PHASE I/RESEARCH & DEVELOPMENT QUESTIONS:

1. Does the NOW device need to optimize the DNA/RNA sequence, or is the input to the “box” a predefined or pre-optimized sequence that is ready to be created?

   No, the device does not need to optimize the DNA/RNA sequence. Proposing teams are responsible for identifying their own pathogen/threat target products to be generated during the capability demonstrations, except for the DARPA-defined sequence in capability demonstration #4.

2. What is DARPA’s attitude towards (fill in the blank) technology?

   We will not comment on specific technologies. Proposed technologies and approaches must fit within the boundaries and spirit of the NOW program.

3. Is it important for the system to be able to make completely arbitrary DNA/RNA sequences?

   It is critical that the NOW device is able to synthesize whatever DNA/RNA sequence is required. In the real world, the sequence may not be known with much lead-time, and therefore the technology should be agnostic.

4. Is there a preference for nucleic acid antibodies over antigens or are vaccines an acceptable test of the platform?

   Targets should be DoD-relevant and any prophylactic/therapeutic approach is appropriate. DARPA uses prophylactic and therapeutic interchangeably in the BAA.

5. Does the program disfavor chemical synthesis approaches? Also – is the use of organic solvents in a synthetic method allowed?

   The NOW program does not favor enzymatic synthesis over chemical synthesis. Proposals should address the practical use of chemical solvents in a distributed setting (i.e. safety, handling, disposal, etc.) if chemical synthesis is the proposed approach.

6. What if the target molecule is smaller than the product length metrics specified in the BAA?

   If the proposal can provide sufficient rationale for the choice of prophylactic target, and that target happens to be smaller than the BAA metrics, the proposal will be considered responsive.

7. Are technologies related to nucleic acid sequence engineering for maximum protein yields (thereby reducing the required quantity of nucleic acid needed to be synthesized) within the scope of the program?

   Yes, as long as all other program metrics/aspects are met.
8. **Does the final product need to simply be a DNA/RNA in buffer, or is a delivery vehicle and/or carrier needed? Is liquid or lyophilized formulation in a vial the only final preparation of interest to DARPA?**

It depends on the therapeutic target product. Ultimately the platform needs to develop products to be used in humans right from the box.

DARPA has no preference as long as the system produces the final product for direct-to-human use.

9. **Does the system have to produce individual doses, or can it produce a single bulk vial?**

The NOW system needs to formulate for direct delivery. This does not necessarily mean that the product is in a vial per se, but the product should be filled into a container from which single doses can be easily drawn. DARPA does not want bulk products in the field; however, a multidose format is allowed as long as sterility can be maintained.

10. **Can DARPA provide more clarity on “100% sequence fidelity” vs “identity.” Given that no sequencing system is 100% accurate, what is the accepted limit of detection of the sequencer used to determine the fidelity of the product? Does the sequence verification need to be part of the machine?**

The product must have 100% sequence identity to reference standard.

The sequencing approach will need to be defined in the proposal, along with its error rates. The proposal will need to address the depth of sequencing coverage, and how the approach will verify that the sequence is accurate at the global level.

Yes, the sequencer needs to be part of the system.

11. **Is de novo DNA synthesis applicable?**

Yes, but the proposal must describe how the technology will scale to meet the BAA metrics.

12. **What types of targets are of most interest to DARPA?**

DARPA is primarily interested in prophylactic products. Targets can include infectious disease targets as well as targets to protect against chemical or radiological threats.

13. **What do the purity metrics mean - DNA/RNA vs all other components? Or desired DNA/RNA vs other DNAs/RNAs?**

The BAA specifies that the final product must contain less than 1% impurities, including raw materials and other nucleic acid byproducts. However, DARPA defers to regulatory agencies for specific requirements.

14. **Will DARPA allow raw materials, such as enzymes and other starting materials, to be made in bulk in the US and then shipped abroad with the NOW device?**

Yes.
15. Why is the early RNA threshold set below DNA, then switches dramatically by the end – Is this because DARPA envisions the average dose of RNA needing to be 2.5 times larger than a DNA dose?

NOW threshold and objective values were set based on current state of the art DNA and RNA technologies for both vaccines and encoded therapeutic proteins, with the threshold typically meeting vaccine doses and the objective meeting encoded therapeutic doses. The ultimate goal of the NOW program is to develop capabilities to manufacture 100s of doses of DNA or RNA. Proposers should provide the rationale for the quantity of nucleic acid they are synthesizing based upon expected dose levels of the proposed medical countermeasure at the end of the program.

16. In challenge #1 there is no quantity mentioned. I assume this can then be any amount?

Yes.

17. In challenges #1 and #2 where we are making the target of our choice, do we have to start from electronic sequence each time, or do we start from the starting template we will have made before? Can the fragments / template be considered starting material?

The goal of the challenges is to test the ability to synthesize nucleic acids from sequence, if the template is something that could be used as a starting material (i.e. template is not product specific) then that could be reused for each challenge.

PHASE II/INTEGRATION QUESTIONS:

1. Who are the “DARPA transition partners” that the team needs to collaborate with to produce the devices?

Reference page 9 of BAA; the proposal should provide a general plan for how the device would be manufactured at scale in the future by other government transition partners from Health and Human Services and the Department of Defense.

2. Is equivalency proven in the animal models?

Yes, but only on a research scale.

3. Is there a shelf life requirement of the final product?

No.

4. Is there a preferred method of delivery of the RNA final product?

No. The delivery method is defined by the product identity.

5. Is the proposer responsible for the mobile unit, or only the 6x6x6 manufacturing equipment? Is the final system size limited to a single 6x6x6 container, or can it be comprised of multiple containers, all of which can fit inside a single shipping container?

The Government will provide the truck and Conex box. The Conex box itself will contain the generator fuel and water, so the NOW system cannot occupy the entire space. Thus, the 6x6x6 system is ideal.
6. Can you please specify the size of the power and water supply that would be needed in the container?

Field standards are difficult to define and requirements will vary depending on the technology. Proposers should address the anticipated size of the system to facilitate mobile use within the 20' ISO 668 container.

7. Who is the intended end-user of the system at the end of the program?

The NOW system is ultimately intended to function with minimal user-training (one week or less). The expected user could be a medic or similar.

8. What is the level of operator skill for month 36 and earlier?

Operator skill for month 36 and earlier – the operators can be highly technical and extensively trained on the instrumentation.

9. Will the system need to be capable of verifying the sterility of final vials?

DARPA intends to deliver a contained system. DARPA fully acknowledges that vialing in a closed system may be quite difficult and that this step will likely occur in an open air environment. Vials will likely need to be held for sterility testing. DARPA hopes that rapid sterility testing technologies will be developed independently of, but concurrently with, this effort that could eventually be utilized.

10. What are the certification requirements around the final system? Are certifications such as UL/CE/MIL required?

A: No certifications are required at the end of the NOW program; however, engagement with stakeholder groups throughout the program will illuminate certifications that may be required during advanced development with transition partners.

PHASE III QUESTIONS

1. Please clarify the timeline for producing the first 100 doses in Capability Demonstration #4 - is it 24 hours or 1-3 days?

DARPA sets a “stretch” goal of 500 doses per day, but aims for 100 doses in the first 24 hours.

2. Clinical Trial
   a. What are the expectations around the clinical trial with respect to SAFETY vs EFFICACY?

   DARPA intends to fund a Phase I clinical safety trial; efficacy will be assessed in animals alone during the scope of the program.

   b. What is the anticipated cost of the clinical trial?

   The clinical trials costs should be proposer-defined.

   c. Is the human subject research data required to be de-identified?

   No, but any Human Subjects Research will need HRPO approval.

   d. Is DARPA looking for novel/newly discovered candidates for the clinical trial?
No. NOW is not a pre-clinical MCM discovery program; the MCM discovery community (whether NOW performer or not) is responsible for determining the sequence to be made. The candidates can be performer-defined or derived from the larger research community.

3. Please clarify in more detail the expectation for the timing and deliverables for the clinical trial within Phase 3, such as completion of the dose regimen for all patients.

A: Given that a clinical study of a nucleic acid product could be associated with an extensive timeline as required by regulatory agencies, the expectation of the NOW program is that an IND will be filed and a clinical study will begin in year 5 of the program, ideally with initial safety and efficacy readouts available by the end of year 5.

4. Can we assume that DARPA transition partners will select the MCM molecule and delivery method for performing teams to carry-out in human safety trial?

A: The MCM molecule for a human safety trial will be determined by the performer team, however, if the team does not have a MCM for clinical study at the proposal stage, there will be opportunities for interactions with DARPA performers in the space of nucleic acid based MCMs to determine a relevant molecule and associated formulation/delivery strategy for clinical studies. This meeting is described on page 9 of the BAA.

5. Producing an MCM via conventional/existing methods would require a separate IND with a different CMC section (relative to methodology developed under DARPA NOW). Can we assume that DARPA transition partners will provide a licensed or very advanced product for comparison in Phase 3 of the program?

A: As part of the interactions described in the above question it is anticipated that clinical material from previous DoD investments will be available for a comparison in a safety study. However, it should be noted that a phase I study of NOW derived material can be performed independent of a phase I study of a traditionally manufactured material if the study is performed in a manner that will allow comparison of the clinical results (i.e. an aligned dosing regimen for both clinical protocols).

6. IN table 3, the timeline for synthesis says it includes animal testing. Most vaccines take many weeks just for a read out. Exactly what animal studies are expected to be completed within the <1 week timeline at 36 months?

The animal studies should be initiated, it is not expected that a final readout from the experiment is completed within 1 week.

7. Have you confirmed with the FDA that DARPA’s ideas for entering clinical trials are acceptable?

DARPA will engage with the FDA throughout the duration of the NOW program.

8. How will the FDA regulate this platform?

DARPA does not influence the regulatory process in any manner, therefore any products made using the NOW system will undergo regulatory approval using standard FDA procedures.

9. Do we need to engage agencies other than the FDA if the system will be distributed worldwide?

A: Although eventual worldwide distribution is a broad goal of the NOW program, the FDA is the only regulatory agency for which engagement is required during NOW.
GENERAL QUESTIONS:

1. Is any program data expected to be Controlled Unclassified Information (CUI)?
No CUI is anticipated for general data, except PII associated with clinical studies.

2. Where will the PPTs from this meeting be posted?
PowerPoint (PPT) presentations will be posted to the NOW Proposers Day website, as well as the DARPA Opportunities page.

3. Will proposers receive extensive feedback on abstracts?
Feedback will be provided in accordance with Section 6.1.1 of the BAA.

4. Are subcontracts part of the direct/indirect costs?
Subcontracts are part of the direct costs of the Prime contractor.

5. Can companies/groups be part of multiple proposals?
Yes, a person, institution, or company may be part of more than one team. DARPA will only pay once for identical work being done under multiple awards so the Performers/DARPA will have to decide which award will be charged.

6. Are there any considerations or limitations regarding ownership of companies by non-US entities?
Per the BAA, “Non-U.S. organizations and/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.”

7. Are we required to have a US subcontractor as a part of the consortium, or can all partners be from Europe?
There is no requirement to have a US subcontractor as part of any consortium.

8. If patentable Intellectual Property (IP) is developed, may the company retain ownership and assignment?
Yes, the company may retain ownership of IP, in which case the Government has a license to it. Assignment may be subject to the written approval of the Government in certain circumstances.

9. What is DARPA’s plan for biosecurity/dual-use sequence concerns? Will a security plan be implemented post-abstract?
Security is a major concern, and should be associated with the NOW system technology package. DARPA plans to address security with each individual performer team as the solutions are anticipated to be technology-specific such that the system won’t be easily hacked.

10. Can you further define specialized handling or disposal? Most DNA processes, even if using non-toxic materials, cannot be poured down the drain. Do we need to build in an autoclave, for example?
Inclusion of an autoclave is not necessary as part of a NOW proposal. Proposers should address any specialized handling and disposal of materials in their proposal and should strive to minimize hazardous
materials that will require extensive safety protocols for the end user. Proposers should be aware that end users will be often be functioning near a field hospital.

11. **What is meant by “regulatory framework” in Section 1.5.2 (Regulatory Strategy)?**

It is expected that proposers will include the anticipated timeline for regulatory interactions and appropriate costs associated with preparing regulatory documents as part of the proposal.

12. **Can the commercially relevant target be anything? i.e. can it be non-prophylactic, for example oncology?**

Yes – anything relevant.

13. **Is there a budget range expected by DARPA? (e.g. max funding)**

To avoid biasing proposals that are submitted, DARPA is not defining an anticipated budget at this time and will not predetermine award amounts; however, typical DARPA BTO program budgets range from $50-100M over 3-5 years. We anticipate funding more than one team.

14. **If a component of the NOW system is receiving funding from an entity external to DARPA, can we still apply to the NOW BAA?**

A: Yes. While the technical approaches to the entire NOW system must be defined and described to meet the metrics set forth in the BAA, components that are receiving external funding should be identified and their cost should not be included in the cost of the proposal. The proposal must identify any restrictions on DARPA's intellectual property rights to components that are funded outside of the NOW program.

15. **What is DARPA policy on the purchase of capital equipment if it is used exclusively or partially for program work?**

A: As stated on page 29 of the BAA, any equipment purchases associated with the proposed research should be included as an: “itemized list, which includes description of equipment, unit price, quantity, and total price. Any equipment item with a unit price over $5,000 must include a vendor quote.” The list will be evaluated in accordance with the criteria set forth in the BAA, just like all other cost proposal elements.

16. **Can national labs lead NOW proposals? How will subcontracts work with national labs?**

National Labs can lead NOW proposal teams, but such proposals cannot be submitted directly against the BAA. Proposals with a National Lab as lead must be submitted directly to the NOW Program Manager. National Labs can be proposed as subawardees, but, since they cannot compete against private industry, the Lab’s work will be removed from any award and treated as Government Furnished services funded directly by the Government. The effort provided by a National Lab will be made available to all NOW performers.