Research ethics and integrity during a pandemic

Committee on Science, Engineering, Medicine and Public Policy, NASEM

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These are my views, and do not represent those of the NIH, DHHS, or the US government

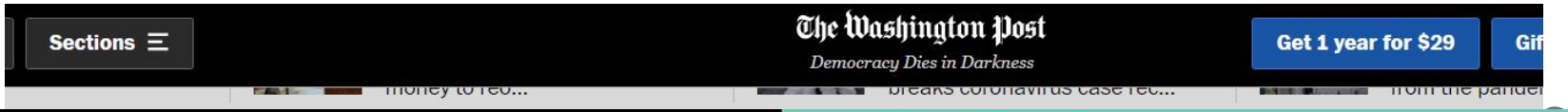
Research

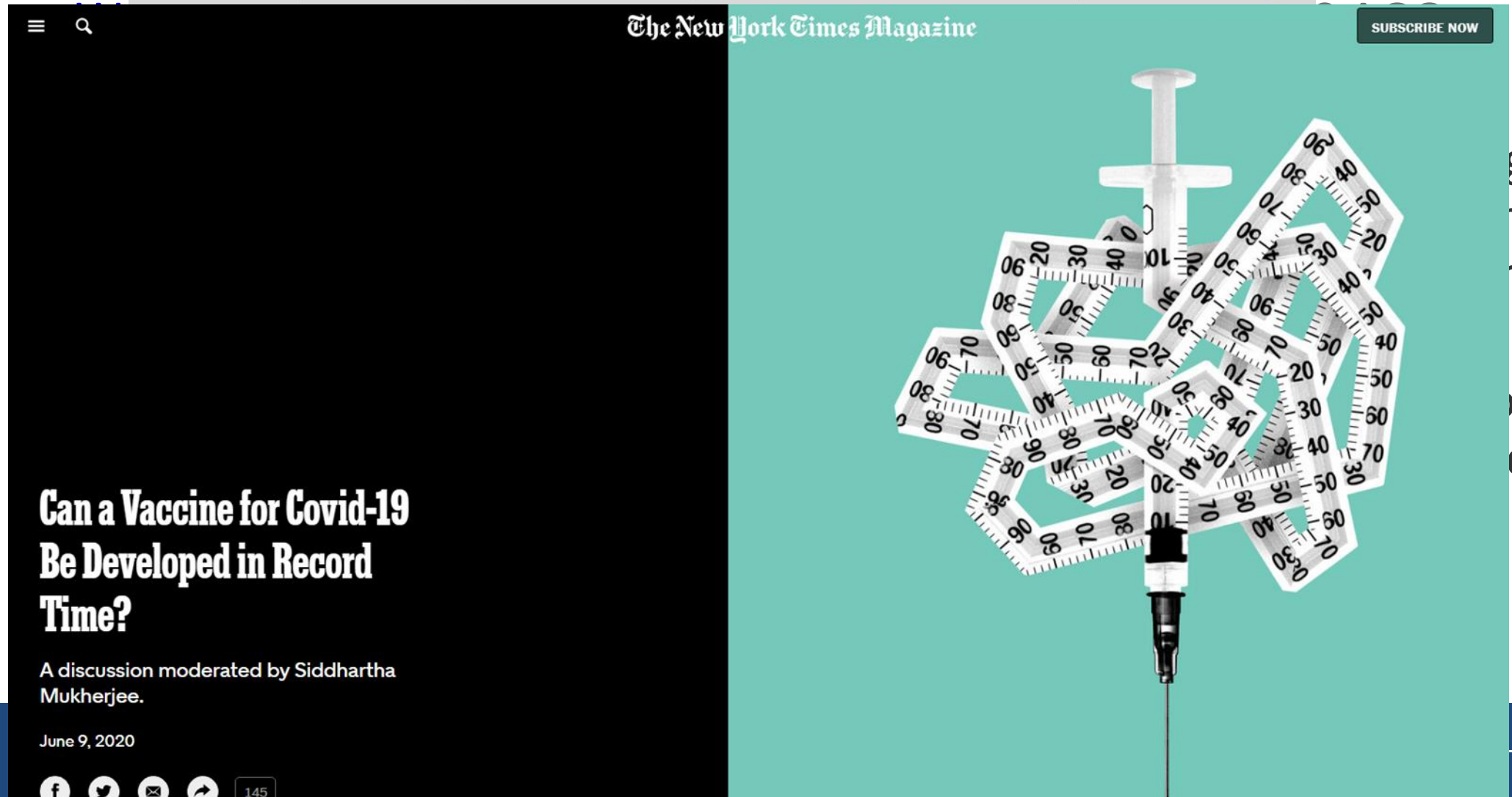
- Ethical imperative to research epidemiology, natural history, pathophysiology, clinical manifestations, and preventative, diagnostic, and therapeutic interventions; and social consequences

- Urgency and complexity

- As of July 20, 482 therapeutic agents and 156 vaccine candidates in the pipeline
- https://www.bioworld.com/COVID19products#vac

Challenge: Speed vs Rigor





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VIEWPOINT

COVID-19: BEYOND TOMORROW

Adverse Consequences of Rushing a SARS-CoV-2 Vaccine
Implications for Public Trust

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Viewpoint
pages 2462, 2458, and 2455

As the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic persists across the US and the world, the spotlight on vaccine science has never been more intense. Researchers across the globe are working rapidly to produce a potential vaccine, and 7 candidates are already in clinical trials.[1] Operation Warp Speed, the vaccine development project announced by President Trump, has advocated for a vaccine to be made available in the US by the beginning of 2021.[1] But for scientists and physicians, the term "warp speed" should trigger concern. Good science requires rigor, discipline, and deliberate caution. Any medical therapy approved for public use in the absence of extensive safeguards has the potential to cause harm, not only for COVID-19 prevention efforts and vaccine recipients, but also for public trust in vaccination efforts worldwide.

Long before coronavirus disease 2019 (COVID-19), vaccine hesitancy and refusal were increasing.[2] In 2019, the World Health Organization listed vaccine refusal as one of the top 10 global health threats.[3] Pediatricians, in particular, frequently encounter resistance to childhood vaccinations, and as a result, outbreaks of measles

> What cannot and must not be allowed is for desperation to result in the suspension of scientific principles and ethical research values.

activated polio vaccine developed by Jonas Salk was declared "safe, potent, and effective" following the largest public health experiment in the nation's history, involving more than a million schoolchildren.[5] Within weeks, however, the miracle vaccine intended to end the scourge of polio stood accused of causing it. Years in development, the Salk vaccine had been rigorously tested in preparation for the massive trials. But the very success of these trials led to an understandable outcry for the immediate, but premature, public release of the vaccine. Five pharmaceutical companies were given Salk's formula and left to produce the vaccine without significant oversight. As speed took precedence over caution, serious mistakes went unreported.[5] One company, Cutter Laboratories, distributed a vaccine so contaminated with live poliovirus that 70 000 children who received that vaccine developed muscle weakness, 164 were permanently paralyzed, and 10 died.[6] Not surprisingly, that incident forced the federal government to directly intervene. The legacy of this event is a regulatory landscape in which vaccines undergo thousands of tests to ensure their safety and effectiveness.[6]

Yet on rare occasions, this vital evidence-based process of vaccine development and testing has still been ignored. In 1976, concerns about the emergence of a new swine flu strain reminiscent of the lethal 1918 version led President Gerald Ford to convene a panel that recommended a government-backed mass vaccination program.[7]

Science

POLICY FORUM

Cite as: A. J. London and J. Kimmelman, *Science* 10.1126/science.abc1731 (2020).

Against pandemic research exceptionalism

By **Alex John London**[1] *and* **Jonathan Kimmelman**[2]

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Crises are no excuse for lowering scientific standards

The global outbreak of coronavirus disease 2019 (COVID-19) has seen a deluge of clinical studies, with hundreds registered on clinicaltrials.gov. But a palpable sense of urgency and a lingering concern that "in critical situations, large randomized controlled trials are not always feasible or ethical" (*1*) perpetuate the perception that, when it comes to the rigors of science, crisis situations demand exceptions to high standards for quality. Early phase studies have been launched before completion of investigations that would normally be required to warrant further development of the intervention (*2*), and treatment trials have used research strategies that are easy to implement but unlikely to yield unbiased effect estimates. Numerous trials investigating similar hypotheses risk duplication of effort, and droves of research papers have been rushed to preprint servers, essentially outsourcing peer review to practicing physicians and journalists. Although crises present major logistical and

The problem with this view is that challenges that rigorous methods address do not disappear in the face of urgent need. Small studies that build on basic science and preclinical research in early phases of drug development routinely generate signals of promise that are not confirmed in subsequent trials. Even when new drugs are established to be safe and effective, rarely are their benefits so massive that they can be detected in small, open-label, nonrandomized trials. The proliferation of small studies that are not part of an orchestrated trajectory of development is a recipe for generating false leads that threaten to divert already scarce resources toward ineffective practices, slow the uptake of effective interventions because of an inability to reliably detect smaller but clinically meaningful benefits, and engender treatment preferences that make patients and clinicians reluctant to participate in randomized trials. These problems are amplified by published reports of compassionate use, which was designed

Lessons, Speed vs Rigor

- Both are important
- Evaluate the trade-offs
- Avoid compromising ethics or science

Averting ethical or scientific compromise

- Ethical standards/principles
- Priority setting
- Coordination/collaboration
- Public engagement

Guided by ethical standards

- "… the best public health policies are guided by and embody rigorous ethical standards at all levels. *Integrating ethics* throughout public health emergency response can serve a problem-solving function by anticipating, identifying, and addressing ethical concerns in the early stages of emergencies.

- Presidential Commission for the Study of Bioethical Issues, Ethics and Ebola: Public Health Planning and Response, 2015. https://bioethicsarchive.georgetown.edu/pcsbi/sites/default/files/Ethics-and-Ebola_PCSBI_508.pdf

World Health Organization

Ethical standards for research during public health emergencies: Distilling existing guidance to support COVID-19 R&D

Introduction

There is an ethical imperative to conduct research during public health emergencies, as some research questions can be adequately investigated only in emergency contexts. Since the 2003 outbreak of the Severe Acute Respiratory Syndrome (SARS), the 2009-2010 H1N1 influenza pandemic, and the 2014-2016 Ebola outbreak in West Africa, authoritative guidance has been produced on how to conduct ethical research during emergencies. To ensure ethical research during the COVID-19 outbreak, we summarize the key universal ethical standards. They should be adhered to by researchers, review bodies, funders, publishers, and manufacturers during an emergency (Table 1).[1]

Table 1: Key ethical guidance documents
World Health Organization. (2016). Guidance for Managing Ethical Issues in Infectious Disease Outbreaks.
Nuffield Council on Bioethics. (2020). Research in Global Health Emergencies: Ethical Issues.
Council for International Organizations of Medical Sciences. (2016). International Ethical Guidelines for Health-Related Research Involving Humans (particularly Guideline 20).
Ezekiel J. Emanuel, David Wendler, Jack Killen, Christine Grady. (2004). What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research. *The Journal of Infectious Diseases*, 189(5): 930–937. https://doi.org/10.1086/381709

Research Priority Setting

- At every level
- Social and scientific value
- Feasibility/capacity
- Transparent and fair process
- Flexibility

GOALS OF THE GLOBAL RESEARCH ROADMAP

Research and innovation play increasingly important roles during, after, and in anticipation of public health emergencies. Conducting research is linked to "a moral obligation to learn as much as possible, as quickly as possible".[1]

It is important to underline that research—implemented as policy and practice—can save lives and needs to be integrated into the response from the start.

The global imperative for the research community is to maintain a high-level discussion platform which enables consensus on strategic directions, nurtures scientific collaborations, and supports optimal and rapid research to address crucial gaps, without duplication of efforts. Importantly there is a decisive pledge to collaboration, solidarity and to equitable access to all innovations developed.

The WHO R&D Blueprint is facilitating such platforms. In addition to the research actions ongoing, a comprehensive collaborative research agenda has been drawn up. The implementation of this collaborative research agenda has started.

Goals of the Global Research Roadmap

A. To facilitate that those affected are promptly diagnosed and receive optimal care; while integrating innovation fully within each research area.

B. To support research priorities in a way that leads to the development of global research platforms pre-prepared for the next disease X epidemic (an unexpected epidemic by a known or previously unknown pathogen); thus, allowing for accelerated research innovative solutions, and enabling R&D for diagnostics, therapeutics and vaccines as well as their timely equitable access.

The intense communications and information sharing among researchers is unprecedented and has resulted in a level of collaboration among scientists that, together with innovation advances, has led to research actions to be implemented faster than ever before during an outbreak.

World Health Organization
Global Research Roadmap

COVID-19 is an emerging, rapidly evolving situation.

- Get the latest public health information from CDC »
- Get the latest research information from NIH »
- NIH staff guidance on coronavirus (NIH Only) »

ACCELERATING COVID-19 THERAPEUTIC INTERVENTIONS AND VACCINES (ACTIV)

Challenge

The COVID-19 pandemic is an unprecedented global crisis that has been met with a swift and extraordinary response. Since the novel coronavirus was first reported in late 2019, institutions and organizations around the world have launched hundreds of research studies on diagnosis, prevention, and treatment strategies—all of which are critical to the world's ability to return to normal.

With limited resources, there is a need to coordinate and streamline processes to make the best use of biomedical research resources and testing of preclinical compounds.

The research community is sifting through more than 100 potential preventives and treatments. However, because so many studies are recruiting patients, many of those studies could fail to enroll enough participants to answer their research questions. In addition, lack of coordination could make interpretation and comparison of the results difficult. Meanwhile, healthcare providers on the front lines are taking care of critically ill patients every day. They need solid information grounded in research.

With limited resources, there is a need to coordinate and streamline processes to make the best use of biomedical research resources and testing of preclinical compounds. There is also a need to prioritize the most promising vaccine candidates and move them into

Priority Setting

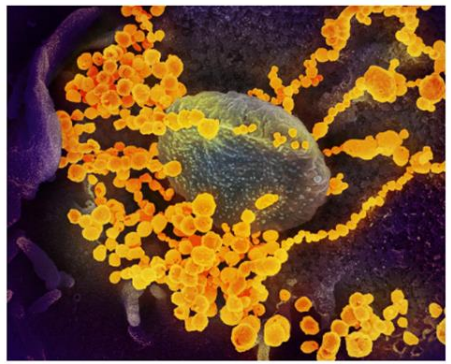
NEWS RELEASES

Media Advisory Thursday, April 23, 2020

NIAID strategic plan details COVID-19 research priorities

What

Urgent public health measures are needed to control the spread of the novel coronavirus (SARS-CoV-2) and the disease it causes, coronavirus disease 2019, or COVID-19. Scientific research to improve our understanding of the virus and how it causes disease, and to develop strategies to mitigate illness and death, is of paramount importance. A new strategic plan from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, details the institute's plan for accelerating research to diagnose, prevent and treat COVID-19.



This scanning electron microscope image shows SARS-CoV-2 (round gold objects) emerging from the surface of cells cultured in the lab. SARS-CoV-2, also known as 2019-nCoV, is the virus that causes COVID-19. The virus shown was isolated from a patient in the U.S. *NIAID-RML*

The *NIAID Strategic Plan for COVID-19 Research* has four key priorities. The first involves improving fundamental knowledge of SARS-CoV-2 and COVID-19, including studies to characterize the virus and better understand how it causes infection and disease. This research includes natural history, transmission and surveillance studies to determine why some individuals experience mild symptoms of infection while others become critically ill. The role of asymptomatic individuals in viral spread and the potential seasonality of viral circulation also need to be explored, according to the report. Additionally, small and large animal models that can recapitulate COVID-19 disease seen in humans must be developed.

Institute/Center

National Institute of Allergy and Infectious Diseases (NIAID)

Contact

NIAID News Office
301-402-1663

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Priority Setting - institutional level

- Feasibility and capacity
- Competing priorities
- Researcher, staff, participant safety
- Process

Coordination and collaboration

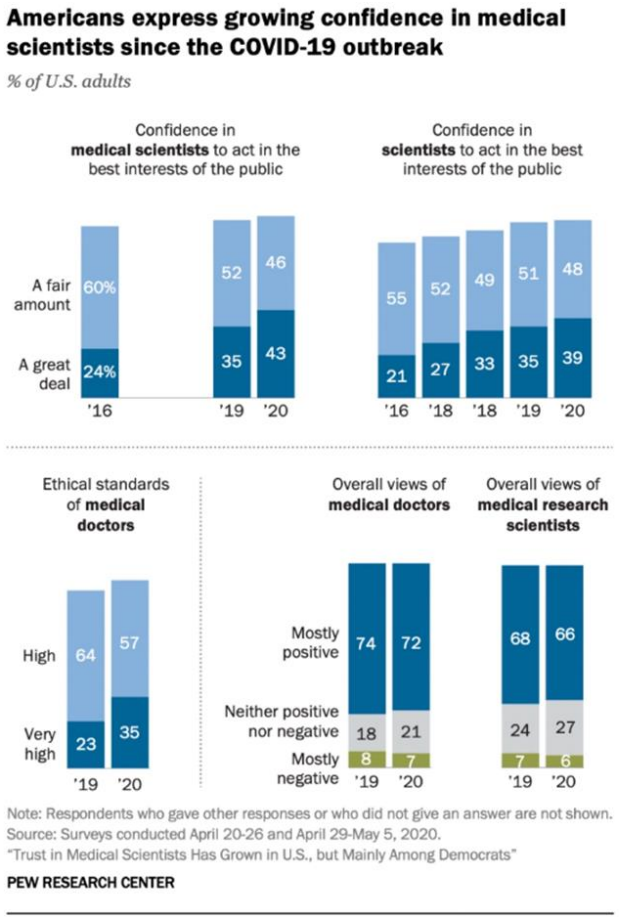
- Partnerships
- Collaboration
- Pooling resources
- Sharing data

Coordination

- “Fortunately, the global scientific community has a long tradition of transcending political and economic differences to coordinate or consult on major scientific challenges for the health and welfare of the world, and to push the frontiers of knowledge beyond what one country can do on its own.”

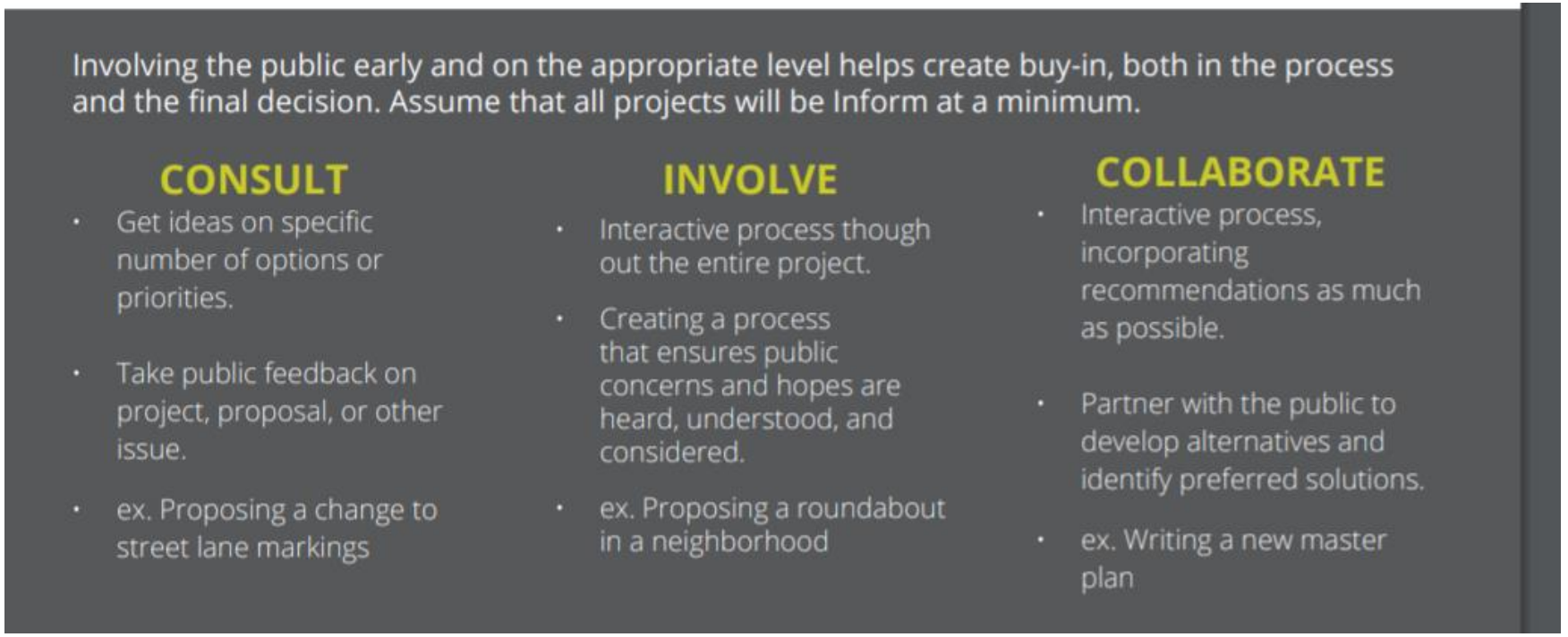
Dr. M. McNutt, testimony to the US Congress, 3/6/19.
https://www.nationalacademies.org/ocga/testimonies/116-session-1/maintaining-us-leadership-in-science-and-technology

Public engagement and trust



Pew Research Center

https://www.pewresearch.org/science/2020/05/21/trust-in-medical-scientists-has-grown-in-u-s-but-mainly-among-democrats/ps_2020-05-21_trust-in-scientists_00-01/



Based on IAP2, International Association for Public Participation, 2018. https://www.slc.gov/can/wp-content/uploads/sites/8/2020/04/Best-Practices-for-Engagement-During-COVID-19.pdf

Rigorous and expeditious research
Averting ethical or scientific compromise

- Ethical standards/principles
- Priority setting
- Coordination/collaboration
- Public engagement