ARPA-H Frequently Asked Questions

I. ARPA-H Overview

What is the motivation for ARPA-H?

America has an extraordinary biomedical ecosystem, which has delivered advances that not long ago would have been inconceivable — such as drugs that unleash the immune system to eliminate certain cancers and COVID-19 vaccines that were rapidly developed and authorized for use in a mere eleven months. These stunning advances underscore that we stand at a moment of unprecedented scientific promise. They challenge us to ask:

- *What can we do to harness this momentum and dramatically accelerate turning this scientific promise into breakthroughs throughout medicine and health?*
- *What will it take to end cancer as we know it?*
    - *To properly protect ourselves from pandemics?*
    - *To prevent the ravages of Alzheimer's disease?*
    - *To develop health solutions that can serve all Americans?*

What is the mission of ARPA-H?

The proposed mission is "to benefit the health of all Americans by catalyzing health breakthroughs that cannot readily be accomplished through traditional research or commercial activity".

What gaps in the biomedical ecosystem is ARPA-H aiming to fill?

The current biomedical research ecosystem has historically been driven by two components:

- the important *fundamental research*, largely supported by NIH, a component of HHS, that has made great progress in uncovering the underlying mechanisms of health and disease
- the vibrant *biopharmaceutical industry* that has created products for patients in a multitude of disease areas
- Often a critical gap remains. Some of the best ideas, which could yield bold breakthroughs, do not fit well into either half of our current system, because:
    - the risk is too high
    - the cost is too large
    - the time frame is too long
    - the focus is too applied for academia
    - there is a need for complex coordination among multiple parties
    - the near-term market opportunity is too small to justify commercial investment
    - the scope is so broad that no company can realize the full economic benefit

The purpose of ARPA-H will be to support promising opportunities that fall in this gap.

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What types of projects could ARPA-H support?

ARPA-H could fund programs and projects that undertake challenges ranging from the molecular to the societal, with the potential to transform entire areas of medicine and health by:

- Tackling bold challenges requiring large scale, sustained coordination, including those which span equities across the US government
- Creating new capabilities (e.g., technologies, data resources, disease models)
- Supporting high-risk exploration that could establish entirely new paradigms
- Overcoming market failures through critical solutions, including financial incentives

Whereas most NIH proposals are "curiosity-driven," ARPA-H ideas would be largely "use-driven" research—that is, research directed at solving a practical problem.

What are examples of transformative progress that ARPA-H could drive?

ARPA-H has the potential to accelerate advances in a range of biomedical and health research areas and diseases – from cancer to hypertension to infectious diseases to population-level behavioral interventions. Some illustrative examples include:

Cancer and Other Chronic Diseases
- *Vaccines that can prevent most cancers*. Use messenger RNA (mRNA) vaccines to teach the immune system to recognize any of 50 common genetic mutations that drive cancers, so that the body will wipe out cancer cells when they first arise.
- *New manufacturing processes to create patient-specific T-cells* to search and destroy malignant cells, decreasing costs from $100,000s to $1000s to make these therapies widely available.
- *Molecular 'zip codes' that target a drug or gene therapy vector to any specific tissue and cell type*, to make treatments much more effective by treating diseases at their source and eliminating side effects due to consequences in other tissues.
- *Small, highly accurate, inexpensive, non-intrusive, wearable 24/7 monitors* (e.g., smart watches) for blood pressure and blood sugar.
- *New approaches to accelerate discovery of brain imaging and blood biomarkers* capable of measuring synaptic loss, neuronal death, and glial inflammatory pathways, as a means of tracking responses to potential Alzheimer's disease therapies.

Healthcare Access, Equity and Quality
- *Platforms to reduce health disparities in maternal morbidity and mortality*, which are among the highest in the world, by identifying those at highest risk for pregnancy complications and providing ethically-integrated, regular virtual house calls by nurses and midwives, from early in pregnancy through at least 6 months postpartum.
- *Platforms to promote better health outcomes through substantially improving how medication is taken*, as recommended, on a regular basis or over a standard course (e.g., for hypertension, diabetes, infections), by engaging community health workers aided by privacy-preserving smart devices and telehealth

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II. Designing ARPA-H Based on Lessons Learned from DARPA

What is DARPA?

Launched in the wake of Sputnik, the Defense Advanced Research Projects Agency (DARPA) has had a singular mission: to make pivotal investments in breakthrough technologies for national security. DARPA has played a key role in generating bold advances that have shaped the world—such as the internet, Global Positioning Systems, and self-driving cars—and has contributed to the development of many others, including mRNA vaccines. For more detail, see: https://www.darpa.mil/about-us/about-darpa

How is DARPA organized and structured?

DARPA has been successful by organizing around the following:

- Encouraging a culture that values a relentless drive for transformative technical results and a willingness to take risks. Notably, it does not focus on merely accelerating ordinary products to the market, but on creating true breakthroughs.
- Maintaining a flat, nimble, and non-bureaucratic organization whose work is driven by approximately 100 term-limited program managers (PMs) and office directors.
- Recruiting PMs from industry or top research universities who bring bold, risky ideas.
- Giving PMs the resources and authority to select a portfolio of projects that pursue multiple approaches (through a competitive process) to achieve a clearly defined goal, while empowering them to promote collaboration and integration across performers.
- Limiting its focus to supporting research done by companies, universities, and others. DARPA does not perform its own internal research.
- Using broad, flexible hiring and procurement authorities, including very flexible contracts and "other transactional authorities" (OTA).
- Attracting extraordinary directors who are nominated by the Secretary of Defense and appointed directly by the President. Their appointment does not require Senate confirmation.

Today, DARPA comprises approximately 220 government employees in six technical offices, including nearly 100 program managers, who together oversee about 250 research and development programs.

How does DARPA determine what risks are worth taking?

DARPA makes use of a set of questions developed by former DARPA director, George H. Heilmeier (1975-1977), known as the "Heilmeier Catechism". These questions help Agency officials consider and evaluate proposed research programs.
- What are you trying to do? Articulate your objectives using absolutely no jargon.
- How is it done today, and what are the limits of current practice?
- What is new in your approach and why do you think it will be successful?

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- Who cares? If you are successful, what difference will it make?
- What are the risks?
- How much will it cost?
- How long will it take?
- What are the mid-term and final "exams" to check for success?

How does DARPA review proposals?

DARPA proposals are rigorously reviewed by a group of experts within the federal government, who do not score or rank the proposals. Rather, they determine whether the proposals are suitable for funding or not ("selectability determination") based on the evaluation criteria outlined in the announcement. The PMs then assemble the portfolio of those applications that are suitable for funding that best accomplishes the goals and objectives of the program.

Is DARPA a good model for biomedical and health research?

DARPA is an excellent inspiration for ARPA-H, but it is not a perfect model for biomedical and health research because:
- It serves the needs of a single customer, the DOD
- Its mission is focused on national security
- Its programs and projects typically involve engineered systems.

By contrast, breakthroughs in health:
- Interact with biological systems that are much more complex and more poorly understood than engineered systems, requiring close coupling to a vast body of biomedical knowledge and experience
- Interact with a complex world of many different customers and users — including hospitals, physicians, individuals/patients, biopharma companies, and payers
- Interact in complex ways with human behavior and social factors
- Require navigating a complex regulatory, reimbursement, and distribution landscape

ARPA-H can learn from DARPA, but will need to pioneer new approaches.

Does DARPA have an intramural research component?

No, DARPA does not have its own laboratories or research facilities

III. Structure of ARPA-H

How will ARPA-H be structured?

ARPA-H will be a relatively lean, flat, and dynamic organization. It will be centered around ensuring risk tolerance and instilling a sense of urgency, nimbleness, and innovation to push the limits of biomedical and health research.

ARPA-H will embrace DARPA's organizational model of having world-class program managers (PMs) who come from industry, academia, or elsewhere for limited periods of time, are chosen

because they bring ideas, and have broad autonomy to fund. The PMs develop and manage their programs, actively engage with their performers, apply thoughtful metrics and milestones, and monitor progress. Leading experts in various business and administrative areas will also be recruited to provide the mechanisms and pathways for PMs to be successful. ARPA-H will be headed by an innovative leader with substantial authority and independence to act.

Will ARPA-H have an intramural research component?

No, ARPA-H likely will not have a typical, standing intramural program. However, where essential for its programs, ARPA-H might draw on and support research elsewhere at Federal or Federally-supported labs for specific programs or projects.

Will ARPA-H be housed within NIH? Why?

Yes, ARPA-H is proposed to be housed within NIH for two reasons:
- The goals of ARPA-H fall squarely within NIH's mission – "to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability".
- ARPA-H will need to draw closely upon NIH's role as a global leader in biomedical research, including its knowledge, expertise, and ongoing activities. Setting up ARPA-H within NIH will ensure scientific collaboration and productivity and avoid unproductive or rival duplication of scientific and administrative effort.

Where will ARPA-H be physically located?

There is broad agreement that ARPA-H should not be located on the NIH main campus in Bethesda, MD. Physical distance from the main campus will facilitate the development of a distinct culture, as well reinforce the independence of ARPA-H. This approach is similar to that of DARPA, which benefits from this same autonomy by being located several miles from the Pentagon.

There are advantages to situating ARPA-H near the NIH campus, including the ability to support its operational and administrative needs, particularly early in its establishment. On the other hand, some people have suggested housing ARPA-H in other cities. We are still discussing the benefits and disadvantages of other locations, such as those with a vibrant entrepreneurial culture and access to large pools of potential program managers.

IV. Ensuring that ARPA-H Takes Risks and Learns from Failure

Will ARPA-H be allowed to take risks?

It is critical that the ARPA-H culture support the program managers in taking risks to accomplish bold goals. The cost of that boldness is that not all programs and projects will be successful. If all of the programs and projects are succeeding, they are not ambitious enough. Indeed, failing and learning from those failures will help to catalyze future successes.

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As an element of embracing risk, how will ARPA-H ensure research failures are not detrimental to the careers of researchers, particularly trainees?

We recognize that ending programs and projects could have an impact on the careers of performers and their trainees. ARPA-H will use approaches to minimize the impact — for example, retaining certain elements of a programs or project, allowing a longer shut-down time, permitting current work to reach the next milestone, and combining teams to enhance efforts. Further, ARPA-H likely will also support a program for investigators at early stages of their career, providing a pathway to enhance their research and career development while building a cohort of ARPA-H investigators.

V. Prioritization of Programs and Disease Areas

Is the focus of ARPA-H limited to specific diseases, such as cancer, Alzheimer's, and diabetes?

No, ARPA-H will not solely focus on any specific diseases or conditions. Moreover, many ARPA-H programs will aim to build and develop capabilities and platforms that are broadly applicable to a wide range of diseases and conditions (including but not limited to cancer, Alzheimer's, and diabetes).

How will ARPA-H develop programs?

Program managers will identify important needs that can't currently be filled through traditional research or commercial activity and/or that requires a high-risk/high-reward solution to a future, projected problem. The ideas for these needs could arise from multiple sources, including the program managers themselves, patients or their advocates, providers, the academic research community, industry, Federal agencies, and others. Ultimately, it will be the responsibility of the program manager to focus on a key problem or idea and develop a bold program to address it.

How will ARPA-H decide which programs and projects it should fund?

Program managers will pitch their ideas for a program to the ARPA-H director. Once approved, ARPA-H will solicit and review applications, adapting the DARPA model for review based on the principle that generating big rewards requires taking big risks. These capable program managers will assemble a portfolio of complementary approaches to pursue the program objective, incorporating experts from multiple disciplines and convening unique teams. Essentially, they will lay out the challenge and the ideal future state, and place bets on different approaches to achieve a transformative solution. The ARPA-H director will give the program managers the independence to implement the program, empowering them to do what they do best – think creatively about science.

Ultimately, the director of ARPA-H will have the authority to decide which programs will be pursued and to set the agency's priorities.

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VI. Fostering Equity, Diversity, and Access

Will health equity be an important aspect of ARPA-H?

Yes, ARPA-H will be committed to improving health equity — including with respect to race, ethnicity, gender/gender identity, sexual orientation, disability, geography, employment and insurance status, and socioeconomic status. This will be an essential element of ARPA-H's programs, operations, and projects.

How can we ensure that ARPA-H funding will reach broadly across the nation geographically, but also in a way that ensures inclusion across race, gender, and ethnicity – especially for those who have historically been underrepresented in biomedical research and development?

This will be a priority for ARPA-H.

We must understand diseases from all lenses and deliver benefits to those who are disproportionately affected by health inequities. Therefore, equity considerations – including race, ethnicity, gender/gender identity, sexual orientation, disability, geography, employment and insurance status, and socioeconomic status – will be woven throughout the ARPA-H mission. Some programs and projects will be directly focused on addressing health equity, and all programs and projects will consider equity in their design. Further, we will identify a senior leader within ARPA-H who will be responsible for ensuring issues of equity are considered in all aspects of ARPA-H's work – from scientific program development to performers receiving awards to staff recruitment and hiring.

Are there opportunities for ARPA-H to address prevention, early detection, and/or environmental factors?

Yes. ARPA-H will be focused on health broadly – from molecular to societal levels. Any program solving a difficult challenge that others are not able to tackle and that has the potential to deliver significant benefits to human health may be considered.

How will equity and diversity in staffing be ensured?

We will identify a senior leader within ARPA-H who will be responsible for ensuring issues of equity are considered in all aspects of ARPA-H's work – from scientific program development to staff recruitment and hiring.

Many health concerns are global in nature. To what extent will ARPA-H have a global focus and partner with global institutions?

Our experience with the COVID-19 pandemic highlighted that diseases and pathogens know no boundaries. ARPA-H will work with global partners to cast the widest net possible when solving challenges to promoting the health and well-being of Americans.

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Organizationally, there are several ARPA-like innovation entities being considered or established in other countries or with a global focus, and ARPA-H will cultivate partnerships and cooperation with these entities, where appropriate.

What is the model for ensuring broad access to the platforms that are developed through ARPA-H funding?

Broad access to the platforms, capabilities, and other innovations arising out of ARPA-H will be critical. Doing so likely will vary depending on the program, including partnerships with industry, Federal agencies, or other stakeholders.

VII. Hiring

What are the characteristics of an ARPA-H director? How will they be selected and who will they report to? The ARPA-H director will be critical to the culture and will inject the principles of risk-tolerance, urgency, and innovation into every decision. The ARPA-H director will be an extraordinary leader and have a proven innovation track-record and a vision for driving transformative change. They will likely have a strong background in the private sector and potentially experience in or working with the government and/or academia. They will be a diplomatic and charismatic leader, who can build partnerships across an array of sectors. They will also have an innate ability to recruit and energize a phenomenal team of experts and then provide the team with the autonomy and independence to carry out their vision, all while being supportive and facilitating their efforts (e.g., preventing or eliminating barriers to success).

The exact process for appointing the director is still being developed and considered. Options include appointment by the President or by the Secretary of Health and Human Services. The reporting structure for the ARPA-H director is still being considered as well.

What will the tenure of the ARPA-H director be?

The ARPA-H director will be term limited, potentially up to 5 years. The possibility of a single extension could be considered in rare circumstances.

How will the program managers be selected and appointed? Will the founding leadership team of ARPA-H be a diverse and inclusive team?

ARPA-H will need to hire innovative, outside-the-box thinkers with a variety of experiences that may cross industry, academia, non-profit, venture philanthropy, federal agencies, or elsewhere. Hiring a diverse and inclusive team will be integral to this process, and a senior leader within ARPA-H will be responsible for ensuring issues of equity are considered in all aspects of ARPA-H's work – from scientific program development to performers receiving awards to staff recruitment and hiring. Further, we envision that program managers will serve as term-limited federal employees for 3-year appointments, with the option to renew for an additional short time period (2-3 years).

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What are the personnel goals for the first year of ARPA-H?

During the first year, ARPA-H will need to identify and hire a director and quickly onboard approximately 30-50 program managers, along with other staff to support the mission.

VIII. Proposed Budget and Authorities

What is the proposed budget for ARPA-H?

The President's FY22 budget (https://www.whitehouse.gov/omb/budget/) proposed the creation of ARPA-H within NIH in the fiscal year 2022 (FY22) budget request. The House Appropriations Subcommittee on Labor, Health, & Human Services released their draft appropriations bill that includes $3 billion for ARPA-H (https://docs.house.gov/meetings/AP/AP00/20210715/113908/BILLS-117--AP--AP00-FY2022LHHSSubcommitteeAppropriationsBill.pdf), and the House Energy and Commerce Committee released their budget reconciliation legislative recommendations and included $3 billion for ARPA-H (https://energycommerce.house.gov/newsroom/press-releases/pallone-announces-full-committee-markup-of-build-back-better-act).

What is the timeline for ARPA-H?

The President's budget request proposes to launch ARPA-H in FY 2022.

What authorities will ARPA-H need to enact the ARPA model and operate efficiently?

ARPA-H will require several authorities to effectively deliver on its mission.
- It will need hiring authorities to rapidly recruit expert program managers outside of the civil service system and pay competitive wages for short 3-5-year terms.
- It will also need broad and flexible funding authorities that could allow it to mix and match ideas and teams with minimal bureaucracy, support projects that do not fit into one-year intervals, distribute funds over multiple years, and challenge teams to compete.
- ARPA-H will also leverage a different approach to peer review and thus will need exemptions from traditional NIH peer review process requirements.

IX. Interfacing with Federal Programs and Preventing Redundancy

How might ARPA-H interact with other federal agencies?

ARPA-H can benefit from suggestions from agencies in HHS and elsewhere about critical needs and opportunities; coordination of complex programs and projects requiring, for example, interaction with the public health infrastructure or medical regulation; expertise in breakthrough innovation; and expertise from other fields of science.

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Will ARPA-H collaborate with existing federal programs, such as the Biomedical Advanced Research and Development Authority (BARDA) and the Biological Technologies Office (BTO) at DARPA?

ARPA-H will embrace the opportunity to partner with agencies across the federal government, including but not limited to BARDA and DARPA, to mitigate any potential for redundancy and to complement each agency's activities. Given the specific missions of both BARDA and DARPA, there may be potential opportunities for ARPA-H to collaborate with them to expand ideas, tools, and platforms beyond the focus of their missions – emergency response and national security, respectively – and ensure their broad use to promote human health.

Why can't NIH just do this kind of work?

ARPA-H programs and projects will employ a radically different approach, culture, and organization, embracing a DARPA-like model of innovation and accountability. Whereas most NIH proposals are 'curiosity-driven', ARPA-H ideas will be largely 'use-driven' research — that is, research directed at solving a practical problem.

NIH has some experience with running large, complex programs using DARPA-like approaches to drive highly managed, use-inspired, breakthrough research. Recently, the NIH Rapid Acceleration of Diagnostics (RADx) initiative utilized an innovation funnel approach to rapidly advance promising COVID-19 diagnostic technologies. Looking further back, the Human Genome Project was an ambitious, bold, and long-term commitment to sequence the human genetic code that was completed ahead of schedule and has resulted in dramatically decreased costs of sequencing a human genome.

While these examples are compelling, they required *ad hoc* approaches. Future advances for diseases, ranging from rare to common, would each benefit from being pursued with this level of ambition. ARPA-H would allow NIH to pursue these needs systematically with an organization that is built for the purpose.

Will funding ARPA-H take funding away from other health initiatives at NIH?

We strongly believe that ARPA-H should not detract from what we know is already working well across NIH. So, ARPA-H funding should be complementary to and distinct from ongoing NIH and other agency efforts in a way that strengthens and helps catalyze transformative discoveries.

How will ARPA-H be different from NCATS and the Common Fund?

ARPA-H's proposed mission – to benefit the health of all Americans by catalyzing health breakthroughs that cannot readily be accomplished through traditional research or commercial activity – is different from the mission of the existing NIH Institutes and Centers.

Both NCATS and the Common Fund are important innovations that serve a defined purpose; they are distinct from the vision and approach for ARPA-H. NCATS' primary focus is to support a national network of clinical research centers and a drug screening hub. These two programs

account for nearly 90% of its resources. A modestly sized component within NCATS, the Cures Acceleration Network, is aligned with the general directions of ARPA-H.

Similarly, the NIH Common Fund is aimed at a different goal from ARPA-H's use-driven objective: it supports programs to explore new areas of foundational research that cut across multiple ICs—for example, the human microbiome effort.

X. Data Ecosystem

How will data generated through ARPA-H be shared with researchers to further advance the work?

ARPA-H will be committed to the principle of broadly sharing data within the constraints of privacy and security. A key metric of success will be the reuse and repurposing of data, which will require making the data available, discoverable, and well-described. This is essential to generating the most value for these federal dollars – a challenging objective given the differences in systems utilized across fields and organizations.

XI. Evaluating the Success of ARPA-H

What are the scientific goals and metrics for the first year of ARPA-H?

The true measure of success will be to identify and support bold, innovative programs and to begin making awards to that end in fiscal year (FY) 2022.

XII. Process for Collecting Feedback

Who was invited to the listening sessions?

OSTP and NIH jointly hosted a series of listening sessions with patients and their advocates, professional societies, industry, philanthropy organizations, venture capital firms, non-biomedical STEM organizations, and others. For a full list of meetings, please refer to: https://www.nih.gov/arpa-h/events.

Formal comments may be submitted to the ARPA-H comment box at arpahcomments@nih.gov.