

1 **FRAMEWORK FOR CONDUCTING RISK AND BENEFIT ASSESSMENTS OF**
2 **GAIN-OF-FUNCTION RESEARCH:**
3 **RECOMMENDATIONS OF THE NSABB WORKING GROUP**
4
5

TABLE OF CONTENTS

Background and Introduction	2
The Charge to the NSABB	4
The NSABB’s Process	5
WG Recommendations Regarding the Design and Conduct of the RA and BA	6
Guiding Principles	6
Pathogens and Pathogen Characteristics	7
Risk Categories	8
Benefit Categories	9
Historical Perspectives from Analysis of Past Experiences	11
Scenarios and Events to be Included in the RA	12
Approaches and Methods for Assessing Risks and Benefits Associated with GOF Studies	14

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8 **BACKGROUND AND INTRODUCTION**

9 Most genetic manipulations of microorganisms do not raise significant safety or security concerns; these
10 studies are routinely conducted for valid scientific purposes using non-pathogenic organisms or biologic
11 systems and are subject to appropriate Federal and institutional oversight. However, safety and security
12 concerns may arise when certain types of manipulations, which introduce stable genetic mutations, are
13 employed to better understand some pathogens or toxins, sometimes enhancing the ability of those
14 agents to harm their hosts.

15
16 Recently, the phrase “gain-of-function (GOF) research” has come to describe certain studies that
17 increase the ability of a pathogen to cause disease. This phrase achieved prominence after two groups
18 published findings demonstrating that highly pathogenic avian influenza H5N1 viruses with a small
19 number of engineered mutations became transmissible between mammals by respiratory droplets.^{1,2}
20 Such studies were undertaken to help define the fundamental nature of human-pathogen interactions,
21 with the goal of enabling assessment of the pandemic potential of emerging infectious agents,
22 informing public health and preparedness efforts, and furthering medical countermeasure
23 development. However, such GOF studies may entail biosafety and biosecurity risks, and significant
24 concerns have been raised about whether these studies generate information that could be misused to
25 cause harm or whether the modified viruses could pose a pandemic threat if they were to be
26 accidentally or intentionally released.

27
28 In 2012, a voluntary suspension of certain GOF studies involving highly pathogenic avian influenza H5N1
29 viruses was undertaken by the influenza research community.³ During that time, policymakers
30 considered whether certain GOF studies should be conducted using Federal funds, and if so, how those
31 studies could be safely conducted. The Centers for Disease Control and Prevention (CDC) and the
32 National Institutes of Health (NIH) issued new biosafety guidelines for working with highly pathogenic
33 avian influenza strains.^{4,5} The U.S. Department of Health and Human Services (HHS) developed a
34 framework for guiding its funding decisions about projects that may generate highly pathogenic H5N1
35 viruses that are transmissible between mammals by respiratory droplets.⁶ This funding framework was
36 later expanded to include H7N9 influenza viruses as well.⁷ Under this framework, HHS considers newly
37 submitted research project proposals involving certain GOF studies for their scientific and public health
38 merits as well as associated biosafety, biosecurity, and dual use risks. HHS also identifies appropriate
39 risk mitigation measures that are required. Studies that are deemed acceptable for funding may then
40 proceed in accordance with any agreed-upon risk mitigation measures.

41

¹ Imai et al. Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. *Nature* 486, 21 June 2012

² Herfst et al. Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets. *Science* 336, 22 June 2012

³ Fouchier et al. Pause on avian flu transmission studies. *Nature* 481, 26 January 2012.

⁴ Gangadharan D, Smith J, and Weyant R. Biosafety Recommendations for Work with Influenza Viruses Containing a Hemagglutinin from the A/goose/Guangdong/1/96 Lineage, Morbidity and Mortality Weekly Report 62(RR06); 1-7. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6206a1.htm>

⁵ NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. <http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines>

⁶ Framework for Guiding Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets, February 21, 2013. <http://www.phe.gov/s3/dualuse/Documents/funding-hpai-h5n1.pdf>

⁷ Jaffe, HW, Patterson, AP, and Lurie, N. Avian Flu: Extra Oversight for H7N9 Experiments. *Nature* 500, 07 August 2013. <http://www.nature.com/nature/journal/v500/n7461/full/500151a.html>

42 Given the biosafety incidents in U.S. Federal laboratories during the summer of 2014 and renewed
43 concerns regarding laboratory safety and biosecurity, the U.S. government (USG) determined that the
44 risks and benefits of GOF research must be re-evaluated.⁸ A robust and broad deliberative process that
45 will result in the adoption of a new Federal GOF research policy (which will apply to research funded by
46 U.S. agencies whether conducted in the U.S. or abroad) has been undertaken. While this process takes
47 place, the USG has instituted a pause in the provision of new USG funding for certain GOF research on
48 influenza, Middle East Respiratory Syndrome coronavirus (MERS) or Severe Acute Respiratory Syndrome
49 coronavirus (SARS)—pathogens determined to have pandemic potential. Restrictions on new funding
50 apply as follows:

51
52 *New USG funding will not be released for gain-of-function research projects that may be*
53 *reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the*
54 *virus would have enhanced pathogenicity and/or transmissibility in mammals via the*
55 *respiratory route. This restriction would not apply to characterization or testing of naturally*
56 *occurring influenza, MERS, and SARS viruses, unless the tests are reasonably anticipated to*
57 *increase transmissibility and/or pathogenicity.*

58
59 In parallel, the USG has encouraged the research community (both those who receive USG funding and
60 those who do not) to join in adopting a voluntary pause on any on-going research that involves the types
61 of studies that are subject to the funding restriction above.

62
63 The ongoing deliberative process involves both the National Science Advisory Board for Biosecurity
64 (NSABB) and the National Academies National Research Council (NRC), and involves explicit evaluation
65 of the possible risks and potential benefits of GOF research with potential pandemic pathogens. The
66 NSABB serves as the official federal advisory body for providing advice on oversight of this area of dual
67 use research. The NSABB is providing the USG with specific recommendations regarding a conceptual
68 approach to the evaluation of proposed GOF studies. The NRC has and will convene forums to engage
69 the life sciences community as well as to solicit feedback from scientists and the public on optimal
70 approaches to ensure effective federal oversight of GOF research. These forums involve discussion of
71 principles important for the design of risk and benefit assessments of GOF research and of NSABB draft
72 recommendations.

73
74 The final NSABB recommendations and the discussions at the NRC forums will be taken into
75 consideration by the USG during the development and adoption of a new USG policy governing the
76 funding and conduct of GOF research.

77
78 Thorough and scientifically rigorous risk and benefit assessments of GOF research involving pathogens
79 with pandemic potential are needed to inform the deliberative process, and to provide the NSABB and
80 the USG with objective and comprehensive information about the risks and benefits associated with
81 certain types of GOF research. The USG has determined that an independent contractor will conduct
82 the risk and benefit analyses (RA and BA). The contractor will provide personnel and expertise for
83 conducting the RA and BA on certain GOF research involving pathogens with pandemic potential. The
84 RA and BA are to be comprehensive, sound, and credible and must be able to withstand rigorous
85 scrutiny by a variety of stakeholders. The contractor's analyses are to be guided by the overall guiding

⁸ U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS viruses, October 17, 2014.

86 principles described herein. In planning and conducting the RA and BA, the contractor will take into
87 account issues raised by recent biosafety incidents in USG laboratories.

88
89 While the funding pause and the RA and BA are limited to selected pathogens,⁹ products of the RA and
90 BA are intended to inform broader NSABB deliberations, which will involve recommendations on a
91 conceptual approach to the evaluation of proposed GOF studies that may extend to other high-
92 consequence pathogens. NSABB recommendations will inform the USG as it develops and adopts
93 policies about whether certain types of GOF studies on high consequence pathogens with pandemic
94 potential should be supported and, if so, how such funding proposals should be evaluated.

95
96 A private contractor will conduct the RA and BA, however, the process is intended to be a cooperative
97 effort involving participation by NIH and the NSABB, and informed by discussion held at the NRC forums.
98 The NIH Office of Science Policy is managing the overall deliberative process, providing the interface and
99 facilitating the communications between the contractor and other entities, and overseeing the work by
100 the contractor. The studies and resulting reports must comply fully with USG requirements, both
101 procedurally and analytically, using existing guidance from federal agencies and peer-reviewed sources
102 and well-established methods; concerns of other stakeholders, in addition to the USG, must be
103 considered.

104

105 **THE CHARGE TO THE NSABB**

106 The NSABB has been charged with providing advice on the design, development, and conduct of risk and
107 benefit assessment studies, and with providing recommendations to the USG on a conceptual approach
108 to the evaluation of proposed GOF studies. In developing its recommendations, the NSABB will
109 consider: the results of the risk and benefit assessments; the spectrum of potential risks and benefits
110 associated with GOF studies; alternative methods that may be employed to yield similar scientific
111 insights or benefits, while reducing potential risks; public discussions hosted by the NRC; and any
112 additional consultations with relevant subject matter experts, as needed, to ensure that all appropriate
113 expertise is brought to bear on the issues. In advising on the design and conduct of the RA and BA, the
114 NSABB will recommend assumptions to be included in the risk assessment; evaluate the scope and
115 methodologies to be used in the risk assessment; consider the adequacy of the scenarios in the risk
116 assessment and propose additional scenarios to address other concerns or factors, as appropriate;
117 advise on the assessment of the benefits, including types of benefits that should be examined and
118 methods for examining them; and provide advice at key milestones in the conduct of the RA and BA.

119
120 To satisfy this charge, The NSABB will convene, deliberate, and provide two deliverables to the USG:

- 121 • **Deliverable 1.** Advice on the design, development, and conduct of risk and benefit assessments.
- 122 • **Deliverable 2.** Formal recommendations on the conceptual approach to the evaluation of
123 proposed GOF studies.

124

125 The framework outlined herein, and subsequent input provided by the NSABB at key milestones
126 throughout the conduct of the RA and BA, are intended to satisfy Deliverable 1.

127

128 **THE NSABB'S PROCESS**

⁹ U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS viruses, October 17, 2014.

129 In order to accomplish its charge regarding Deliverable 1, the NSABB established a Working Group (WG),
130 composed of 13 NSABB members with a broad range of expertise including microbiology, biodefense,
131 ethics, biosecurity, national security, biosafety, public health, and other relevant areas. The WG also
132 included *ex officio* members from Federal agencies who contributed expertise in virology, national
133 security, ethics, foreign policy, and other areas. The group convened during the period of December
134 2014 through April 2015 by telephone conference calls and held a one-day in-person meeting to discuss
135 the design and conduct of the risk and benefit assessments and to begin to identify the information
136 necessary to inform the Board’s final recommendations to be issued in Deliverable 2. The discussions
137 ranged broadly and included general concepts of overall importance as well as specific details that the
138 contractor should consider and include as the RA and BA proceed. The WG’s findings were consolidated
139 into a series of recommendations that are presented below. The recommendations in this Framework
140 are intended to guide the NIH as it works with the contractor performing the RA and BA such that the
141 assessments will be conducted in a way that will provide information that allows the NSABB to make
142 sound, evidence-based recommendations. The WG acknowledged the strengths and limitations
143 associated with such assessments, which primarily involve scientific and technical input, and has noted
144 that other information, such as consideration of ethical, legal, and other viewpoints, should inform its
145 final recommendations (Deliverable 2).

146
147 In guiding the design of the RA and BA, the WG attempted to focus its attention on issues specific to
148 GOF studies, although it agreed that some other directly relevant studies are important for comparison
149 and should be included. Although the RA and BA focus on specific experiments and scenarios, the scope
150 is intended to be sufficient to allow evaluation of the risks and benefits of not just single experiments,
151 but also whole research programs to inform decisions pertaining to the entire USG research portfolio
152 related to GOF studies with high consequence pathogens with pandemic potential.

153
154 Finally, an issue of central importance to the entire deliberative process is public trust in the scientific
155 enterprise. A possible negative outcome associated with the GOF issue is the loss of public trust if a
156 laboratory accident involving modified strains were to occur or if GOF research were intentionally
157 misused to cause harm. Loss of public trust is a serious concern and its impact could be felt more widely
158 across the scientific community. The deliberative process should be conducted with an eye toward
159 maintaining public trust in the scientific enterprise and oversight of scientific research. To help ensure
160 public trust, and to ensure the NSABB’s deliberations are informed by broad input and diverse
161 perspectives, the NSABB seeks to maximize stakeholder input and public engagement during the
162 deliberative process. Of note, the deliberative process includes public forums hosted by the NRC that
163 are intended to gather input and foster broad discussions by the scientific and other stakeholder
164 communities. The first forum was held in December 2014;¹⁰ the second will be held later in the process.
165 Additionally, NSABB meetings are open to the public and the Board encourages attendees to provide
166 comments, either verbally or in writing. The NSABB encourages comments and input at any time, which
167 can be submitted by emailing NSABB@od.nih.gov.

168

169

170 **WG RECOMMENDATIONS REGARDING THE DESIGN AND CONDUCT OF THE RA AND BA**

¹⁰ Risks and Benefits of Gain-of-Function Research: A Symposium. National Academy of Sciences Board on Life Sciences, December 15, 2014 – December 16, 2014.

171 *Guiding Principles*

172 Listed below (not necessarily in order of importance) are guiding principles that should underpin the risk
173 and benefit assessments. These principles should inform and guide the contractor’s efforts in
174 performing the risk and benefit assessments.

175

176 1. There are potential risks and benefits associated with certain GOF life sciences research that
177 should be formally and rigorously identified and analyzed. The possible risks and benefits of not
178 doing this work also need to be thoroughly examined.

179

180 2. Alternative experimental approaches to GOF experiments that may provide the same or similar
181 outcomes or additional/different benefits, without the same risks, should be identified and their
182 relative risks, benefits, and limitations thoroughly and impartially analyzed. There may be
183 different risks and benefits of these alternatives.

184

185 3. The RA and BA processes should start with a clear articulation of their purposes. The issues
186 must be framed appropriately, with specific, relevant questions to be answered. The RA and BA
187 should be conceptualized so as to provide information that is useful and informative for guiding
188 NSABB recommendations about whether or not and how to pursue the types of scientific
189 studies that are the subject of the assessments.

190

191 4. The scope of the RA and BA must be sufficiently comprehensive and delineated, with all aspects
192 of the problem being clearly defined and considered at the outset. While the scope must be
193 sufficiently detailed, it also must be appropriately narrowed to the particular subset of studies
194 whose risks may be especially significant.

195

196 5. The concepts of clarity, transparency, consistency, and reasonableness must underpin the RA
197 and BA. The processes must be well-documented and the final results and their interpretations
198 should be clearly described and presented.

199

200 6. The assessments must be objective, scientifically rigorous, comprehensive, credible, and
201 reasonable. Analyses of potential risks and benefits should be based on existing guidance, use
202 real data to the extent possible, and employ established, tested, and peer-accepted methods.
203 The RA and BA should include both qualitative and quantitative analyses to the extent feasible.

204

205 7. Analyses should examine the impact of risk mitigation strategies and practices, the effect of
206 public health interventions, and whether countermeasures are effective against novel strains, as
207 well as how these strategies are actually employed, which may involve human error, crisis
208 conditions, or other factors that decrease their effectiveness.

209

210 8. The data used are critical to conducting the risk and benefit assessments. Sources of data,
211 quality of data, assumptions made in analyses, limitations of data, and areas where more data
212 are needed all require explicit documentation. Insufficient or lack of quality data should not be
213 grounds for not addressing issues pertinent to the goals of the assessments. Particular

214 consideration must be given to issues of uncertainty¹¹ and sensitivity¹² in presenting results.
215 Ranges and bounds should be used to reflect the level of confidence in the results.
216

- 217 9. The RA should address what could go wrong as a result of conducting GOF research, and the
218 probability and consequences of such events. The BA should address what beneficial outcomes
219 might result from such research, how probable they are, the magnitude of their effects, and a
220 realistic timeframe for realizing the benefits. Both risks and benefits may depend on other
221 factors and have different timeframes. Any assumptions regarding factors that must be present
222 for the risks or benefits to be realized should be explicitly identified.
223
- 224 10. The focus of the assessments should be on research studies conducted within the U.S. or
225 supported by US funding and conducted outside of the U.S., but should take into account the
226 fact that laboratories throughout the world that are not funded by the U.S. government may
227 also be conducting similar studies.
228
- 229 11. These principles largely apply to both the RA and BA; however, the benefits are not just
230 reduction of the risks included in the risk assessment. It may not always be feasible to express
231 risks and benefits in the same terms, but an effort should be made to do so when possible.
232
- 233 12. The RA must encompass a range of scenarios including “maximum reasonable foreseeable
234 events” (i.e., worst case) as well as those with a range of probabilities. Low probability, but high
235 consequence events deserve particular attention. Both intentional (malevolent) and accidental
236 events should be included in the analyses.

237
238 *Pathogens and Pathogen Characteristics*

239 Listed below are pathogens that the WG recommends for inclusion in the RA and BA to provide
240 information about the risks and benefits associated with GOF research involving these specific agents;
241 however, the NSABB’s ultimate policy recommendations need not be limited to these specific
242 pathogens. The risks and benefits analyzed in the assessments are intended to be representative of
243 those associated with similar agents and experiments that may arise in the future. Most pandemics are
244 associated with respiratory transmission, so agents in this category are of overarching concern. The WG
245 considered adding a variety of agents, viral and bacterial, as well as agents having different transmission
246 routes that might gain the property of respiratory transmission. The WG also discussed the pathogen
247 characteristics that are most concerning.
248
249
250

¹¹ Uncertainty is the lack or incompleteness of information. Quantitative uncertainty analysis attempts to analyze and describe the degree to which a calculated value may differ from the true value; it sometimes uses probability distributions. Uncertainty depends on the quality, quantity, and relevance of data and on the reliability and relevance of models and assumptions used to fill data gaps. From *Science and Decisions: Advancing Risk Assessment*. National Research Council of the National Academies, The National Academies Press; Washington DC. 2009.

¹²Sensitivity is the degree to which the outputs of a quantitative assessment are affected by changes in selected input parameters or assumptions. From *Science and Decisions: Advancing Risk Assessment*. National Research Council of the National Academies, The National Academies Press; Washington DC. 2009.

251 **Pathogens that should be included in the RA and BA because they are the subjects of the funding**
252 **pause:**

253

254 **1. Influenza viruses.** Because of the significant differences among influenza strains, the WG
255 recommends that three distinct strains be analyzed. These are:

256

257 a. Seasonal influenza (e.g., currently circulating or historical H1N1, H3N2, and influenza B
258 strains for which a significant portion of the general population has pre-existing immunity)

259 b. Highly pathogenic avian influenza virus H5N1

260 c. Low pathogenic avian influenza virus H7N9

261

262 **2. SARS-CoV**

263

264 **3. MERS-CoV**

265

266 **Pathogen characteristics that are recommended for consideration in the RA and BA:**

267

268 The RA and BA should include analysis of the risks and benefits associated with GOF experiments that
269 are anticipated to increase the pandemic potential of the above agents. Toward this end, the following
270 characteristics, which may be conferred to the pathogens in GOF studies, should be considered:

271

272 1. Enhanced virus production as a result of changes in any step of the virus replication cycle.

273

274 2. Enhanced morbidity and mortality in appropriate animal models.

275

276 3. Enhanced transmission in mammals (e.g., increased host or tissue range, altered route of
277 transmission, infectivity above a certain threshold determined in an appropriate animal model).

278

279 4. Evasion of existing natural or induced immunity or evasion of the effects of countermeasures.

280

281 *Risk Categories*

282 In order for the contractor to plan and conduct the risk assessment so that it will ultimately meet the
283 needs of the NSABB, the scope of possible risks must be defined at the outset. It is important that all
284 reasonable categories of risks be examined. There is some overlap between the categories, and of note,
285 there are national security elements associated with most of the categories that should be considered.
286 Listed below are the risk categories that the WG recommends be considered in the RA. For each of the
287 risk categories, both intentional and accidental events that lead to risk should be considered, as
288 appropriate. In addition, the analysis should consider the risks associated with certain GOF studies in
289 the context of currently existing risks associated with the broader, national biomedical research
290 portfolio and from the perspective of past experience. The RA should also consider the additive risks
291 associated with conducting relevant GOF studies at multiple locations. Where there are case studies or
292 known examples of events that document various risks, these should be compiled and selected
293 examples incorporated into the RA report.

294

- 295 1. **Biosafety:** Biosafety risks are those generally associated with laboratory accidents. Assessing
296 these risks should include the magnitude of exposures, initial infections, transmission leading to
297 secondary infections, and outbreaks in humans or animals. The issue of novel pathogenic
298 strains for which we may be unprepared needs particular attention. The association of
299 laboratory personnel with intermediary hosts (such as pets and livestock) should also be
300 considered. The risk assessment should evaluate the effect that public health interventions and
301 occupational health and staff monitoring programs have on risk from novel pathogens resulting
302 from GOF studies, as compared to existing pathogens. The assessment should consider how the
303 capabilities and containment features of the lab doing the work influence risk. The risks to lab
304 workers and to the general public should be analyzed separately.
305
- 306 2. **Physical and personnel security (biosecurity):** Biosecurity risks are those associated with crime
307 and terrorism and would take into account the physical security of pathogens, risks associated
308 with shipping and transporting pathogens, and personnel security. Biosecurity risks include
309 physical breach, theft, loss or intentional release by lab personnel, malevolent acts, and
310 terrorism. The RA should include consideration of the types of actors who would seek to misuse
311 life sciences research information and materials as well as their capabilities to do so. The
312 analysis should also consider specifically how the studies in question could be misused, whether
313 terrorists might target labs to gain access to materials or scientific expertise, and include
314 estimates of how great the threats may be.
315
- 316 3. **Proliferation:** The risk assessment should consider how pursuing certain GOF studies may lead
317 to expanded amounts of that research and, as a result, increased risk (biosafety, biosecurity, and
318 others). Proliferation might occur if certain studies become standard or typical, or, conversely, if
319 unpublished studies (due to safety or security concerns) are repeated, unwittingly by others.
320 This analysis should take into account that biosafety standards vary in different countries and
321 settings.
322
- 323 4. **Information risk:** Information risks are those associated with how the information generated by
324 GOF studies, if made publically available, could enable others throughout the world to replicate
325 such studies or generate pathogens for malevolent actions or threats to national security.
326 Intellectual property threats may also be considered here.
327
- 328 5. **Agricultural:** This involves the risks to agriculturally-relevant animals such as pigs or chickens if
329 a laboratory-modified pathogen were to be intentionally or accidentally released. This also
330 includes risks resulting from laboratory workers keeping intermediate hosts as pets.
331
- 332 6. **Economic risks:** Economic risks include monetary costs associated with releases, including loss
333 of productivity, agricultural damage, liability, and the issue of accountability. Opportunity costs
334 might also be considered.
335

336 *Benefit Categories*

337
338 In order for the contractor to plan and conduct the BA so that it will ultimately meet the needs of the
339 NSABB, the scope of potential benefits that may result from GOF research must be defined at the
340 outset. It is important that all reasonable categories of benefits be examined. Listed below are several

341 benefits categories that the WG recommends for inclusion in the benefit assessment. It should be noted
342 that there are national security dimensions to the benefits associated with several categories that
343 should be considered. The WG notes that some benefits may only accrue if subsequent events also take
344 place. The WG also acknowledges the difficulty of analyzing some benefits, particularly those with long-
345 term timeframes.

346

347 1. **Scientific knowledge:** These benefits include analysis of the types of scientific information that
348 could be generated from GOF research, and an assessment of the value of such information for
349 understanding the agents/diseases being studied (or other agents/diseases). The assessment
350 should consider ways to quantify these benefits if possible. The benefit assessment should also
351 analyze whether GOF research generates (or is likely to generate) unique scientific information
352 that expands the knowledge base in ways that other research approaches cannot.

353

354 2. **Biosurveillance:** These benefits would include those relevant to the processes of gathering,
355 integrating, analyzing, interpreting, and communicating essential information that might relate
356 to disease activity and threats to human, animal, or plant health.¹³ Specifically, the potential
357 benefits of relevant GOF studies should be examined for benefits to:

358

359 a. **Public Health Surveillance¹⁴:** How GOF research may contribute to the improvement of
360 public health efforts by aiding detection and monitoring of pathogens in the real world, or
361 help to better recognize or predict outbreaks in human populations, and inform decision-
362 making.

363

364 b. **Agricultural and domestic animal surveillance:** How GOF research may contribute to the
365 improvement of agricultural health efforts by aiding detection and monitoring of pathogens
366 in food-producing, domestic, or other animals so as to help to better recognize or predict
367 outbreaks in such animals, and inform decision-making.

368

369 c. **Wildlife surveillance:** How GOF research may contribute to the improvement of
370 surveillance in wildlife by aiding detection and monitoring of pathogens, or help to better
371 recognize or predict outbreaks in such animals, and inform decision-making.

372

373 3. For the following three benefits in particular, the benefit assessment should examine the
374 relative benefits of GOF research compared to alternative approaches. The assessment should

¹³ National Association of County and City Health Officials, <http://naccho.org/topics/emergency/biosurveillance/index.cfm>
Biosurveillance is a process of gathering, integrating, interpreting, and communicating essential information that might relate to disease activity and threats to human, animal, or plant health. For the public health professional, biosurveillance activities range from standard epidemiological practices to advanced technological systems, utilizing complex algorithms.

¹⁴ World Health Organization defines public health surveillance as the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice. Such surveillance can serve as an early warning system for impending public health emergencies; document the impact of an intervention, or track progress towards specified goals; and monitor and clarify the epidemiology of health problems, to allow priorities to be set and to inform public health policy and strategies. CDC defines public health surveillance as the ongoing, systematic collection, analysis, and interpretation of health data, essential to the planning, implementation and evaluation of public health practice, closely integrated with the dissemination of these data to those who need to know and linked to prevention and control.

375 also consider whether, and if so, how, GOF research yields unique information that may not
376 otherwise be possible:

377
378 a. **Therapeutics:** How the research is likely to aid discovery and development of new or more
379 effective therapeutics.

380
381 b. **Vaccines:** How the research is likely to aid development and selection of new or more
382 effective vaccines.

383
384 c. **Diagnostics:** How the research is likely to aid development of new or better diagnostic
385 methods and products.

386
387 4. **Informing policy decisions:** How information gained from GOF studies contributes, or is likely to
388 contribute, to public health preparedness decisions such as informing countermeasure
389 stockpiling decisions, guiding decisions about strain selection for vaccine development, or
390 informing decisions about whether and how to mobilize resources or issue guidance in response
391 to a newly emergent pathogen.

392
393 5. **Economic benefits:** Possible gains (monetary, employment, labor productivity, etc.) and cost
394 savings associated with the results/outcomes of GOF studies, such as diminished health care
395 costs due to vaccines or therapeutics, or other positive impacts on the economy.

396

397 *Historical Perspectives from Analysis of Past Experiences*

398

399 Naturally-occurring epidemics and pandemics can provide helpful background information that might
400 inform the discussion about the risks associated with the infectious agents that are subjects of RA and
401 BA. There is significant historical data on the mortality and morbidity associated with seasonal and
402 pandemic influenza, as well as more recent data on the other pathogens recommended for inclusion the
403 RA and BA studies. However, there are complexities and limitations to interpreting these data and
404 trends that require further analysis. Valuable historical perspectives about past outbreaks of seasonal
405 and pandemic influenza, SARS, and MERS viruses could be obtained by conducting quantitative analyses
406 of global pathogen-associated morbidity and mortality. This information will supplement the RA and BA
407 being undertaken as part of the deliberative process on GOF research, and will help inform the
408 development of the NSABB's final recommendations (Deliverable 2).

409

410 Specifically, the WG recommends that an analysis be done for each pathogen, which summarizes
411 existing data and information and, to the extent possible, includes:

412

413 1. Global morbidity and mortality data associated with seasonal influenza, pandemic influenza,
414 SARS, and MERS, and trends in these data over time.

415

416 2. Comparison of the morbidity and mortality associated with seasonal influenza and pandemic
417 influenza.

418

419 3. Historical information about the impact of influenza on food production, particularly the swine
420 and poultry industries.

- 421
422 4. Description of how the data utilized were collected, interpreted, and analyzed.
423
424 5. Qualitative review of the impact of vaccines and therapeutics on pathogen associated morbidity
425 and mortality.
426

427 *Scenarios and Events to be Included in the RA*

428 The RA should be based on a series of events that might occur during the course of conducting GOF
429 research. It is anticipated that the contractor will develop a large list of possible events and scenarios
430 that might be included. Because of time and resource constraints, only a subset will be analyzed in
431 depth; however, it is important to define the total range of reasonably likely events so that the ones that
432 are analyzed will be representative of the risks anticipated to be associated with GOF research more
433 broadly. Scenarios should include analysis of the effects of risk mitigation approaches and include
434 realistic examples where mitigation is effective and where it fails in some way. The analyses should
435 incorporate examples that account for variability between labs and their practices.
436

437 **Development and Selection of Events and Scenarios**

438 Listed below are recommendations, derived from the Guiding Principles identified above which should
439 guide the contractor as specific scenarios are developed and proposed for analysis.
440

- 441 1. Scenarios and events should be scientifically, politically, and socially accurate and credible.
442 2. To the extent possible, events and scenarios should be realistic and based on actual examples,
443 possibly including the recent laboratory accidents at Federal facilities.
444 3. The overall range of scenarios should encompass high and low risk events, high and low
445 probability events, and maximum reasonably foreseeable (highly unlikely, but still credible)
446 events.
447 4. The scenarios should involve events that are of concern to stakeholders, including the public,
448 and include types that involve experimental manipulations that ultimately may be determined
449 to be prohibited under any circumstances.
450 5. Scenarios involving security threats should be plausible but not necessarily based on specific,
451 real-life examples, given that the security landscape is constantly evolving. Such scenarios
452 should involve consideration of the prior actions or expressed intent of certain groups, current
453 and reasonably achievable technical capabilities of these groups, and how readily security
454 threats could be achieved or enabled by a certain type of GOF study.
455

456 **Categories of Events and Scenarios**

457 Listed below are types of events and scenarios that the WG recommends for consideration in the RA.
458 The contractor should propose more specific scenarios based on these categories to be evaluated by the
459 WG.

- 460 1. Accidents due to equipment failure, human error, and system malfunction

- 461 2. Events that lead to direct infection of lab worker(s)
- 462 3. Accidental direct release into the environment, with possible exposure of the public
- 463 4. Scenarios that lead to secondary transmission of disease in the community, starting with an
464 infected lab worker
- 465 5. Incidents that result from security failures, either building systems or personnel
- 466 6. Incidents stemming from inventory errors and those involved with laboratory transitions, such
467 as laboratories relocating, PIs retiring, students graduating, etc.
- 468 7. Scenarios involving the escape of an infected animal
- 469 8. Scenarios that result in health and/or economic impacts on important animal species,
470 particularly those important to the food supply
- 471 9. Insider threats: an internal breach of security (e.g., disgruntled lab worker, infiltration of a lab by
472 an individual with nefarious intent)
- 473 10. External threats: an external breach of security (e.g., crime, targeting of a lab for theft of agents
474 or materials)
- 475 11. Production of novel pathogens, for malevolent acts or other illegitimate purposes, based on
476 information published about the results of GOF research
- 477 12. Natural disasters (e.g., earthquake, hurricane, tornado)
- 478 13. Accidents resulting from conduct of GOF research under sub-standard biosafety/biocontainment
479 conditions or practices, either in the U.S. or internationally
- 480 14. Scenarios based on alternative experimental approaches to GOF research

481

482 **Types of Experiments in RA**

483

484 The scope of research that is of concern must be clearly defined at the outset. Not all research that
485 involves genetic manipulations to alter a pathogen's phenotype should be examined in the RA and BA.
486 Listed below are types of experiments that the WG recommends for consideration in the RA and BA, but
487 the NSABB's ultimate policy recommendations need not be limited to the specific experiment types
488 included in the assessments. The following list includes experiment types that the WG recommends be
489 incorporated into scenarios to be modeled in the RA. Importantly, inclusion of these types of
490 experiments is not intended to condemn or condone them. The goal is to get a broad sense of the risks
491 and benefits associated with different experimental manipulations in the context of the pathogens
492 identified above, recognizing that not all permutations of risks, agents, and scenarios can practically be
493 analyzed in depth.

494

- 495 1. Passage in animals with the intent to alter host range and generate mammalian adapted strains
496 or to develop an animal model of disease
- 497
- 498 2. Genetic modifications and/or selection for traits that may increase pathogenicity or
499 transmissibility

500

- 501 3. Manipulations resulting in better growth or enhanced replication, for example, to make a
502 vaccine strain
503
504 4. Selection for antiviral resistant mutants
505
506 5. Antigenic escape studies, i.e., selecting for viruses that are not neutralized by certain antibodies,
507 such as those generated in response to a vaccine or monoclonal antibodies
508
509 6. Alternative experiments to GOF that may yield similar scientific information
510

511 **Biosafety Assumptions for the RA**

512 In order to assess the risks of GOF experiments it is necessary to define the biosafety level (BSL) and
513 other related conditions under which the work may take place because differences in working
514 conditions may significantly affect the risk of an experiment and possible adverse results. In the U.S.,
515 the *Biosafety in Microbiological and Biomedical Laboratories* and the *NIH Guidelines for Research
516 Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*¹⁵ provide biosafety guidance
517 regarding the conduct of risk assessments, and determination of appropriate laboratory practices and
518 physical containment for research conducted with specific agents. These guidelines apply to certain
519 federally-funded research conducted in the U.S. and abroad and are frequently used by non-federally-
520 funded institutions and other countries as the model for biosafety guidance. The WG discussed the
521 containment, practices, training, and occupational health plans required at various BSLs.
522

523 Because other countries have varying biosafety standards and individuals intending to misuse biological
524 materials may not abide by biosafety standards, the WG recommends that for each agent analyzed in
525 the RA multiple BSLs be assessed so that the effects of different levels of mitigation can be determined.
526 Also, the WG recommends that the effects of adequate or inadequate occupational medicine/medical
527 surveillance programs, training, standard operating procedures, and administrative controls be
528 examined. This approach will provide information the NSABB needs to make recommendations about
529 the conditions under which certain GOF studies might be performed to maximize safety and minimize
530 unnecessary burden on the research. Finally, the WG recommends that the contractor investigate the
531 status of biosafety guidance and biocontainment capabilities in other parts of the world, including
532 guidance issued by the World Health Organization, and provide a summary of the findings.
533

534 *Approaches and Methods for Assessing Risks and Benefits Associated with GOF*
535 *Studies*

536 The WG recommends that the following approaches be explored and employed by the contractor, as
537 appropriate and reasonable, to assess the risks and benefits associated with relevant GOF studies as well
538 as other important issues. The contractor should examine these and other possible methods and
539 identify those which might best be used to assess the specific categories of risks and benefits
540 recommended above. Efforts to identify risks and benefits that are unique to GOF research should be
541 included.
542

- 543 1. Literature reviews and examination of knowledge indicators (e.g., science citation index),
544 including consideration of quality and impact of information on the field.

¹⁵ <http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines>

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2. Examination of commercialization indicators (e.g., number of patents), including considerations for quality and utility.
3. Interviews and consultations with a broad range of relevant experts about risks and benefits associated with GOF studies are highly recommended. Relevant experts might include those in various scientific disciplines, public health, agriculture, private sector, global health, and public policy, and should include experts both within and outside the U.S. Consultations should include discussion of the important scientific questions remaining specifically for the pathogens being analyzed in the RA and BA and whether and how information from GOF studies may be utilized by relevant sectors. Discussions of how GOF studies contribute to research involving other pathogens with pandemic potential may also be useful. Interviews should also incorporate discussion of the perceived risks and benefits of alternatives to GOF studies.
4. Development of illustrative case studies or descriptions of instances where a GOF study has resulted in a specific risk or benefit.
5. Quantitative approaches to modeling the risks and benefits, particularly to public health. For instance, morbidity and mortality may be modeled for various scenarios of laboratory accidents, security breaches or intentional misuse, and/or public health responses. Additionally, if a GOF study were to accelerate vaccine or therapeutic production, it may be possible to model the positive effects on public health.
6. Quantitative approaches to modeling economic benefits and risks. For instance, if a GOF study would accelerate the development of a therapeutic or vaccine, the potential positive effects on jobs or productivity, as well as reduced health care costs in the event of a pandemic, might be estimated. In addition, the costs associated with an accidental release or malevolent act should be modeled.
7. Development of “event trees” illustrating processes leading to tangible events from GOF studies, employing expert elicitation to bound key events/nodes in processes.