Historical Case Studies for the Opportunity Cost Analysis

from

ROADMAP FOR IMPEMENTING BIOSECURITY AND BIODEFENSE POLICY IN THE UNITED STATES

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Historical Case Studies for Opportunity Cost Analysis

Biosecurity policies, such as the BSAT regulations and export controls, promote national security by preventing theft, diversion, and deliberate malicious use of biological knowledge, skills, technologies, materials, and/or pathogens and toxins. At the same time, the restrictions imposed by these policies may have indirect effects on biodefense and health security activities (e.g., research, medical countermeasure development, and biosurveillance), which inadvertently could present barriers to achieving U.S. biodefense objectives. However, no policy-agnostic framework exists for analyzing the opportunity costs of biosecurity policies.

To identify the types of data (i.e., parameters) that should be incorporated into an analysis of opportunity costs of new policies, the authors conducted historical case studies on the opportunity costs of existing biosecurity policies. Findings from these case studies were developed into an analytic framework for analyzing the opportunity costs of new or changing biosecurity policies, which is intended to be used to evaluate direct costs, the indirect effects resulting from these costs, and their downstream consequences to U.S. biodefense objectives. By evaluating new policies using this framework, policy-makers can evaluate potential opportunity costs than what currently exists and to identify policy strategies that could mitigate anticipated costs before they unintentionally counteract investments. The framework also can guide the collection of data for evaluating implemented policies to understand fully the effects of a given policy.

Approach to Case Studies

Two historical case studies were conducted on the following policies: (1) Biological Select Agent and Toxin Regulations (SAR), and (2) U.S. government dual use research of concern (DURC) policies. To enable the systematic identification of data types needed to assess opportunity costs, a variety of stakeholders affected by these policies were engaged. The stakeholders included:

- Academia and government research community, including researchers and environmental health and safety (EH&S) personnel;
- Professionals in public health laboratories and veterinary diagnostic laboratories;
- Experts from industry, including medical countermeasure (MCM) development companies and contract research organizations (CROs); and
- Public health and environmental health stakeholders at the state, local, territorial, and tribal (SLTT) levels.

The goal of these discussions was to capture the *types* of opportunity costs that *individuals* and *institutions* have experienced as a result of the SAR and federal DURC policies. Information on two types of costs was gathered:

1) Direct costs: Time, money, and other resources required to comply with the policy.

2) Indirect opportunity costs: Indirect costs (“*trade-offs”)* arising from the direct costs and the *downstream consequences* of these indirect costs. For example, indirect costs may include abandoned research and development activities, the loss of opportunities for training and career development, and the loss of institutional capabilities to conduct select agent research. These indirect costs may impair advancements in select agent research and diminish capabilities for preparedness and response of biological incidents. Collectively, the indirect costs and their downstream effects on U.S. biodefense objectives represent opportunity costs of the policy.

Opportunity Costs are indirect costs (“*trade-offs*”) arising from the direct costs and the *downstream consequences* of these trade-offs.

Members of the experts working group also provided recommendations for evaluating how the indirect costs may affect U.S. biodefense objectives.
Based on the information collected from stakeholder discussions and the experts working group, key data needs for assessing the costs of biosecurity policies were identified, including:

- The direct costs for complete and accurate policy compliance, and
- Potential trade-offs caused by resources directed to policy compliance activities and their downstream effects on U.S. biodefense objectives.

The data needs/parameters were organized into an analytic framework that involves an ordered series of questions about direct compliance costs, indirect effects, and downstream consequences, which can be evaluated quantitatively or semi-quantitatively for new or changing biosecurity policies in the future.

Because such an effort previously has not been undertaken, no attempt has been made in these case studies to conduct a quantitative or semi-quantitative assessment. Furthermore, although some quantitative data exist for administrative burden and financial cost of initial and ongoing implementation of regulations, little, if any, quantitative data exist for the indirect effects of those costs and the downstream consequences (e.g., lost workforce or scientific knowledge). However, now that an analytic framework has been developed, data on direct costs and indirect effects can be collected and analyzed.

This effort has several limitations. First, the prevalence of a particular cost or challenge across various types of institutions could not be evaluated because a limited number of stakeholders were engaged in this study. However, several individuals discussed the frequency with which their colleagues at other institutions experienced the similar costs. Therefore, the analyses are not intended to be quantitative or comprehensive, but rather illustrative of the costs incurred by various stakeholders to help develop an opportunity cost analysis framework. Second, the findings described in this report may not represent

all opportunity costs associated with the 2012 and 2017 SAR updates and the federal DURC policies. Engagement with additional stakeholders affected by these policies may reveal additional costs. Third, stakeholder discussions focused on elucidating costs arising from the policies themselves (i.e., what is written explicitly in the policy), but costs also may arise from policy implementation (i.e., activities that are not mandated by the policy, but are necessary for compliance or implementation).

Despite these limitations, the case studies captured a wide range of direct and indirect costs experienced by stakeholders who were affected by the SAR and DURC policies, enabling the development of a robust framework for evaluating the opportunity costs of biosecurity policies. Opportunity costs and data needs identified through future discussions with biosecurity policy stakeholders can be incorporated into this framework.

Summary of Findings: Implications for Opportunity Cost Analysis

The case study findings, described in detail below, provide insight into the data needs and analytic approach needed for an accurate assessment of the opportunity costs of biosecurity policies, including: 1) the types of direct costs, indirect costs, and downstream consequences that stakeholders experienced while complying with or implementing these policies; 2) factors to consider for an accurate assessment of these costs; and 3) strategies for mitigating opportunity costs that stakeholders shared.

Direct Costs

Stakeholders described three types of direct costs associated with implementation or compliance with biosecurity policies: financial costs, time costs, and frustration of researchers and other affected stakeholders. Table 1 summarizes the key findings associated with direct costs of policy implementation.

Table 1. Key findings related to the direct costs of policy implementation or compliance.

Categories of Cost	Findings
Financial Resources and Time	The direct financial and time costs of complying with a new biosecurity policy are influenced by whether, and to what extent, the policy likely requires changes to the infrastructure or operation of affected institutions. Determining these changes requires consideration of two factors: 1) overlapping requirements of guidelines established by other policies; and 2) existing laboratory architectures, workflows, and procedures. These elements vary systematically between different types of institutions (e.g., research institutions versus diagnostic reference laboratories).
	Cost assessments of policies related to research procedures should consider whether affected entities need to conduct new experiments to satisfy the record-keeping and/or inspection requirements of the policy, even if those experiments explicitly are not required by the policy. Evaluations of the direct financial and time cost of policy compliance should account for the cost of those experiments (labor, consumables, etc.).
Financial Resources	A realistic accounting of financial costs associated with biosecurity infrastructure, including physical, cyber, and other security measures, must consider the costs of equipment maintenance and upfront purchase and installation costs.

Time	To address the direct time cost of a new biosecurity regulation, assessing both the upfront and ongoing level of personnel effort needed for compliance is critical. This assessment also should include regulations that codify practices or systems that already are being followed by regulated entities.
	Assessments of the time costs for ongoing compliance with research review policies should account for the total number of research proposals that are reviewed, not simply those projects deemed to fall within scope of the policy.
	To assess the direct time cost of a new biosecurity regulation that involves exemptions, the level of administrative effort needed for documenting exemptions should be considered.
	Delays in research or other biodefense activities can have adverse effects on research even if affected stakeholders are not engaged actively in compliance with policies. These activities include: 1) delays in review or approval processes for regulated activities; and 2) lengthy security vetting processes for newly-hired personnel. These delays should be considered a direct *time* cost of biosecurity policies.
Frustration	Researchers have experienced frustration arising from several different types of biosecurity policies, such as: 1) personnel security policies, because of their intrusiveness; and 2) dual use research policies, because of perceived redundancy with other research review policies and stigmatization of the research by some members of the public and biosecurity communities.

Indirect Effects

Stakeholders described three types of indirect effects arising from the direct time costs, financial costs, and frustration experienced by affected stakeholders: 1) costs to research and other biodefense activities; 2) costs to workforce, including costs to workforce development and the loss of individual capabilities; and 3) the loss of institutional capabilities. Table 2 summarizes the key findings associated with indirect effects resulting from the direct costs of policy implementation.

Table 2. Key findings related to the indirect costs of policy implementation or compliance.

Categories of Cost	Finding
Regulated Activities	The source of funding for compliance activities (e.g., direct federal funding, institutional overhead funding, or research funding) influences the indirect effects of compliance expenses on research activities at affected institutions. For example, using money dedicated for research to fund compliance activities may prevent researchers from achieving their project outcomes, potentially affecting the overall funding initiative.
Regulated Activities **Workforce (Development)**	The direct time and financial costs of complying with or implementing biosecurity policies may limit opportunities for training in regulated research areas, which can impede workforce development. For example, many institutions have limited the number of personnel in their select agent programs and reduced visiting scientist programs to minimize the costs of personnel security programs required by the SAR. Reduced training opportunities, including visiting scientist programs, also may adversely affect research collaborations.
	The time needed to comply with new biosecurity policies may stall or slow the progress of research or other biodefense activities. Additionally, research delays may have consequences for workforce development by impeding researchers' ability to advance their careers by publishing papers, obtaining grants, or achieving promotions.

	Time delays for research reviews or other compliance activities may cause researchers to re-direct their research to activities that are not regulated, which may limit research capabilities and have adverse consequences for workforce development by reducing training opportunities.
Regulated Activities, Loss of Institutional Capabilities	Hiring challenges arising from lengthy personnel vetting processes can lead to research delays and contribute to institutional decisions to not support regulated activities such as select agent research.
Workforce (Loss of Individual Capabilities)	Frustration with biosecurity policies may contribute to the decisions of some affected stakeholders to leave their fields, potentially leading to loss of subject matter expertise in a given field.
Loss of Institutional Capabilities	The financial and time costs of compliance with biosecurity policies have contributed to institutional decisions to cease supporting select agent research because of: 1) the expense for maintaining security infrastructure and personnel reliability programs; and 2) escalating administrative burdens. The loss of institutional biodefense capabilities leads to a loss of critical research and training activities.
Workforce (Export of Capabilities Overseas)	The loss of individual biodefense capabilities may result in the export of these capabilities and knowledge overseas, if trained individuals move from U.S. to foreign institutions to continue their research or other regulated biodefense activities.
Regulated Activities **Workforce** **Loss of Institutional Capabilities**	Costs to workforce, institutional capabilities, and/or research activities may result in the U.S. abandoning or significantly curtailing certain biodefense research and development activities, limiting the United States' ability to keep pace with scientific and technological advances and applications occurring in other countries.

Downstream Consequences (Opportunity Costs)

Stakeholders described two types of downstream consequences arising from indirect costs, which represent the opportunity costs of biosecurity policies: 1) adversely affected or lost national capabilities; and 2) shift in balance of power between the U.S. and adversary countries. Table 3 summarizes the key findings associated with downstream consequences resulting from the indirect effects of policy implementation.

Table 3. Key findings related to the downstream consequences of policy implementation or compliance. The downstream consequences of institutions ceasing to support regulated activities varies between institution types, depending on the institution's mission, and training and research activities.

Categories of Cost	Findings
Lost National capabilities	Indirect effects on workforce development, including the loss of individual and institutional biodefense capabilities, adversely affect the ability to meet U.S. biodefense objectives by *reducing the number of trained personnel* available for critical biodefense activities (e.g., basic and applied research on pathogens, biosurveillance, MCM development, and forensics).
	Indirect effects on biodefense activities, including the loss of individual or institutional biodefense capabilities, can adversely affect the ability to meet U.S. biodefense objectives by *delaying or preventing critical research activities* for detection of new zoonotic diseases, characterization of pathogens, development of new MCM, and microbial forensics.
Shift in Balance of Power	Reduced global competitiveness in biodefense fields arising from the loss of individual and institutional capabilities and the export of biodefense

	capabilities and knowledge could lead to a shift in the balance of power between the U.S. and adversary nations.

Mitigation Strategies

Stakeholders proposed or had implemented a variety of solutions to mitigate the direct or opportunity costs of biosecurity policies. These strategies include:

- Solutions to limit direct financial costs.
  - Provide dedicated funding for institutions to implement or comply with biosecurity policies. For example, ensuring sufficient funding from the CDC's Public Health Emergency Preparedness (PHEP) grants can be used to support SAR compliance activities at public health laboratories.

- Solutions to limit direct time costs.
  - Split administrative work between multiple senior researchers, which reduces administrative burden on any single person in the laboratory, limiting adverse effects on research productivity.
  - Centralize compliance activities in one place such as Environmental Health and Safety (EH&S) offices, provided that institutions secure sufficient funding for EH&S personnel.
  - Increase financial support to the implementing federal agency(-ies) to enhance consistency between inspections, if applicable, and shorten response times of inquiries. This support could reduce administrative burdens arising from differences in interpretation of the regulations between inspectors or between federal agencies and institutions.

- Solutions to limit frustration of affected stakeholders.
  - Improve communication between the scientific community and the public about the benefits and risks involved in research that elicit biosafety and biosecurity concerns, and strategies for risk mitigation. This outreach effort could help to alleviate the stigmatization of some life sciences research.

- Approaches for mitigating indirect effects from reduced or ceased select agent research activities.
  - Encourage researchers to conduct their research at a different facility, if their home institutions or supervisors choose to stop supporting regulated research, including research with BSAT. For this strategy to be feasible, existing challenges for visiting scientists (i.e., arising from personnel security requirements) must be addressed.
  - Serve as a contract research organization or collaborating institution for laboratories that choose not to support regulated research.

Opportunity Cost Historical Analysis: Biological Select Agents and Toxins Regulations

The Federal Select Agent Program (FSAP) regulates the possession, use, and transfer of biological select agents and toxins (BSAT), which are pathogens and toxins that could cause significant damage to public health and safety if accidentally or deliberately released. The U.S. Centers for Disease Control and Prevention and the U.S. Animal and Plant Health Inspection Service jointly oversee and administer the program. The program derives its legal authorities from the BSAT Regulations (a.k.a., Select Agent Regulations or SAR), authority for which was created by the Antiterrorism and Effective Death Penalty Act of 1996. This law was passed after Larry Wayne Harris (a member of the Aryan Nations) illegally acquired the bacteria that causes plague from a U.S.-based culture collection. The initial regulations focused on the transfer of BSAT between approved entities. The regulations were enhanced significantly after the events of 2001. The USA PATRIOT Act of 2001 defined restricted persons and illegitimate uses of BSAT. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 expanded the BSAT list to include agricultural pathogens, established a security risk assessment process for vetting individuals seeking access to BSAT, and required registration of individuals and facilities possessing, using, and transferring BSAT. The changes included in these laws were finalized in 2005. Shortly thereafter, two significant events occurred that precipitated additional changes to the SAR: 1) the identification by the Federal Bureau of Investigation (FBI) of Dr. Bruce Ivins, a 30-year researcher at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), as the perpetrator of the 2001 anthrax letters; and 2) the revelation that a researcher, who was not registered as a select agent-approved researcher, at Texas A&M contracted brucellosis after coming into contact with a contaminated animal infection chamber in a select agent-approved laboratory. These events resulted in a flurry of policy debate on personnel reliability of BSAT researchers and support staff, and security in BSAT facilities. The White House established an interagency working group to review existing laws, regulations, and policies related to the FSAP, oversight and security of high-containment laboratories, and personnel security measures as directed by Executive Order 13486, Strengthening Laboratory Biosecurity in the United States. Following this review, the White House established the Federal Experts Security Advisory Panel (FESAP), to evaluate and provide recommendations on the tiering of BSAT, removal or additions of BSAT, personnel reliability practices, physical and cyber security measures, and other relevant policy issues as directed in Executive Order 13546, Optimizing the Security of Biological Select Agents and Toxins in the United States. The recommendations were considered and incorporated into the 2012 final rule of the SAR.

Table 4 summarizes key regulatory changes included in the 2012 and 2017 updates to the SAR.

Table 4. Selected Regulatory Changes in the 2012 Updated BSAT Regulations.		
Requirement Category	**Prior Requirements**	**New requirements**
	2012 Updates	
Physical security	Two physical barriers protecting select agent storage units	*Tier 1 agents*: Three physical barriers protecting select agent storage units; all registered space must be protected by an intrusion detection system
Personnel reliability	Security risk assessments: electronic records check to determine whether individual meets any of the statutory restrictions that prohibit access to select agents	*Tier 1 agents*: initial and ongoing suitability assessments, including more thorough investigation of individuals and the establishment of a system for self and peer reporting of incidents that might compromise suitability
Occupational Health	No requirement	*Tier 1 agents*: occupational health monitoring for individuals with access to Tier 1 agents
Training	Standard biosecurity training	*Tier 1 agents*: additional insider threat awareness training
Coordination with local law enforcement	No requirement	*Tier 1 agents*: 15-minute response time for security forces or local police following a security breach
Listed agents	-	Addition of SARS-Coronavirus, Chapare virus, and Lujo virus to the list
	2017 Updates	
Agent inactivation	Non-viable select agents are excluded from SAR, but no requirements regarding inactivation procedures for rendering agents non-viable	New requirement that inactivated select agents or regulated nucleic acids intended for future use must be subjected to an in-house validated inactivation procedure that is confirmed through a viability testing protocol
Note: This table does not include all changes issued in the 2012 and 2017 updates to the SAR but rather highlights those changes that led to opportunity costs for affected stakeholders.		

Findings

The findings of these case studies are organized around the following policy elements:

- Enhanced security requirements for Tier 1 agents, issued in 2012;
- Baseline security requirements for non-Tier 1 agents, as required after the 2012 Final Rule and which apply to laboratories that conduct SARS-CoV work;
- Policy elements that apply to both Tier 1 and non-Tier 1 agents, such as the new inactivation guidelines issued in the 2017 SAR Final Rule.

Although our discussions focused on the 2012 and 2017 updates to the SAR, some of the costs described dated back to the 2005 Final Rule, including institutions that relinquished select agent status following the 2005 updates. Analytic parameters reflecting these costs were identified and wherever possible effects associated with the 2005 Final Rule were indicated.

Information from stakeholder discussions was supplemented with data described in published literature, including data from published surveys and articles on the costs associated with the SAR. However, most of these studies were conducted prior to 2012, and so evaluated a select agent regime that looks quite different from that of today.(3-6) Further, most do not distinguish between the direct effects of the SAR and effects arising from other scientific or political issues, such as fluctuation in research funding levels and changes in publication priorities and standards.

Within each policy element, the direct costs of compliance with the policy are first discussed, followed by the trade-offs for individuals and institutions and the downstream consequences for select agent research and preparedness.

Enhanced physical security measures

This category includes costs incurred by select agent-registered institutions to upgrade the physical security systems of their Tier 1 labs to meet the enhanced requirements issued in the 2012 SAR final rule and the cost to retrofit or move laboratories when new agents are added to the select agent list. The direct costs and financial burden associated with physical security infrastructure varied systematically between different types of institutions, in part depending on whether the institution supported its own physical security expenses or had outside sources of funding.

Direct Financial Costs

Research institutions generally incurred the direct financial costs of establishing or upgrading physical security barriers, as opposed to the federal government. At some research institutions, upgrading the physical security systems of Tier 1 laboratories required significant upfront investments. For example, one academic institution highlighted the expense of the intrusion-detection system. In contrast, some research institutions previously implemented stringent security measures that met the enhanced requirements issued in 2012 and therefore incurred minimal (or no) new expenses. Research institutions receiving DoD funding had to establish stringent physical security systems prior to 2012 to comply with DoD regulations, whereas some academic institutions implemented these measures voluntarily.

Multiple public health and veterinary diagnostic laboratory stakeholders indicated that the financial costs of installing the physical security measures outlined in the SAR, in particular the enhanced security requirements for Tier 1 agents, represent a significant financial burden for this cohort of laboratories. In part, this burden reflects the older age of many of these laboratories – the average age of a veterinary diagnostic laboratory is about 40 years old – such that significant infrastructure upgrades would be required to make the facility SAR-compliant. Further, public health and veterinary diagnostic labs support most of their laboratory infrastructure expenses themselves, and budgets are already stretched thin.

Small and mid-sized companies that support medical countermeasure (MCM) development generally engage contract research organizations (CROs) to perform select agent studies (e.g., challenge testing) to reduce the high costs of establishing and

maintaining a select agent laboratory and to leverage an experienced CRO workforce. Some large MCM development companies have their own select agent laboratories, but at least one pharmaceutical company recently has closed some of its select agent laboratories in favor of outsourcing their select agent studies, in large part because of the high costs of physical security maintenance and upgrades. In contrast, the financial costs associated with maintaining physical security infrastructure at CROs is offset by the fees of their select agent research services. Because the development of MCM for select agents is funded primarily by the government, through contracts from agencies such as NIAID, BARDA and various DoD components, these expenses are passed on to the government (i.e., in the form of higher overhead fees on contracts). Because government agencies have been willing to pay industry for the escalating costs of select agent research as physical security and other BSAT requirements have increased, the expenses associated with physical security infrastructure for select agent research have been minimally borne by industry. However, absent increases in government biodefense funding, these increases in the security costs effectively decrease government funding for biodefense research.

For all types of select agent laboratories, the costs of maintaining physical security infrastructure are significant. The maintenance costs are on par with upfront equipment costs at their institutions. At institutions that support their own laboratory infrastructure, which includes most academic institutions and public health and veterinary diagnostic laboratories, securing funding for maintenance of security equipment poses significant challenges. No federal grants for this purpose are available to academic institutions or veterinary diagnostic laboratories, and minimal federal money is available to public health laboratories through the Public Health Emergency Preparedness (PHEP) grants distributed by the CDC. In contrast, at other institutions (e.g., National Biocontainment Laboratories, USG research institutions), maintenance of physical security is directly or indirectly supported by the USG.

Trade-offs of Financial Costs

The cost of maintaining and upgrading physical security infrastructure to remain compliant with the SAR was a major factor in the decisions of many academic institutions, public health laboratories, veterinary diagnostic laboratories, and MCM development companies to shut down their select agent programs. Many labs let their select agent registration lapse after the 2005 SAR updates. Additional laboratories working on Tier 1 agents or SARS-CoV relinquished their status following the 2012 updates. Moreover, this cost has deterred non-registered institutions from joining (or re-joining) the FSAP. The implications of a reduction in the number of select agent laboratories for research and preparedness against biothreats are discussed further below.

Take-aways

- The direct financial costs of maintaining physical security equipment are on par with the upfront purchase and installation costs.
- The direct financial costs and financial burden of policies involving laboratory infrastructure vary systematically between different types of institutions. In part,

the financial burden depended on the source of funding for compliance activities (e.g., direct federal funding versus institutional funding).
- The costs of maintaining and upgrading physical security infrastructure to remain compliant with the SAR has deterred non-registered labs from joining the Federal Select Agent Program and was a major factor in the decisions of many registered institutions to withdraw from the program.

Personnel reliability

This category includes requirements for personnel security risk assessments (SRAs), required for all individuals with access to select agents, and personnel suitability programs, required for individuals with access to Tier 1 agents only. SRAs, which are conducted by the FBI Criminal Justice Information Services (CJIS), comprise an electronic records check to determine whether an individual meets one of the statutory restrictions that prohibits access. Beginning in 2005, individuals were required to undergo an SRA to gain approval for accessing select agents, which was valid for five years. In 2012, the duration of approvals was shortened to three years, and institutions were required to assess suitability of personnel working with Tier 1 agents. Personnel suitability programs comprise a more thorough pre-suitability assessment of an individual's background and behavior history than the SRA alone, as well as ongoing monitoring to identify behaviors of concern.

Direct Financial and Time Costs

Personnel reliability requirements have not prevented the institutions consulted for this project from hiring skilled individuals, but the long timeframes for clearance investigations pose significant logistical challenges for hiring. Clearance investigations for SRAs may take one to a few months for U.S. citizens, but can be much longer for foreign nationals, in large part because information required to conduct a thorough background check often is not available or hard to obtain.

Institutions with Tier 1 labs spent significant amounts of time and money developing and maintaining new personnel suitability programs for personnel with access to Tier 1 agents following the 2012 updates to the SAR. In part, the costs of program development arose from the need to engage a diverse set of institutional and community stakeholders in the program, including the research community, environmental health and safety, university health services, the institution's legal department, human resources, and the local police department. Many of these stakeholder groups continued to be involved in personnel assessment, and some institutions also incorporate annual psychiatrist reviews into their programs, which can be a significant expense. Based on comments from stakeholders, the cost of background checks and suitability assessments for Tier 1 personnel can be over $2,000 per individual. Most institutions fund their personnel suitability programs through institutional funding mechanisms rather than drawing from the research grants of select agent principal investigators.

In contrast, most companies developing select agent MCM have not incurred direct costs from the SAR personnel reliability requirements because they outsource their select agent studies to CROs, which are required to comply with personnel security

requirements. As discussed above, ultimately this cost is borne by government contracts for biodefense MCM, in the form of higher overhead fees. Although quality assurance/quality control (QA/QC) personnel from the MCM development companies audit CROs through on-site visits to ensure that CRO practices meet company standards, their audit activities do not require accessing laboratory spaces where select agents are stored. As a result, the QA/QC personnel do not need to obtain clearance.

Trade-offs of Financial and Time Costs

The direct time and financial costs associated with personnel reliability requirements have led many institutions to limit the number and type of personnel conducting research with select agents at their institutions.

The time burden of the SRAs poses challenges for hiring and can lead to research delays. Because non-registered individuals must be escorted continuously by a registered individual in areas with access to select agents, the non-registered individuals can contribute minimally, or not at all, to select agent research activities while waiting for clearance. (During this waiting period, these individuals are often trained in standard operating procedures (SOPs) in non-registered, BSL-2 spaces.) Some select agent labs have ceased hiring foreign individuals because supporting their salaries during this long waiting period poses a financial burden. Alternatively, for one large, university-associated veterinary diagnostic lab, this situation has contributed to the lab's decision to not obtain select agent status, because the hiring of the spouses of foreign students as laboratory technicians is a common practice in the laboratory (and some other university-associated diagnostic laboratories). The concern that lengthy clearance investigations may delay research was previously identified in a 2004/2005 survey of select agent researchers; this survey queried U.S. researchers about direct and indirect costs associated with the 2003 interim rule for the SAR, which were nearly identical to the Final Rule released in 2005.(7) These delays are problematic for research laboratories and institutions because grants are time-sensitive, grantees cannot carry over more than 25% of costs in any given year of a grant, and no cost extensions are only automatic for one year. Therefore, an inability to hire new staff quickly may compromise a grantee's ability to achieve the research milestones in their grant.

Multiple academic institutions deliberately limit the number of personnel in their select agent programs to minimize the *time* and *expense* of maintaining the personnel reliability components of the program. For example, many institutions re-configured lab spaces to limit the number of personnel with access to Tier 1 select agents following the 2012 SAR updates. However, this strategy is not possible in many public health laboratories (PHLs) and veterinary diagnostic laboratories because of the open, shared structure of these labs and the need for high-containment lab spaces to be available for testing many different agents. As a result, these laboratories would need to enroll all (or nearly all) of their staff in their personnel security programs to comply with the regulations, which would be expensive and time-consuming. The time and financial burdens of developing and maintaining these programs were a major factor in the decisions of multiple PHLs and veterinary diagnostic laboratories to relinquish their Tier 1 status or their select agent registration altogether. Similarly, the costs of

personnel reliability programs contributed to the decision of at least one large MCM development company to shut down their own select agent labs and shift to outsourcing their select agent studies to CROs. Although CROs must incur these costs, the costs minimally affect their business because they are passed on to their clients in the form of higher fees, as described in the previous section. Alternatively, laboratories that retain their select agent registration but control costs by limiting the number of registered personnel may need to curtail training of non-registered students, fellows, and postdocs that would otherwise occur in the registered space.

Multiple research institutions have eliminated or greatly reduced visiting scientist programs for their select agent laboratories (including Tier 1 and non-Tier 1 laboratories) because of the *expense* and *time* required to clear personnel through the institution's select agent program. Most institutions require that visitors to select agent laboratories participate in the host institution's select agent program even if those individuals are enrolled in their home institution's program to minimize safety, security, and liability concerns for the host institution. When participation in these programs becomes significantly difficult (or impossible), the lost training opportunities impede development of a sufficient and qualified select agent workforce. Visiting scientist programs provide important training opportunities in select agent research techniques, including informal opportunities through research sabbaticals, formal training opportunities such as the BSL-4 training course offered by the International Biosafety Training Center at the Galveston National Laboratory, and other arrangements. Visiting scientist programs also foster research collaborations that are critical to technology and scientific advances that help to push forward scientific research. For example, these programs allow select agent researchers to host visiting scientists with specialized skills to apply new techniques that could enhance their research. Without this capability, the research may be delayed (i.e., if the select agent researchers have to learn the new technique themselves rather than leverage their colleagues' expertise), or a particular line of research may be discontinued. Previous surveys of select agent researchers, conducted in 2004/2005 (described above) and 2009 found that the SAR had hampered researchers' ability to collaborate both domestically and internationally, in part by making visits to select agent laboratories slower and more tedious.(3-6)

Researcher Frustration: Direct Costs and Trade-offs

Responsible officials from several academic institutions shared that their Tier 1 select agent researchers were frustrated by the intrusiveness of the suitability program and/or by the time needed for participation in the suitability program (for example, for annual psychological assessments). Although these stakeholders had not observed any of their researchers drop out of the select agent program to avoid participating in these programs, they suggested that researcher frustration contributes to the overall resentment of the "big brother" nature of the select agent program that plays a role in some researchers' decisions to leave the field.

Take-aways

- Laboratory architectures and workflows influence the direct costs of policies related to agent access, in particular the ability of laboratories to re-configure

their space or processes to limit the number of personnel with access to restricted agents. An inability to control the costs of personnel reliability programs by limiting the number of personnel enrolled may lead institutions to relinquish their select agent registration.
- Hiring challenges arising from lengthy personnel vetting processes can lead to research delays and contribute to institutions' decisions not to participate in the FSAP.
- The time and expense of personnel reliability programs may limit the number of personnel participating in an institution's select agent program, including visitors and individuals at the home institution. This effect may lead to the loss of training opportunities and impede research collaborations, which could have broader consequences for the research community's ability to conduct basic research for characterizing pathogens and developing early-stage countermeasures, both critical aspects of U.S. biodefense objectives.
- Frustration with the perceived intrusiveness of personnel reliability programs may contribute to some researchers' decisions to leave select agent research, thereby impeding the development and maintenance of the select agent workforce.

New regulatory requirements for the inactivation of select agents

In January 2017, the Federal Select Agent Program issued a new provision stating that inactivated select agents or regulated nucleic acids that can produce infectious forms of any select agent virus must be subjected to an *in-house validated* inactivation procedure that is confirmed through a viability testing protocol. Previously, the regulations provided that non-viable select agents and genetic material were excluded from the requirements of the SAR but did not include any requirements regarding the procedures for rendering agents non-viable. This new provision was introduced in response to the 2015 discovery that failures to fully inactivate *B. anthracis* spore samples by Department of Defense laboratories led to the inadvertent transfer of potential live *B. anthracis* samples.

The new regulations also established requirements for record-keeping of validation data for inactivation procedures. Registered institutions are responsible for evaluating their own inactivation protocols; this review is conducted by the local Institutional Biosafety Committee (IBC). During inspections, inspectors may verify that institutions have validated their inactivation protocols and review validation data. Although the new regulation does not explicitly require registered entities to re-validate their agent inactivation procedures, in practice entities had to do so to generate *in-house* validation data and satisfy the record-keeping requirement.

The regulations do not set specific performance standards, but accompanying guidance encourages institutions to demonstrate that the risk of live agent remaining in an inactivated sample is "as low as realistically possible." Local IBCs have sought clarity from the FSAP on their interpretation of the performance standard, to ensure that the standards they apply when evaluating inactivation procedures will be approved by FSAP inspectors. However, multiple institutional stakeholders have stated that the FSAP has

not provided sufficient clarity on this issue. Consequently, multiple IBCs have been reluctant to approve inactivation procedures or have applied extremely stringent performance standards, to avoid the perception that their institution does not take biosafety seriously. This approach is problematic for viruses because of technical challenges for validating the efficacy of virus inactivation procedures.[1] Nearly one year after the issuance of the new regulation, multiple select agent virus laboratories had not yet had their virus inactivation procedures approved.

Direct Financial Costs and Trade-offs

Institutions have dedicated significant time and money to re-validating all of their select agent inactivation procedures. The costs of validating inactivation procedures, including labor and consumables costs, can range from ~$100,000 to validate procedures for two BSL-2 agents to several millions of dollars to validate multiple procedures for each of several different agents. Institutions receive no funding to comply with this new requirement. Because the regulation involves experimental procedures, funding for compliance was drawn from research grants or budgets rather than institutional overhead funding, which is typically used to fund compliance with requirements that do not directly involve the process of research, such as physical security. The diversion of research funds to validate inactivation procedures may prevent researchers from achieving the outcomes of their research projects because they have less money available for planned experiments. This effect may impede researchers' career advancement and undermine the ability of research funders to meet their missions.

Direct Time Burden and Trade-offs

Institutions consulted for this study spent weeks re-validating their inactivation protocols for bacteria. However, technical challenges for validating the efficacy of virus inactivation procedures have taken many months to resolve, as described above.[2] During this time, researchers were diverted from their normal research activities to generate the validation data, and inactivated samples could not be taken out of the BSL-3 suite for follow-up experiments until the inactivation procedures were approved by an institution's Institutional Biosafety Committee. This led to delays in research. Even though delays of weeks to months may be considered short given the long timescales of research (including basic and applied research), these delays can have significant consequences for individual researchers, laboratories, or institutions. Academic training and hiring cycles, grant deadlines, and the tenure process are not adjusted to account for unexpected research delays that may be caused by changes in research policies. The delays can stall the career development of researchers at all levels.[3] Consequently, some

[1] Thorough inactivation of virus-containing samples is typically established by infecting cells with the inactivated sample to confirm that no infectious virus remains. However, the chemical agents used for inactivation are toxic to cells, so that inactivated samples must be diluted prior to infection of cells. This need for dilution practically affects assessments of the limit of detection of the inactivation assay.

[2] Thorough inactivation of virus-containing samples is typically established by infecting cells with the inactivated sample to confirm that no infectious virus remains. However, the chemical agents used for inactivation are toxic to cells, so that inactivated samples must be diluted prior to infection of cells. This practical need for dilution affects assessments of the limit of detection of the inactivation assay.

[3] At academic institutions, research professors are hired on a probationary basis and evaluated after a set number of years (typically four to eight years) to determine whether they should be granted a permanent position or leave the institution; this evaluation is called the tenure process. At most institutions, tenure decisions primarily consider the researcher's grant and publication records, while service to the university and community are given less weight. Therefore, any reduction in the number of grants and papers a researcher can obtain during their probationary period could negatively impact their tenure

researchers likely are to leave the field; some voluntarily, out of frustration, and some involuntarily, because of an inability to secure funding or progress their career. Additionally, research delays could impede an emergency response to a biological incident that requires a flexible and rapid scientific capability, which researchers often support.

Take-aways

- FSAP-registered institutions dedicated significant time and money to re-validating their agent inactivation procedures to satisfy the record-keeping requirement of the 2017 provision on select agent inactivation, even though the policy did not explicitly require the conduct of new experiments.
- Institutions diverted research funds for re-validation of their inactivation procedures, which may have limited researchers' abilities to meet their project outcomes.
- The time needed for re-validation of select agent inactivation procedures delayed research projects involving select agents. These delays can have consequences for workforce development by impeding researchers' ability to advance their careers by publishing papers, obtaining grants, or achieving promotions, and by compromising emergency response capabilities.

Administrative aspects of compliance

All aspects of the SAR require accompanying compliance documentation, including experimental procedures, incident response plans, and records for occupational health, personnel clearance and suitability, and training for all individuals in the select agent program. This administrative work is carried out primarily by principal investigators (PIs) of select agent laboratories (and/or their researchers) and responsible officials, depending on the type of documentation.

Direct time burden

Documenting compliance with the SAR requires significant time investments from principal investigators, researchers, responsible officials, or select agent program managers. The upfront time needed to document compliance with new security measures is substantial, particularly when new agents are added to the select agent list and compliance documents for all elements of the SAR must be prepared. Even if a new regulation codifies a practice or system that already is in place, formally documenting compliance with that regulation requires significant time.

The administrative burden associated with ongoing compliance activities is as severe as documenting initial compliance. For example, one select agent researcher estimated that as much as 20-25% of his time is dedicated to administrative work. One contributing factor is that inspectors sometimes interpret regulations differently from year to year, which can result in administrative effort to revise experimental protocols, response plans, and other documentation to comply with new or different

prospects. Although the public health and national security relevance of select agent research may be considered a positive service to the community, this is not likely to off-set any deficiencies in grants or publications.

interpretations of the regulations. Underscoring the administrative burden of ongoing compliance, EH&S personnel at multiple institutions with research on SARS-CoV and Tier 1 agents stated that their departments hired new personnel to help comply with the additional requirements issued in the 2012 SAR updates, who have since stayed busy with ongoing administrative compliance duties.

Indirect Costs

The amount of administrative work required to conduct select agent research slows the pace of research. This effect arises from two factors: (1) the diversion of researchers' time from experiments to administrative activities; and (2) delays in initiating experiments caused by the approval processes at the institutional (i.e., approval by Responsible Officials and Institutional Biosafety Committees) and federal (i.e., FSAP) levels for SAR research. These delays may diminish the productivity of select agent researchers at all levels. For example, the length of a graduate degree involving select agent research is one to two years longer than average. Junior faculty spend significant time on upfront administrative work in setting up their new select agent laboratories rather than conducting research, which can adversely affect their research progress and career advancement.

The administrative burden of select agent compliance also contributes to senior researchers' decisions to re-direct their efforts toward research on non-select pathogens. Many SARS-CoV researchers shut down their SARS-CoV research programs when the virus was added to the select agent list in 2012 to pursue research with non-select agents. One researcher, who chose to redirect her research efforts primarily to avoid the administrative burden of select agent research, had previously conducted select agent research on a different pathogen and therefore, had a realistic understanding of the regulatory challenges associated with this type of research. Alternatively, researchers may maintain their select agent research portfolio but use non-select pathogens (e.g., to use surrogate or attenuated strains) for some experiments, the results from which may not be translatable to the select agent.

Several stakeholders described concerns about receiving penalties for mistakes on documentation. The risk of fines for compliance mistakes can drive some researchers to abandon their select agent research or redirect certain experiments to non-restricted pathogens. Additionally, the potential to incur penalties for administrative mistakes has contributed to the decisions of multiple veterinary diagnostic laboratories to relinquish their select agent status.

Non-registered diagnostic laboratories, which may identify a select agent in the course of testing unknown samples, are exempted from the SAR, but must document any detection of a select agent within seven days. Several stakeholders affiliated with non-registered veterinary diagnostic laboratories also raised concerns about the time burden, penalties for mistakes in documentation, and liability associated with select agent requirements, especially during an animal outbreak of a disease caused by a select agent. These concerns have led some veterinary diagnostic laboratories to stop offering

diagnostic services for select agents, potentially impeding early detection and biosurveillance of pathogens.

Take-aways

- The direct time costs of administrative effort needed for compliance varies by stakeholder and responsibility, resulting in different types and levels of lost opportunities.
- Institutions may spend significant time documenting compliance with systems or practices that are already in place at the institution.
- The administrative burden associated with ongoing compliance activities is significant and has caused some researchers to re-direct their research to non-regulated pathogens.
- The administrative burden of documenting exempt activities (e.g., detection of select agents in clinical samples by diagnostic reference laboratories) has deterred some institutions from engaging in those activities.
- Penalties for documentation mistakes, including documentation of compliance with regulated or exempted activities, have deterred some institutions from engaging in those activities.

Loss of institutional select agent capabilities: Downstream consequences

Direct financial and time costs of compliance with the SAR may contribute to an institution's decision to relinquish or not obtain their select agent registration. These costs include: 1) expense for maintaining physical security infrastructure and personnel reliability programs; 2) hiring challenges imposed by personnel reliability requirements; and 3) escalating administrative burdens. Recent Annual Reports of the Federal Select Agent Program indicated that 27 institutions withdrew their registrations in 2015 and 16 institutions withdrew in 2016, because their research focus changed, select agent research was transferred to another institution, or a desire to reduce administrative burden.(8, 9)[4] These institutions included academic, commercial, federal government, and non-federal government entities. The sections below describe the consequences of a loss of institutional select agent capabilities.

Research institutions. Research institutions provide research and training opportunities for researchers at all levels, from students to experienced scientists. Through grants, cooperative agreements, and contracts, academic and government researchers help to address knowledge and capability gaps in a variety of sectors, including biodefense. Furthermore, research institutions provide a setting to educate and train scientists in various fields, techniques, and biosafety and biosecurity practices.
Stakeholders from institutions that no longer have active select agent programs stated that their institutions are unlikely to re-start these programs to accommodate new hires (or existing researchers) who would like to conduct research with select agents, resulting in limited job opportunities for select agent researchers. The competitive market may drive some researchers out of the field. As the field shrinks, so do training opportunities for junior researchers, further hampering workforce development. Although

[4] At the end of 2015, 291 institutions were select-agent registered, and at the end of 2016, 276 institutions were registered.

quantitative data on the number of new select agent faculty members or senior research staff hired by U.S. government or academic research institutions over the past several years are lacking, multiple academic stakeholders noted that their institutions had hired few or no select agent researchers in recent years. **These institutions had continued to hire researchers to study non-select, BSL-3 organisms such as *M. tuberculosis*, indicating that this trend is specific to select agents, not high-containment research in general.** Ultimately, the decreases in select agent researchers and training opportunities could curtail basic research on select agents in the U.S. This consequence will limit the knowledge base needed for developing new medical countermeasures, detecting and characterizing emerging pathogens, and transferring best practices for biosafety and biosecurity, which are critical to U.S. biodefense objectives.

Industry. Biotechnology companies lead the development and commercialization of medical countermeasures, including vaccines, therapeutics, and diagnostics, a primary contribution of industry to the biodefense sector. Companies also develop other technologies used for biodefense (e.g., sensors for environmental detection of biothreat agents) and may conduct applied research to inform the development of biodefense products.

Take-aways

- The downstream consequences of institutions withdrawing from the select agent program varies for different institutions, depending on their mission and training and research activities.
- The loss of institutional select agent research capabilities adversely affects the ability to meet the U.S. biodefense objectives in the near- and long-terms: (1) in the near-term, the loss of critical research activities and training opportunities; and (2) in the longer-term, inability to detect new zoonotic diseases, characterize pathogens, develop new MCM, and conduct microbial forensics.
- The ability to outsource select agent research is a workaround for the loss of in-house capabilities that has been employed successfully by the MCM development industry.

Opportunity Cost Historical Analysis: United States Government Policy on Review and Oversight of Dual Use Life Sciences Research of Concern

The U.S. government released two policies for oversight of dual use research of concern (DURC) in 2012 and 2014: 1) USG Policy for Oversight of Life Sciences DURC (2012); and 2) USG Policy for Institutional Oversight of Life Sciences DURC (2014). These policies define DURC broadly as "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security." However, the scope of the polices is limited to research involving fifteen listed agents and seven experiments of concern. All listed agents are subject to the Biological Select Agents and Toxins Regulations (SAR) with one exception: research involving small quantities of botulinum neurotoxin (BoNT) is exempt from the SAR at quantities lower than one milligram, but included in the DURC policies.(10) The DURC policies apply to USG-funded research only.

The 2012 policy describes DURC oversight responsibilities for federal departments and agencies that conduct or fund life sciences research, while the 2014 process describes institutional responsibilities for identification, assessment, and management of life sciences DURC. Because stakeholders from funding departments and agencies were not consulted in preparation of this case study, it focuses on opportunity costs experienced by institutional stakeholders only and arising from implementation of and compliance with the 2014 Institutional Oversight Policy. However, the authors did engage federal policy-makers during the project, informing them of this case study.

The 2014 Institutional Oversight Policy outlines a process for institutional identification and assessment of life sciences DURC by a dedicated committee (the institutional review entity, or IRE) in collaboration with the principal researcher. This process includes a risk assessment that underpins the identification of DURC and the development of a risk mitigation plan for conducting the research that preserves the benefits of the research while minimizing risks. Institutions must report the outcomes of all DURC reviews to the relevant USG funding agency, and the USG funding agencies must approve the risk mitigation plan prior to the conduct of research that is designated as having dual use potential.

When the policy first was released, research institutions undertook the following activities to become compliant with it:

- Establish an IRE and develop processes for institutional identification, review, and oversight of life sciences DURC.
- Develop DURC training materials and train IRE members and researchers.

- Review ongoing life sciences research projects to identify, assess, and report life sciences DURC to funding agencies.

Subsequently, newly proposed research projects or experiments have been reviewed for potential DURC according to the institution's established review process. Some institutions limit their DURC oversight to the fifteen agents and seven experiments outlined in the policy, while others evaluate DURC more broadly.

Findings

The financial costs of complying with the 2014 Institutional Oversight Policy, beyond personnel time, were found to be minor for most institutions. Therefore, this section focuses on two types of direct costs associated with this policy and their indirect effects: time and frustration. These costs may influence researchers' interest in pursuing research with dual use potential.

Time: Opportunity Costs

Direct time costs associated with *initial* compliance activities

The development of DURC review processes following the release of the 2014 Institutional Oversight Policy did not place a significant time burden on regulatory compliance officials at most institutions. These institutions already were reviewing experimental protocols to identify and mitigate DURC, typically through the Institutional Biosafety Committee (IBC), and adapted their existing practices to comply with the 2014 policy. For example, one institution shifted from using a rotating sub-group of IBC members to a permanent group for DURC reviews to satisfy the IRE requirement in the policy, but their review process remained the same otherwise.
The main costs of initial compliance with the 2014 policy arose from institutional review of ongoing life sciences research to identify, assess, and report projects involving DURC to the relevant funding agencies. One key challenge was in harmonizing institutions' and funding agencies' interpretations of DURC. One academic institution's initial DURC reviews for ongoing projects was delayed because the National Institutes of Health (NIH) did not agree fully with their determinations of which projects fell within the scope of the policy, requiring several rounds of discussion to clarify the definition of DURC and resolve the disagreement. This effort helped to define the research considered in scope of the policy, which promoted agreement between the NIH and the institution on its DURC assessments of newly-proposed experiments.

Institutions also spent time developing DURC training materials and training researchers and IRE members.

Direct time costs associated with *ongoing* compliance activities

Ongoing review of DURC requires a minimal-to-moderate time investment by members of the IRE, depending on the nature of research occurring at the institution and the institution's review process. Some institutions enroll all investigators working with listed agents in their DURC programs and subject *all* of their proposed research to a DURC review, even though only a small fraction of the reviewed research is determined to constitute DURC. For example, one academic institution estimated that fewer than

half of the projects reviewed by their IRE are elevated to the IBC and Biosecurity Task Force (larger committees) for further discussion, and only some of the referred projects are determined to be DURC. This encompassing approach to DURC review places a time burden on IRE members because of the high volume of proposed experiments that need to be reviewed, particularly at institutions with extensive research programs involving the listed agents. To accommodate the dual use reviews, some institutions have hired dedicated professionals to conduct initial research reviews to identify potential DURC, which subsequently is elevated to the IRE to limit the burden on IRE members.[5] Stakeholders also noted that reviewing research at the pre-proposal or proposal stage is inherently inefficient because some of the research is not funded because of scientific merit or research priority considerations that are independent of DURC.

From the perspective of researchers conducting dual use research, the direct time cost of policy compliance reflects the time needed for the DURC review and approval process. If a researcher would like to conduct a new experiment that may constitute DURC in between scheduled IRE meetings, that research will be delayed unless an emergency meeting can be convened. At one academic institution, this situation has arisen multiple times over the past several years; emergency IRE meetings could not be held in all cases because of the busy schedules of the committee members. For research that is deemed to be DURC, the processes of developing the risk mitigation plan and securing approval from the U.S. government funding agency have a significant time cost. The duration can be up to five months from the IRE's determination that the research is DURC according to the time frames detailed in the 2014 Institutional Oversight Policy.

Indirect Effects and Downstream Consequences Arising from Direct Time Costs

The direct time costs of *initial* and *ongoing* compliance affected stakeholders differently. Affected individuals and institutions experienced few indirect effects from the time needed to *establish* DURC review programs to comply with the 2014 Institutional Oversight Policy because most institutions could leverage their existing DURC review processes and experiences. Additionally, institutions did not experience significant costs associated with the time needed to develop DURC training materials and train researchers. Some ongoing research projects may have been paused while institutions clarified the funding agencies' interpretation of DURC (i.e., what research falls within scope of the policy), which could have adverse effects on the ability of researchers at all levels to meet career milestones (see below).

In contrast, researchers, reviewers (i.e., IRE members), and institutions have experienced indirect costs arising from the time required for *ongoing* oversight of DURC. Because IRE members have other professional responsibilities in addition to their service on the IRE, the time dedicated to IRE reviews may stress their ability to complete their other work. Institutions that hired new personnel to conduct initial DURC reviews used overhead or research funds originally marked for other purposes because outside sources of funding for compliance with the DURC policies are

[5] IRE members are drawn from a variety of positions within an institution and the community and typically have other professional responsibilities in addition to their work on the IRE, for example, other biosafety and biosecurity activities, training, and/or research.

unavailable. This diversion of funds may challenge the institution's ability to meet its research mission.

For researchers conducting dual use research, delays arising from the DURC review process may stall the career advancement of researchers at all levels. Even though delays of weeks-to-months may be considered short given the long timescales of research, these delays can have significant consequences for individual researchers, laboratories, or institutions if the delays occur around deadlines for academic training, hiring, tenure decisions, and grant award. Research delays that cause researches to miss important career milestones may cause some researchers to leave the field – some voluntarily, out of frustration, and some involuntarily, because of an inability to secure funding or progress their career.

Researcher Frustration: Opportunity Costs

Some researchers were frustrated by the need to dedicate time and effort to "yet another review" because they felt their research already was subject to a more rigorous level of review than that of their peers who study non-listed agents. Research subject to DURC review is reviewed by the IBC (i.e., to assess biosafety and other biosecurity considerations), the Institutional Animal Care and Use Committee (IACUC), and/or the Environmental Health and Safety (EH&S) Department, depending on the nature of the research.

Another source of researcher frustration is a perception that DURC is stigmatized by some members of the public, research, and policy communities as having outsize risks without significant benefit, suggesting that the researchers, institutions, and funding agencies involved in the research are irresponsible.(11-16) EH&S personnel leading their institutions' DURC programs shared examples of researchers who were offended that their research was considered potential DURC or frustrated by the need to "defend" the value of their research to the IRE (despite assurances that the process would not be antagonistic). A few of these researchers chose to not conduct experiments with listed agents to avoid the DURC review.

Researcher frustration arising from the perceived redundancy in institutional review processes for life sciences research and the stigma associated with DURC caused some researchers to redirect their research to non-listed agents. This effect was most pronounced for researchers working with small quantities of BoNT, which are exempt from the SAR. For example, at two academic institutions, 5-of-10 and 9-of-10 investigators working with exempt quantities of BoNT withdrew from the institutions' exempt toxins programs because of the DURC policies.[6] These investigators, who were using BoNT as a research tool, either sought out other biological reagents that could serve a similar experimental purpose or adjusted their research if suitable alternatives were unavailable. EH&S personnel from these institutions speculated that so many researchers withdrew from their exempt toxins programs because this group of

[6] These programs were established voluntarily by institutions to track research involving exempt quantities of select agent toxins at their institutions.

researchers was less accustomed to biosecurity regulations than select agent researchers.

Take-aways

The key findings from this care study are:

- The ability of institutions to leverage existing research review practices reduced the time burden of developing formal DURC review processes to comply with the 2014 Institutional Oversight Policy.
- Several IREs review all research proposals involving *potential* DURC, a fraction of which are deemed to constitute DURC as defined in the 2012 and 2014 federal DURC policies.
- Time spent on DURC reviews and delays arising from the scheduling of research review meetings at the institutional and federal levels contributed to the time burden of compliance with the 2014 Institutional Oversight Policy. This time burden caused some researchers to re-direct their research to non-regulated activities.
- Researcher frustration arising from perceived inefficiencies because of redundancy in research reviews and/or stigma associated with DURC contributed to some researchers' decisions to re-direct their research to non-regulated activities.

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