Principal Investigator Responsibility for Flagging Research with Dual-Use or Pandemic Risk

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ABSTRACT: The new US Government Policy on Dual Use and Pathogens with Enhance Pandemic Potential places primary responsibility on the proposing principal investigator to flag potential need for special review. This may be a risky approach in light of incentives on investigators to undervalue the types of risk the policy seeks to mitigate and of given significant opposition to the policy from many virologists. However, this commentary argues that such an approach is much more consistent with proven models of research oversight for protecting human subjects and animals and may be essential in the long run. It identifies the need for several independent but potentially mutually reinforcing preconditions for success – which will require creativity and investment not fully specified in the regulations: researcher training on dual use and population-level biosafety risks, effective institutional-level support for and scrutiny of investigator evaluation, cultural change, checks and balances, and speedy evaluation of low-risk research.

Research activities that harm or risk harm to persons or animals, should be regulated to protect the interests of the latter, even if this means circumscribing the options available to researchers. This principle is widely accepted in relation to animals: while many scientists use and claim ethical justification for using animals in research (including the author of this article, when he had a wet lab), efforts to replace, and reduce, and refine are codified in both regulations and routine training of scientists who plan to use animals [1]. Ongoing consideration of ways to implement these principles [2] has led for example to a ban on funding for chimpanzee research from the US NIH [3] and even more restrictive policies in Europe [4].

For humans, the principle is similarly entrenched in the scientific community where direct harms to research participants are involved. Foundational documents such as the Nuremberg Code, the Declaration of Helsinki, and (in the US) the Belmont Report, as well as their implementation in the form of Institutional Review Boards, are part of the routine training of human subjects researchers. Infamous examples of abuses in the past are widely known and condemned as examples of how research cannot morally be performed. and while evidence of researcher attitudes about the process is scarce, it appears from this limited evidence and personal experience that the need for such regulation is widely appreciated, although the details of its implementation are often criticized [5,6].

The same cannot be said for risks to humans other than research participants. Risk to individuals who have no direct connection to a research endeavor and may be unaware of it (third-party risk) has received much less attention, and regulatory stances range from extremely restrictive to extremely permissive, with many gradations in between [7]. Such risks take many forms but are particularly salient in research with infectious agents, including research to enhance potential pandemic pathogens [8]. Concerns about such risks are rarely discussed in scientific training, and there is no comprehensive regulatory scheme for such risks equivalent analogous to institutional review boards (IRBs) for human research participants or institutional animal care and use committees (IACUCs) for research animals. Institutional Biosafety Committees (IBC) in the US are the closest parallel, but the primary concern of these committees is the safety of laboratory personnel (occupational biosafety), transmission to close contacts where the agent is capable of such, and the prevention of environmental releases, rather than the potential for widespread transmission following infection of a laboratory worker (population-level biosafety) or the misapplication of knowledge from the study (dual use risk/biosecurity) [8]. The performance in Wuhan, China, of experiments on SARS-like coronaviruses at biosafety level 2 exemplifies that this lack of proper precaution to mitigate population-level risks extends – and indeed may be more acute -- beyond the United States [9].

In this context, a striking aspect of the May, 2024, “United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential” [10] is the key role afforded to principal investigators in identifying whether their research falls under the policy, and if so, whether it is in Category 1 (roughly, dual use research of concern, DURC) or Category 2 of the policy (roughly, research reasonably anticipated to create an enhanced potential pandemic pathogen or revive an extinct pandemic pathogen). This commentary proposes recommendations for how this key role for investigators can become a feature rather than a shortcoming of the policy.

Large groups of virologists have written numerous editorials asserting that adopting policies similar to those in the newly released policy will “make widespread disruption to affected fields

of study unavoidable"[11] and similar sentiments [12,13]. These have been printed simultaneously in several journals of the American Society for Microbiology.
With such opposition to the new regulation from many members of the affected community, one could question the wisdom of a policy that places on principal investigators the responsibility to identify their own potential for dual use or accidental pandemic risk. This is especially so given the statement in one of these commentaries that minor modifications to institutional biosafety committees should be the solution, while any analogy to regulation of human subjects research is to be avoided [11]. Skepticism about relying on principal investigators could also be a reasonable reaction to comments in another that amount to gatekeeping and a suggestion that only those with specific technical knowledge and experience (i.e., virologists) should have a voice in designing regulations [12], which arguably denies the legitimate role of the larger society in regulating the risks that research may impose on it [14].

With such reactions from many scientists whose work will fall under the policy, is it wise to place primary responsibility on the investigator for the crucial first step in the process of flagging research that may pose dual use or accidental pandemic risk? x think that this responsibility should not be left scientists who have in many cases been resistant to the regulations that have been adopted.

This view may be correct, and only time will tell. Indeed, prior work has suggested that there are significant incentives for individuals (as well as firms) to undervalue low-probability, high-consequence risks of exactly the kind the policy seeks to mitigate [15]. But if the US government gets the details of implementation right, the increased responsibility for principal investigators may be in fact a major strength of the policy rather than a weakness. The relative success of protections for human subjects and animals, and of occupational biosafety, is built on just such a model: principal investigators on federal grants must assess whether they are conducting human subjects research (a question that is somewhat technical due to the precise definitions of the terms, but relatively clear in nearly all cases);whether they are experimenting on vertebrate animals, a straightforward question; and whether their work requires institutional biosafety committee (IBC) review (also straightforward). If so, their research plan must be vetted by the appropriate institutional committee(s), and their plans for addressing risks to human subjects, harms to animals, and occupational biosafety are part of the proposal's scientific review by the funder. Training on the principles undergirding the regulation in each of these areas is required for any scientist engaging in human subjects research, vertebrate animal research, or pathogen research, respectively.

While the system for these reviews does not work perfectly and indeed can be extremely frustrating to some researchers [5,6], there is a virtuous cycle created by the combination of (i) researcher training, (ii) a widely shared view that such regulation serves an important role even if not always well implemented, and (iii) a system within research institutions (IRBs, IACUCs, and IBCs) and within funding agencies to assess the decisions of the principal investigator.

To be successful, the OSTP policy will need a similar combination of factors, all of which will require creativity and resources.

- **Researcher training on dual use and population-level biosafety risks**. This is currently very scarce. Responsible conduct of research (RCR) training and other aspects of the training environment will need to build curriculum on these topics that reaches or exceeds the level of sophistication of current human subjects training, where trainees are expected to understand the principles at stake, the consequences of not having such

protections, and their obligations under the current regulation. They are also, in the best cases, asked to reason about cases to exercise their ability to think about risks they may not have previously considered. As technological developments including artificial intelligence proliferate and add to the potential for misuse or accident with pathogens, such flexible thinking is at a premium [16].

- **Effective institutional-level support for and scrutiny of investigator evaluation.** The OSTP policy calls on institutions to establish an Institutional Review Entity "to execute the institutional oversight responsibilities described in Section 5.2, with the attributes described in Section 5.2.B." Few details are given, and importantly it is unclear what resources or training must be available to members of this Entity. While there may be an implied reference to the Dual Use Research of Concern Policy of 2014, which also called for Institutional Review Entities, that policy[17] (and the NIH Implementation Guidance for it)[18] are not explicitly referenced and are themselves vague about expertise required and not designed for population-level biosafety (which at that time was not an aspect of DURC). Remarkably, that implementation guidance explicitly rejects the notion of quantifying risk and suggests that the goal is to make "rational, defensible statements," not an inspiringly high standard. Given the lack of consensus on what types of protection are needed, how to assess risks and benefits, and other fundamental questions, this is a major omission. Much more effort needs to be devoted to making such entities successful.
- **Cultural change.** It is essential that researchers develop the same level of appreciation and concern for risks to third parties of the kinds addressed by the OSTP policy that are currently widespread for individual-level biosafety risks, animal harms, and human subjects risks. To some degree, training and institutional arrangements can help. Discussions of these topics at professional meetings and in journals can help raise awareness. Respectful dialogue between parties with different views is essential [19]. Indeed some basic points of agreement emerge in one of the ASM journal articles cited above: "There must be a path in which everyone involved can work together to develop a scheme for ensuring that research that addresses important societal problems can move forward. Might there be some experiments that address questions that are more purely academic in nature than practical? Most definitely yes. Such experiments should have a lower level of risk tolerance, and we need to admit that. Conversely, we must acknowledge that not every gain-of-function experiment carries the risk of global catastrophe" [19].

  The recent report of the Pathogens Project [20] presents a view of the issues at a global scale from a group of well-known experts in relevant fields, and suggests that the principles can be articulated in a clear way that gains assent from many specialists including those whose work would be regulated.
- **Checks and balances.** The OSTP policy describes a complex process by which proposals flagged by the principal investigator as presenting potential Category 1 or 2 risk will be reviewed as it goes through the institution and funder. Less clear is what will happen in cases where a proposal that does in fact pose these concerns is not flagged, for whatever reason, including perverse incentives on the researchers in question [15]. Effective guardrails are needed to ensure that the policy does not fail if the proposer fails to flag a proposal as needing review. These are not yet evident in the policy.
- **Speedy evaluation of low-risk research.** At present and for the foreseeable future, research posing DURC or PEPP risks is a very small minority of virology research. And the remaining research that does not fall into these categories has tremendous potential

for saving lives. To facilitate such research, as well as to improve efficiency of oversight of the small proportion that does pose exceptional risks, it is critical to find ways to rapidly and accurately assess which studies do and do not pose these risks and avoid delaying research that poses no extraordinary risks. The approaches described above will all be helpful in doing so, but this should be maintained as an explicit goal [21], with the caveat that research can and does change direction and may require continuing review to assess whether it has ventured into the realm of concern of the policy [22].

With these elements in place, the policy can be a major step forward and a model for how to improve biosafety and biosecurity in an era of increasing technological abilities to benefit society through research and also to do harm, by deliberately misusing well-intentioned research results or by accident.

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