A Path Forward: Framework for Guiding U.S. Department of Health and Human Services Funding Decisions about Highly Pathogenic Avian Influenza H5N1 Gain-of-Function Research

I. Issue and Task at Hand

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.[1] The public debate that ensued over the communication of the research findings raised questions as to whether the Federal government should fund research that alters key biological properties of HPAI H5N1 viruses—specifically, research that increases transmissibility, increases pathogenicity, and/or alters the host range—and if so, under what conditions. For the purposes of this paper, studies that enhance these biological properties are referred to as "gain-of-function" research.[2]

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 HA reassortant viruses already shown to be transmissible in ferrets.[3,4] The international scientific community and policy makers have 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.[5,6]

The U.S. Department of Health and Human Services (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 white paper proposes a framework for guiding HHS funding decisions on individual proposals involving HPAI H5N1 gain-of-function research. The decision-making framework aims to ensure a robust review by HHS funding agencies—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 may be implemented. Gain-of-function studies that raise particular concern are those that generate mammalian-transmissible HPAI H5N1 viruses. Therefore, the HHS framework requires that proposals that are anticipated to generate mammalian-transmissible strains (as well as viruses with other gain-of-function attributes) require Department-level review in order to be deemed acceptable for funding by HHS. As part of developing this proposed funding framework for HPAI H5N1 gain-of-function research, HHS is interested in hearing the perspectives of the various stakeholders at an international consultative workshop that

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[1] Herfst S *et al*. Science. 336(6088):1534-1541 (22 June 2012); and Imai M *et al*. Nature 486: 420–428 (21 June 2012).

[2] "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.

[3] Fouchier RA, *et al.* Nature. 481:443 (26 January 2012).

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

[5] 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

[6] 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

HHS is hosting in December 2012, and, in particular, learning how other governments and research funders are approaching decisions about pursuing HPAI H5N1 gain-of-function research.

II. The Benefits and Risks of HPAI H5N1 Gain-of-Function Research

HPAI H5N1 and the role of influenza research

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 between mammals. Approximately 600 human cases have been reported since 2003, resulting in a fatality rate of up to 60% of laboratory-confirmed cases, and hundreds of millions of birds have died as a result of infection or were culled to prevent further spread of outbreaks among domestic flocks.[7]

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. This information may 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.

Risks associated with HPAI H5N1 gain-of-function research

Like other research involving pathogens, HPAI H5N1 gain-of-function studies involve inherent risks, and are therefore subject to a number of extant guidelines, policies, laws, and international agreements that govern biosafety, physical security, personnel reliability, informational risks, and nonproliferation. Biosafety risks involve laboratory-acquired infections or accidental releases of a virus outside of the laboratory setting, which could threaten public health or agriculture. Biosecurity risks involve the intentional misuse of research products or information to threaten public health, the environment, agriculture, or other aspects of national security. Biosafety and biosecurity risks may be amplified as more laboratories conduct these types of studies.

Risks associated with conducting HPAI H5N1 gain-of-function research cannot be eliminated entirely. Any decisions regarding what types and how much HPAI H5N1 gain-of-function research to support should be based on a balance between these risks and the potential benefits from conducting this research.

It should be noted that there also may be risks associated with not conducting HPAI H5N1 gain-of-function studies. The information generated by such studies is intended to provide the foundation for developing effective vaccines, therapeutics, diagnostics, and other countermeasures, and enhances our surveillance capabilities. To not engage in this type of research could introduce its own risks by compromising the ability of the scientific and public health communities to prepare for and respond to outbreaks—both naturally-occurring and those stemming from intentional misuse—of influenza viruses with pandemic potential.

[7] http://www.cdc.gov/flu/avianflu/h5n1-virus.htm

III. A Proposed Path Forward

This paper sets forth HHS' proposed framework for making funding decisions about HPAI H5N1 gain-of-function research proposals. It describes the process by which HHS funding agencies (e.g., National Institutes of Health, Centers for Disease Control and Prevention) will identify potentially high-risk gain-of-function projects at the funding proposal stage and determine whether they are acceptable for HHS funding, and if so, under what conditions. For HPAI H5N1 gain-of-function research proposals that are determined to be acceptable for funding, the HHS funding agencies are to designate any additional and applicable biosafety, biosecurity, and DURC risk mitigation measures, as deemed appropriate.

Applicability of the proposed framework

The intent of this proposed framework is to capture funding applications that include or are likely to generate HPAI H5N1 viruses with gain-of-function attributes.[8] However, it is not anticipated that all proposals within this scope would necessarily result in gain-of-function studies. Funding agencies will apply this framework to proposals fitting the description in Box 1.

Box 1. Applicability of the proposed framework for guiding HHS funding decisions about HPAI H5N1 gain-of-function research

HHS will apply this review framework to proposals that are reasonably anticipated to confer gain-of-function attributes to influenza viruses expressing the virulent form of the hemagglutinin (HA) gene from highly pathogenic H5N1.

The scope of the framework does not include routine characterization studies[9] of naturally occurring[10] H5N1 viruses; it is important to ensure that the properties of H5N1 viruses that circulate in nature are identified and characterized as quickly as possible. Such 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.

Overview: Proposed Framework for guiding HHS funding decisions about HPAI H5N1 gain-of-function research

The proposed framework for reviewing HPAI H5N1 gain-of-function research proposals is outlined in Figure 1. Following reviews for both scientific merit and DURC,[11] the HHS funding agency will determine if the proposal falls within the scope of the framework (Box 1). If the framework applies, the funding agency then determines whether the proposed research is in accord with the criteria for guiding HHS funding decisions (Box 2). Next, if the funding agency is considering funding the proposal, it will determine whether the research is reasonably anticipated to confer any of the specified characteristics to HPAI H5N1 viruses (Box 3) that warrant an additional Department-level review. HHS will include a term and condition of award for all HPAI H5N1 research that requires researchers to report any unanticipated gain-of-function findings to HHS so that this framework can be applied throughout the

[8] This framework would apply to extramural as well as intramural research.
[9] "Characterization studies" include sequencing and testing of antigenicity, antiviral drug susceptibility, and pathogenicity.
[10] "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 virus.
[11] *U.S. Government Policy for the Oversight of Life Sciences DURC*, March 29, 2012.

course of the research. In addition, HPAI H5N1 gain-of-function studies are considered DURC and will also receive periodic DURC review.[12]

Of note, this framework does not supersede any extant policies, regulations, rules, or guidelines. For example, funding proposals undergo local biosafety reviews and are subject to the select agent regulations and Federal DURC oversight policy. In recognition of the fact that influenza research is a highly dynamic field and that the scientific and regulatory basis for review will change over time, HHS will periodically revisit this framework and make modifications as necessary.

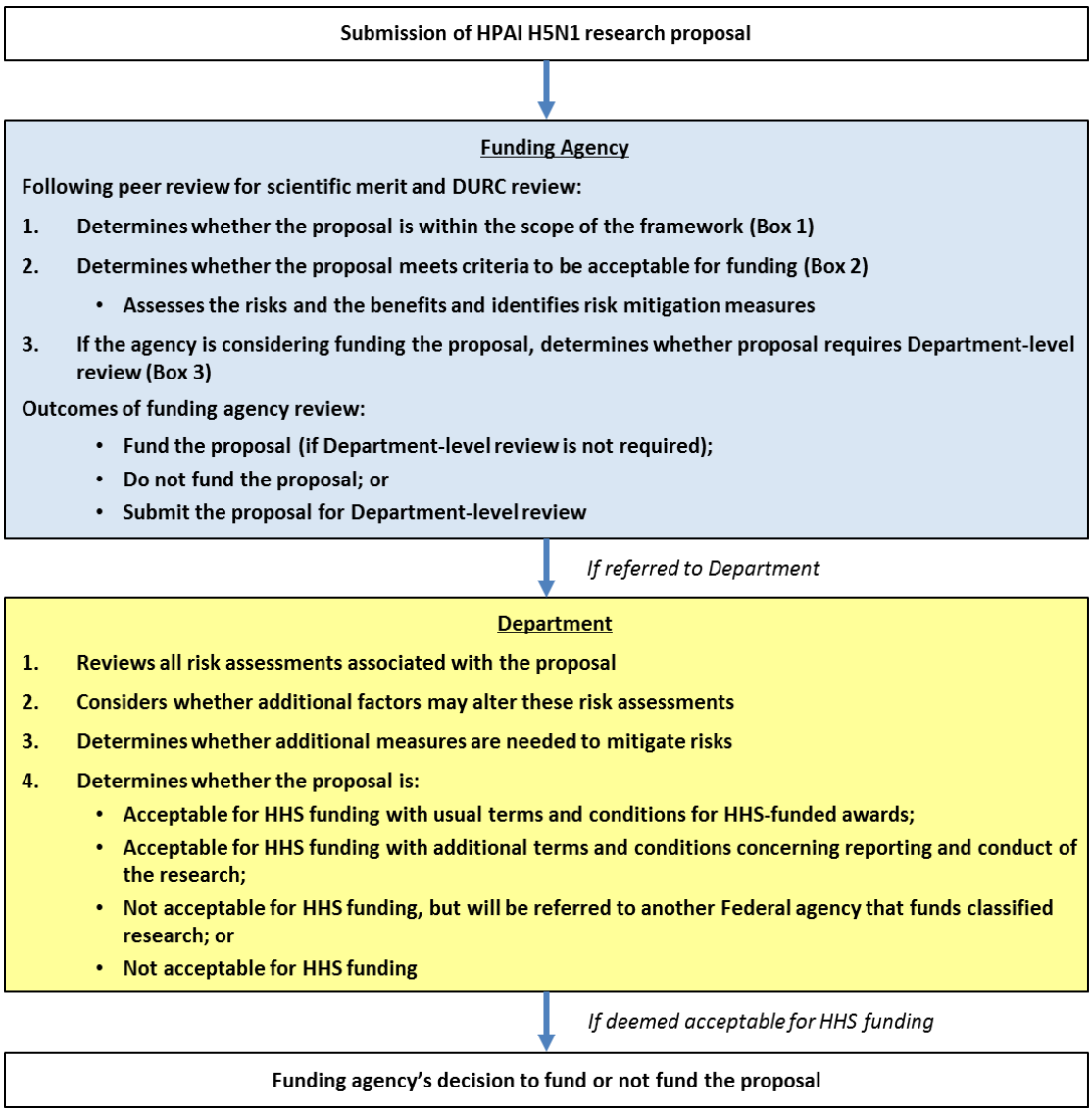

Figure 1. Overview of the framework for guiding HHS funding decisions about HPAI H5N1 gain-of-function research. An HPAI H5N1 gain-of-function research proposal is to be reviewed by the HHS funding agency to ensure that the proposal meets the applicability of the framework and is in line with the criteria for guiding HHS funding decisions. Gain-of-function research

[12] *U.S. Government Policy for the Oversight of Life Sciences DURC*, March 29, 2012.

proposals that involve experiments conferring certain attributes to HPAI H5N1 require Department-level review prior to being funded.

Upon Department-level review, when applicable, HHS will determine whether the proposal is acceptable for funding, and may recommend additional terms and conditions of awards to address risks associated with conducting the research. As a general matter, HHS should only fund research that is reasonably anticipated at the proposal stage, to generate information, products, and technologies that can be broadly shared and openly communicated. The Department may recommend that certain HPAI H5N1 gain-of-function research is not appropriate for HHS funding because the associated risks cannot be adequately managed if the research were conducted and communicated openly. However, research that is deemed unacceptable for HHS funding, yet is determined to have high scientific and public health merit, could be referred to another department for possible funding under classified conditions. In any case, the HHS funding agency makes the final determination of whether a research proposal receives funding, after taking into account the findings of the Department-level review, when applicable. An overview of the process by which this framework will be applied is provided in Figure 1; further explication of this process is provided in the text below.

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

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 HPAI H5N1 gain-of-function research proposals

HPAI H5N1 gain-of-function research proposals are acceptable for HHS funding only if:

1. The research addresses a scientific question with high significance to public health;
2. The research does not intend, nor is reasonably anticipated to yield an HPAI H5N1 experimental virus that has increased transmissibility, pathogenicity, or expanded host range, unless there is evidence that such a virus could be produced through a natural evolutionary process in the foreseeable future;
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.

HHS funding agencies will apply the above criteria when considering a funding proposal for a gain-of-function HPAI H5N1 research project. HHS funding agencies, researchers, and institutions will 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.

Risk assessments for HPAI H5N1 gain-of-function research proposals

Risk assessments should include careful consideration of the scope and magnitude of the potential risks and benefits associated with research, including the ease with which the research could be misused and the possible timeframe for such misuse. 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).

The funding agency will determine whether the proposed risk mitigation strategies identified by the biosafety and biosecurity reviews are adequate and 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 of HPAI H5N1 gain-of-function research proposals by the HHS funding agency may result in one of three outcomes. The HHS funding agency may:

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

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

If an HPAI H5N1 research proposal is in accord with all of the criteria in Box 2, and the HHS funding agency is considering funding the proposal, additional Department-level HHS review is required if the proposal exhibits any of the characteristics in Box 3 to determine if the proposal is acceptable for HHS funding.

Box 3. Characteristics of HPAI H5N1 gain-of-function research proposals that warrant Department-level HHS review

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 if the studies intend or are reasonably anticipated to:

- Increase pathogenicity, virulence, and/or transmissibility of a virus in mammals; or
- Disrupt the induction of a host's innate immunity; or
- Interfere with the effectiveness of an available vaccine; or
- 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.

The purpose of the Department-level review is to examine particularly high-risk HPAI H5N1 gain-of-function research proposals to identify risks and benefits associated with the research as well as any additional risk mitigation measures that may be implemented to help manage those risks. The Department-level review will provide multidisciplinary expertise—including security, intelligence, countermeasures, or preparedness and response—to evaluate certain proposals. Such review will also

consider proposals in the context of the entire HHS research portfolio. For instance, HHS is in a good position to 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 determine whether a given proposal is acceptable for HHS funding, and in such cases, the funding agency within HHS makes 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.

As part of the evaluation process for certain gain-of-function proposals, HHS will establish a Departmental-level review mechanism that allows the Department to perform the functions summarized in Box 4.

Box 4. Department-level HHS 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;
- Determine whether additional measures are needed to mitigate risks;
- Take into account the overall HHS portfolio of HPAI H5N1 gain-of-function research; and
- Determine whether the proposal is acceptable for HHS funding.

After Departmental-level review, HHS may determine that the HPAI H5N1 gain-of-function research proposal is:

- Acceptable for HHS funding with usual terms and conditions for HHS-funded awards;
- Acceptable for HHS funding with additional terms and conditions concerning conduct of the research;
- Not acceptable for HHS funding, but will be referred to another Federal agency that funds classified research;[13] or
- Not acceptable for HHS funding.

In making its funding decision, the HHS funding agency will consider the findings and recommendations from the Department-level review. 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 proposed framework and work with the research institution to determine the appropriate path forward.

IV. Next Steps

HPAI H5N1 gain-of-function research is an international endeavor, and the risks and benefits associated with such research are global. HHS is sponsoring an international consultative workshop to provide a forum for multidisciplinary and multinational perspectives on the types, if any, of "gain of function" research on highly pathogenic avian influenza H5N1 that should be conducted. As part of developing its

[13] As a general matter, HHS does not fund classified research, but the Department-level review could recommend that a scientifically meritorious proposal that was likely to generate sensitive information be referred to other Federal agencies that support classified research. Such cases are anticipated to be extremely rare.

own proposed funding framework for this type of research, HHS is interested in hearing the perspectives of the various stakeholders at this meeting and, in particular, learning how other governments and research funders are approaching decisions about pursuing HPAI H5N1 gain-of-function research. These discussions will make an important contribution to the ongoing global dialogue on this issue.