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Risk Evaluation for Identification and Intervention in Dual Use Research of Concern (DURC) for International Biological R&D Activity (LDRD 192787)

Katherine A. Jones, Mercy B. DeMenno, Matthew J. Hoffman, Susan A. Caskey, Lisa Astuto Gribble, Jared L. Gearhart, Bryan Arguello, Lozanne M. Chavez, Adam J. Pierson, Elizabeth M. Lopez, Linda K. Nozick, Chad E. Davis

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Abstract

This report summarizes the work performed as part of a Laboratory Directed Research and Development project focused on evaluating and mitigating risk associated with biological dual use research of concern. The academic and scientific community has identified the funding stage as the appropriate place to intervene and mitigate risk, so the framework developed here uses a portfolio-level approach and balances biosafety and biosecurity risks, anticipated project benefits, and available mitigations to identify the best available investment strategies subject to cost constraints. The modeling toolkit was designed for decision analysis for dual use research of concern, but is flexible enough to support a wide variety of portfolio-level funding decisions where risk/benefit tradeoffs are involved. Two mathematical optimization models with two solution methods are included to accommodate stakeholders with varying levels of certainty about priorities between metrics. An example case study is presented.

ACKNOWLEDGMENTS

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NOMENCLATURE

APHIS	Animal and Plant Health Inspection Service
CDC	Centers for Disease Control
DOC	Department of Commerce
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DURC	Dual Use Research of Concern
EPA	Environmental Protection Agency
GOF	Gain of Function
GOFROC	GOF Research of Concern
HHS	Department of Health and Human Services
LDRD	Laboratory Directed Research and Development
MERS	Middle East Respiratory Syndrome
NIAID	National Institute for Allergy and Infectious Diseases
NIH	National Institutes of Health
NSABB	National Science Advisory Board for Biosecurity
NSDD	National Security Decision Directive
OSHA	Occupational Safety and Health Administration
PHE	Public Health Emergency
SARS	Severe Acute Respiratory Syndrome
SNL	Sandia National Laboratories
USDA	U.S. Department of Agriculture
USG	United States Government
WHO	World Health Organization

1. INTRODUCTION

1.1. Dual Use Research of Concern (DURC)

Dual Use Research of Concern (DURC) refers to research involving biotechnologies that can be used legitimately or maliciously, and hence may pose major national security and public safety threats.[1] The identification of life science experiments necessitating further government oversight has evolved through a series of policy documents. In 2004, the National Academies of Science identified the following seven classes of experiments identified as warranting further review and oversight: 1) "demonstrating how to render a vaccine ineffective," 2) "conferring resistance to antibiotics or antiviral agents," 3) "enhancing virulence of a pathogen or rendering a nonpathogen virulent," 4) "increasing transmissibility of a pathogen," 5) "altering the host range of a pathogen," 6) "enabling the evasion of diagnostic/detection modalities," and 7) "enabling the weaponization of a biological agent or toxin."[2] In 2012, the United States Government (USG) released a *Policy for Oversight of Life Science Dual Use Research of Concern*[3] which defines the scope of DURC as the 15 agents and toxins belonging to the Federal Select Agent Program[4] and the following seven classes of experiments, which reflect those described in the 2004 National Academies of Science report: 1) "enhances the harmful consequences of the agent or toxin," 2) "disrupts immunity or the effectiveness of an immunization against the agent or toxin without clinical or agricultural justification," 3) "confers to the agent or toxin resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies," 4) "increases the stability, transmissibility, or the ability to disseminate the agent or toxin," 5) "alters the host range or tropism of the agent or toxin," 6) "enhances the susceptibility of a host population to the agent or toxin," and 7) "generates or reconstitutes an eradicated or extinct agent or toxin."

In recent years, a sub-set of DURC, gain-of-function (GOF) research—which involves experiments that are intended to, or may result, in a gain of function, such as achieving airborne transmission of a virus that was not transmissible—has become of particular concern. GOF research "provides insight into the fundamental nature of human-pathogen interactions, enables the assessment of the pandemic potential of emerging infectious agents, and informs public

[1] The NIH provides the following definition: "Dual Use Research of Concern (DURC) is 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." http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/dual-use-research-concern

[2] National Academy of Sciences, *Biotechnology Research in an Age of Terrorism, A Report of the Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology,* National Research Council of the National Academies, 2004.

[3] Department of Health and Human Services, *United States Government Policy for Oversight of Life Science Dual Use Research of Dual Use Research of Concern,* 2012. http://www.phe.gov/s3/dualuse/Documents/us-policy-durc-032812.pdf

[4] These agents and toxins are (7 C.F.R. 331, 9 C.F.R. 121, and 42 C.F.R. 73): Avian influenza virus (highly pathogenic); *Bacillus anthracis;* Botulinum neurotoxin; *Burkholderia mallei*; *Burkholderia pseudomallei;* Ebola virus; Foot-and-mouth disease virus; *Francisella tularensis;* Marburg virus; Reconstructed 1918 Influenza virus; Rinderpest virus; Toxin-producing strains of *Clostridium botulinum;* Variola major virus; Variola minor virus; and *Yersinia pestis*.

health and preparedness efforts, including the development of medical countermeasures,"[5] but it also introduces significant biosecurity and biosafety risks. Recent GOF research has called attention to both these risks and the lack of an appropriate decision framework to analyze the relative benefits and risks of this type of work as well as possible mitigation strategies.

1.2. GOF Pause and NSABB Process

In 2012, two studies published in *Science*[6] and *Nature*[7] detailed GOF research involving highly pathogenic avian influenza (H5N1) conducted at two influenza laboratories, one at Erasmus MC in Rotterdam, the Netherlands, and the other at University of Wisconsin-Madison. These studies raised concerns among policymakers about the conduct of GOF research using federal funds and the role of the federal government in addressing the biosafety and biosecurity concerns raised by this research.[8] In response, in January 2012, the scientific community initiated a pause of certain GOF studies;[9] specifically, "39 virus experts from around the globe announced a voluntary 60-day pause on research that would potentially lead to the generation of highly pathogenic avian influenza (HPAI) H5N1 viruses with increased respiratory transmission in mammals."[10] In parallel, the World Health Organization (WHO) convened a "technical consultation" to analyze key issues associated with conducting, and publishing of, research involving H5N1.[11] In addition, several U.S. federal agencies issued additional guidance regarding GOF work with certain pathogens, including H5N1[12,13,14] and H7N9.[15] For example, the U.S. Department of Health and Human Services' (HHS) 2013 framework for funding decisions related to H5N1 describes the following evaluative criteria for funding decisions: "scientific and public health

[5] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity,* p.1, 2016.
[6] S. Herfst et al., Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets, in *Science,* vol. 336(6088), pp. 1534-1541, 22 June 2012.
[7] M. Imai et al., Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets, in *Nature* vol. 486(7403), pp. 420-428, 21 June 2012.
[8] National Science Advisory Board for Biosecurity, *Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research, Recommendations of The National Science Advisory Board for Biosecurity*, 2015.
[9] R. A. M. Fouchier et al., Pause on avian flu transmission studies, in *Nature* vol. 481, 26 January 2012.
[10] R. A. M. Fouchier, A. García-Sastreb, and Y. Kawaoka, The Pause on Avian H5N1 Influenza Virus Transmission Research Should Be Ended, in *mBio* vol. 3 no. 5 e00358-12, 9 October 2012.
[11] World Health Organization, Technical consultation on H5N1 research issues—consensus points, World Health Organization, Geneva, Switzerland, February 2012. http://www.who.int/influenza/human_animal_interface/consensus_points/en/index.html.
[12] D. Gangadharan, J. Smith, and R. Weyant, 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, p. 1-7, 28 June 2013. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6206a1.htm
[13] National Institutes of Health, *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules,* April 2013. http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines
[14] Department of Health and Human Services, *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*, 21 February 2013. http://www.phe.gov/s3/dualuse/Documents/funding-hpai-h5n1.pdf
[15] H. W. Jaffe, A. P. Patterson, and N. Lurie, Avian Flu: Extra Oversight for H7N9 Experiments, in *Nature* vol. 500, 7 August 2013. http://www.nature.com/nature/journal/v500/n7461/full/500151a.html

benefits of the proposal; the biosafety and biosecurity risks associated with the proposal; and the risk mitigation measures that are required."[16]

Despite these policy developments and the voluntarily 60-day pause on research initiated by the scientific community, several laboratory incidents in 2014 refocused attention on the need for comprehensive assessment of GOF policy. The U.S. government issued a pause on funding for new GOF research involving influenza, Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) viruses in October 2014.[17] In addition, the National Science Advisory Board for Biosecurity (NSABB) and the National Academies of Science were tasked with advising on the "design, development, and conduct of risk and benefit assessments for GOF studies" and providing "recommendations to the U.S. government on a conceptual approach to the evaluation of proposed GOF studies."[18] In support of the NSABB deliberative process, the National Research Council and the Institute of Medicine of the National Academies conducted stakeholder consultations with the life sciences community and general public.[19] The NSABB surveyed existing domestic and international policies and guidelines, which are discussed in more detail in Section 2. The NSABB also commissioned two studies from external experts, which are discussed in more detail in Section 3. The first study, conducted by Gryphon Scientific, LLC., documented a detailed risk and benefit assessment of GOF research involving pathogens with pandemic potential. The second study, conducted by Professor Michael Selgelid, analyzed the ethical issues and decision strategies associated with GOF research. The findings of these analyses fed into a deliberative process, which included the opportunity for public comment, resulting in the NSABB's production of recommendations[20] regarding a new federal policy on GOF research. These recommendations, published in May 2016,[21] will inform an interagency policy formation process; the Office of Science and Technology Policy and the National Research Council will lead the interagency policy formation processes. The resulting polices will add specificity to the broader set of policies governing DURC research, discussed in Section 2.

1.3. LDRD Contribution

This Laboratory Directed Research and Development (LDRD) effort focuses on incorporating risk and benefit assessments into an overarching optimization framework which considers available mitigations and funding to recommend a portfolio level risk mitigation strategy.

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[16] *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*, 21 February 2013. http://www.phe.gov/s3/dualuse/Documents/funding-hpai-h5n1.pdf

[17] Department of Health and Human Services, *U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS viruses*, 17 October 2014.

[18] National Science Advisory Board for Biosecurity, *Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research, Recommendations of The National Science Advisory Board for Biosecurity*, p. 2, 2015.

[19] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, 2016.

[20] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, 2016.

[21] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, 2016.

Progress has been made in developing methods of both biosafety and biosecurity risk assessment (i.e., producing the data required to conduct risk-benefit analysis) and USG policies for DURC and the NSABB deliberative process for GOF produced a conceptual approach and set of principles to guide funding decisions (i.e., producing the parameters required for prioritization of benefits and risks). Yet, a gap remains in bringing together these developments in a comprehensive decision analysis framework that integrates risk evaluation and mitigation. To address this gap, we develop a mathematical optimization framework for assessing and mitigating risks associated with DURC. This framework provides a defensible approach for converting qualitative assessments of risk into quantitative metrics and supports identification of optimal risk mitigation strategies that consider tradeoffs between benefits and multiple dimensions of risk. This framework, which we operationalize in a tool called the "Risk Informed Funding Toolkit," is designed to enable interventions at the stage of prospective risk analysis, which in the U.S. occurs at the funding stage. The importance of policy intervention at the funding stage is underscored by the NSABB's first recommendation: "*Research proposals involving GOF research of concern entail significant potential risks and should receive an additional, multidisciplinary review, prior to determining whether they are acceptable for funding. If funded, such projects should be subject to ongoing oversight at the federal and institutional levels."*[22] Even prior to the NSABB, the HHS deemed intervention at the funding stage to be the most viable approach; in 2012 it developed a framework for guiding its funding decisions for H5N1 and H7N9 GOF projects.[23,24]

This report discusses the development and implementation of robust mathematical framework using complex systems analysis algorithms and techniques to evaluate the risk associated with potential dual-use biological research and to recommend mitigation measures. This framework advances the state of the art in dual use risk evaluation and mitigation in an integrated manner which incorporates high levels of uncertainty. We demonstrate this approach using a case study of DURC involving three pathogens with pandemic potential.

[22] National Science Advisory Board for Biosecurity, *Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research, Recommendations of The National Science Advisory Board for Biosecurity*, p. 2, 2015.
[23] Department of Health and Human Services, *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*, 21 February 2013. http://www.phe.gov/s3/dualuse/Documents/funding-hpai-h5n1.pdf
[24] H. W. Jaffe, A. P. Patterson, and N. Lurie, Avian Flu: Extra Oversight for H7N9 Experiments, in *Nature* vol. 500, 7 August 2013. http://www.nature.com/nature/journal/v500/n7461/full/500151a.html

2. POLICY LANDSCAPE

The NSABB deliberative process described in Section 1 aims to provide policy recommendations for a more unified framework for GOF research of concern. While the resulting policy will address a clear gap in the governance of GOF research of concern, it will also be layered in the broader set of policies addressing DURC research. The NSABB report documents[25] the complexity of current policy landscape for DURC research, as depicted in Figure [1] below.

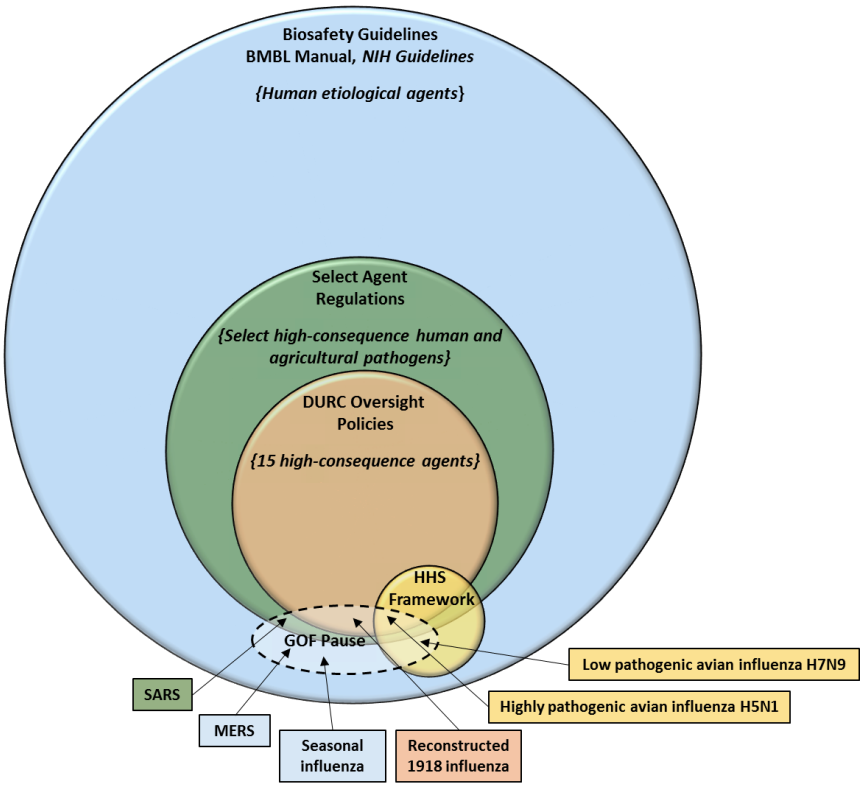

Figure 1: Comparison of the Scope of Different Policies for the Oversight of Life Sciences Research Involving Pathogens. Image source: NSABB, 2016.[26]

A variety of federal and international stakeholders are involved in the governance of DURC, which is codified in legislative statutes,[27] regulations,[28] executive directives,[29] guidance

[25] Gryphon Scientific, LLC., *Risk and Benefit Analysis of Gain of Function Research*, NIH Contract# HHSN263201500002C, 2015.
[26] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, p. 28, 2016.
[27] Federal statutes—developed and enacted by the U.S. Congress, and codified in the U.S. Code (U.S.C.)—permit and prohibit certain activities and/or delegate policymaking authority to federal regulatory agencies.
[28] Federal rules and orders—developed and enacted by the U.S. federal agencies, and codified in the Code of Federal Regulations (CFR)—dictate specific requirements.
[29] Executive Office of the President (EOP) may issue memoranda, presidential policy directives, or executive orders.

documents,[30] grants and contracts,[31] and international agreements.[32] In addition, laboratories carrying out DURC research have their own policies and practices, and these laboratories and their stakeholders share best practices, often facilitated through professional organizations (e.g., American Biological Safety Association).[33]

In the United States, the primary regulatory agencies of DURC research are the Department of Health and Human Services (HHS) Centers for Disease Control (CDC), the U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS), and the Department of Labor (DOL) Occupational Safety and Health Administration (OSHA). Several other federal agencies—such as the Department of Transportation (DOT), Department of Commerce (DOC), and Environmental Protection Agency (EPA)—may also issue rules and orders that affect the conduct of DURC. In addition, several federal agencies issue guidance documents which, through incorporation by reference in funding contracts or laboratory operating procedures, often carry the weight of federal policies. As Figure [1] from the NSABB final report[34] depicts, these different types of policies are relevant at different stages of the research lifecycle. At the proposal and funding stage, scientific merit review is the primary selection criterion for federally funded research. Each funding agency establishes its own internal policies for funding decisions, but these policies are informed by frameworks governing the conduct of research and will presumably be informed by the policies derived from the NSABB recommendations. Finally, in advance of the NSABB deliberative process, several agencies have developed frameworks for GOF: the HHS Framework for guiding funding decisions about certain GOF studies applies to H5N1 and H7N9[35] and the NIH National Institute for Allergy and Infectious Diseases (NIAID) developed a process for considering on a case-by-case basis studies that might be subject to the GOF pause.

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[30] Guidance documents—issued by federal agencies and non-governmental professional organizations—add specificity to federal regulations via best practices, recommendations, and operational baselines; although guidance documents do not hold legal standing, they may become *de facto* requirements via regulatory agency adoption by reference or contractual requirements (e.g., in federal funding).

[31] Government funding, in the forms of grants and contracts, may contain terms and conditions which dictate additional requirements.

[32] Federal government policy may implement international commitments, such as those dictated by the Biological Weapons Convention, Nations Security Council Resolution, World Health Organization (WHO) parallel guidance documents (e.g., WHO Laboratory Biosafety Manual).

[33] "A thorough examination of current practices in influenza and coronavirus biosafety level 3 (BSL-3) was conducted through site visits and interviews with researchers, public health officials, and institutional representatives. Best practices in biosafety and biosecurity pertaining to gain-of-function research were identified that exceed recommendations or requirements from various bodies, including the Occupational Safety and Health Administration (OSHA), select agent regulations, recommendations of the Federal Experts Security Advisory Panel (FESAP), and Institutional Animal Care and Use Committees (IACUC). Practices either unique to specific institutions or commonly found across institutions are highlighted and were found to be especially beneficial/optimal/useful in training, exercises and drills, laboratory practices, health precautions, physical security, and institutional culture." (Gryphon Scientific 2015: 100)

[34] National Science Advisory Board for Biosecurity, *Working Paper Prepared by the NSABB Working Group on Evaluating the Risks and Benefits of Gain-of-Function Studies to Formulate Policy Recommendations*, 2015. The NSAAB considers specifically the applicability of these policies to GOF research of concern.

[35] Department of Health and Human Services, *Framework for Guiding U.S. 852 Department of Health and Human Services Funding Decisions about Research Proposals with the 853 Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among 854 Mammals by Respiratory Droplets*, 2013.

At the research conduct stage, federal and institutional biosafety oversight and guidance provides biosafety practices and containment features based on risk assessments for specific projects. Examples of guidelines that are relevant to the conduct of DURC include HHS *Biosafety in Microbiological and Biomedical Laboratories (BMBL),*[36] NIH *Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines),*[37] and NRC *Prudent Practices in the Laboratory: Handling and Management of Chemical Hazards.*[38] In addition to these guidelines, a number of federal regulations govern certain DURC projects and processes. For example, the Federal Select Agent Program, which is jointly administered by HHS CDC and USDA APHIS, dictates the requirements for physical and personnel security for certain pathogens, some of which may be considered DURC. In addition, in response to the 2012 studies, HHS Public Health Emergency (PHE) developed policies for federal and institutional oversight of life science DURC. These policies—*USG Policy for Oversight of Life Science Dual Use Research of Concern* (March 2012)[39] and *USG Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern* (September 2014)[40]—focus oversight on research involving 15 high-consequence pathogens and toxins and seven categories of experimental activity. The *2012 DURC Policy*[41] outlines a process for the regular review of federally-funded or -conducted life sciences research to both identify DURC and to assess its risks, benefits, and oversight processes. The *2014 Policy for Institutional DURC Oversight*[42] complements the *2012 DURC Policy* and established specific review procedures and oversight requirements for federally funded life science research. HHS also issued a Companion Guide—*Tools for the Identification, Assessment, Management, and Responsible Communication of Dual Use Research of Concern*—, case studies, training slides, posters, and brochures to support researchers and institutions with compliance.[43]

While the U.S. government has many *ex ante* mechanisms to minimize biosafety and biosecurity risks associated with DURC, the *ex post* controls are limited. For example, following the conduct of research, there is very limited government control over the sharing and communication of scientific findings and research publications. Research is often published in academic journals and, pursuant to the National Security Decision Directive (NSDD) 189, is unrestricted to the "maximum extent possible." However, most biological research activities that are subject to

[36] Centers for Disease Control and Prevention, *Biosafety in Microbiological and Biomedical Laboratories (BMBL),* 5th Edition, December 2009. http://www.cdc.gov/biosafety/publications/bmbl5/

[37] National Institutes of Health, *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines),* April 2016. http://osp.od.nih.gov/sites/default/files/NIH_Guidelines.html

[38] National Research Council, *Prudent Practices in the Laboratory: Handling and Management of Chemical Hazards, Updated Version*, Washington, DC: The National Academies Press, 2011. doi:10.17226/12654. https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical

[39] Department of Health and Human Services, *United States Government Policy for Oversight of Life Science Dual Use Research of Dual Use Research of Concern,* 2012. http://www.phe.gov/s3/dualuse/Documents/us-policy-durc-032812.pdf

[40] Department of Health and Human Services, *United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern,* 2014. http://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf

[41] Department of Health and Human Services, *United States Government Policy for Oversight of Life Science Dual Use Research of Dual Use Research of Concern,* 2012. http://www.phe.gov/s3/dualuse/Documents/us-policy-durc-032812.pdf

[42] Department of Health and Human Services, *United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern,* 2014. http://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf

[43] Department of Health and Human Services Public Health Emergency, *Institutional Policy Companion Guide & Resources*. http://www.phe.gov/s3/dualuse/Pages/companion-guide.aspx

export controls fall under the DOC's Export Administration Regulations. Figure [2] from the NSABB report depicts the stage at which various government policies are relevant, demonstrating that agencies have the most control at the research proposal and funding stage.

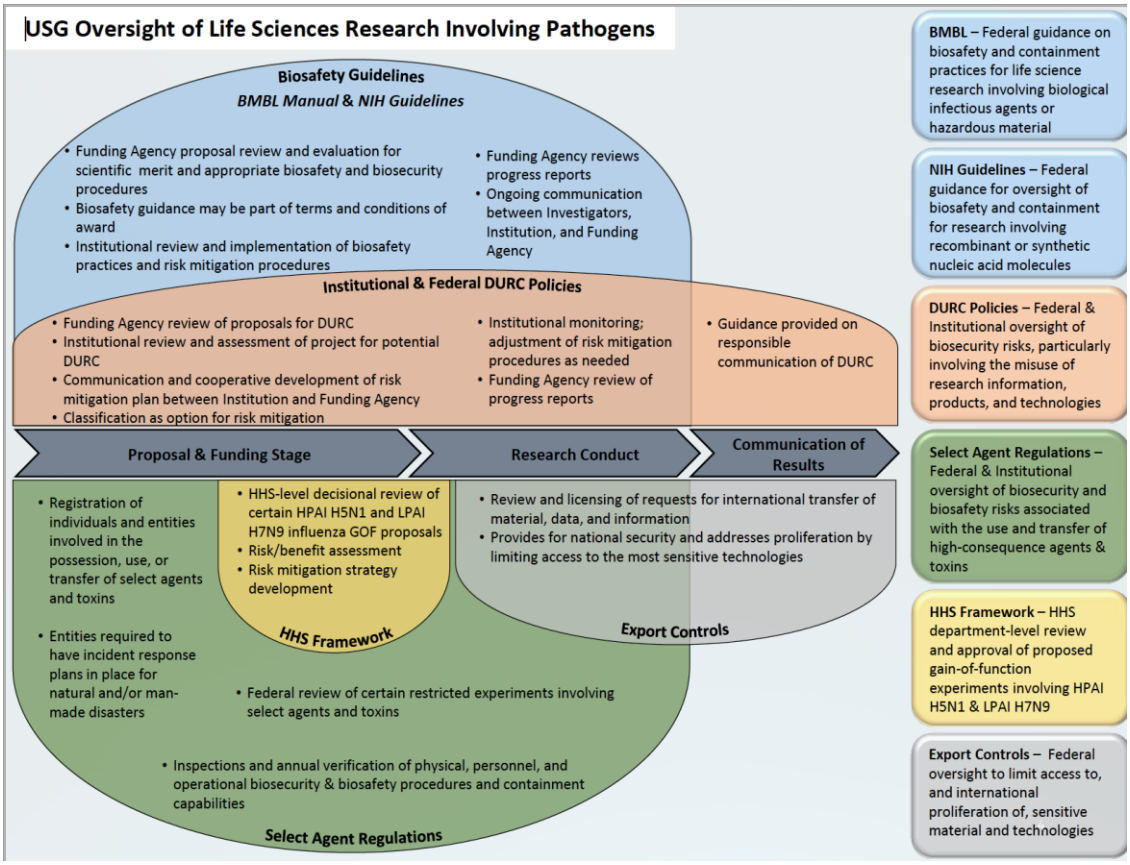

Figure 2: U.S. Government Oversight of Life Sciences Research Involving Pathogens. Image source: NSABB, 2016.[44]

[44] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, p. 22, 2016.

3. DEVELOPMENTS IN RISK-BENEFIT ANALYSIS

As Section 2 demonstrates, the current policy landscape provides a clear opportunity for government intervention at the funding stage and well as oversight throughout the research lifecycle. Yet, there are myriad technical, scientific, and policy issues that may affect decision-making at this stage. This section describes developments in risk-benefit analysis for biological and life sciences research.

There have been a number of developments in the methods of risk, benefit, and mitigation assessment, yet the applications to life sciences research, and the biosecurity and biosafety threats therein, are still being developed. Further, as summarized by Gaudioso et al.,[45] tools of biological risk assessment, which are utilized in the planning phase, are less developed that those implemented as part of biological risk management frameworks. Although certain general approaches to risk assessment—such as SWIFT analysis, Hazard and Operability (HAZOP), and Safety Integrity Level (SIL)—may be applied, with sufficient contextual expertise, to biological risk assessment, Gaudioso et al. note:

> *"While some would benefit from being better adapted to biosafety and possibly biosecurity, their purpose, relevance, advantages and drawbacks when applied to biorisk issues should in general be better known and documented. The same overall observations can be made for incident and accident investigation: general tools such as the causal tree (or root cause) analysis or the bow tie approach (which also allows identifying corrective actions) are available and useful, but they need to be used with the specific knowledge and experience of biorisk management."*[46]

Certain tools have begun to address these gaps in the *ex ante* measurement of the "performance of biosafety and biosecurity management in an institution," through tools that "quantify, visualize and simulate the effects of changes in the biorisk control measures." For example, Sandia National Laboratories has developed a series of Biorisk Assessment Models (BioRAMs) to identify and prioritize biosecurity and biosafety risks as well as mitigations. Specifically, BioRAMs include a scoring process for each component based on "Multi Criteria Decision Analysis (MCDA)" which relies on qualitative data from subject matter experts.[47] These scores are then aggregated into quantitative consequence and likelihood scores, which in turn can be multiplied to determine the relative risks of particular agents and mitigations.[48] BioRAM is highlighted by the Federal Select Agent program as a tool for biological risk assessment.[49]

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[45] J. Gaudioso, S. A. Caskey, L. Burnett, E. Heegaard, J. Owens, and P. Stroot, *Strengthening Risk Governance in Bioscience Laboratories*, Sandia National Laboratories report SAND2009-8070, pp. 78-79, Albuquerque, NM, 2009.

[46] J. Gaudioso, S. A. Caskey, L. Burnett, E. Heegaard, J. Owens, and P. Stroot, *Strengthening Risk Governance in Bioscience Laboratories*, Sandia National Laboratories report SAND2009-8070, p. 79, Albuquerque, NM, 2009.

[47] Sandia National Laboratories, *Biorisk Assessment Models (BioRAMs).* http://www.biosecurity.sandia.gov/BioRAM/

[48] *Biorisk Assessment Models (BioRAMs),* Sandia National Laboratories report SAND2008-2865, Albuquerque, NM, 2008. http://www.biosecurity.sandia.gov/BioRAM/BioRAM%20Intro.pdf

[49] Federal Select Agent Program, *Security Risk Assessment Tool.* http://www.selectagents.gov/guidance-securityrisk.html

As noted in the introduction, recent laboratory incidents and policy responses have spurred considerable debate among the scientific community regarding the conduct of DURC, resulting in numerous articles in the academic literature discussing the relative benefits and risks associated with such work.[50,51,52,53,54] Yet, current papers largely focus on the consequences of a release of a novel biological agent and any acknowledgement of likelihood is not based upon actual laboratory processes or procedures.[55,56,57] The National Academy of Sciences undertook an effort to define steps to minimize risk associated with such research, but the report does not provide concrete guidance beyond the need for review of experiments in seven areas of concern.[58]

As part of the NSABB deliberative process, Gryphon Scientific, LLC. undertook a comprehensive risk-benefit assessment of GOF studies and pathogens with "different enhanced phenotypes."[59] The report includes an assessment of biosafety risk, biosecurity risk (including risks associated with information disclosure), and the benefits of these studies; the report also considers other methods to achieve the same benefits. The report quantifies the key biosafety risks associated with coronaviruses, seasonal influenza, and pandemic influenza noting that studies of the latter were predicated to produce fewer risks than the former two. With respect to biosecurity risks, the study concludes that insider threats are the most prevalent and that information risks for influenza are small (because of the extent to which these studies are already published) but that there are some information risks associated with certain coronavirus studies. A number of benefits are also described—many of which are "unique," such as those associated with the development of seasonal influenza vaccines—in addition to those associated with surveillance and preparedness efforts. The NSABB notes that because risks and benefits are not presented in comparable terms it is difficult to determine from the risk-benefit assessment the instances in which certain risks justify the associated benefits. Therefore, a gap remains in bringing together these developments in a comprehensive decision analysis framework that

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[50] R. A. M. Fouchier, A. García-Sastreb, and Y. Kawaoka, The Pause on Avian H5N1 Influenza Virus Transmission Research Should Be Ended, in *mBio* vol. 3 no. 5 e00358-12, 9 October 2012.
[51] M. Lipsitch and B. R. Bloom, Rethinking biosafety in research on potential pandemic pathogens, in *mBio* vol. 3 no. 5 e00360-12, 9 October 2012. doi:10.1128/mBio.00360-12.
[52] M. Lipsitch and A. P. Galvani, Ethical Alternatives to Experiments with Novel Potential Pandemic Pathogens, in *PLoS Med* vol. 11(5): e1001646, May 2014. doi:10.1371/journal.pmed.1001646
[53] L. C. Klotz and E. J. Sylvester, The consequences of a lab escape of a potential pandemic pathogen, in *Frontiers* in *Public Health* vol. 2(116), August 2014.
[54] W. P. Duprex, R. A. M. Fouchier, M. J. Imperiale, M. Lipsitch and D. A. Relman, Gain-of-function experiments: time for a real debate, in *Nature* vol. 13, January 2015.
[55] L. Klotz, *The Human Fatality and Economic Burden of a Man-made Influenza Pandemic: A Risk Assessment*, Center for Arms Control and Non-Proliferation, 2014.
[56] S. Merler et al., Containing the Accidental Laboratory Escape of Potential Pandemic Influenza Viruses, in *BMC Medicine* (2013).
[57] S. Wain-Hobson et al., *Response to the letter by the European Society for Virology on 'Gain of Function' Influenza Research and proposal to organize a scientific briefing for the European Commission and conduct a comprehensive risk-benefit assessment*, Letter to the European Commission, 2013.
[58] National Academy of Sciences, *Biotechnology Research in an Age of Terrorism, A Report of the Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology*, National Research Council of the National Academies, 2004.
[59] Gryphon Scientific, LLC., *Risk and Benefit Analysis of Gain of Function Research*, NIH Contract# HHSN263201500002C, 2015.

integrates risk evaluation and mitigation; as will be discussed below, this is one area in which this LDRD advances the state of the art.

In addition to these developments in the conduct of risk-benefit assessment, USG policies for DURC and the NSABB deliberative process for GOF research of concern have produced a conceptual approach and set of principles to guide funding decisions (i.e., producing the parameters requires for prioritization of benefits and risks). These guidelines are important because the data produced via the aforementioned methods may feed into a variety of decision frameworks. The NSABB report[60] also identifies several frameworks from the broader literature on risk analysis that can be used to guide complex decisions with ethical implications and high degrees of uncertainty, such as GOF studies: "maximax," "maximin," "expected utility theory," "precautionary approach," "permissive approach," "planned adaptation or risk-based approach," "threshold approach," and "point-source approach." As the analysis of ethical issues associated with GOF commissioned by Professor Michael Selgelid describes[61] there are a number of substantive—"non-maleficence," "beneficence," "social justice," "respect for persons," "scientific freedom," and "responsible stewardship"—and procedural—"public participation and democratic deliberation," "accountability," and "transparency"—values that may influence the choice of decision framework, and in turn, funding decisions. Further, according to NSABB,[62] these values supplement other sources, such as the HHS *Belmont Report*[63] and the academic literature.[64] The findings of the NSABB risk-benefit assessment, along with the assessment of ethical issues, survey of existing policies and decision frameworks, and stakeholder interactions led to the findings and recommendations depicted in Table 1 below.

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[60] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, pp. 19-21, 2016.

[61] M. J. Selgelid, *Gain-of-Function Research: Ethical Analysis*, White Paper Prepared for NSABB, 2016.

[62] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, p. 16, 2016.

[63] Department of Health and Human Services, *The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects Research*, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979. http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

[64] Specifically, the NSABB (2016:16) calls for consideration of the following literatures and studies: "public health ethics" (N. E. Kass, An Ethics Framework for Public Health, in *American Journal of Public Health*, vol. 91(11), pp. 1776-1782, 2001. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1446875/); "oversight of emerging technologies"(*New Directions. The Ethics of Synthetic Biology and Emerging Technologies*. Presidential Commission for the Study of Bioethical Issues, December 2010. http://bioethics.gov/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10_0.pdf); and "literature specifically debating appropriate approaches to overseeing dual use research of concern (DURC) and GOF research" (D. B. Resnik, H5N1 Avian flu research and the ethics of knowledge, in *Hastings Center Report*, vol. 43(2) pp. 22-33, 2013; A. Kelle, Beyond patchwork precaution in the dual-use governance of synthetic biology, in *Sci Eng Ethics*, vol. 19(3), pp. 1121-39, September 2013; F. Kuhlau, A. T. Höglund, K. Evers, and S. Eriksson, A precautionary principle for dual use research in the life sciences, in *Bioethics*, vol. 25(1) pp. 1-8., January 2011; *Biotechnology Research in the Age of Terrorism*, The National Academies, 2004. http://www.nap.edu/catalog/10827/biotechnology-research-in-an-age-of-terrorism; National Science Advisory Board for Biosecurity, *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*, June 2007. http://osp.od.nih.gov/sites/default/files/resources/Framework%20for%20transmittal%20duplex%209-10-07.pdf)

Table 1: NSABB Findings[65] and Recommendations[66]

Findings	Recommendations
"Finding 1. There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF research—GOF research of concern (GOFROC)—entail risks that are potentially significant enough to warrant additional oversight."	**"Recommendation 1.** Research proposals involving GOF research of concern entail significant potential risks and should receive an additional, multidisciplinary review, prior to determining whether they are acceptable for funding. If funded, such projects should be subject to ongoing oversight at the federal and institutional levels."
"Finding 2. The U.S. government has several policies in place for identifying and managing risks associated with life sciences research. There are several points throughout the research life cycle where, if the policies are implemented effectively, risks can be managed and oversight of GOF research of concern could be implemented."	**"Recommendation 2.** An advisory body that is designed for transparency and public engagement should be utilized as part of the U.S. government's ongoing evaluation of oversight policies for GOF research of concern."
"Finding 3. Oversight policies vary in scope and applicability, and do not cover all potential GOFROC, therefore, current oversight is not sufficient for all GOF research of concern."	**"Recommendation 3.** The U.S. government should pursue an adaptive policy approach to help ensure that oversight remains commensurate with the risks associated with the GOF research of concern."
"Finding 4. An adaptive policy approach is a desirable way to ensure that oversight and risk mitigation measures remain commensurate with the risks associated with the research and that the benefits of the research are being fully realized."	**"Recommendation 3.1.** The U.S. government should develop a system to collect and analyze data about laboratory safety incidents, near-misses, and security breaches as well as the effectiveness of mitigation measures to inform GOF research of concern policy development over time."
"Finding 5. There are life sciences research studies, including possibly some GOF research of concern, that should not be conducted because the potential risks associated with the study are not justified by the potential benefits. Decisions about whether specific GOFROC should be permitted will entail an assessment of the potential risks and anticipated benefits associated with the individual experiment in	**"Recommendation 3.2.** The U.S. government should develop or facilitate the development of a system to collect and analyze data about Institutional Review Entity (IRE) challenges, decisions, and lessons learned to provide feedback to the IRE community and to inform policy development for GOF research of concern over time."

[65] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, p. 34, 2016.
[66] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, p. 40, 2016.

question. The scientific merit of a study is a central consideration during the review of proposed studies but other considerations, including legal, ethical, public health, and societal values are also important and need to be taken into account."	
"Finding 6. Managing risks associated with GOF research of concern, like all life sciences research, requires both federal and institutional oversight, awareness and compliance, and a commitment by all stakeholders to safety and security."	**"Recommendation 4.** In general, oversight mechanisms for GOF research of concern should be incorporated into existing policy frameworks when possible."
"Finding 7. Funding and conducting GOF research of concern encompasses many issues that are international in nature."	**"Recommendation 5.** The U.S. government should consider ways to ensure that all GOF research of concern conducted within the U.S. or by U.S. companies be subject to oversight, regardless of funding source."

Expanding on Recommendation 1, which is of clear relevance to this LDRD, the NSABB report[67] details "guiding principles" and a "conceptual approach" for funding decisions for GOF research of concern. The principle for guiding review and funding decisions[68] provide important inputs to any decision framework for GOF research of concern and arguably DURC research more broadly. Of particular relevance to this project is guiding principle iii:

> *"An assessment of the overall potential risks and benefits associated with the project determines that the potential risks as compared to the potential benefits to society are justified. Prior to funding GOFROC, the anticipated risks and potential benefits must be carefully evaluated. In general, the potential benefits associated with a research project should be commensurate with or exceed the presumed risks. Projects involving significant risks and little anticipated benefits are ethically unacceptable and should not be funded. If the potential risks appear high, the possible benefits should also appear high. Risks should be managed and should be mitigated whenever possible. The extent to which risks can be mitigated should factor into the assessment."*[69]

This principle clearly embodies the expected utility framework described above, suggesting that any decision analysis tool must be able to compare risks and benefits in such a way that enables identification of the Pareto optimal solution(s). In addition, the NSABB provides a conceptual approach for funding decision, which include the following steps:

[67] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, pp. 41-48, 2016.
[68] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, pp. 43-44, 2016.
[69] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, p. 43, 2016.

> *"1. Investigators and research institutions identify proposed GOFROC, as described by the two attributes for identifying GOFROC.*
>
> *2. Funding agencies identify or confirm proposed GOFROC.*
>
> *3. A Department-level panel of U.S. government experts reviews proposals involving GOFROC to determine whether the proposal meets the 8 principles for guiding funding decisions and to make recommendations as to whether the proposed research is acceptable for funding.*
>
> *4. Funding agencies make a funding decision, and if the proposal is funded, establish risk mitigation plans and issue the funding award with appropriate terms and conditions to help ensure ongoing oversight.*
>
> *5. Investigators and institutions conduct the research in accordance with any applicable federal, state, and local oversight policies and employ any necessary additional mitigation strategies. Federal agencies provide oversight to ensure adherence to established risk mitigation plans and funding terms."*[70]

As Step 4 highlights, any decision analysis framework must include, in addition to risks and benefits of a given project, potential mitigations. While this framework is focused on a subset of DURC, GOF Research of Concern (GOFROC), it is largely consistent with that developed by HHS PHE in its guidance policies for DURC, which envisage a similar review process. For example, in describing the roles and responsibilities of USG funding agencies, the *2014 Policy for Institutional DURC Oversight* also states that the benefits and risks of DURC, along with mitigations (enumerated in a "risk mitigation plan") should be evaluated at the funding stage. Further, the decision framework identified in the *2014 Policy for Institutional DURC Oversight* describes guiding principles for oversight of DURC, which also calls on the expected utility framework, stating that:

> *"Oversight of DURC must recognize both the need for security and the need for research progress; as such, the degree of oversight should be commensurate with the possible consequences of misuse."* [71]

Despite these advancements in the production of data there is a need for a comprehensive framework that brings together this disparate data on risks, benefits, and mitigations and enables users to analyze these data in a framework that is adaptable to the various decision criteria identified above.

[70] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, p. 45, 2016.
[71] National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, p. 22, 2016.

4. R&D APPROACH

This LDRD seeks to advance the state of the art in portfolio-based risk-benefit analysis. It seeks to provide a defensible approach for converting qualitative assessments of risks, benefits, and mitigations into quantitative metrics. It does so by establishing a new mathematical framework for risk evaluation of potential DURC research projects. This framework is operationalized through a user-friendly optimization model, which identifies interventions which best control relevant dimensions of risk while supporting scientific advancement. This section describes the framework, including the user interface, data sources, and the underlying model. The next section demonstrates this capability using a case study of DURC involving three pathogens with pandemic potential.

4.1. Risk-Informed Funding Toolkit

We develop a mathematical model and associated software interface, the Risk-Informed Funding Toolkit (RIFT), to enable policymakers to evaluate a portfolio of DURC projects. This model, which is optimization-based, assesses not only the biosafety and biosecurity risks and benefits of each DURC project in the portfolio, but also the possible mitigations and resulting risk reductions, all under a consideration of costs and available funding. As such, this framework provides a defensible approach for converting qualitative assessments of risk into quantitative metrics, and supports identification of optimal risk mitigation strategies that consider tradeoffs between benefits and multiple dimensions of risk.

4.1.1. User Interface

The RIFT user interface is designed to accommodate a wide range of data input types. Figures [3]-[12] below depict the input screens for the RIFT user interface, populated with notional data derived from prior studies and policies related to DURC. The facilities input screen (Figure [3]) depicts the names of all facilities in which projects might be executed. In addition, this screen captures the maximum amount each facility would be willing and able to pay for any required safety or security mitigations, both as a hard dollar limit and as the percentage of funding received that they might be willing to pay for mitigations. Any values shown in the screens in this section are placeholder values, not real data.

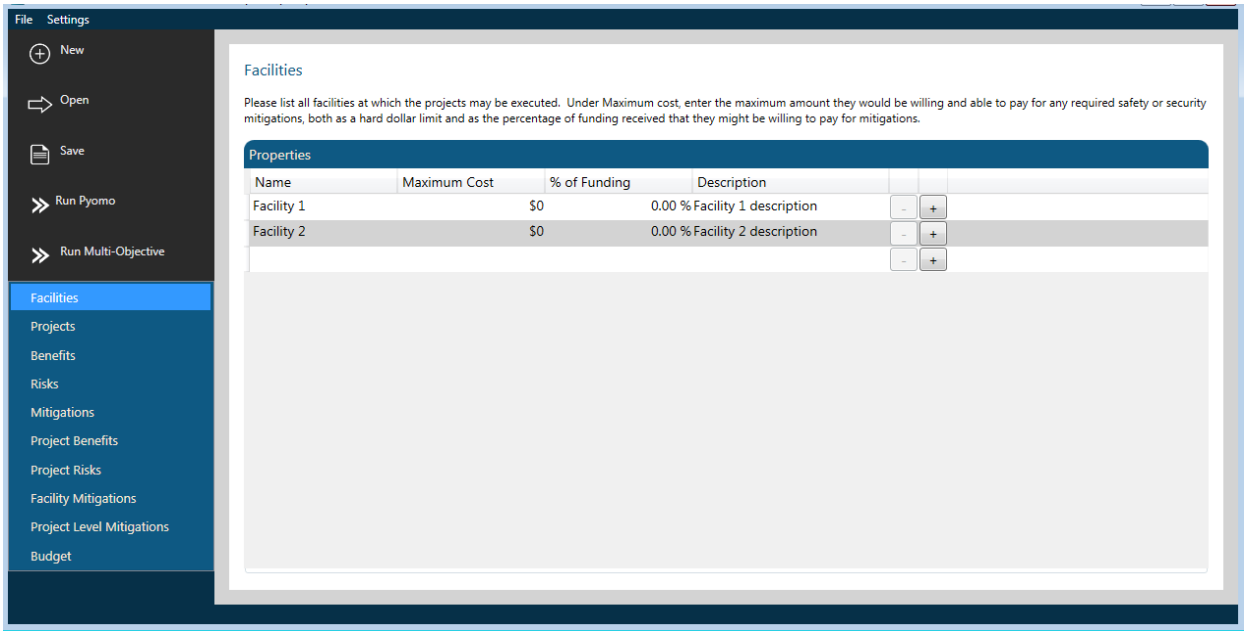

Figure 3: Facilities Input Screen

The projects input screen (Figure [4]) depicts all proposed projects names, types of research, the facility at which each project would be performed, the funding being requested, and a brief description. The funding amount is the cost of the project exclusive of any risk mitigation investments, which are entered separately.

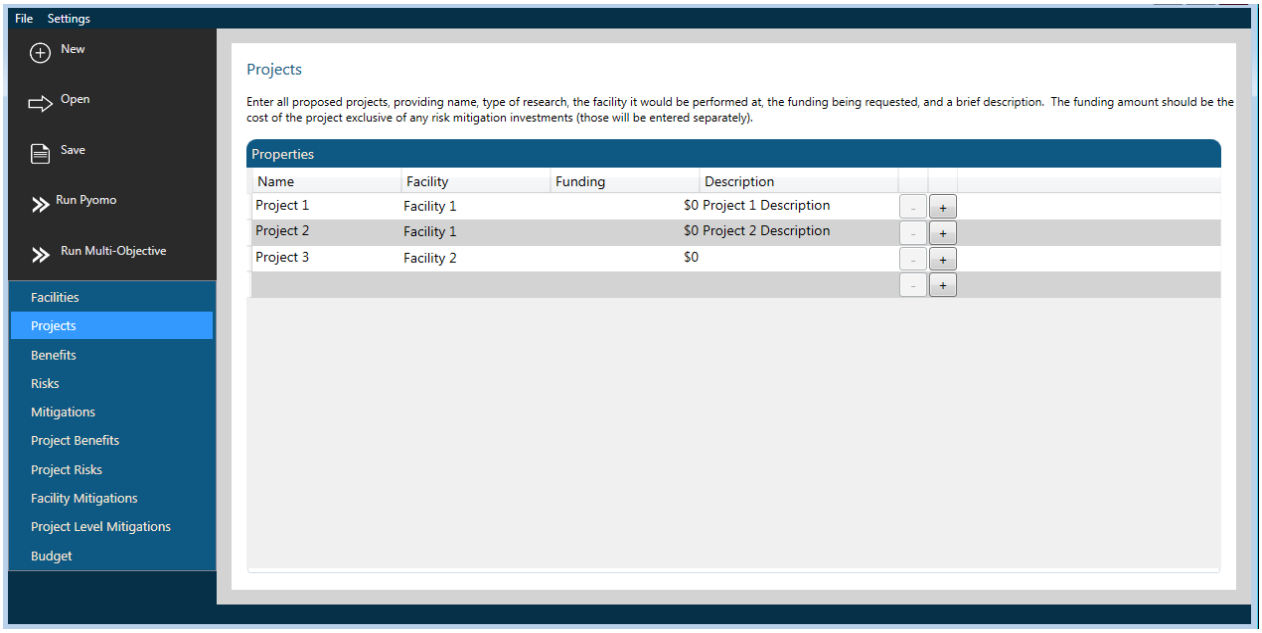

Figure 4: Projects Input Screen

The benefits input screen (Figure [5]) captures the various benefits that may be associated with a given project portfolio. Basic Research and Applied Research are provided as default benefit categories, but it is possible to add additional categories if desired. Basic research benefits focus on scientific discovery (e.g., understanding pathways, mechanisms, relationships, utility of surrogates, immune responses) for potential applied benefit further out in the future than the time horizon of the analysis. Applied research benefit examples include product development, vaccine development, therapeutics, delivery, and decontamination. Benefits can be quantified in any relative scale, as long as all benefit types share the same scale. If not, they need to be normalized prior to entry. The "Importance" column is only used in the closed form mode of the model, and needs to be between 0 and 1.

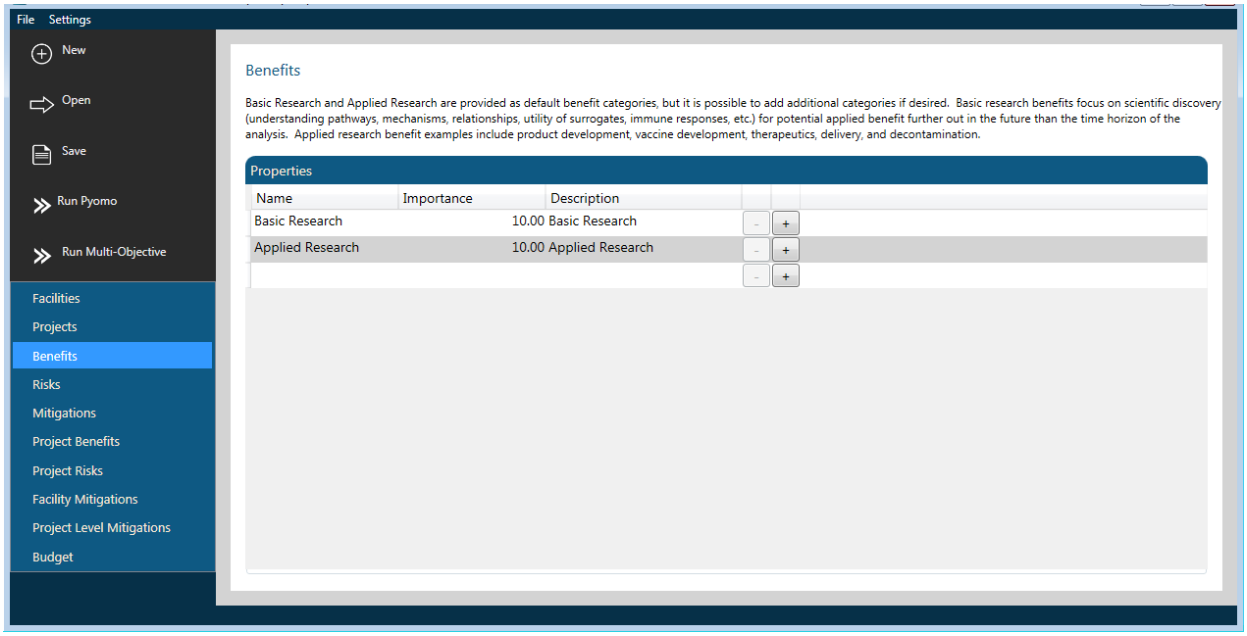

Figure 5: Benefits Input Screen

The risk input screen (Figure [6]) captures the various risks that may be associated with a given project portfolio. Biosafety and Biosecurity are provided as default risk categories, but it is possible to add additional categories if desired. An available mechanism (i.e., subject matter expert evaluation, models, simulations, or checklists) must be available to provide anticipated risk levels in all categories listed for all projects listed, but risks can be quantified in any relative scale, as long as all risk types share the same scale. If not, they need to be normalized prior to entry. The "Importance" column is only used in the closed form mode of the model, and needs to be between 0 and 1.

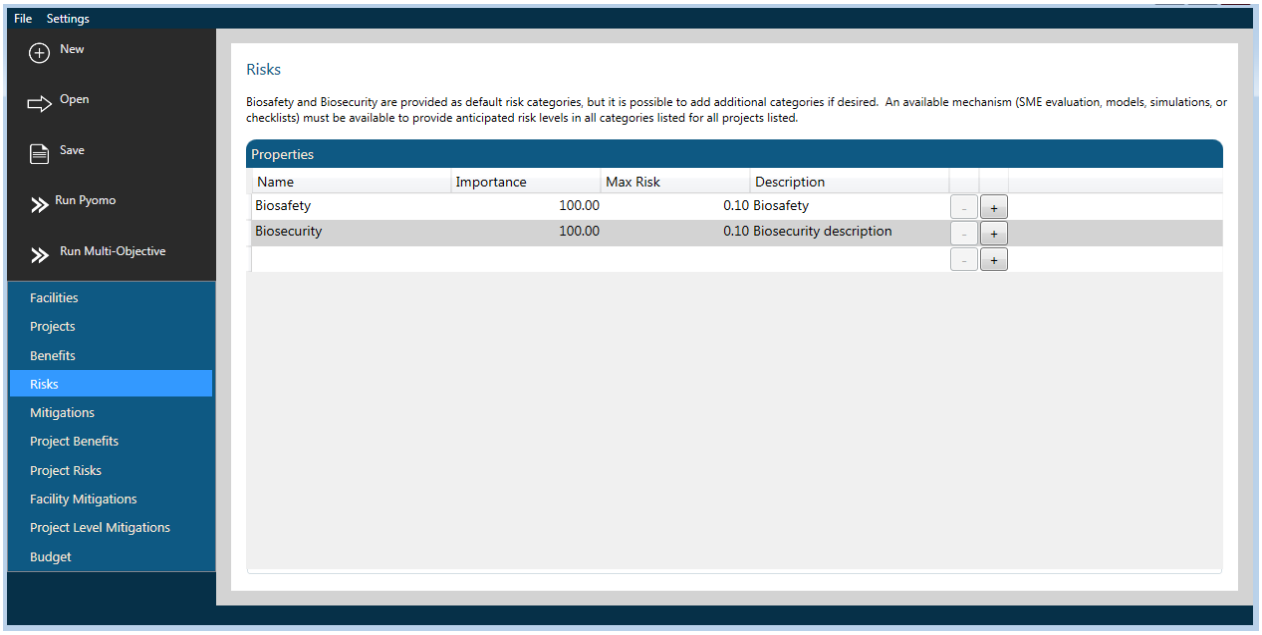

Figure 6: Risks Input Screen

The mitigations input screen (Figure [7]) captures all potential biosecurity and biosafety risk mitigations available. This information includes the name of the mitigation (e.g. biosafety cabinet), the anticipated cost, and whether facility overhead or the project grant would be expected to cover the cost of the mitigation. There is optional space to provide a mitigation description.

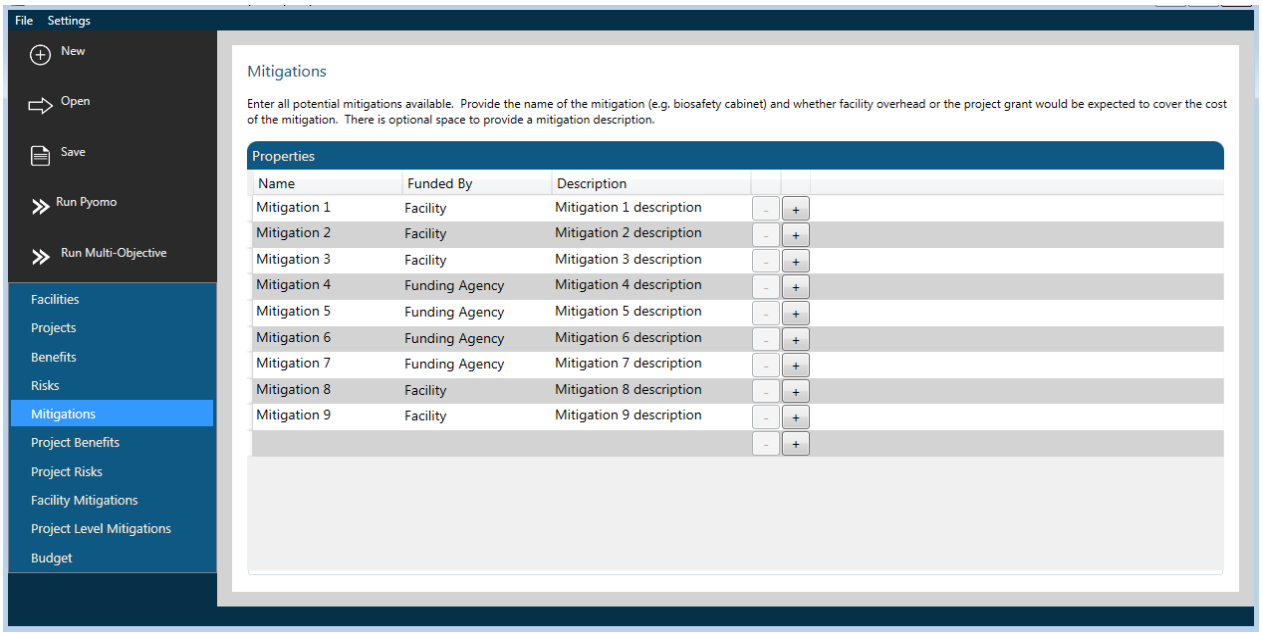

Figure 7: Mitigations Input Screen

The project benefits screen (Figure [8]) captures the anticipated benefit level for each category (by default, Basic Research and Applied Research) for each project. The user enters 0 if there is no anticipated benefit in a category. For example, a scientific discovery effort with no applied benefit in the near term would have a 0 for Applied Research.

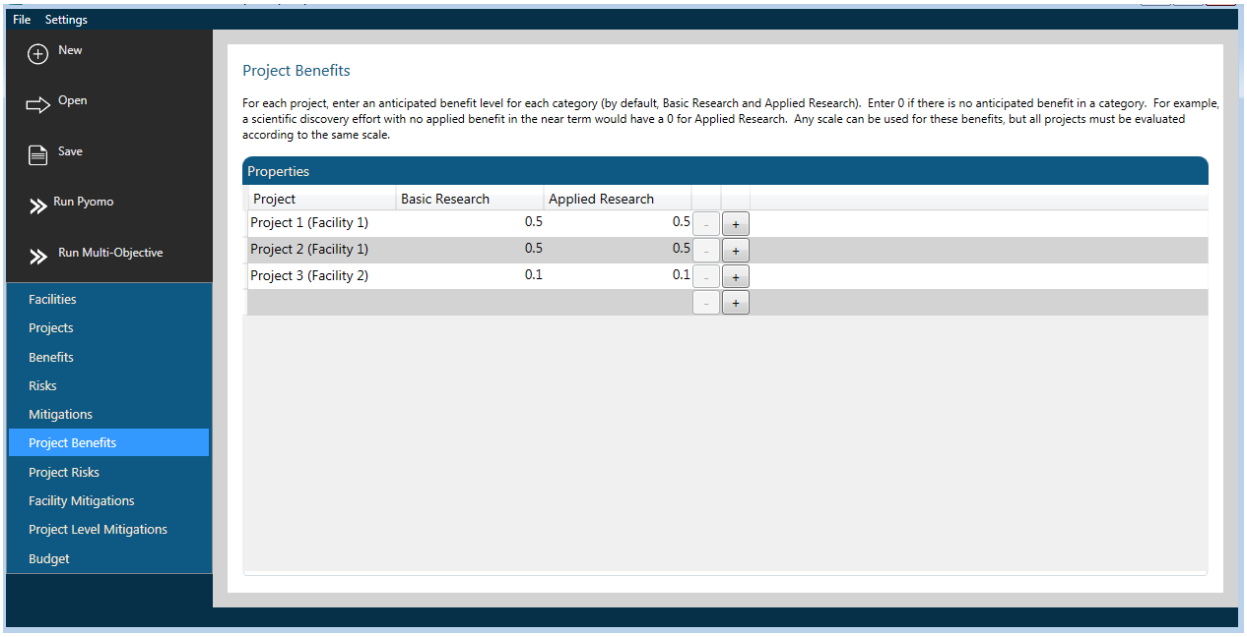

Figure 8: Project Benefits Input Screen

The project risks screen (Figure [9]) captures the anticipated risk level for each category (by default, Biosafety and Biosecurity) if no mitigation measures beyond existing equipment or processes were required for each project. An available mechanism (i.e., subject matter expert evaluation, models, simulations, or checklists) must be available to provide anticipated risk levels in all categories listed for all projects listed.

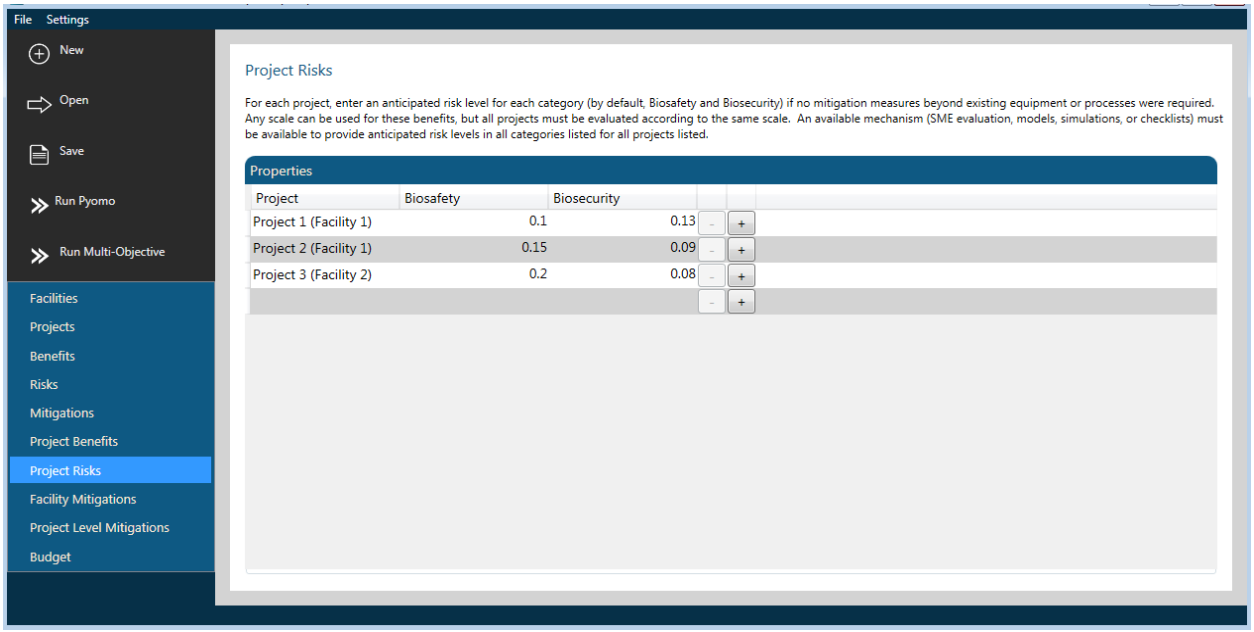

Figure 9: Project Risks Input Screen

The facility mitigations screen (Figure [10]) captures anticipated reduction in risk (using the same metric/scale(s) as on the previous step) anticipated if the mitigation were invested in at that facility. A simplifying assumption is made that all projects at that facility will receive the same risk reduction level under the mitigation. For example, an entry control system at a facility would provide biosecurity risk reduction to all projects funded at that facility.

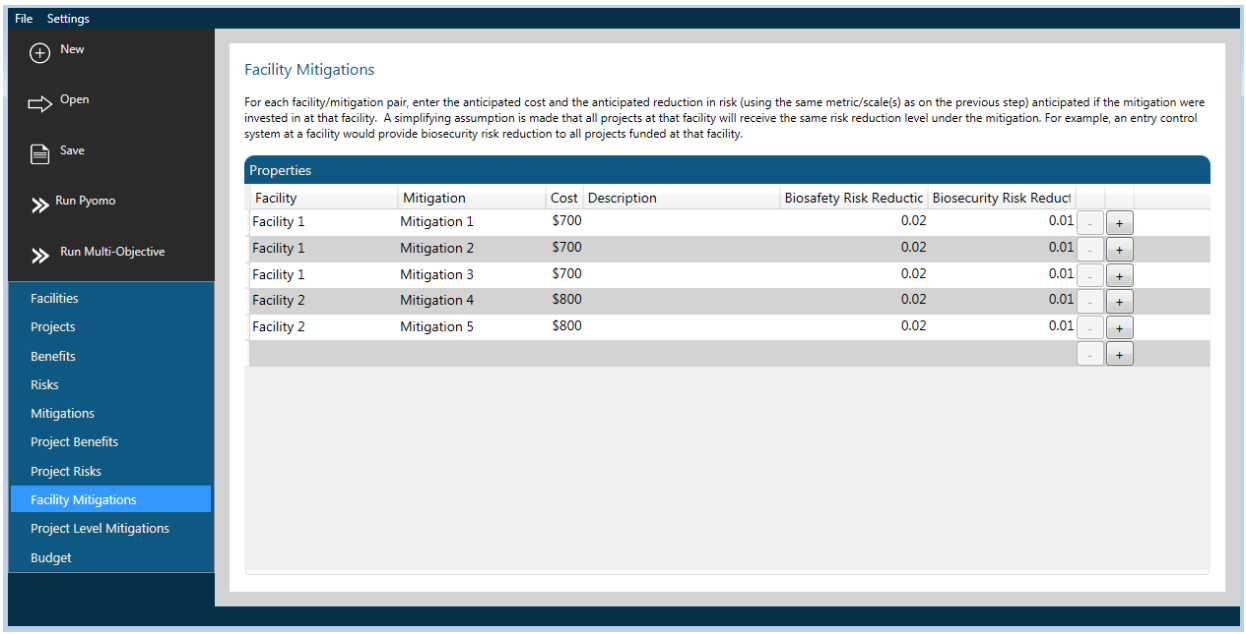

Figure 10: Facility Mitigations Input Screen

The project mitigations screen (Figure [11]) captures anticipated reduction in risk (using the same metric/scale(s) as on the previous step) if the mitigation were funded and implemented as part of that project.

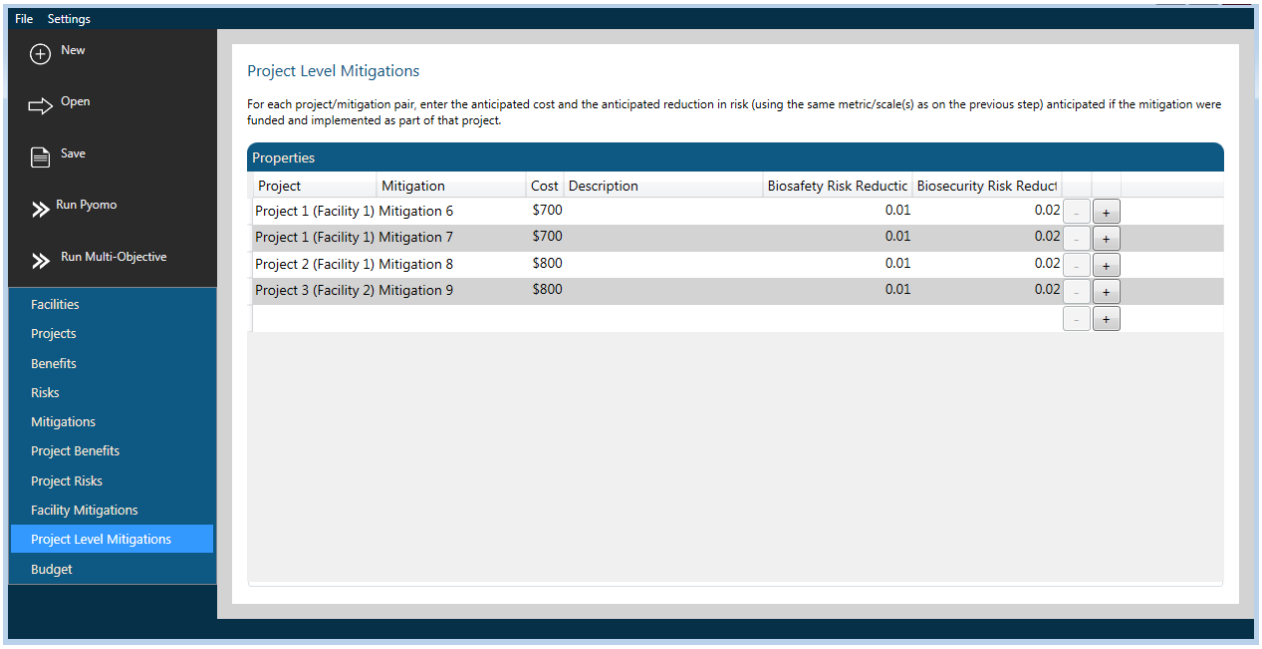

Figure 11: Project Mitigations Input Screen

The budget input screen (Figure [12]) captures the total funding available for all projects from the funding agency. The facility budgets entered in the Facilities section is displayed here as a reminder of the available mitigation budget at each facility.

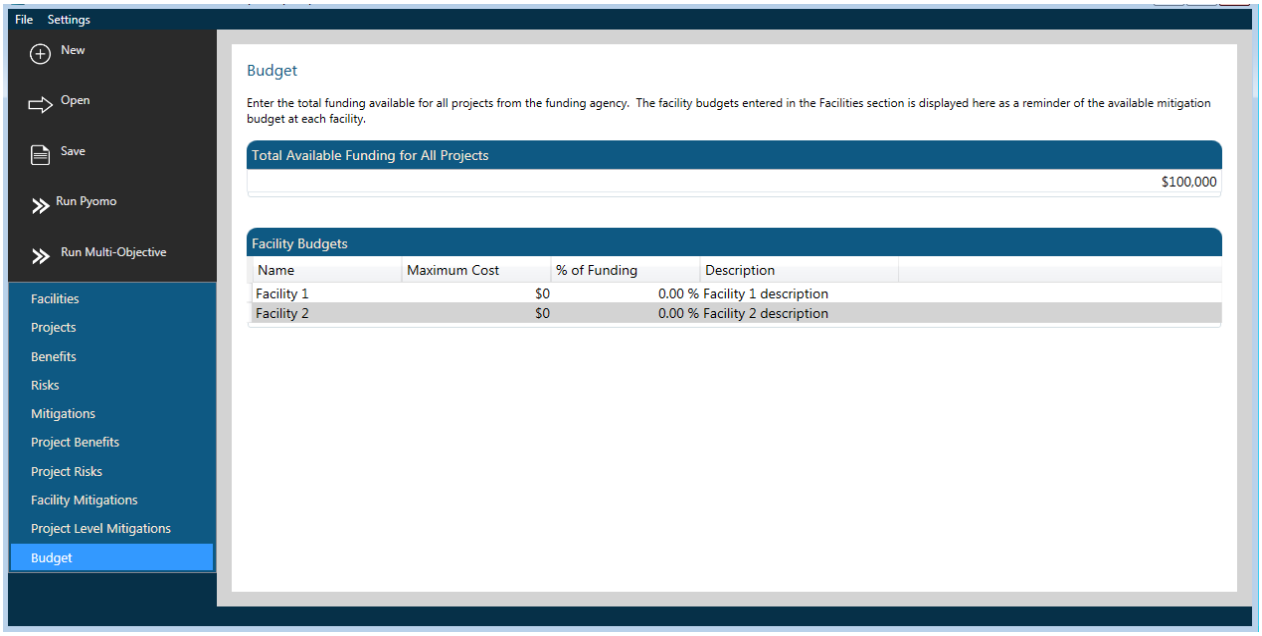

Figure 12: Budget Input Screen

As described in more detail below, RIFT enables users to run a closed form a priori weighted or heuristic multi-objective optimization. For each mode, RIFT produces a visualization of solution(s) and a detailed view of each solution in the solution set. Figures [13] and [14] depict the output screens using the multi-objective optimization. The solutions output screen (Figure [13]) provides sliders that filter the available solutions to show only a set that meet acceptable values on each metric. For example, if you want to see all the possible optimal solutions that have a Biosafety risk level below 3, move the top slider down to 3. Then select a specific solution (represented by a line) to pull up the details of that solution and select the one which represents the best balance of risks and benefits for the stakeholders' preferences.

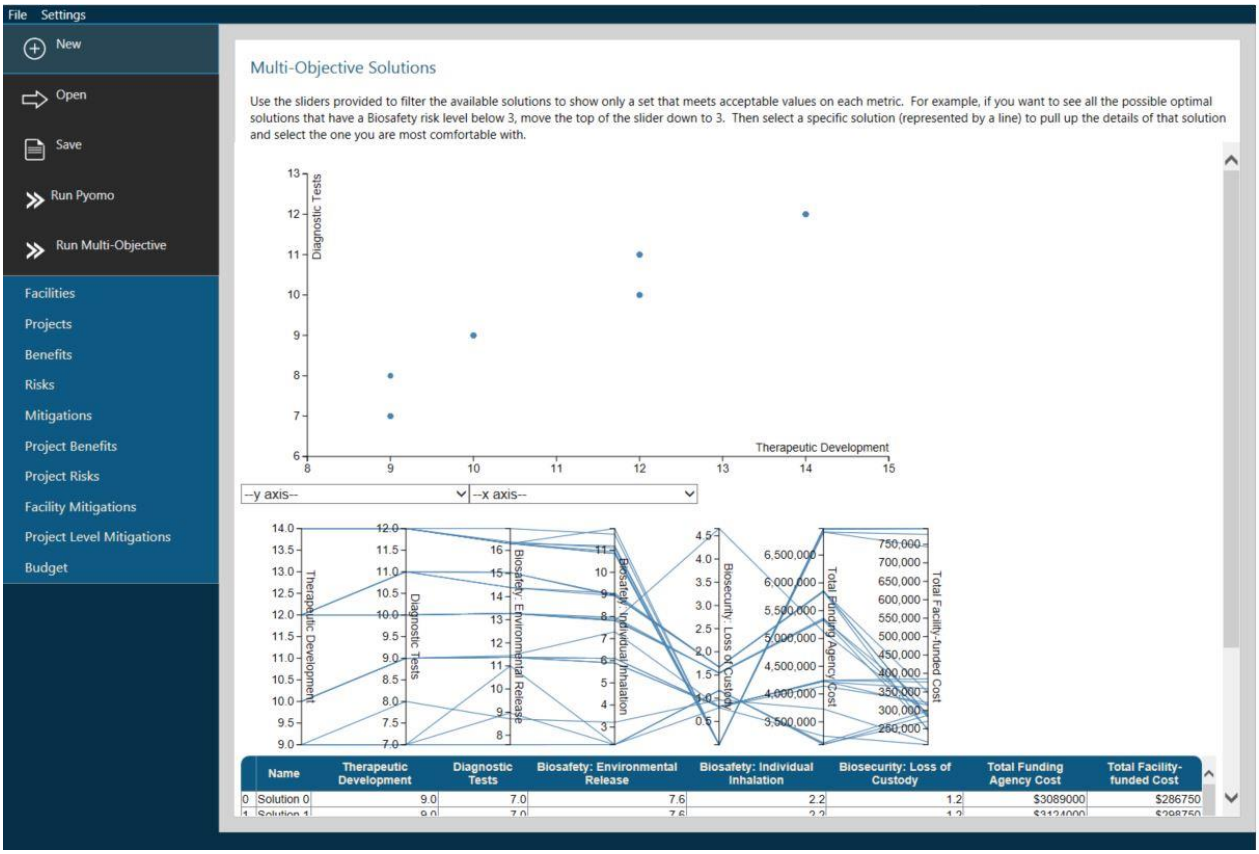

Figure 13: Solution Output Screen

The solution details output screen (Figure [14]) depicts the projects that are selected for funding under this solution, along with the recommended mitigations and associated cost, benefit, and risk levels assuming implementation of those mitigations.

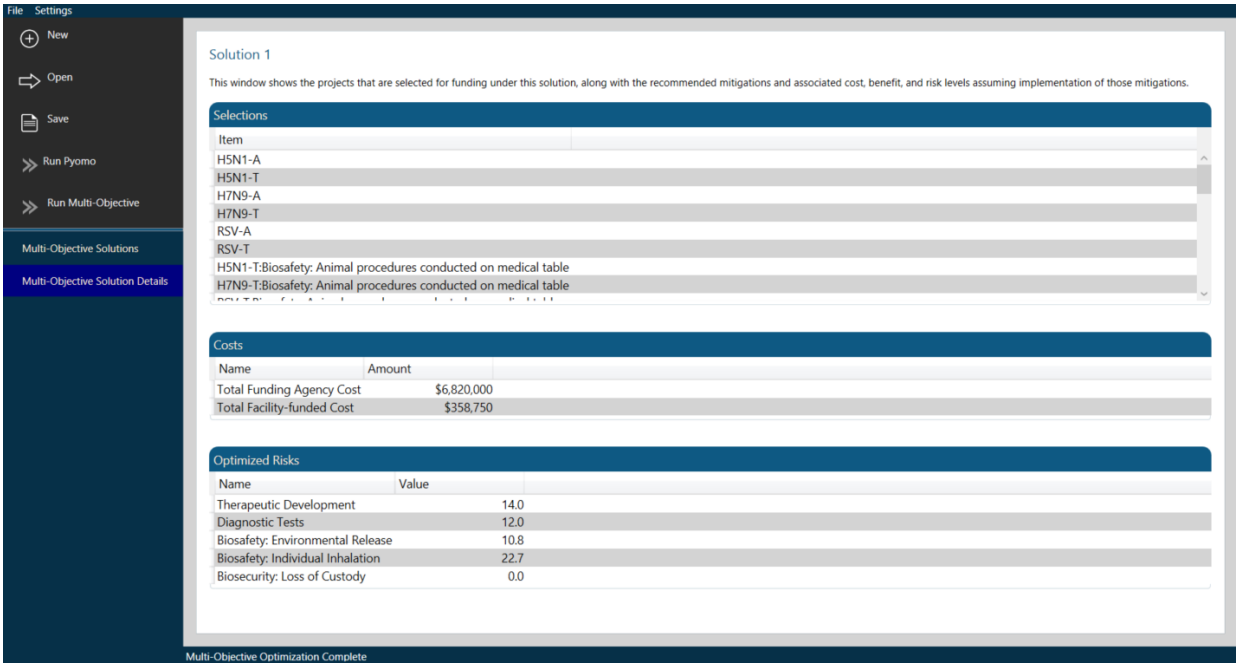

Figure 14: Solution Details Output Screen

4.1.2. Data Sources

A key contribution of RIFT is the ability to integrate various qualitative and quantitative data sources and compare risks, benefits, mitigations, and associated costs in a comprehensive framework. For example, recent policy guidance has enumerated a number of potential biosecurity and biosafety mitigations.[72] To quantify both the risks and benefits of a given project as well as the risk reductions as a result of these mitigations, tools and methods of risk analysis described in Section 3, such as BioRAM, can be integrated into RIFT. Notwithstanding recent developments in risk analysis, potential societal benefits and risks of DURC research projects are inherently probabilistic, so a stochastic representation of the problem is needed. We overcome the significant technical challenges around developing probability distributions for key inputs through uncertainty quantification and advanced expert elicitation techniques. For the purposes of the test case, we relied on subject matter experts within Sandia, but subject matter experts could come from a wide range of institutional settings, including the National Institutes of Health (NIH), World Organisation for Animal Health (OIE), and the European biosafety community. RIFT is further amenable to a variety of elicitation approaches such as the Analytic Hierarchy Process, the Delphi technique, and Multi-Attribute Utility Theory, as well as statistical

[72] National Science Advisory Board for Biosecurity, Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity, p. 48, 2016.

methods.[73,74,75,76] Further, the approach takes into account uncertainty in assessments and correlations between benefits and multiple dimensions of risk.

4.1.3. Applicability of Different Decision Frameworks

RIFT is designed to enable interventions at the stage of prospective risk analysis, which in the U.S. occurs at the funding stage. As noted in the introduction, the importance of policy intervention at the funding stage is underscored by the recent NSABB recommendations, which draw on multiple decision frameworks. For example, Recommendation 1 draws on a "threshold" approach in identifying GOF research of concern but in describing funding decisions draws on expected utility theory (risk-benefit assessment), point-source, and precautionary approaches. Recommendation 3 also draws on the planned adaptive approach. This suggests that the resulting policy framework may embody multiple decision-making frameworks and as such any decision-support tool must be sufficiently flexible. RIFT is sufficiently flexible to allow it to be used pursuant to a number of different decision frameworks:

- Expected utility theory[77]
- Point source[78]
- Precautionary[79]

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[73] T. Saaty and K. Peniwati, *Group decision-making: drawing out and reconciling differences*, RWS Publications, Pittsburg, PA, 2007.
[74] T. Saaty, *Mathematical Principles of Decision Making*, RWS Publications, Pittsburg, PA, 2014.
[75] E. Triantaphyllou, *Multi-criteria Decision Making Methods: A Comparative Study*, Kluwer Academic Publishers, Netherlands, 2000.
[76] P. Garthwaite et al., Statistical Methods for Eliciting Probability Distributions, *in Journal of the American Statistical Association*, 100.470, pp. 680-700, 2005.
[77] "Expected Utility Theory: choosing the option that maximizes expected utility, where expected utility for a possible outcome = probability x utility. Expected utility theory involves a quantitative balancing of risks and benefits and is inherently a more complex process. Cost-benefit analysis in economics is a form of expected utility theory. A problem with expected utility theory is that sufficient evidence may not always be available to confidently estimate the probabilities involved in the utility calculus. When this is the case, other approaches may be appropriate. For GOF studies, use of expected utility theory would require quantitatively determining the likelihood of risks and benefits and calculating the resulting utility." (National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, pp. 19-20, 2016.)
[78] "Point-source approach: involves controlling where certain studies are conducted and under what conditions. This approach would centralize certain research activities, restricting them to designated locations or facilities. For GOF studies that raise concerns this might involve requiring that certain studies only be conducted in facilities with certain biocontainment conditions, biosafety practices, and security measures." (National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, p. 21, 2016.)
[79] "Precautionary approach: involves taking reasonable measures to prevent, minimize, or mitigate risks that are significant and plausible. A measure is "reasonable" if it: 1) appropriately balances the values at stake in the risk management; 2) is proportional to nature of the risk (i.e. greater risks require stronger measures); and 3) is likely to be effective. A risk is "plausible" if there is some scientific evidence that it could occur even if the probability of the risk cannot be confidently estimated. There are many versions of the precautionary principle, including ones that are more or less risk-averse. A precautionary approach, in general, would limit an activity unless the environment, health, or security, are clearly protected. This approach can recognize a potential problem early and prevent harm from occurring but may lead to regulatory burdens or unnecessarily limit activities. This approach might restrict potential GOF research unless the studies are demonstrated to be safe." (National Science Advisory Board for

- Threshold approach[80]
- Planned adaptation or risk-based[81]

4.2. Model

4.2.1. Multi-Objective Full Frontier

4.2.1.1. Formulation

A multi-objective optimization is used to identify the optimal investment strategy for reducing risks while considering both the potential benefits of a given project and the costs of potential mitigations. This approach draws on both closed form and heuristic methods. Assume that a portfolio of research projects is under consideration. The funding agency is interested in minimizing the total portfolio risk while maximizing the benefit gained through the portfolio, subject to available funding. The model is intended to recommend which projects to fund and which mitigations to fund in order to minimize risk and maximize benefit subject to a number of constraints. The goal of the model is to identify the trade-off frontier between the different elements of risk and benefits. This results in the objective function given in equation (1a) and (1b).

Projects for this research have multiple types of risk (such as biosafety or biosecurity) indexed by *r* and multiple types of benefit (such as basic research or applied research) indexed by *b.* The baseline level of risk for a project is given by S_{pr}. There are mitigations available, such as biosafety cabinets or alarm systems, which can reduce the risk associated with a project, either by directly impacting the project laboratory or by protecting the entire facility in which the project takes place. Suppose there are two separate pools of funding available: the funding agency and the facilities applying for funding to carry out the research. The mitigations funded

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Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, pp. 20-21, 2016.)

[80] "Threshold approach: identifying a risk threshold beyond which, certain studies are given special attention or subject to additional scrutiny or oversight and might preclude certain studies. Implementation would involve defining or describing the studies that would require additional oversight as well as a description of what that oversight would entail. This approach would allow for the identification of studies of concern but might need to be reevaluated if the risk landscape changes and the threshold that was identified is no longer appropriate. For GOF studies, this would entail identifying the characteristics of studies involving significant risks that may not be adequately managed and then stipulating further oversight or determining that they should not be conducted." (National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, pp. 20-21, 2016.)

[81] "Planned adaptation or risk-based approach: provides a systematic way to deal with managing risks in the face of uncertainty. It involves: 1) preparation to identify the risks and regulatory gaps, including input from a broad range of perspectives; 2) putting measures in place to control risk based on the best information available at the time; 3) systematically gathering data and observing the effects of policies; and 4) updating and revising policies as needed. An example of an adaptive approach is the life cycle approach taken by the Food and Drug Administration when making decisions about whether to approve drugs, when that includes post-market surveillance. For GOF studies, this approach might entail allowing studies that raise concerns to proceed under defined conditions, then evaluating the risk-benefit landscape periodically to determine whether the studies that are permitted should continue, be expanded, or be restricted." (National Science Advisory Board for Biosecurity, *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research, A Report of the National Science Advisory Board for Biosecurity*, p. 20, 2016.)

by the agency are indexed by *a* and the mitigations which must be funded by individual facilities are indexed by *l*. Risk reductions from facility-funded mitigations are given by e_{lfr} and risk reductions from agency-funded mitigations are given by e_{apr}. These reductions in risk must result in per-project risk levels below the maximum level of acceptable risk H_r as shown in equation (2). The value that is minimized in equation (1a) is a submodular set function over all facility-funded and agency-funded risk mitigations, which is intended to emulate diminishing returns that will occur when many mitigations are funded.

Let *V* be the agency funds available and let K_f be the funds facility *f* is willing to spend. The agency funds must cover the project-specific mitigations as well as the cost of the research project. Let c_p be the cost of research project *p*. These constraints are given in equations (3) and (4) below. Suppose each facility *f* is unwilling to exceed a given fraction of the total project grant funding they receive, where that percentage is given by g_f . This restriction is given in equation (5).

Variables:

x_p - binary which takes on 1 if project *p* is to be carried forth and 0 otherwise

y_{ap} - binary which takes on 1 if agency mitigation *a* for project *p* is to be carried forth and 0 otherwise

z_{lf}- binary which takes on 1 if facility funded mitigation *l* for facility *f* is to be carried forth and 0 otherwise

Indices/Sets:

f	facility
p	project
l	mitigation funded by laboratory facility
a	mitigation funded by agency
r	risk type (e.g. biosafety risk or biosecurity risk)
b	benefit type (e.g. basic or applied research)
l(p)	set of projects which benefit from mitigation l
$\varphi(p)$	set of projects which take place at a facility

Constants:

H_r	maximum acceptable risk for risk type *r* on any individual project
S_{pr}	baseline risk for project *p* of risk type *r*
e_{lpfr}	facility-funded mitigation risk reduction for mitigation l at facility f on risk type r
e_{apr}	agency-funded mitigation risk reduction for mitigation a on project p on risk type r
j_{bp}	benefit score for benefit type *b* on project *p*
c_{ap}	cost for the mitigation in mitigation -project pair (a, p)
c_{lf}	cost for the mitigation in mitigation- facility pair (l, f)
c_p	cost of project *p*
K_f	budget for mitigations at facility *f*
V	agency budget (for projects and mitigations)
g_f	maximum fraction of total grant money that facility f is willing to spend on mitigations

$min \sum_p S_{pr}\, x_p e^{-\sum_{ap} e_{apr} y_{ap} - \sum_{lfp} e_{lpfr} z_{lf}}$	$\forall r$	(1a)
$max \sum_p j_{bp}\, x_p$	$\forall b$	(1b)
such that		
$S_{pr}\, x_p e^{-\sum_{ap} e_{apr} y_{ap} - \sum_{lfp} e_{lpfr} z_{lf}} \leq H_r$	$\forall r, p$	(2)
$\sum_l c_{lf}\, z_{lf} \leq K_f$	$\forall f$	(3)
$\sum_{ap} c_{ap}\, y_{ap} + \sum_p c_p x_p \leq V$		(4)
$\sum_l c_{lf}\, z_{lf} \leq g_f \sum_{p\|\varphi(p)=f} c_p x_p$	$\forall f$	(5)
$y_{ap} \leq x_p$	$\forall p, (a,p)$	(6)
$z_{lf} \leq \sum_{p\|\varphi(p)=f, p\in l(p\prime)} x_p$	$\forall f, (l,f)$	(7)
$x_p \in \{0,1\}$	$\forall p$	(8)
$y_{ap} \in \{0,1\}$	$\forall\, ap$	(9)
$z_{lf} \in \{0,1\}$	$\forall\, lf$	(10)

4.2.1.2. Solution Method (TMO)

Technology Management Optimization (TMO) is a multi-objective optimization application designed for Trade Space exploration and optimization. The multi-objective nature of TMO allows for multiple user goals to be considered simultaneously. This is important since there is likely not a single design that best meets all of the objectives. Given this, RIFT is focused on seeking a collection of funding profiles that together provide insights, trends, and trade-off information to support decision making and reduce the space of funding profiles.

TMO accesses an external solver to perform the optimization. In RIFT, the search algorithm used by TMO is a genetic algorithm (GA) called JEGA. This algorithm operates on a population of individual solutions, where each solution is a funding recommendation represented by an array that identifies the selected funding choices. During each iteration of the algorithm, new solutions, referred to as "children", are created by selecting and combining individual solutions, or "parents," from the existing population. These "child" solutions inherit traits from the "parent" solutions. For each new solution, fitness is determined by calculating each objective as well as whether strict constraints are satisfied. Objectives are created for each type of risk as well as each type of benefit, and strict constraints created for budgets and risk thresholds are satisfied. Only a subset of the solutions carries over to the next iteration of the algorithm. Those solutions that have a better fitness "score" (i.e., perform well with respect to one or more of the benefits or objectives compared to other solutions), and do not violate strict constraints, are more likely to carry over to the next iteration of the algorithm. Additionally, the algorithm occasionally "mutates" individuals to introduce diversity into the population. An example of "mutation" would be randomly selecting an individual from the population and randomly changing the funding choice for one of the funding profile elements.

The primary output of TMO is a set of efficient trade-off funding profiles, also referred to as a Pareto frontier. These designs have the quality that no other solution was found during the search that is better with respect to any one objective without being worse with respect to another objective. Typically, the solution set will include funding profiles that have relatively high benefit scores and high risk scores, low benefit scores and low risk scores, and a range of options

in between. Since the objective is to minimize risks and maximize benefits, none of these solutions are inherently better or worse than any other solution. However, since these results show the trade-offs between solutions they can help decision makers identify solutions or characteristics of solutions that best meet their needs.

4.2.2. Pyomo single solution version

4.2.2.1. Formulation

The a priori weighted version of the optimization is implemented in Pyomo, a Python-based mathematical optimization language. The difference between the formulation shown previously and this version is that the Pyomo formulation includes importance weights in the objective function for each type of risk and benefit. This means that rather than producing the entire Pareto frontier of solutions, it uses a priori information about the importance of each metric as part of the optimization and produces a single recommended solution.

4.2.2.2. Solution Method

The Pyomo version of the model is solved using COIN-OR Branch-and-Cut (CBC), an open-source mixed integer program solver.

4.2.3. Verification and Validation

Relative lack of historical examples of DURC incidents makes validation difficult, but the team had access to internal and external subject matter experts who assisted in validation of input data for the case study as well as validation of mathematical formulation assumptions.

5. TEST CASE

To demonstrate the RIFT capability, we carry out a test case, in which a hypothetical funding agency is choosing among six DURC projects and has a total budget to fund projects and mitigations of $7M. The data for this case are generated through subject matter expert elicitation and are based subject matter expert's real-world experience evaluating laboratories and the risks and benefits of research carried out therein. The test case involves three pathogens with pandemic potential: highly pathogenic avian influenza (H5N1), avian influenza (H7N9), and respiratory syncytial virus (RSV). Projects can be conducted in two different laboratory settings—a typical or an advanced laboratory—creating a total of six unique project/laboratory combinations. The profiles for these laboratories are based on two laboratory evaluations carried out by Sandia National Laboratories. The "typical" laboratory is a relatively small laboratory based in a developing country; it has the basic infrastructure required to carry out some DURC research but no advanced mitigations in place. As a result, its operating costs are relatively low and as such the requesting funding for each DURC project is lower than that of the advanced lab (see Table [2] below). The advanced laboratory is a relatively large laboratory based in an industrialized country; it has the required infrastructure to carryout DURC research as well as a number of pre-existing biosecurity and biosafety mitigations in place (e.g., biosafety cabinets). As a result, its operating costs are relatively high and as such the requesting funding for each DURC project is higher than that of the typical lab (see Table [2] below). Facility-funded mitigations are assumed to be capped at 20% of the grant for the advanced facility and 15% for the typical facility. These numbers are optimistic and probably reflect a greater willingness to pay than a funding agency could expect from many applicants.

The test case considers two types of benefits: therapeutic development and development of diagnostic tests. Subject matter experts assessed the relative importance of these two benefits, and deemed them to be of equal importance. The test case considers two types of risks: biosafety and biosecurity. The biosafety risks identified by subject matter experts include the risk of individual inhalation and the risk of environmental release. Quantitative estimates for the likelihoods of inhalation/release at each facility and the consequence of inhalation/release for each strain were derived from BioRAM, and, when multiplied, provide a baseline biosafety score for each project/laboratory pair. The biosecurity cost estimates were based on a mix of real examples and subject matter expert evaluation, and the relative risk reductions are notional subject matter expert judgement based values. One important note is that for biosecurity mitigations, the "typical" lab often had both a lower cost for the mitigation and a lower effectiveness of that mitigation (to reflect differences in the facility design, equipment, or supporting infrastructure). For this example, when using the Pyomo version it was assumed that the two biosafety risks are of equal importance to each other. The biosafety risks were assumed to each be twice as importance as the biosecurity risk.

Table 2 below depicts the six project/facility pairs along with the costs, benefits, and risks posed by each. Benefits of each project/facility pair were assessed by subject matter experts on a three-point scale, with three being the most important and one being the least important.

Table 2: DURC Test Case Baseline Costs, Benefits, and Risks

Project	Facility	Project Cost	Project Benefits		Project Risks		
			Therapeutic Development	Diagnostic Tests	Biosafety: Individual Inhalation	Biosafety: Environmental Release	Biosecurity: Loss of Custody
H5N1	Advanced	$2,000,000	3	3	5.7188	5.684	3.48
H5N1	Typical	$750,000	3	3	8.99	6.8875	8.7
H7N9	Advanced	$1,500,000	2	2	3.03688	3.0184	1.848
H7N9	Typical	$600,000	2	2	4.774	3.6575	4.62
RSV	Advanced	$1,000,000	2	1	1.91284	1.9012	1.164
RSV	Typical	$500,000	2	1	3.007	2.30375	2.91

The test case considers a series of biosafety and biosecurity mitigations, including both their costs and impacts on overall levels of risk. This data is derived from subject matter expert elicitation, reviews of existing policies and laboratory practices, and prior applications of risk assessment tools such as BioRAM. The test case considers 11 biosafety mitigations, of which six are facility-level mitigations and five are project-level mitigations. Table [3] below depicts each mitigation, the anticipated funding source, and the total cost (assuming a five-year project).

Table 3: Biosafety and Biosecurity Mitigations

	Mitigations	Funding Source	Typical Facility Cost	Advanced Facility Cost [82]
Biosafety	Surfaces solid, some wooden cabinets	Facility	$10,000	n/a
	Biological safety cabinets (not validated)	Facility	$25,000	n/a
	HEPA filtered exhaust	Facility	$5,000	n/a
	Decontaminated in lab (not validated)	Facility	$16,000	n/a
	Sharps housed in puncture resistant container, autoclaved, then incinerated	Facility	$250	n/a
	Animal procedures conducted on medical table	Funding Agency	$15,000	n/a
	HEPA filtered animal housing (not validated)	Funding Agency	$15,000	n/a
	Powered Air Purifying Respirators	Funding Agency	$50,000	n/a
	Gloves	Funding Agency	$25,000	n/a
	Goggles	Funding Agency	$25,000	n/a
	Gowns	Funding Agency	$25,000	n/a
Biosecurity	Self-closing lockable doors	Facility	$5,500	n/a
	Personnel background checks	Funding Agency	$36,000	$120,000
	Access control	Facility	$17,000	$30,000
	Visitor escort	Facility	$2,000	n/a
	Cameras	Facility	$20,000	$30,000
	Security station in lobby	Facility	$3,000	$4,500

[82] The advanced facility is assumed to have all biosafety mitigations already in place, as well as self-closing lockable doors, visitor escort, the intrusion detection system, and the secured freezers.

	Pharmacy security	Facility	$20,000	$24,000
	Utility security	Funding Agency	$14,000	$14,000
	Secured freezers	Facility	$50,000	n/a
	Intrusion detection system	Facility	$10,000	n/a
	Material accountability system	Facility	$12,000	$18,000
	Information security system	Facility	$3,000	$3,000
	Accident, injury, and incident response plans	Facility	$5,000	$5,000
	Reporting and communication plans	Facility	$75,000	$125,000
	Training and practice drills	Facility	$100,000	$150,000
	Security updates and re-evaluations	Facility	$5,500	$7,000

Tables [4] and [5] below depicts the average risk reduction associated with each mitigation. As noted above, these data are derived from prior assessment using BioRAM and subject matter expert evaluation. Averages for project-level mitigations are depicted in the table, but they are operationalized at the project-level in the model.

Table 4: Effects of Biosafety Mitigations

Mitigations	Mitigation Level	Individual Inhalation Risk Reduction	Environmental Release Risk Reduction
Surfaces solid, some wooden cabinets	Facility	0	0
Biological safety cabinets (not validated)	Facility	0.2164	0
HEPA filtered exhaust	Facility	0	0.468866667
Decontaminated in lab (not validated)	Facility	0	0.1082
Sharps housed in puncture resistant container, autoclaved, then incinerated	Facility	0	0.1082
Animal procedures conducted on medical table	Project	1.172166667	0
HEPA filtered animal housing (not validated)	Project	1.5148	0.1082
Powered Air Purifying Respirators	Project	2.686966667	0
Gloves	Project	0	0
Goggles	Project	0	0
Gowns	Project	0	0

Table 5: Effects of Biosecurity Mitigations

Mitigations	Mitigation Level	Loss of Custody Risk Reduction (Typical Lab)	Loss of Custody Risk Reduction (Advanced Lab)
Self-closing lockable doors	Facility	0.450833333	0.901666667
Personnel background checks	Project	0.450833333	0.901666667
Access control	Facility	0.901666667	1.3525
Visitor escort	Facility	0.901666667	0.901666667

Cameras	Facility	0.901666667	0.901666667
Security station in lobby	Facility	1.3525	1.3525
Pharmacy security	Facility	0.450833333	0.450833333
Utility security	Project	0.450833333	0.450833333
Secured freezers	Facility	1.3525	1.3525
Intrusion detection system	Facility	0.901666667	0.901666667
Material accountability system	Facility	1.3525	1.3525
Information security system	Facility	0.450833333	0.450833333
Accident, injury, and incident response plans	Facility	0.450833333	0.450833333
Reporting and communication plans	Facility	1.127083333	1.127083333
Training and practice drills	Facility	0.901666667	0.901666667
Security updates and re-evaluations	Facility	1.3525	1.3525

For the case described above, the multi-objective optimization generated a frontier of 25 solutions when 50 generations of the algorithm were run. The parallel coordinates chart shown in Figure [15] allows the decision maker to filter the solutions based on preference. Note that there are several low-cost and low-risk options, but these solutions also have low benefit for therapeutic development and diagnostic tests because they do not fund many projects. The highlighted line is an example of the solution a funding agency might select achieve an even balance of benefits and risks at a medium level of cost to the agency. This particular solution involves investment in H5N1 projects at both laboratories, H7N9 at the typical laboratory, and RSV projects at both laboratories, along with a variety of biosafety and biosecurity mitigations which are listed for the user for each solution.

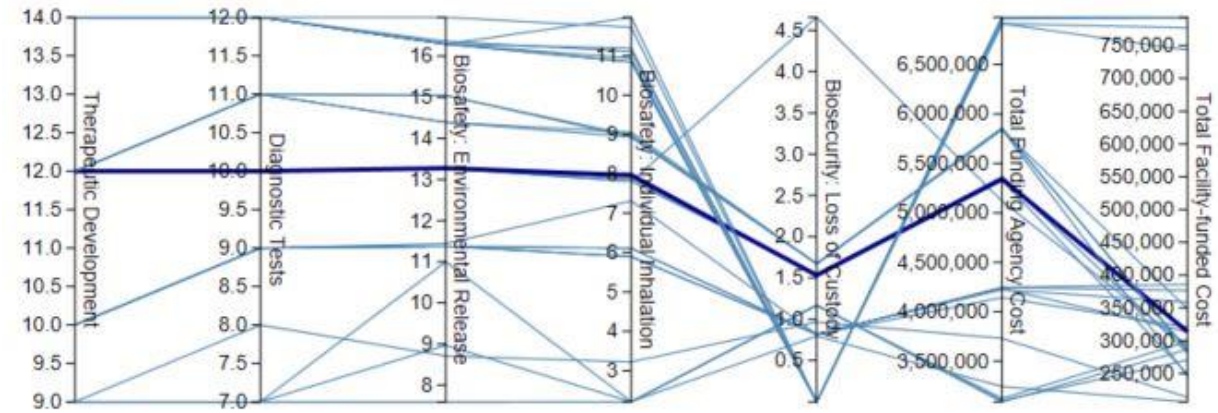

Figure 15: Results Shown in Parallel Coordinates Chart

Another view of the results is shown in Figure [16], in this case plotting the biosafety risk metric of "environmental release" against the benefit metric of "diagnostic tests." As is expected, they are positively correlated, with risk rising along with the benefit as more budget is dedicated to project funding.

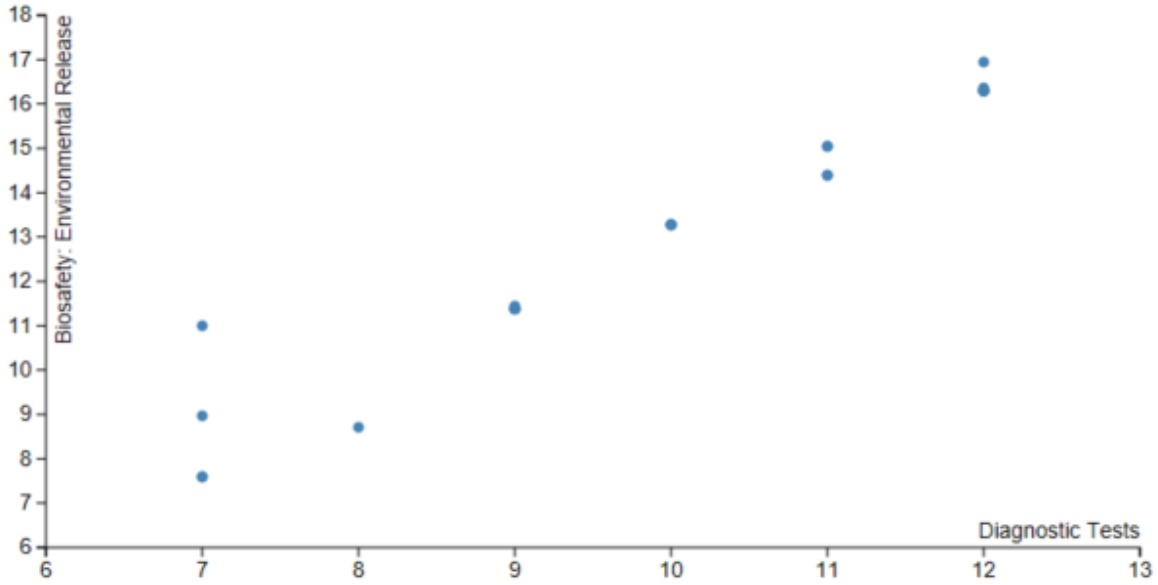

Figure 16: Plot of Environmental Release Risk Against Diagnostic Test Benefit

Displaying the full frontier of solutions to the decision maker in this fashion means that there does not have to be an a priori determination about the value of one metric over another, and the benefit and risk metrics can be on two different scales. The visual allows the user to choose the solutions that have a relative risk and benefit relationship that they are comfortable with, as well as being able to quickly see cost impacts.

CONCLUSIONS

5.1. Significance of Results

The LDRD produced a mathematical framework with the ability to identify optimal risk mitigation strategies that consider tradeoffs between research benefits and multiple dimensions of risk in an integrated manner. This analytical framework could be used to quantitatively evaluate and reduce risk associated with DURC that could be used by customers and stakeholders worldwide to evaluate their portfolios of potential projects and protect the safety and security of their workers and the general public.

5.2. Potential Extensions

This model could be used for portfolio-level risk evaluation beyond DURC, either in other biological research applications or could be adapted to a broad number of contexts where risk, benefit, and mitigation options need to be evaluated against available budgets. A version with explicit representation of uncertainty incorporated was formulated but not yet implemented in the model, so that is an additional extension that should be explored.

While this toolkit provides an overarching decision model, it would be beneficial to build in optional evaluation tools for the user to choose from for safety and security risk and for benefit evaluation. The goal would never be to require that a specific model be used for input to RIFT, but to provide a suite of options for stakeholders that don’t have that capability in-house.

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