A Framework for Guiding U.S. Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets

Executive Summary

In 2011, two studies funded by the National Institutes of Health (NIH), which examined the mammalian transmissibility of highly pathogenic avian influenza (HPAI) H5N1 viruses, raised concerns regarding the potential for a global pandemic due to accidental or intentional release of an engineered virus or misuse of the research information. To address these concerns, the U.S. Department of Health and Human Services (HHS), a major funder of influenza research, has developed this Framework for guiding HHS funding decisions on individual proposals involving HPAI H5N1 research with specific attributes. The Framework aims to ensure a robust review of research proposals—prior to making a funding decision—that considers the scientific and public health benefits of the proposal; the biosafety and biosecurity risks associated with the proposal; and the risk mitigation measures that are required.

The HHS Framework requires additional review for research proposals that are anticipated to generate HPAI H5N1 viruses that are transmissible among mammals by respiratory droplets. Such proposals will undergo additional funding agency review as well as Department-level review in order to determine its acceptability for funding by HHS. Following reviews for both scientific merit and dual use research of concern (DURC),[1] the HHS funding agency will determine if the proposal is reasonably anticipated to generate an HPAI H5N1 virus[2] that is transmissible among mammals by respiratory droplets.[3] If so, the funding agency will determine whether the proposed research is in accord with the following criteria:

1) The virus anticipated to be generated could be produced through a natural evolutionary process;
2) The research addresses a scientific question with high significance to public health;
3) There are no feasible alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach;
4) Biosafety risks to laboratory workers and the public can be sufficiently mitigated and managed;
5) Biosecurity risks can be sufficiently mitigated and managed;
6) The research information is anticipated to be broadly shared in order to realize its potential benefits to global health; and
7) The research will be supported through funding mechanisms that facilitate appropriate oversight of the conduct and communication of the research.

If a proposal meets these criteria and is being contemplated for funding, the agency will submit the proposal for Department-level review. The Department-level review will provide multidisciplinary expertise—including public health, scientific, security, intelligence, countermeasures, and preparedness and response—to evaluate these proposals. The Department-level review will also identify any additional risk mitigation measures that are required, and determine whether a given proposal is acceptable for HHS funding. For proposals that are deemed acceptable for HHS funding, the funding agency within HHS will make the final funding decision. Proposals that have been determined to be unacceptable for HHS funding through Department-level review are not eligible for funding agency support. Figure 1 outlines the review process described by the Framework.

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[1] The *U.S. Government Policy for Oversight of Life Science Dual Use Research of Concern* (March 29, 2012) defines dual use research of concern as "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security."

[2] HPAI H5N1 viruses are defined here as influenza viruses that express the virulent form of the hemagglutinin (HA) gene from highly pathogenic H5N1 virus.

[3] Proposals aimed at characterizing naturally occurring strains are exempt from this Framework.

I. Purpose

To address concerns raised by studies that alter the mammalian transmissibility of highly pathogenic avian influenza (HPAI) H5N1 viruses, the U.S. Department of Health and Human Services (HHS) has developed a Framework for guiding HHS funding decisions on individual proposals involving HPAI H5N1 research with specific attributes. The Framework described here is intended to ensure a robust review of research proposals—prior to making a funding decision—that considers the scientific and public health benefits of the proposal; the biosafety and biosecurity risks associated with the proposal; and the risk mitigation measures that are required.

II. Issue and Task at Hand

In 1997, the HPAI H5N1 virus appeared in Hong Kong, and since 2006, descendants of this virus have posed a smoldering threat in many regions of the world. Humans are infected primarily by contact with infected birds, but naturally occurring HPAI H5N1 viruses do not appear well-adapted for transmission among mammals. Approximately 600 laboratory-confirmed human cases have been reported since 2003, with a fatality rate of nearly 60%, and hundreds of millions of birds have died as a result of infection or culling to prevent further outbreaks among domestic flocks.[4]

Today, the public health community remains vigilant as HPAI H5N1 influenza viruses continue to evolve and potentially gain the ability to spread efficiently in humans. One of the goals of HPAI H5N1 research is to identify the genetic changes that correlate with transmission or enhanced virulence of these viruses in mammals. For the purposes of this paper, studies that enhance these biological properties are referred to as "gain-of-function" research.[5] Information gained from these studies is intended to contribute to pandemic preparedness efforts. Such research may also enable the development and evaluation of countermeasures, such as vaccines, antivirals, and diagnostics for HPAI H5N1 strains that have the potential to spread among humans. The question that ensues is whether HPAI H5N1 gain-of-function research is needed to achieve these aims, and if so, under what conditions such studies should be conducted.

In 2011, two studies funded by the National Institutes of Health (NIH), which examined the mammalian transmissibility of HPAI H5N1 viruses, raised concerns regarding the potential for a global pandemic due to accidental or intentional release of an engineered virus or misuse of the research information.[6,7] Others argued that the risk of not conducting HPAI H5N1 gain-of-function studies would compromise the ability of the scientific and public health communities to prepare for and respond to potential influenza pandemics—both naturally-occurring and those stemming from intentional misuse.
In light of the difficult and important questions raised by the debate over whether and how to conduct and communicate gain-of-function studies, the influenza research community initiated a voluntary moratorium in January 2012 on research with HPAI H5N1 viruses that could generate new viruses with increased transmissibility in mammals, or any research with H5N1 or H5 hemagglutinin (HA) reassortant viruses already shown to be transmissible in ferrets.[8,9] The international scientific community and policy

[4] http://www.cdc.gov/flu/avianflu/h5n1-virus.htm
[5] "Gain-of-function" is typically defined more broadly as a mutation that confers a new or enhanced activity to a protein. For the purposes of this paper, "gain-of-function" studies refer specifically to those that increase the transmissibility, increase the pathogenicity, or alter the host range of HPAI H5N1 viruses.
[6] Herfst S, *et al*. Science. 336(6088):1534-1541 (22 June 2012).
[7] Imai M, *et al*. Nature 486: 420–428 (21 June 2012).
[8] Fouchier RA, *et al.* Nature. 481:443 (26 January 2012).

makers called for a discussion of the future direction of this research that includes experts in the life sciences, public health, biosecurity, biosafety, law, and science policy.[10,11]

III. A Path Forward

Framework for guiding HHS funding decisions

HHS is a major funder of influenza research, and as such will need to determine which, if any, HPAI H5N1 gain-of-function research projects are acceptable for HHS funding. This Framework will be used by HHS and its funding agencies to guide funding decisions on individual proposals involving certain HPAI H5N1 gain-of-function research. Figure 1 provides a comprehensive outline of this process. The Framework is intended to ensure a robust review by HHS—prior to making a funding decision—that considers the scientific and public health benefits of the proposal; the risks associated with biosafety, biosecurity, and dual use; and the appropriate risk mitigation measures that are required.

As part of developing this funding Framework for HPAI H5N1 gain-of-function research, HHS solicited the perspectives of the various stakeholders at an international consultative workshop held at NIH in Bethesda, Maryland on December 17-18, 2012. An international group of influenza and non-influenza scientists, as well as experts in biosafety, biosecurity, public health, and representatives from other governments and international organizations were present at this public workshop and provided input on the proposed Framework. The workshop included a full and open discussion by the participants and audience members of the draft Framework document and of representative case studies. During these discussions, it became evident that a subset of research generated enough concern to warrant special consideration prior to its funding—namely, research that is anticipated to generate HPAI H5N1 viruses that are transmissible by respiratory droplets among mammals.

When considering whether to fund certain HPAI H5N1 gain-of-function proposals, it is important that HHS analyze the potential risks and benefits associated with each proposal on a case-by-case basis. Risk assessments will include careful consideration of the scope and magnitude of the potential risks and benefits associated with the research proposal, evaluation of whether the risks outweigh the benefits, and strategies for mitigating potential risks. Such assessments will consider the risks associated with the intrinsic nature of the virus used in the proposal (i.e., the transmissibility, pathogenicity, and host range of the starting viral strain) as well as the risks associated with any experimental manipulations outlined in the proposal (i.e., the likelihood that the virus will become more transmissible or more virulent in mammals). Risk assessments will also consider the ease with which the research could be misused and the possible timeframe for such misuse.

Risk assessments will also occur during other reviews, such as review by the Institutional Biosafety Committee and funding agency review for dual use research of concern (DURC).[12] Such assessments will

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[9] Fouchier RA, *et.al*. Science. Vol. 335, no. 6067. (26 January 2012)

[10] Technical consultation on H5N1 research issues – consensus points. World Health Organization, Geneva, 16-17 February 2012. http://www.who.int/influenza/human_animal_interface/consensus_points/en/index.html

[11] Fauci AS. 2012. Research on highly pathogenic H5N1 influenza virus: the way forward. mBio 3(5):e00359-12. doi:10.1128/mBio.00359-12 http://mbio.asm.org/content/3/5/e00359-12.full

[12] The *U.S. Government Policy for Oversight of Life Science Dual Use Research of Concern* (March 29, 2012) defines dual use research of concern as "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security."

factor into the risk-benefit assessments performed specifically for HPAI H5N1 gain-of-function research proposals. Risk-benefit assessments will occur during the funding agency's review of the proposal to determine whether it meets the funding criteria (see Box 2) and the Department-level review (see Box 3).

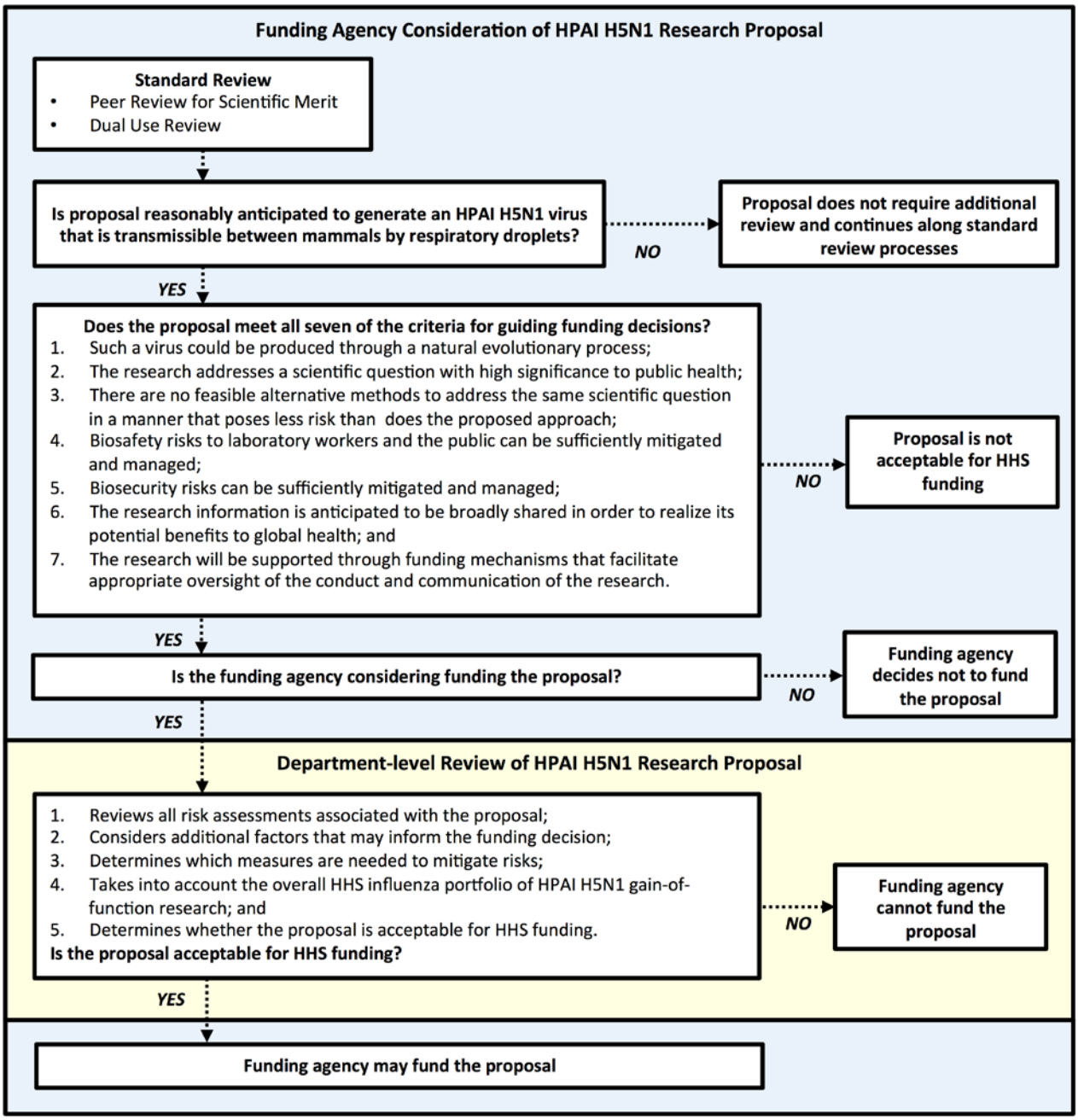

Figure 1. Overview of HHS Review of HPAI H5N1 Gain-of-Function Research Proposals

Applicability of the Framework

The HHS Framework requires higher-level review for funding applications that include or are reasonably anticipated to generate HPAI H5N1 viruses with gain-of-function attributes that enable respiratory droplet transmission of the virus among mammals (Box 1).[13]

> **Box 1. Applicability of the Framework.**
>
> HHS will apply this review Framework to proposals that are reasonably anticipated to confer gain-of-function attributes that enable influenza viruses expressing the virulent form of the hemagglutinin (HA) gene from highly pathogenic H5N1 to be transmissible among mammals by respiratory droplets.
>
> The scope of the Framework does not include routine characterization studies of naturally occurring H5N1 viruses.

"Characterization studies" of naturally occurring H5N1 viruses, including studies that examine the virus's potential for transmissibility among mammals by respiratory droplets, are intentionally exempted from the Framework. Characterization studies include sequencing and testing of antigenicity, antiviral drug susceptibility, and pathogenicity. "Naturally occurring" is intended to refer to mutations that arise in nature or through a natural process, and were not engineered by researchers or obtained by serial passaging of viruses. Characterization studies do not intend, nor are they reasonably anticipated to generate, novel viruses with gain-of-function attributes. In addition, the characterization of naturally occurring viruses does not introduce the risks associated with generating or engineering new H5N1 viruses.

To ensure that this Framework can be applied throughout the course of the research, HHS will include a term and condition of award for all HPAI H5N1 projects that requires researchers to report to HHS any unanticipated results that involve the generation of a virus that is transmissible among mammals by respiratory droplets. Of note, this Framework does not supersede any existing policies, regulations, rules, or guidelines.

Criteria for guiding HHS funding decisions about HPAI H5N1 gain-of-function research proposals

As part of the funding decision, and after scientific merit and DURC reviews, HHS funding agencies will determine whether HPAI H5N1 gain-of-function research proposals meet the criteria listed in Box 2. Proposals that do not accord with all of these criteria are not acceptable for HHS funding.

> **Box 2. Criteria for guiding HHS funding decisions for research proposals with the potential to produce HPAI H5N1 viruses that are transmissible among mammals by respiratory droplets.**
>
> Gain-of-function research proposals that are anticipated to produce HPAI H5N1 strains that are transmissible among mammals by respiratory droplets are acceptable for HHS funding only if:
>
> 1. Such a virus could be produced through a natural evolutionary process;
> 2. The research addresses a scientific question with high significance to public health;
> 3. There are no feasible alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach;
> 4. Biosafety risks to laboratory workers and the public can be sufficiently mitigated and managed;
> 5. Biosecurity risks can be sufficiently mitigated and managed;
> 6. The research information is anticipated to be broadly shared in order to realize its potential benefits to global health; and
> 7. The research will be supported through funding mechanisms that facilitate appropriate oversight of the conduct and communication of the research.

[13] This Framework will apply to extramural as well as intramural research.

HHS funding agencies will apply the above criteria when considering a funding proposal for a gain-of-function research project and will continue to consider the principles inherent in these criteria throughout the lifespan of the research to inform the planning of its conduct and oversight. Researchers and institutions should be mindful of these criteria when submitting research proposals and when conducting research that may be covered under this Framework. Researchers and institutions should continue to apply these criteria throughout the lifespan of any HPAI H5N1 research project that receives HHS funding when determining how to conduct the research and whether to continue conducting certain studies.

The funding agency will make an initial determination of whether the proposed risk mitigation strategies identified by the biosafety and biosecurity reviews are adequate, and it will incorporate any additional measures into the terms and conditions of award, as necessary. Risk mitigation measures may include, but are not limited to, those described in the *U.S. Government Policy for Oversight of Life Sciences Dual Use Research of Concern*.

Review by the HHS funding agency of a gain-of-function research proposal with the potential for generating an HPAI H5N1 virus that is transmissible among mammals by respiratory droplets may result in one of two outcomes. The HHS funding agency may:

- Not fund the research proposal; or
- Refer the research proposal for Department-level review.

HPAI H5N1 gain-of-function research proposals that warrant Department-level HHS review

If a research proposal that has the potential to produce HPAI H5N1 strains that are transmissible among mammals by respiratory droplets has satisfactorily undergone peer review and DURC review, is in accord with all of the criteria in Box 2, and is being considered for funding by the HHS funding agency, then additional Department-level HHS review is required to determine if the proposal is acceptable for HHS funding (Box 3). For NIH awards, Department-level review will occur before NIH council review.

Box 3. Department-level review of research proposals with the potential to produce HPAI H5N1 viruses that are transmissible among mammals by respiratory droplets.

HPAI H5N1 gain-of-function research proposals that meet the criteria in Box 2, and that the HHS funding agency is considering funding, require Department-level review.

The purpose of the Department-level HHS review is to:

- Review the funding agency's risk assessments;
- Provide additional and multidisciplinary expertise to consider whether additional factors may alter assessment of whether the research can be funded;
- Carefully consider proposals that are reasonably anticipated to:
  - Increase pathogenicity in mammals;
  - Disrupt the induction of a host's innate immunity;
  - Interfere with the effectiveness of an available vaccine;
  - Confer to the agent resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent; or
  - Facilitate the virus' ability to evade detection methodologies.
- Determine which measures are needed to mitigate risks;
- Take into account the overall HHS influenza portfolio of HPAI H5N1 gain-of-function research; and
- Determine whether the proposal is acceptable for HHS funding.

The purpose of the Department-level review is to provide balanced, multidisciplinary expertise and perspectives to the consideration of proposals that involve HPAI H5N1 gain-of-function studies. This will include expertise in countermeasure development and availability, national security, law, public health preparedness and response, biodefense, select agent regulations, and science and public health policy, as well as funding agency perspectives and other areas. A core review group will draw on relevant expertise within HHS, as well as *ad hoc* consultants from other departments and agencies as necessary. In some cases, HHS may wish to seek additional expertise from within HHS and/or from additional departments or agencies. Moreover, there may be cases in which additional consultation with outside *ad hoc* experts or consultation with Federal advisory bodies (such as the National Science Advisory Board for Biosecurity, the NIH Recombinant DNA Advisory Committee, and the National Biodefense Science Board) is desirable.

The Department-level review will consider proposals in the context of the entire HHS research portfolio of HPAI H5N1 research. For instance, HHS can determine whether the proposal meets a critical, unmet research need that requires HHS investment, or whether the risks associated with the project in question are not justified, given the other, perhaps similar, research being supported by HHS and/or other Federal agencies. The Department-level review will also help to address real or perceived conflicts of interest with respect to the funding agency.

Within 14 working days of receipt of a proposal with supporting information from a funding agency, the Office of the Assistant Secretary for Preparedness and Response, with assistance from the HHS Office of General Counsel, will convene the core review group and, as necessary, any *ad hoc* consultants. Funding agency staff will describe the proposal, its importance, its relevance to the field and to the agency's portfolio, and the results of applying the Framework. The core review group and *ad hoc* consultants will discuss the proposal and consider the implications for national security, public health, international agreements, and any other issues and relevant information. Summary observations and recommendations from the Department-level review will be sent to the Assistant Secretary for Preparedness and Response to determine whether a given proposal is acceptable for HHS funding. The decision will be transmitted to the funding agency within HHS to make the final funding decision. Proposals that have been determined to be unacceptable for HHS funding after Department-level review are not eligible for funding agency support. Of note, if the research project generates results that are both unanticipated and concerning during the course of the research, the funding agency will apply the Framework and work with the research institution to determine the appropriate path forward.

If a proposal is determined to be unacceptable for HHS funding, applicants will be provided with a brief justification explaining why a proposal was determined to be unacceptable. If the investigators so choose, they may address concerns and resubmit their proposal during a future grant cycle.

IV. Next Steps

Investigators who submit proposals that fall within the scope of the Framework are encouraged to be mindful of the Criteria listed in Box 2 and to develop their proposals accordingly. The Framework will be reevaluated periodically and modified as necessary to reflect scientific advances and changes in the regulatory landscape.