting Cooperative Agreements:**

Proposers requesting cooperative agreements may submit proposals through one of the following methods: (1) hard copy mailed directly to DARPA; or (2) electronic upload per the instructions at http://www.grants.gov/applicants/apply-for-grants.html. Cooperative agreement proposals may not be submitted through any other means. If proposers intend to use Grants.gov as their means of submission, then they must submit their entire proposal through Grants.gov; applications cannot be submitted in part to Grants.gov and in part as a hard-copy. Proposers using the Grants.gov do not submit paper proposals in addition to the Grants.gov electronic submission.

Grants.gov requires proposers to complete a one-time registration process before a proposal can be electronically submitted. If proposers have not previously registered, this process can take between three business days and four weeks. See the Grants.gov registration checklist at http://www.grants.gov/web/grants/applicants/organization-registration.html for registration requirements and instructions.

Once Grants.gov has received a proposal submission, Grants.gov will send two email messages to advise proposers as to whether or not their proposals have been validated or rejected by the system; IT MAY TAKE UP TO TWO DAYS TO RECEIVE THESE EMAILS. The first email will confirm receipt of the proposal by the Grants.gov system; this email only confirms receipt, not acceptance, of the proposal. The second will indicate that the application has been successfully validated by the system prior to transmission to the grantor agency or has been rejected due to errors. If the proposal is validated, then the proposer has successfully submitted their proposal. If the proposal is rejected, the proposed must be corrected and resubmitted before DARPA can retrieve it. If the solicitation is no longer open, the rejected proposal cannot be resubmitted. Once the proposal is retrieved by DARPA, the proposer will receive a third email from Grants.gov. To avoid missing deadlines, proposers should submit their proposals in advance of the final proposal due date with sufficient time to receive confirmations and correct any errors in the submission process through Grants.gov. For more information on submitting proposals to Grants.gov, visit the Grants.gov submissions page at: http://www.grants.gov/web/grants/applicants/apply-for-grants.html

Upload six (6) separate documents, the SF424; Volume I, Technical and Management Proposal; Volume II, the Cost Proposal; Attachment 2, Summary Slides; Attachment 3, Gantt Chart; and,

Attachment 4, Budget (as attachments to the application package). **No other Grants.gov forms are required.** Please note that Grants.gov does not accept zipped or encrypted proposals. More detailed instructions for using Grants.gov can be found on the Grants.gov website.

Proposers electing to submit cooperative agreement proposals as hard copies must complete the SF 424 R&R form (Application for Federal Assistance, Research and Related) available on the Grants.gov website http://apply07.grants.gov/apply/forms/sample/RR_SF424_2_0-V2.0.pdf. Technical support for Grants.gov submissions may be reached at 1-800-518-4726 or support@grants.gov.

Please note that submitters to Grants.gov will still need to visit https://baa.darpa.mil to register their organization concurrently to ensure the BAA office can verify and finalize their submission.

**For All:**

All administrative correspondence and questions on this solicitation, including requests for information on how to submit a proposal to this BAA, should be directed to one of the administrative addresses below; e-mail is preferred.

BAA Administrator
E-mail: SafeGenes@darpa.mil

DARPA/BTO
ATTN: DARPA-BAA-16-59
675 North Randolph Street
Arlington, VA 22203-2114
Office Website: http://www.darpa.mil/about-us/offices/bto
Solicitations Page: http://www.darpa.mil/work-with-us/opportunities

DARPA intends to use electronic mail for correspondence regarding DARPA-BAA-16-59. Proposals may not be submitted by fax or e-mail; any so sent will be disregarded. DARPA encourages use of the Internet for retrieving the BAA and any other related information that may subsequently be provided.

### 4.2.3. Restrictive Markings on Proposals

All proposals should clearly indicate limitations on the disclosure of their contents. Proposers who include in their proposals data that they do not want disclosed to the public for any purpose, or used by the Government except for evaluation purposes, shall-

(1) Mark the title page with the following legend:

> This proposal includes data that shall not be disclosed outside the Government and shall not be duplicated, used, or disclosed-in whole or in part-for any purpose other than to evaluate this proposal. If, however, a contract is awarded to this proposer as a result of, or in connection with, the submission of this data, the Government shall have the right to duplicate, use, or disclose the data to the extent provided in the resulting contract. This restriction does not limit the Government's right to use information contained in this data if

it is obtained from another source without restriction. The data subject to this restriction are contained in sheets [insert numbers or other identification of sheets]; and

(2) Mark each sheet of data it wishes to restrict with the following legend:

Use or disclosure of data contained on this sheet is subject to the restriction on the title page of this proposal.

NOTE (classification and handling markings): Confidential, Secret and Top Secret are classification markings used to control the dissemination of US Government National Security Information (NSI) as dictated in Executive Order 13526 - "Classified National Security Information". When referencing business proprietary information in a response to this BAA, please refrain from using any combination of the NSI caveats unless the content is classified.

## 4.3. FORMATTING CHARACTERISTICS

### 4.3.1. Proposal Abstract Format

Proposers are highly encouraged to submit an abstract in advance of a proposal to minimize effort and reduce the potential expense of preparing an out of scope proposal. DARPA will respond to abstracts providing feedback and indicating whether, after preliminary review, there is interest within BTO for the proposed work. DARPA will attempt to reply within 30 calendar days of receipt. Proposals may be submitted irrespective of comments or feedback received in response to the abstract. Proposals are reviewed without regard to feedback given as a result of abstract review. The time and date for submission of proposal abstracts is specified in Section 4.4.1 below.

The abstract is a concise version of the proposal comprising a maximum of **8** pages including all figures, tables, and charts. The cover sheet and (optional) submission letter is not included in the page count. All pages shall be formatted for printing on 8-1/2 by 11 inch paper with font size not smaller than 12 point. Smaller font sizes may be used for figures, tables, and charts.

Submissions must be written in English.

The page limit does NOT include:
1. Official transmittal letter (optional);
2. Cover sheet;
3. Executive summary slide;
4. Resumes; and,
5. Bibliography (optional).

Abstracts must include the following components:

**A. Cover Sheet** (LABELED “ABSTRACT”):

1. BAA number (DARPA-BAA-16-59);
2. Lead organization (prime contractor);

3. Other team members/subcontractors (if applicable);
4. Proposal Abstract title;
5. Technical point of contact (Program Manager or Principle Investigator) to include: salutation, last name, first name, street address, city, state, zip code, telephone, fax, e-mail;
6. Administrative point of contract to include: salutation, last name, first name, street address, city, state, zip code, telephone, fax, e-mail;
7. Estimated cost; and
8. Estimated period of performance

**B. Executive Summary**: Clearly describe what is being proposed and what difference it will make (qualitatively and quantitatively), including brief answers to the following questions:

1. What are you trying to do?
2. How is it done today? And what are the limitations?
3. What is innovative in your approach and how does it compare to the state of the art?
4. Who will care and what will the impact be if you are successful?
5. How much will it cost and how long will it take?

**C. Executive Summary Slide (does not count towards page limit):** Provide a one-slide summary in PowerPoint that effectively and succinctly conveys the information requested in the slide template provided as **Attachment 1**. Use of this template is required.

**D. Technical Plan:** Identify the Technical Area(s) to be addressed in the proposal and summarize your plan for accomplishing the program technical goals. Proposers that pursue gene drive technologies (or any other self-perpetuating gene editing technology that may bias the outcome of reproductive inheritance) must address TA1 and at least one additional Technical Area. Outline and address all technical challenges inherent in the approach and possible solutions for overcoming potential problems. In addition:

1. Describe the genome editor(s), the target cell lines and/or organisms, and the DoD-relevant application that will be addressed.
2. Describe the methods for assaying any and all genome editing systems *in vitro*, *in vivo*, and/or *in situ* to determine on- and off-target genome editing, failure modes, etc.
3. Provide qualitative and quantitative metrics and milestones that will be used to measure progress against program goals
4. For experiments involving gene drives or performed in non-BSL2 or equivalent safety levels, describe the methods and technical challenges to ensure biocontainment and/or bioconfinement of genetically modified organisms or cell lines.

**E. Management and Capabilities:** It is expected that proposals will involve multidisciplinary teams that include expertise from multiple complementary disciplines, for example, synthetic biology, computational biology, and ecology. Provide a brief summary of expertise of the team, including subcontractors and key personnel.

A principal investigator for the project must be identified, and a description of the team's organization. All teams addressing more than one TA are encouraged to identify a Project Manager to serve as the primary point of contact to communicate with the DARPA Program Manager and Contracting Officer Representative, coordinate effort across performer teams, organize regular performer meetings or discussions, facilitate data sharing, and ensure timely completion of milestones and deliverables.

Include a description of the team's organization including roles and responsibilities. Team member descriptions should address the Technical Plan and delineate individuals to avoid duplication of efforts. Teams addressing more than one TA should describe the time and percent effort divisions for members participating across multiple TAs. Describe the organizational experience in this area and existing intellectual property required to complete the project.

Describe any specialized facilities to be used as part of the project, the extent of access to these facilities, and any biological containment, biosafety, and certification requirements.

List Government-furnished materials or data assumed to be available.

**F. Cost and Schedule:** Provide a cost estimate for resources over the proposed timeline of the project, broken down by Phase and major cost items (*e.g.*, labor, materials, etc.). Include cost estimates for each potential subcontractor (may be a rough order of magnitude).

**G. Resumes (do not count towards page limit):** Include resumes of key team members.

**H. Bibliography (Optional, does not count towards page limit):** If desired, include a brief bibliography with links to relevant papers and reports. The bibliography should not exceed two (2) pages.

### 4.3.2. Proposal Format

All full proposals must be in the format given below. Nonconforming proposals may be rejected without review. Proposals shall consist of two volumes. All pages shall be printed on 8-1/2 by 11 inch paper with type not smaller than 12 point. Smaller font may be used for figures, tables and charts. The page limitation for full proposals includes all figures, tables, and charts. Volume I, Technical and Management Proposal, may include an attached bibliography of relevant technical papers or research notes (published and unpublished) which document the technical ideas and approach upon which the proposal is based. Copies of not more than three (3) relevant papers may be included with the submission. The bibliography and attached papers

are not included in the page counts given below. The submission of other supporting materials along with the proposals is strongly discouraged and will not be considered for review. The maximum page count for Volume 1 is **20** pages for proposals that address a single Technical Area. Up to **10** pages can be added for each additional Technical Area. A submission letter is optional and is not included in the page count. The time and date for submission of full proposals is specified in Section 4.4.2 below. Volume I should include the following components:

**a. Volume I, Technical and Management Proposal**

Section I. Administrative

**A.** Cover Sheet (LABELED "PROPOSAL: VOLUME I"):

1. BAA number (DARPA-BAA-16-59);
2. Technical area;
3. Lead organization (prime contractor);
4. Type of organization, selected from among the following categories: "LARGE BUSINESS," "SMALL DISADVANTAGED BUSINESS," "OTHER SMALL BUSINESS," "HBCU," "MI," "OTHER EDUCATIONAL," OR "OTHER NONPROFIT";
5. Proposer's reference number (if any);
6. Other team members (if applicable) and type of business for each;
7. Proposal title;
8. Technical point of contact (Program Manager or Principle Investigator) to include: salutation, last name, first name, street address, city, state, zip code, telephone, fax, e-mail;
9. Administrative point of contact (Contracting Officer) to include: salutation, last name, first name, street address, city, state, zip code, telephone, fax, e-mail;
10. Award instrument requested: procurement contract, cooperative agreement, or other transaction;
11. Place(s) and period(s) of performance;
12. Proposal validity period;
13. DUNS number (http://www.dnb.com/get-a-duns-number.html);
14. Taxpayer ID number (https://www.irs.gov/Individuals/International-Taxpayers/Taxpayer-Identification-Numbers-TIN;
15. CAGE code (https://www.dlis.dla.mil/bincs/FAQ.aspx);

Information on award instruments is available at http://www.darpa.mil/work-with-us/contract-management.

**B.** Official Transmittal Letter.

**C.** Executive Summary Slides: Provide a three-slide summary in PowerPoint that effectively and succinctly conveys the main objective, key innovations, expected impact, and other unique aspects of the proposed project. The slide template is provided as **Attachment 2**. Use of this template is required.

Section II. Detailed Proposal Information

**A.** Executive Summary: Provide a synopsis of the proposed project, including answers to the following questions:

- What is the proposed work attempting to accomplish or do?
- How is it done today, and what are the limitations?
- What is innovative in your approach?
- What are the key technical challenges in your approach and how do you plan to overcome these?
- Who or what will be affected and what will be the impact if the work is successful?
- How much will it cost, and how long will it take?

**B.** Goals and Impact: Clearly describe what the team is trying to achieve and the difference it will make (qualitatively and quantitatively) if successful. Describe the innovative aspects of the project in the context of existing capabilities and approaches, clearly delineating the uniqueness and benefits of this project in the context of the state of the art, alternative approaches, and other projects from the past and present. Describe how the proposed project is revolutionary and how it significantly rises above the current state of the art. Describe the deliverables associated with the proposed project and any plans to commercialize the technology, transition it to a customer, or further the work.

**C.** Technical Plan: Outline and address technical challenges inherent in the approach and possible solutions for overcoming potential problems. This section should provide appropriate measurable milestones (quantitative if possible) at intermediate stages of the program to demonstrate progress, and a plan for achieving the milestones. The technical plan should demonstrate a deep understanding of the technical challenges and present a credible (even if risky) plan to achieve the program goal. Discuss mitigation of technical risk.

**D.** Management Plan: It is expected that proposals will involve multidisciplinary teams that include expertise from multiple complementary disciplines, for example, synthetic biology, computational biology, and ecology. Provide a summary of expertise of the team, including any subcontractors, and key personnel who will be doing the work. Resumes do not count against the proposal page count.

Identify a principal investigator for each Technical Area to be addressed by the project. It is also highly recommended that teams addressing more than one TA also identify a Program Manager to coordinate day-to-day activities, serve as a primary point-of-contact for the project, and integrate team inputs. Provide a clear description of the team's

organization including an organization chart that includes, as applicable: the programmatic relationship of team members; the unique capabilities of team members; the task responsibilities of team members, the teaming strategy among the team members; and key personnel with the amount of effort to be expended by each person during each year. Provide a detailed plan for coordination including explicit guidelines for interaction among collaborators/subcontractors of the proposed effort. Include risk management approaches. Describe any formal teaming agreements that are required to execute this program. Describe existing intellectual property required to complete the project and how the team will manage these arrangements.

**E.** Capabilities: Describe organizational experience in relevant subject area(s), existing intellectual property, specialized facilities, and any Government-furnished materials or information. Discuss any work in closely related research areas and previous accomplishments. Descriptions of any specialized facilities to be used as part of the project should include size and scale that will enable the proposed activities, the extent of access to these facilities, and any biological containment, biosafety, and certification requirements.

**F.** Statement of Work (SOW): The SOW should provide a concise task breakdown, citing specific tasks and their connection to the interim milestones and program metrics. Each phase of the program should be separately defined. The SOW must not include proprietary information.

For each task/subtask, provide:

- A brief description of the approach to be taken to accomplish each defined task/subtask.
- Identification of the primary organization responsible for task execution (prime contractor, subcontractor(s), consultant(s), by name).
- A measurable milestone, i.e., a deliverable, demonstration, or other event/activity that marks task completion. Include quantitative metrics.
- A definition of all deliverables (e.g., data, reports, software) to be provided to the Government in support of the proposed tasks/subtasks.
- It is recommended that the SOW be developed so that each Technical Area and Phase of the program is separately defined.
- Do not include any proprietary information in the SOW.

The Government requires proposers to complete an editable Excel Gantt Chart template that outlines the proposed tasks, subtasks, metrics, and milestones by each Phase; download and complete the template provided in **Attachment 3**, Gantt Template, posted with the BAA.

**G.** Schedule and Milestones: Provide a detailed schedule showing tasks (task name, duration, work breakdown structure element as applicable, performing organization), milestones, and the interrelationships among tasks. The task structure must be consistent with that in the SOW. Measurable milestones should be clearly articulated and defined in time relative to the start of the project.

Section III. Additional Information (Note: Does not count towards page limit)

A resume or "Biosketch" is required for key personnel.

A brief bibliography of relevant technical papers and research notes (published and unpublished) which document the technical ideas upon which the proposal is based. Copies of not more than three (3) relevant papers can be included in the submission.

**b. Volume II, Cost Proposal (No Page Limit)**

All proposers, including FFRDCs, must submit the following:

**A.** Cover Sheet (LABELED "PROPOSAL: VOLUME II"):

1. BAA number (DARPA-BAA-16-59);
2. Technical area(s);
3. Lead organization (prime contractor);
4. Type of organization, selected from among the following categories: "LARGE BUSINESS," "SMALL DISADVANTAGED BUSINESS," "OTHER SMALL BUSINESS," "HBCU," "MI," "OTHER EDUCATIONAL," OR "OTHER NONPROFIT";
5. Proposer's reference number (if any);
6. Other team members (if applicable) and type of business for each;
7. Proposal title;
8. Technical point of contact (Program Manager or Principle Investigator) to include: salutation, last name, first name, street address, city, state, zip code, telephone, fax, e-mail;
9. Administrative point of contact (Contracting officer) to include: salutation, last name, first name, street address, city, state, zip code, telephone, fax, e-mail;
10. Award instrument requested: procurement contract, cooperative agreement, or other transaction;
11. Place(s) and period(s) of performance;
12. Total proposed cost separated by basic award and option(s) (if any);
13. Name, address, and telephone number of the proposer's cognizant Defense Contract Management Agency (DCMA) administration office (*if known)*;
14. Name, address, and telephone number of the proposer's cognizant Defense Contract Audit Agency (DCAA) audit office (*if known*);
15. Date proposal was prepared;
16. DUNS number (http://www.dnb.com/get-a-duns-number.html);
17. Taxpayer ID number (https://www.irs.gov/Individuals/International-Taxpayers/Taxpayer-Identification-Numbers-TIN);

18. CAGE code (https://www.dlis.dla.mil/bincs/FAQ.aspx);
19. Proposal validity period;

**Note that nonconforming proposals may be rejected without review.**

**Proposers without an accounting system considered adequate for determining accurate costs must complete an SF 1408 if a cost type contract is to be negotiated.** To facilitate this process, proposers should complete the SF 1408 found at http://www.gsa.gov/portal/forms/download/115778 and submit the completed form with the proposal. To complete the form, check the boxes on the second page, then provide a narrative explanation of your accounting system to supplement the checklist on page one. For more information, please see http://www.dcaa.mil/preaward_accounting_system_adequacy_checklist.html.

The Government encourages proposers to complete an editable MS excel budget template that covers items 1.a, 1.d, 3, 4, 5 and 6 discussed below. This template document is provided as **Attachment 4** to this BAA. If you choose to use **Attachment 4**, submit the MS Excel template in addition to Volume I and II of your proposal. Volume II must include all other items discussed below that are not covered by the editable MS excel budget template. Proposers are welcome to utilize an alternative format, provided the information requested below is clearly and effectively communicated.

(1) Total program cost broken down by major cost items to include:
   a. Direct Labor – Including individual labor categories with associated labor hours and direct labor rates. If selected for award, be prepared to submit supporting documentation to justify labor rates. (i.e., screenshots of HR databases, comparison to NIH or other web-based salary database);
   b. Consultants – If consultants are to be used, proposer must provide a copy of the consultant's proposed SOW as well as a signed consultant agreement or other document which verifies the proposed loaded daily / hourly rate, hours and any other proposed consultant costs (e.g., travel);
   c. Indirect Costs – Including Fringe Benefits, Overhead, General and Administrative Expense, Cost of Money, Fee, etc. (must show base amount and rate), if available, provide current Forward Pricing Rate Agreement or Forward Pricing Rate Proposal. If not available, provide 2 years historical data to include pool and expense costs used to generate the rates. For academia, provide DHHS or ONR negotiated rate package or, if calculated by other than a rate, provide University documentation identifying G&A and fringe costs by position;
   d. Travel – Provide the purpose of the trip, number of trips, number of days per trip, departure and arrival destinations, number of people, estimated rental car and airfare costs, and prevailing per diem rates as determined by gsa.gov, etc.; Quotes must be supported by screenshots from travel websites;
   e. Other Direct Costs – Itemized with costs including tuition remission, animal per diem rates, health insurance/fee; back-up documentation is to be submitted to support proposed costs;

f. Equipment Purchases – Itemization with individual and total costs, including quantities, unit prices, proposed vendors (if known), and the basis of estimate (e.g., quotes, prior purchases, catalog price lists, etc.); any item that exceeds $5,000 must be supported with back-up documentation such as a copy of catalog price lists or quotes prior to purchase (NOTE: For equipment purchases, include a letter stating why the proposer cannot provide the requested resources from its own funding); and
g. Materials – Itemization with costs, including quantities, unit prices, proposed vendors (if known), and the basis of estimate (e.g., quotes, prior purchases, catalog price lists, etc.); any item that exceeds $5,000 must be supported with back-up documentation such as a copy of catalog price lists or quotes prior to purchase.

(2) A summary of major program tasks by Government Fiscal Year (GFY = Oct 1 – Sep 30)
(3) A summary of total program costs by phase and task;
(4) A summary of projected funding requirements by month;
(5) An itemization of any information technology (IT) purchase (including a letter stating why the proposer cannot provide the requested resources from its own funding), as defined in FAR Part 2.101;
(6) An itemization of Subcontracts. **All subcontractor cost proposal documentation must be prepared at the same level of detail as that required of the prime.** Subcontractor proposals should include Interdivisional Work Transfer Agreements (IWTA) or evidence of similar arrangements (an IWTA is an agreement between multiple divisions of the same organization);
(7) The source, nature, and amount of any industry cost-sharing. Where the effort consists of multiple portions which could reasonably be partitioned for purposes of funding, these should be identified as options with separate cost estimates for each;
(8) Identification of pricing assumptions of which may require incorporation into the resulting award instrument (e.g., use of Government Furnished Property/Facilities/Information, access to Government Subject Matter Expert/s, etc.);
(9) Any Forward Pricing Rate Agreement, DHHS rate agreement, other such approved rate information, or such documentation that may assist in expediting negotiations (if available); and
(10) Proposers with a Government acceptable accounting system who are proposing a cost-type contract, must submit the DCAA document approving the cost accounting system.

The proposer should include supporting cost and pricing information in sufficient detail to substantiate the summary cost estimates and should include a description of the method used to estimate costs and supporting documentation. Per FAR 15.403-4, certified cost or pricing data shall be required if the proposer is seeking a procurement contract award per the referenced threshold, unless the proposer requests an exception from the requirement to submit cost or pricing data. "Certified cost or pricing data" are not required if the proposer proposes an award instrument other than a procurement contract (e.g., a cooperative agreement or other transaction).

The prime contractor is responsible for compiling and providing all subcontractor proposals for the Procuring Contracting Officer (PCO). Where the effort consists of multiple portions which could reasonably be partitioned for purposes of funding, these should be identified as options with separate cost estimates for each.

The prime and subcontractor proposals should be uploaded together if possible to DARPA's BAA Website (https://baa.darpa.mil/). If the subcontractor proposal contains proprietary information not releasable to the prime, the subcontractor may upload their proposal separately but identify the proposal as a subcontract proposal and provide the name and proposal title of the prime contractor. Subcontractor proposals submitted by hard copy can be submitted in a sealed envelope by the prime or directly by the subcontractor. If submitted directly by the subcontractor the subcontractor must identify the proposal as a subcontract proposal and provide the name and proposal title of the prime contractor. Subcontractors must provide the same number of hard copies and/or electronic proposals as is required of the prime contractor.

All proposers requesting an Other Transaction (OT) for Prototypes must include a detailed list of milestones. Each milestone must include the following: milestone description, completion criteria, due date, and payment/funding schedule (to include, if cost share is proposed, contractor and Government share amounts). It is noted that, at a minimum, milestones should relate directly to accomplishment of program technical metrics as defined in the BAA and/or the proposer's proposal. Agreement type, fixed price or expenditure based, will be subject to negotiation by the Agreements Officer; however, it is noted that the Government prefers use of fixed price milestones with a payment/funding schedule to the maximum extent possible. Do not include proprietary data. If the proposer requests award of an OT for Prototype as a non-traditional contractor (defined as an entity that is not currently performing or has not performed in the last one-year period any contract or subcontract for the Department of Defense that is subject to full CAS coverage), information must be included in the cost proposal to support the claim.

## 4.4. SUBMISSION DATES AND TIMES

### 4.4.1. Proposal Abstract Submission Deadline

The proposal abstract (original and (designated number) of hard and electronic copies) must be submitted to DARPA/BTO), 675 North Randolph Street, Arlington, VA 22203-2114 (Attn.: DARPA-BAA-16-59) **on or before 4:00 p.m., ET, October 6, 2016**. Proposal abstracts received after this time and date may not be reviewed.

### 4.4.2. Full Proposal Submission Deadline

The full proposal (original and (designated number) of hard and electronic copies) must be submitted to DARPA/BTO), 675 North Randolph Street, Arlington, VA 22203-2114 (Attn.: DARPA-BAA-16-59) **on or before 4:00 p.m., ET, November 17, 2016.**

Failure to comply with the submission procedures may result in the submission not being evaluated. DARPA will acknowledge receipt of complete submissions via email and assign control numbers that should be used in all further correspondence regarding proposals.

DARPA will post a consolidated Question and Answer list in response to any relevant and/or BAA clarification question(s) after October 4, 2016, before final full proposals are due. In order

to receive a response to your question, submit your question by November 10, 2016 to SafeGenes@darpa.mil.

### 4.5. FUNDING RESTRICTIONS

Not applicable.

### 4.6. OTHER SUBMISSION REQUIREMENTS

Not applicable.

## 5. Application Review Information

### 5.1. EVALUATION CRITERIA

Evaluation of proposals will be accomplished through a scientific/technical review of each proposal using the following mandatory criteria, listed in descending order of importance:

5.1.1 Overall Scientific and Technical Merit; 5.1.2 Potential Contribution and Relevance to the DARPA Mission; 5.1.3 Biological Safety and Containment; and 5.1.4 Cost Realism.

#### 5.1.1. Overall Scientific and Technical Merit

The proposed technical approach is feasible, achievable, complete and supported by a proposed technical team that has the expertise and experience to accomplish the proposed tasks.

Task descriptions and associated technical elements provided are complete and in a logical sequence with all proposed deliverables clearly defined such that a final outcome that achieves the goal can be expected as a result of award. The proposal identifies major technical risks and planned mitigation efforts are clearly defined and feasible.

The proposal clearly explains the technical approach(es) that will be employed to meet or exceed performer and program defined metrics and milestones and provides ample justification as to why the approach(es) is/are feasible. Other factors to be considered will include the structure, clarity, and responsiveness to the statement of work; the quality of proposed deliverables; and, the linkage of the statement of work, technical approach(es), risk mitigation plans, costs, and deliverables of the prime contractor and all subcontractors through a logical, well-structured, and traceable technical plan that results in the achievement of the technical program goals. Proposer team capabilities and/or related experience to the proposed effort efforts must clearly demonstrate an ability to deliver products that meet the proposed technical performance within the proposed budget and schedule. The proposed team has the expertise to manage the cost and schedule.

#### 5.1.2. Potential Contribution and Relevance to the DARPA Mission

The potential contributions of the proposed effort are relevant to the national technology base. Specifically, DARPA's mission is to maintain the technological superiority of the U.S. military and prevent technological surprise from harming our national security by sponsoring revolutionary, high-payoff research that bridges the gap between fundamental discoveries and their application.

### 5.1.3. Biological Safety and Containment

The proposer must adhere to strict biosafety and biosecurity guidelines and regulations by complying with national guidelines for manipulation of genes and organisms and demonstrating that all biological laboratory work is conducted in compliance with applicable federal regulations to protect human health and the environment; the latest edition of the CDC/NIH *Biosafety in Microbiological and Biomedical Laboratories;* the American Society of Tropical Medicine and Hygiene (ASTMH) Arthropod Containment Guidelines (if applicable); the Biological Weapons Convention; and any local institutional policies that may apply for the proposer's institution facilities.

The proposal thoroughly addresses any potential health and environmental biosecurity, biosafety, and biocontainment issues that may arise from the development of the proposed tools, capabilities, or strategies. If the proposal involves gene drive organisms, it includes additional measures of biosafety and biosecurity by delineating and justifying all methods of biocontainment and bioconfinement, such as physical, ecological, and molecular barriers. The proposal also includes a discussion on managing, mitigating, and monitoring during the development of gene drive technologies. The proposal clearly explains the training, procedures, and engineering that will be employed with the proposed technical approach(es) to meet or exceed regulations and policies. The proposal will include plans for controls against exposure or release, as well as environmental safety planning.

### 5.1.4. Cost Realism

The proposed costs are realistic for the technical and management approach and accurately reflect the technical goals and objectives of the solicitation. The proposed costs are consistent with the proposer's Statement of Work and reflect a sufficient understanding of the costs and level of effort needed to successfully accomplish the proposed technical approach. The costs for the prime proposer and proposed subawardees are substantiated by the details provided in the proposal (e.g., the type and number of labor hours proposed per task, the types and quantities of materials, equipment and fabrication costs, travel and any other applicable costs).

It is expected that the effort will leverage all available relevant prior research in order to obtain the maximum benefit from the available funding. For efforts with a likelihood of commercial application, appropriate direct cost sharing may be a positive factor in the evaluation. DARPA recognizes that undue emphasis on cost may motivate proposers to offer low-risk ideas with minimum uncertainty and to staff the effort with junior personnel in order to be in a more competitive posture. DARPA discourages such cost strategies.

## 5.2. REVIEW AND SELECTION PROCESS

DARPA will conduct a scientific/technical review of each conforming proposal. Proposals will not be evaluated against each other since they are not submitted in accordance with a common work statement. DARPA's intent is to review proposals as soon as possible after they arrive; however, proposals may be reviewed periodically for administrative reasons.

Award(s) will be made to proposers whose proposals are determined to be the most advantageous to the Government, all factors considered, including the potential contributions

of the proposed work to the overall research program and the availability of funding for the effort.

It is the policy of DARPA to ensure impartial, equitable, comprehensive proposal evaluations and to select the source (or sources) whose offer meets the Government's technical, policy, and programmatic goals. Pursuant to FAR 35.016, the primary basis for selecting proposals for acceptance shall be technical, importance to agency programs, and fund availability. In order to provide the desired evaluation, qualified Government personnel will conduct reviews and (if necessary) convene panels of experts in the appropriate areas.

For evaluation purposes, a proposal is the document described in "Proposal Information", Section 4.4.2. Other supporting or background materials submitted with the proposal will be considered for the reviewer's convenience only and not considered as part of the proposal.

Restrictive notices notwithstanding, proposals may be handled for administrative purposes by support contractors. These support contractors are prohibited from competition in DARPA technical research and are bound by appropriate non-disclosure requirements.

Subject to the restrictions set forth in FAR 37.203(d), input on technical aspects of the proposals may be solicited by DARPA from non-Government consultants /experts who are strictly bound by the appropriate non-disclosure requirements.

# 6. Award Administration Information

## 6.1. SELECTION NOTICES

As soon as the evaluation of a proposal is complete, the proposers will be notified that 1) the proposal has been selected for funding pending contract negotiations, or 2) the proposal has not been selected. These official notifications will be sent via email to the Technical POC identified on the proposal coversheet.

## 6.2. ADMINISTRATIVE AND NATIONAL POLICY REQUIREMENTS

### 6.2.1. Meeting and Travel Requirements

There will be a program kickoff meeting and semi-annual program-wide meetings in a location central to the performer teams (assume central US for budgeting purposes), and all key participants are required to attend. Performers should also anticipate periodic site visits at the Program Manager's discretion to the performers location (approximately once per year). Proposers shall include within the content of their proposal details and costs of any travel or meetings they deem to be necessary throughout the course of the effort. Performers should anticipate at least quarterly meetings, including teleconference calls, in-person program reviews, and site visits by the DARPA Program Manager and/or Government team. For travel budgeting purposes, proposers may assume program reviews at six (6) month intervals with alternating locations in Arlington, VA and a location central to the performer team.

### 6.2.2. Human Subjects Research

All research selected for funding involving human subjects, to include use of human biological specimens and human data, must comply with the federal regulations for human subjects protection. Further, research involving human subjects that is conducted or supported by the DoD must comply with 32 CFR 219, Protection of Human Subjects (and DoD Instruction 3216.02, Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research (http://www.dtic.mil/whs/directives/corres/pdf/321602p.pdf).

Institutions awarded funding for research involving human subjects must provide documentation of a current Assurance of Compliance with Federal regulations for human subjects protection, such as a Department of Health and Human Services, Office of Human Research Protection Federal Wide Assurance (http://www.hhs.gov/ohrp). All institutions engaged in human subjects research, to include subawardees, must also hold a valid Assurance. In addition, all personnel involved in human subjects research must provide documentation of completion of human subjects research training.

For all proposed research that will involve human subjects in the first year or phase of the project, the institution must provide evidence of or a plan for review by an Institutional Review Board (IRB) upon final proposal submission to DARPA as part of their proposal, prior to being selected for funding. The IRB conducting the review must be the IRB identified on the institution's Assurance of Compliance with human subjects protection regulations. The protocol, separate from the proposal, must include a detailed description of the research plan, study population, risks and benefits of study participation, recruitment and consent process, data collection, and data analysis. It is recommended that you consult the designated IRB for guidance on writing the protocol. The informed consent document must comply with federal regulations (32 CFR 219.116). A valid Assurance of Compliance with human subjects protection regulations along with evidence of completion of appropriate human subjects research training by all investigators and personnel involved with human subjects research should accompany the protocol for review by the IRB.

In addition to a local IRB approval, a headquarters-level human subjects administrative review and approval is required for all research conducted or supported by the DoD. The Army, Navy, or Air Force office responsible for managing the award can provide guidance and information about their component's headquarters-level review process. Note that confirmation of a current Assurance of Compliance with human subjects protection regulations and appropriate human subjects research training is required before headquarters-level approval can be issued.

The time required to complete the IRB review/approval process varies depending on the complexity of the research and the level of risk involved with the study. The IRB approval process can last between one and three months, followed by a DoD review that could last between three and six months. Ample time should be allotted to complete the approval process. DoD/DARPA funding cannot be used towards human subjects research until ALL approvals are granted.

### 6.2.3. Animal Use

Award recipients performing research, experimentation, or testing involving the use of animals shall comply with the rules on animal acquisition, transport, care, handling, and use as outlined in: (i) 9 CFR parts 1-4, Department of Agriculture rules that implement the Animal Welfare Act of 1966, as amended, (7 U.S.C. § 2131-2159); (ii) National Institutes of Health Publication No. 86-23, "Guide for the Care and Use of Laboratory Animals" (8th Edition); and (iii) DoD Instruction 3216.01, "Use of Animals in DoD Programs."

For projects anticipating animal use, proposals should briefly describe plans for Institutional Animal Care and Use Committee (IACUC) review and approval. Animal studies in the program will be expected to comply with the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals, available at http://grants.nih.gov/grants/olaw/olaw.htm.

All award recipients must receive approval by a DoD-certified veterinarian, in addition to an IACUC approval. No animal studies may be conducted using DoD/DARPA funding until the United States Army Medical Research and Materiel Command (USAMRMC) Animal Care and Use Review Office (ACURO) or other appropriate DoD veterinary office(s) grant approval. As a part of this secondary review process, the award recipient will be required to complete and submit an ACURO Animal Use Appendix, which may be found at https://mrmc-www.army.mil/index.cfm?pageid=Research_Protections.acuro&rn=1.

### 6.2.4. Export Control

Per DFARS 225.7901-4, all procurement contracts, other transactions and other awards, as deemed appropriate, resultant from this solicitation will include the DFARS Export Control clause (252.225-7048).

### 6.2.5. Subcontracting

Pursuant to Section 8(d) of the Small Business Act (15 U.S.C. § 637(d)), it is the policy of the Government to enable small business and small disadvantaged business concerns to be considered fairly as subcontractors to contractors performing work or rendering services as prime contractors or subcontractors under Government contracts, and to assure that prime contractors and subcontractors carry out this policy. Each proposer who submits a contract proposal and includes subcontractors is required to submit a subcontracting plan in accordance with FAR 19.702(a) (1) and should do so with their proposal. The plan format is outlined in FAR 19.704.

### 6.2.6. Employment Eligibility Verification

As per FAR 22.1802, recipients of FAR-based procurement contracts must enroll as federal contractors in E-verify and use the system to verify employment eligibility of all employees assigned to the award. All resultant contracts from this solicitation will include FAR 52.222-54, "Employment Eligibility Verification." This clause will not be included in grants, cooperative agreements, or Other Transactions.

### 6.2.7. System for Award Management (SAM) and Universal Identifier Requirements

Unless the proposer is exempt from this requirement, as per FAR 4.1102 or 2 CFR 25.110 as applicable, all proposers must be registered in the System for Award Management (SAM) and have a valid Data Universal Numbering System (DUNS) number prior to submitting a proposal. All proposers must maintain an active registration in SAM with current information at all times during which they have an active Federal award or proposal under consideration by DARPA. All proposers must provide the DUNS number in each proposal they submit.

Information on SAM registration is available at www.sam.gov.

### 6.2.8. Reporting Executive Compensation and First-Tier Subcontract Awards

FAR clause 52.204-10, "Reporting Executive Compensation and First-Tier Subcontract Awards," will be used in all procurement contracts valued at $25,000 or more. A similar award term will be used in all grants and cooperative agreements.

### 6.2.9. Updates of Information Regarding Responsibility Matters

Per FAR 9.104-7(c), FAR clause 52.209-9, Updates of Publicly Available Information Regarding Responsibility Matters, will be included in all contracts valued at $500,000 or more where the contractor has current active Federal contracts and grants with total value greater than $10,000,000.

### 6.2.10. Representations by Corporations Regarding an Unpaid Delinquent Tax Liability or a Felony Conviction under any Federal Law

The following representation will be included in all awards:

(a) In accordance with section 101(a) of the Continuing Appropriations Act, 2016 (Pub. L. 114-53) and any subsequent FY 2016 appropriations act that extends to FY 2016 funds the same restrictions as are contained in sections 744 and 745 of division E, title VII, of the Consolidated and Further Continuing Appropriations Act, 2015 (Pub. L. 113-235), none of the funds made available by this or any other Act may be used to enter into a contract with any corporation that —

> (1) Has any unpaid Federal tax liability that has been assessed, for which all judicial and administrative remedies have been exhausted or have lapsed, and that is not being paid in a timely manner pursuant to an agreement with the authority responsible for collecting the tax liability, where the awarding agency is aware of the unpaid tax liability, unless the agency has considered suspension or debarment of the corporation and made a determination that this further action is not necessary to protect the interests of the Government; or
>
> (2) Was convicted of a felony criminal violation under any Federal law within the preceding 24 months, where the awarding agency is aware of the conviction, unless the agency has considered suspension or debarment of the corporation and made a determination that this action is not necessary to protect the interests of the Government.

(b) The Offeror represents that –

(1) It is [ ] is not [ ] a corporation that has any unpaid Federal tax liability that has been assessed, for which all judicial and administrative remedies have been exhausted or have lapsed, and that is not being paid in a timely manner pursuant to an agreement with the authority responsible for collecting the tax liability,

(2) It is [ ] is not [ ] a corporation that was convicted of a felony criminal violation under a Federal law within the preceding 24 months.

### 6.2.11. Cost Accounting Standards (CAS) Notices and Certification

As per FAR 52.230-2, any procurement contract in excess of the referenced threshold resulting from this solicitation will be subject to the requirements of the Cost Accounting Standards Board (48 CFR 99), except those contracts which are exempt as specified in 48 CFR 9903.201-1. Any proposer submitting a proposal which, if accepted, will result in a CAS compliant contract, must submit representations and a Disclosure Statement as required by 48 CFR 9903.202 detailed in FAR 52.230-2. The disclosure forms may be found at http://www.whitehouse.gov/omb/procurement_casb.

### 6.2.12. Controlled Unclassified Information (CUI) on Non-DoD Information Systems

Controlled Unclassified Information (CUI) refers to unclassified information that does not meet the standards for National Security Classification but is pertinent to the national interests of the United States or to the important interests of entities outside the Federal Government and under law or policy requires protection from unauthorized disclosure, special handling safeguards, or prescribed limits on exchange or dissemination. All non-DoD entities doing business with DARPA are expected to adhere to the following procedural safeguards, in addition to any other relevant Federal or DoD specific procedures, for submission of any proposals to DARPA and any potential business with DARPA:

- Do not process DARPA CUI on publicly available computers or post DARPA CUI to publicly available webpages or websites that have access limited only by domain or Internet protocol restriction.
- Ensure that all DARPA CUI is protected by a physical or electronic barrier when not under direct individual control of an authorized user and limit the transfer of DARPA CUI to subawardees or teaming partners with a need to know and commitment to this level of protection.
- Ensure that DARPA CUI on mobile computing devices is identified and encrypted and all communications on mobile devices or through wireless connections are protected and encrypted.
- Overwrite media that has been used to process DARPA CUI before external release or disposal.

### 6.2.13. Safeguarding of Covered Defense Information and Cyber Incident Reporting

Per DFARS 204.7304, DFARS 252.204-7012, "Safeguarding of Covered Defense Information and Cyber Incident Reporting," applies to this solicitation and all FAR-based awards resulting from this solicitation.

#### 6.2.14. Prohibition on Contracting with Entities that Require Certain Internal Confidentiality Agreements

(a) In accordance with section 101(a) of the Continuing Appropriations Act, 2016 (Pub. L. 114-53) and any subsequent FY 2016 appropriations act that extends to FY 2016 funds the same restrictions as are contained in section 743 of division E, title VII, of the Consolidated and Further Continuing Appropriations Act, 2015 (Pub. L. 113-235), none of the funds appropriated (or otherwise made available) by this or any other Act may be used for a contract with an entity that requires employees or subcontractors of such entity seeking to report fraud, waste, or abuse to sign internal confidentiality agreements or statements prohibiting or otherwise restricting such employees or contactors from lawfully reporting such waste, fraud, or abuse to a designated investigative or law enforcement representative of a Federal department or agency authorized to receive such information.

(b) The prohibition in paragraph (a) of this provision does not contravene requirements applicable to Standard Form 312, Form 4414, or any other form issued by a Federal department or agency governing the nondisclosure of classified information.

(c) *Representation*. By submission of its offer, the Offeror represents that it does not require employees or subcontractors of such entity seeking to report fraud, waste, or abuse to sign or comply with internal confidentiality agreements or statements prohibiting or otherwise restricting such employees or contactors from lawfully reporting such waste, fraud, or abuse to a designated investigative or law enforcement representative of a Federal department or agency authorized to receive such information.

### 6.3. REPORTING

The number and types of reports will be specified in the award document, but will include as a minimum monthly financial status reports and quarterly technical status reports. The reports shall be prepared and submitted in accordance with the procedures contained in the award document and mutually agreed on before award. Reports and briefing material will also be required as appropriate to document progress in accomplishing program metrics. A Final Report that summarizes the project and tasks will be required at the conclusion of the performance period for the award, notwithstanding the fact that the research may be continued under a follow-on vehicle.

### 6.4. ELECTRONIC SYSTEMS

#### 6.4.1. Representations and Certifications

In accordance with FAR 4.1201, prospective proposers shall complete electronic annual representations and certifications at https://www.sam.gov/portal/SAM.

### 6.4.2. Wide Area Work Flow (WAWF)

Unless using another approved electronic invoicing system, performers will be required to submit invoices for payment directly via the Internet/WAWF at http://wawf.eb.mil. Registration to WAWF will be required prior to any award under this BAA.

### 6.4.3. i-EDISON

The award document for each proposal selected for funding will contain a mandatory requirement for patent reports and notifications to be submitted electronically through i-Edison (http://s-edison.info.nih.gov/iEdison).

## 7. Agency Contacts

Administrative, technical or contractual questions should be sent via e-mail to SafeGenes@darpa.mil.

Points of Contact
The BAA Coordinator for this effort may be reached at:
SafeGenes@darpa.mil
DARPA/BTO
ATTN: DARPA-BAA-16-59
675 North Randolph Street
Arlington, VA 22203-2114

## 8. Other Information

### 8.1. INTELLECTUAL PROPERTY

### 8.1.1. Procurement Contract Proposers

#### 8.1.1.1 Noncommercial Items (Technical Data and Computer Software)

Proposers responding to this BAA requesting a procurement contract to be issued under the FAR/DFARS, shall identify all noncommercial technical data, and noncommercial computer software that it plans to generate, develop, and/or deliver under any proposed award instrument in which the Government will acquire less than unlimited rights, and to assert specific restrictions on those deliverables. Proposers shall follow the format under DFARS 252.227-7017 for this stated purpose. In the event that proposers do not submit the list, the Government will assume that it automatically has "unlimited rights" to all noncommercial technical data and noncommercial computer software generated, developed, and/or delivered under any award instrument. If mixed funding is anticipated in the development of noncommercial technical data, and noncommercial computer software generated, developed, and/or delivered under any award instrument, then proposers should identify the data and software in question, as subject to Government Purpose Rights (GPR). In accordance with DFARS 252.227-7013 Rights in Technical Data - Noncommercial Items, and DFARS 252.227-7014 Rights in Noncommercial Computer Software and Noncommercial Computer Software Documentation, the Government will automatically assume that any such GPR restriction is limited to a period of five (5) years in accordance with the applicable DFARS clauses, at which time the Government will acquire

"unlimited rights" unless the parties agree otherwise. Proposers are advised that the Government will use the list during the source selection evaluation process to evaluate the impact of any identified restrictions, and may request additional information from the proposer, as may be necessary, to evaluate the proposer's assertions. If no restrictions are intended, then the proposer should state "NONE." It is noted an assertion of "NONE" indicates that the Government has "unlimited rights" to all noncommercial technical data and noncommercial computer software delivered under the award instrument, in accordance with the DFARS provisions cited above. Failure to provide full information may result in a determination that the proposal is not compliant with the BAA – resulting in nonselectability of the proposal.

A sample list for complying with this request is as follows:

| NONCOMMERCIAL | | | | |
|---|---|---|---|---|
| Technical Data Computer Software To be Furnished With Restrictions | Summary of Intended Use in the Conduct of the Research | Basis for Assertion | Asserted Rights Category | Name of Person Asserting Restrictions |
| (LIST) | (NARRATIVE) | (LIST) | (LIST) | (LIST) |

**8.1.1.2 Commercial Items (Technical Data and Computer Software)**
Proposers responding to this BAA requesting a procurement contract to be issued under the FAR/DFARS, shall identify all commercial technical data, and commercial computer software that may be embedded in any noncommercial deliverables contemplated under the research effort, along with any applicable restrictions on the Government's use of such commercial technical data and/or commercial computer software. In the event that proposers do not submit the list, the Government will assume that there are no restrictions on the Government's use of such commercial items. The Government may use the list during the source selection evaluation process to evaluate the impact of any identified restrictions, and may request additional information from the proposer, as may be necessary, to evaluate the proposer's assertions. If no restrictions are intended, then the proposer should state "NONE." Failure to provide full information may result in a determination that the proposal is not compliant with the BAA – resulting in nonselectability of the proposal.

A sample list for complying with this request is as follows:

| COMMERCIAL | | | | |
|---|---|---|---|---|
| Technical Data Computer Software To be Furnished With Restrictions | Summary of Intended Use in the Conduct of the Research | Basis for Assertion | Asserted Rights Category | Name of Person Asserting Restrictions |
| (LIST) | (NARRATIVE) | (LIST) | (LIST) | (LIST) |

### 8.1.2. Non-Procurement Contract Proposers - Noncommercial and Commercial Items (Technical Data and Computer Software)

Proposers responding to this BAA requesting an Other Transaction for Prototype shall follow the applicable rules and regulations governing that instrument, but in all cases should appropriately identify any potential restrictions on the Government's use of any Intellectual Property contemplated under that award instrument. This includes both Noncommercial Items and Commercial Items. Although not required, proposers may use a format similar to that described in Paragraphs 1.a and 1.b above. The Government may use the list during the source selection evaluation process to evaluate the impact of any identified restrictions, and may request additional information from the proposer, as may be necessary, to evaluate the proposer's assertions. If no restrictions are intended, then the proposer should state "NONE." Failure to provide full information may result in a determination that the proposal is not compliant with the BAA – resulting in nonselectability of the proposal.

### 8.1.3. All Proposers – Patents

Include documentation proving your ownership of or possession of appropriate licensing rights to all patented inventions (or inventions for which a patent application has been filed) that will be utilized under your proposal for the DARPA program. If a patent application has been filed for an invention that your proposal utilizes, but the application has not yet been made publicly available and contains proprietary information, you may provide only the patent number, inventor name(s), assignee names (if any), filing date, filing date of any related provisional application, and a summary of the patent title, together with either: 1) a representation that you own the invention, or 2) proof of possession of appropriate licensing rights in the invention.

### 8.1.4. All Proposers-Intellectual Property Representations

Provide a good faith representation that you either own or possess appropriate licensing rights to all other intellectual property that will be utilized under your proposal for the DARPA program. Additionally, proposers shall provide a short summary for each item asserted with less than unlimited rights that describes the nature of the restriction and the intended use of the intellectual property in the conduct of the proposed research.

## 8.2. PROPOSERS DAY

DARPA will host a Proposers Day in support of the Safe Genes program on **Friday, September 30, 2016** at the United States Institute of Peace in Washington, DC. The purpose is to provide potential proposers with information on the Safe Genes program, promote additional discussion on this topic, address questions, provide a forum to present their capabilities, and to encourage team formation.

Interested proposers are not required to attend to respond to the Safe Genes BAA, and relevant information and materials discussed at Proposers Day will be made available to all potential proposers in the form of a FAQ posed on the FBO.gov website.

DARPA will not provide cost reimbursement for interested proposers in attendance.

An online registration form and various other meeting details can be found at the registration website, http://www.sa-meetings.com/SafeGenesproposersday.

To encourage team formation, interested proposers are encouraged to submit information to be shared with all potential proposers through the Proposers Day website and the FBO.gov website. This information may include contact information, relevant publications, and a slide or poster to summarize the proposer's interests.

Participants are required to register no later than **Friday, September 23, 2016**. This event is not open to the Press. The Proposers Day will be open to members of the public who have registered in advance for the event; there will be no onsite registration.

In-person attendance will be accepted on a first come first serve basis, subject to room restrictions.

All foreign nationals, including permanent residents, must complete and submit a DARPA Form 60 "Foreign National Visit Request," which will be provided in the registration confirmation email.

**Proposers Day Point of Contact: DARPA-SN-16-67@darpa.mil.**

# 9. APPENDIX 1 – Volume II checklist

**Volume II, Cost Proposal**
**Checklist and Sample Templates**

**The following checklist and sample templates are provided to assist the proposer in developing a complete and responsive cost volume. Full instructions appear in Section 4.3.2.b beginning on Page 36 of DARPA-BAA-16-59. This worksheet must be included with the coversheet of the Cost Proposal.**

1. Are all items from Section 4.3.2.b (Volume II, Cost Proposal) of DARPA-BAA-16-59 included on your Cost Proposal cover sheet?
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]
   If reply is "No", please explain:

2. Does your Cost Proposal include (1) a summary cost buildup by Phase, (2) a summary cost buildup by Year, and (3) a detailed cost buildup of for each Phase that breaks out each task and shows the cost per month?
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

   If reply is "No", please explain:

3. Does your cost proposal (detailed cost buildup #3 above in item 2) show a breakdown of the major cost items listed below:
   Direct Labor (Labor Categories, Hours, Rates)
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

   Indirect Costs/Rates (i.e., overhead charges, fringe benefits, G&A)
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

   Materials and/or Equipment
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

   Subcontracts/Consultants
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

   Other Direct Costs
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

   Travel
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

   If reply is "No", please explain:

4. Have you provided documentation for proposed costs related to travel, to include purpose of trips, departure and arrival destinations and sample airfare?
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

If reply is "No", please explain:

5. Does your cost proposal include a complete itemized list of all material and equipment items to be purchased (a priced bill-of-materials (BOM))?
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

   If reply is "No", please explain:

6. Does your cost proposal include vendor quotes or written engineering estimates (basis of estimate) for all material and equipment with a unit price exceeding $5000?
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

   If reply is "No", please explain:

7. Does your cost proposal include a clear justification for the cost of labor (written labor basis-of-estimate (BOE)) providing rationale for the labor categories and hours proposed for each task?
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

   If reply is "No", please explain:

8. Do you have subcontractors/consultants? If YES, continue to question 9. If NO, skip to question 13.
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

9. Does your cost proposal include copies of all subcontractor/consultant technical (to include Statement of Work) and cost proposals?
   ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

   If reply is "No", please explain:

10. Do all subcontract proposals include the required summary buildup, detailed cost buildup, and supporting documentation (SOW, Bill-of-Materials, Basis-of-Estimate, Vendor Quotes, etc.)?
    ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

    If reply is "No", please explain:

11. Does your cost proposal include copies of consultant agreements, if available?
    ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

    If reply is "No", please explain:

12. If requesting a FAR-based contract, does your cost proposal include a tech/cost analysis for all proposed subcontractors?
    ○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

    If reply is "No", please explain:

13. Have all team members (prime and subcontractors) who are considered a Federally Funded Research & Development Center (FFRDC), included documentation that clearly demonstrates work is not otherwise available from the private sector AND provided a letter on letterhead from the sponsoring organization citing the specific authority establishing their eligibility to propose to government solicitations and compete with industry, and compliance with the associated FFRDC sponsor agreement and terms and conditions.

○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

If reply is "No", please explain:

14. Does your proposal include a response regarding Organizational Conflicts of Interest?

○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

If reply is "No", please explain:

15. Does your proposal include a completed Data Rights Assertions table/certification?

○ **YES** ○ **NO** **Appears on Page(s)** [Type text]

If reply is "No", please explain: