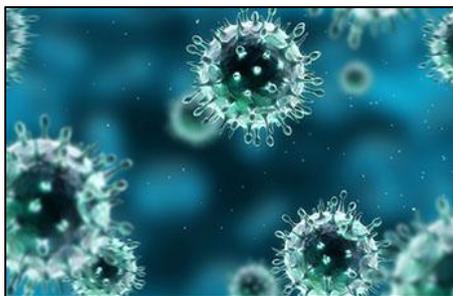


A Case Study Approach to the Institutional DURC Oversight Policy



Prepared by NIH Office of Science Policy and HHS ASPR on behalf of the U.S. Government

July 22, 2015

Institutional Oversight of Life Sciences Dual Use Research of Concern Draft Case Study Narrative

PART ONE

Boyle University is a medium-sized private academic institution in the USA with a robust research program in the life sciences. Boyle University receives sponsored research grant and contract awards from several U.S. Government agencies including the U.S. Department of Health and Human Services (i.e. the National Institutes of Health) the U.S. Department of Defense, the U.S. Department of Agriculture, and the National Science Foundation, as well as from privately funded sources.

Dr. Jameson has recently been hired as a new faculty member in the Department of Microbiology and is in the process of establishing his research program in the Department's BSL 2 and BSL 3 laboratories to conduct research on *Francisella tularensis*, the causative agent for tularemia—a rare but serious infectious disease. *F. tularensis* can be transmitted to humans through the skin, eyes, mouth, throat, or lungs and infections that are acquired by inhaling dust or aerosols contaminated with *F. tularensis* can result in pneumonic tularemia, which can be severe. Wild type *F. tularensis* is listed as a Tier 1 Select Agent with the Federal Select Agent Program.

Dr. Jameson's research involves the characterization of *F. tularensis* proteins that are involved in the assembly of the Type III Secretion System (T3SS). The secretion system enables *F. tularensis* to avoid clearance by the host of the bacteria from cells it invades. A better understanding of how this secretion system works may help enable the development of new therapeutics for tularemia.

Before the initiation of his research, Dr. Jameson contacts Ms. Locke, the institutional biosafety officer, to submit a registration for Institutional Biosafety Committee (IBC) review and approval. In his correspondence he outlines his intention to conduct a series of gene modification experiments aimed at characterizing the T3SS. The experiments would be carried out using the attenuated strain *F. tularensis* subspecies *novicida*, strain Utah 112. He notes in his registration submission that due to this attenuation, *F. tularensis novicida* Utah 112 has been excluded from the Federal Select Agent List. The IBC consults with the NIH Office of Biotechnology Activities (OBA) for guidance regarding Dr. Jameson's registration. Based on OBA guidance, the IBC approves Dr. Jameson's research on *F. tularensis novicida* Utah 112 under BSL 2 conditions.

For Discussion:

Question 1: Would this newly proposed research be subject to the U.S. Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern? If so, for what reason?

After nine months of conducting research on *F. tularensis novicida* Utah 112, Dr. Jameson decides that use of a non-attenuated, virulent *F. tularensis strain*, SHUS4, would allow him to more accurately identify the biochemical and structural features that are most important in the T3SS pathway, with hopes that this knowledge would accelerate the development of new therapeutics or vaccines. Dr. Jameson consults with Dr. Greenore, an experienced bacteriologist and Chair of the university's IBC, to learn how he can get the necessary approval from the IBC to begin a new set of experiments using non-attenuated, virulent *F. tularensis tularensis* SHUS4. Dr. Jameson explains to Dr. Greenore that he intends to mutate SHUS4 genes that encode proteins of interest to investigate whether he is able to disrupt the T3SS secretion mechanisms. He will then evaluate these proteins in the SHUS4 bacterial isolates that show altered survival in host cells. Since Dr. Jameson's research was registered with the Federal Select Agent Program at his prior institution, and since he has access to Boyle University's BSL3 space, Dr. Jameson is confident that he should be able to secure institutional approval to conduct these studies on *F. tularensis* SHUS4 under BSL3 conditions.

For Discussion:

Question 2: At this point, aside from the information about IBC registration, what additional information should Dr. Greenore convey to Dr. Jameson?

Question 3: Would this newly proposed research be subject to the U.S. Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern? If so, for what reason?

Dr. Greenore explains the process to amend Dr. Jameson's initial IBC registration and mentions to Dr. Jameson that the new experimental aims using non-attenuated, virulent *F. tularensis* may be subject to the scope of the new *USG Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern* (DURC policy). Dr. Jameson is advised to submit his research proposal to the newly established Institutional Review Entity (IRE) so that the proposal may be reviewed for its applicability to the Policy.

Dr. Jameson states he has heard of "dual use research of concern" but does not think anything he is working on constitutes dual use research of concern. Dr. Greenore explains to Dr. Jameson that not all research subject to the DURC policy is necessarily DURC but that research involving any of the 15 agents or toxins listed in the Policy must be reviewed for its potential to be DURC. She explains that since Dr. Jameson plans to conduct studies involving non-attenuated, virulent *F. tularensis*—one of the DURC policy's listed agents— the proposed research is subject to the policy. Dr. Greenore advises Dr. Jameson to consult the Institutional Contact for Dual Use Research (ICDUR), who can provide him with more information about the DURC policy and Boyle University's institutional requirements for compliance with the Policy.

For Discussion:

Question 4: What are some methods the university can utilize to help ensure all investigators conducting work with any of the 15 agents or toxins listed in the policy are familiar with the policy and understand its requirements?

Question 5: How can the institution identify those individuals who need specific DURC training?

Question 6: What are effective strategies for conducting DURC training?

Question 7: At an institution, who acts in the role of the ICDUR? At what point should a PI reach out to the ICDUR?

Dr. Jameson contacts Mr. Middleton, the University's ICDUR, to discuss the university's implementation of the institutional DURC Policy and the role of the IRE. Mr. Middleton explains how the university's plan to implement the institutional DURC policy was developed and provides Dr. Jameson with a roster of IRE members, as follows:

- Dr. Millar, Professor in the Department of Immunology, who will chair the IRE
- Dr. Greenore, Professor in the Department of Microbiology, and IBC Chair
- Dr. Teeling, Associate Professor in the Department of Neurology
- Ms. Locke, the institutional Biological Safety Officer
- Mr. Middleton, Director of Research Compliance, who will serve as the ICDUR

At the end of the conversation, Dr. Jameson summarizes his understanding of the IRE review process. He states that since he is performing research with non-attenuated, virulent *F. tularensis*, his research is DURC and that additional risk mitigation measures may be necessary for his project.

For Discussion:

Question 8: At this point, is Dr. Jameson's understanding correct? How would you best communicate the functions of the IRE to Dr. Jameson?

Question 9: Is the IRE appropriately constituted? What other subject matter expertise do you believe should be represented on the IRE?

Mr. Middleton explains to Dr. Jameson that research on one of the 15 agents listed in the Policy does not *in and of itself* mean that the research constitutes DURC. Mr. Middleton tells Dr. Jameson that there are three factors that need to be considered before research might be determined to be DURC under the Policy:

1. Whether research will involve one of the 15 agents or toxins listed
2. Whether research will produce any of the seven experimental effects listed in the Policy
3. For projects meeting the first two criteria, the IRE will then evaluate whether the research meets the policy's definition of DURC.

Only when all three of these criteria are met will the research be considered DURC under the Policy and a risk mitigation plan required to be developed. Mr. Middleton informs Dr. Jameson that since his project involves one of the 15 agents or toxins he will need to complete a registration document to submit this project to the IRE for further evaluation of its DURC potential.

Dr. Jameson goes back to his office, goes to the IRE's website and fills out the application. He receives an email confirmation that discussion of his research project will be on the IRE's agenda for their next meeting in two weeks.

Dr. Jameson attends the IRE meeting and his proposal comes up for review. It has been established that Dr. Jameson proposes to use non-attenuated, fully virulent *F. tularensis*. Based on the experimental aims Dr. Jameson described in his application to the IRE, the committee determines that the proposed research is not anticipated to produce any of the seven experimental effects listed in the Policy. The IRE asks Dr. Jameson to alert them if any of the experimental details of his project change in the future.

For Discussion:

Question 10: What are some of the important messages to take from the IRE's review of Dr. Jameson's research?

PART TWO

It has now been one year since Dr. Jameson's tularemia research project was initially reviewed by Boyle University's IRE. Dr. Jameson has conceptualized a new experiment involving *F. tularensis* which could have significant public health benefit. The experiment would involve specific gene mutations that would enhance the ability of *F. tularensis* to survive and replicate in host immune cells. One proposed mutation would result in changing the antigenicity of a *F. tularensis* surface protein. This mutation could potentially affect the ability of neutralizing antibodies, derived from the serum of tularemia patients, to recognize *F. tularensis* infection - allowing *F. tularensis* to potentially evade host immunity.

For Discussion:

Question 11: Since Dr. Jameson is planning a modification of his existing research plan, when would be the most appropriate time for him to consult with the IRE?

Dr. Jameson feels it would be prudent to have a discussion with the IRE chair about his new proposed experiment. Dr. Jameson meets with Dr. Millar, the IRE Chair, and they discuss the proposed project. After hearing the experimental details from Dr. Jameson, Dr. Millar believes the new proposal should be reviewed by the IRE to determine if the new experimental aims may be anticipated to produce any of the seven experimental effects listed in the Policy, and if so, has the potential to be DURC. Dr. Millar informs Dr. Jameson that once the proposal is completed he should send the proposal to the IRE for review.

A month later, Dr. Jameson submits his proposal to the IRE. It is obvious that Dr. Jameson's research meets the first criterion since he is working with a strain of *F. tularensis* covered by the Select Agent Regulations.

For Discussion:

Question 12: Based on the experimental details provided above, which, if any, of the seven listed experimental effects in the Policy might Dr. Jameson's research aim to produce?

Question 13: If the research does involve one or more of the seven experimental effects, what next steps are required?

Based on the information Dr. Jameson provided to the IRE, the committee determines that the experiments he is proposing involve two of the seven experimental effects listed in the policy:

1. **The experiments specifically aim to increase the pathogenesis of *F. tularensis*, thus “Enhances the harmful consequences of an agent or toxin;” and**
2. **The experiments may result in *F. tularensis* having an increased ability to avoid clearance by the host immune system, thus “Disrupts immunity or the effectiveness of an immunization against the agent or toxin without clinical and/or agricultural justification.”**

Since the IRE has determined that Dr. Jameson’s research meets the first two criteria of the Policy, the IRE must then apply the definition of DURC to see if the proposed project will be considered DURC. The Policy lists the definition of DURC 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.”

For Discussion:

- Question 14: Based on the experimental details provided, and considering the definition of DURC, what are your thoughts on whether Dr. Jameson’s research meets the threshold for constituting DURC?**
- Question 15: Is any additional information needed in order for the IRE to determine whether this research meets the definition of DURC?**
- Question 16: Does everyone in your breakout group concur with the assessment? If not, what are the differing opinions and the rationales behind them?**

After carefully considering the definition of DURC and the details of Dr. Jameson's latest proposed experiment and conducting a detailed assessment of the risks and benefits of the research, the IRE determines that the proposed research meets the definition of DURC. The IRE arrived at this conclusion because the research aims to change the antigenicity of a *F. tularensis* protein that could potentially allow *F. tularensis* to evade host immunity and because such a mutated strain could be directly misapplied to pose a significant threat with broad potential consequences to public health.

Dr. Jameson and the institution will need to prepare a risk mitigation plan to submit to Dr. Jameson's federal funding agency. Since Dr. Jameson's proposed research project has not yet begun, the IRE informs him to refrain from starting the element of his project that involves DURC until the risk mitigation plan has been submitted to and approved by the funding agency.

For Discussion:

Question 17: Since the IRE has determined that this research is DURC, what notifications are required to be made and in what timeframe?

Question 18: Would the IRE have to take any action if they had determined the research did NOT meet the definition of DURC?

Question 19: How is a risk assessment completed? How do you weigh the benefits against the risks to conducting such research?

The IRE, in conjunction with Dr. Jameson, begins to prepare a draft risk mitigation plan to submit to Dr. Jameson's federal funding agency. The plan will include the risks identified and the anticipated benefits of the research. It will also include proposed risk mitigation measures.

For Discussion:

Question 20: How long after determining a project constitutes DURC must a draft risk mitigation plan be submitted to the funding agency?

PART THREE

The IRE and Dr. Jameson meet to begin writing the risk mitigation plan for his tularemia research. They are unsure how to begin writing this document. While searching on the U.S. Government's S3 website (<http://www.phe.gov/s3/>) the IRE identifies multiple educational tools related to DURC to help institutions implement the Policy, including the USG's Companion Guide to the institutional DURC policy, which provides points to consider when drafting a risk mitigation plan. After reviewing the Companion Guide, the IRE begins to prepare the risk mitigation plan.

RESEARCH RESOURCE MANAGEMENT

As the first step in developing the draft risk mitigation plan, the IRE looks at the biosafety and biosecurity measures associated with Dr. Jameson's research, including ways in which risk might be mitigated through changing the experimental design, increasing the biosafety containment level in the facility, adding additional security enhancements to the facility, and using additional administrative controls, including enhanced cyber security precautions.

Dr. Jameson provides the IRE with the following information about the biosafety and biosecurity precautions being employed for this particular experiment: laboratory staff will conduct cell-based antigenic escape assays with virulent *F. tularensis* mutant strains in BSL-3 containment with physical and administrative enhancements that include dedicated single pass directional air handling systems that are interlocked and HEPA filtered on both supply and exhaust; double door autoclaves and dunk tanks; and the addition of shower-in and shower-out requirements for personnel.

For Discussion:

Question 21: Based on Dr. Jameson's description of the biosafety and biosecurity measures that he plans to employ during the conduct of the research, do you believe there are any additional biosafety or biosecurity measures that should be requested by the IRE? If so, what might these measures be? If not, why do you believe the existing measures are sufficient?

Based on the IRE's review of Dr. Jameson's proposed biosafety and biosecurity measures, the committee requires that Dr. Jameson characterize the mutated virulent strains in cell-based assays and then contact the IRE with the outcomes of the cell-based assays before proceeding with studies in animal models.

The IRE continues to prepare the draft risk mitigation plan by evaluating the applicability of existing countermeasures. For this section, the IRE considers how the existence or absence of countermeasures impacts the degree of risk posed by the conduct of the research and the communication of results generated. For the purposes of developing the risk mitigation plan, the IRE defines a countermeasure as a drug, biological product, or device intended for diagnosis, detection, mitigation, prevention or treatment. Dr. Jameson's protocol contains the following information regarding existing medical countermeasures: No new antibiotic resistance traits are being introduced during the course of the experiments. The mutant strains should still be susceptible to existing antibiotics but the effectiveness of the antibiotics against a strain with significantly higher virulence is unknown.

For Discussion:

Question 22: Based on the description of the existing medical countermeasures provided by Dr. Jameson, do you think the IRE should conclude that existing countermeasures are sufficient? If so, why?

After much debate back and forth between the IRE members and in consultation with Dr. Jameson, the IRE makes the determination that because no therapeutically relevant antibiotic resistance traits are being introduced, there is no evidence to indicate that existing countermeasures would be insufficient due to the susceptibility of the strain to available antibiotics used to treat tularemia.

INFORMATION MANAGEMENT

The IRE then turns its attention to how the research Dr. Jameson is performing should be responsibly communicated. The members of the IRE believe that the results of life sciences research should be communicated openly and to the fullest extent possible. They begin to explore how Dr. Jameson can best communicate his potential results.

For Discussion:

Question 23: What are some of the potential ways in which Dr. Jameson can communicate the results of his research in a responsible manner?

The IRE meets with Dr. Jameson to discuss the optimal way for communicating the results of his research in a responsible manner. After discussing the matter, Dr. Jameson and the IRE come to the following agreement. Before publishing his research, Dr. Jameson will first request his funding agency to review his manuscript in order to provide any guidance on responsibly communicating his research results. It was also agreed that when Dr. Jameson presents his research results, he will describe all of the biosafety and biosecurity measures that were in place throughout the course of his research; emphasize the public health benefits that may derive from his studies, including how the finding may inform **the development of new countermeasures against *F. tularensis*** and communicate the implications of the research results in a manner consistent with best practices in the responsible conduct of research.

For Discussion:

Question 24: The IRE has outlined responsible communication strategies for publishing the results of the research; however the committee should also be concerned with communications that may occur before the publication stage. At what stages in the research continuum might communication about the research occur?

Question 25: What else might the IRE consider in developing a responsible communication strategy?

To complete the draft risk mitigation plan, the IRE and Dr. Jameson also discuss the need for Dr. Jameson to ensure his laboratory staff is trained on the elements of the research that are considered DURC.

For Discussion:

Question 26: What are some methods Dr. Jameson could employ to ensure that his staff members are aware that elements of the research they are conducting constitute DURC?

Question 27: Are there any other conditions that should be incorporated into the risk mitigation plan?

Dr. Jameson's laboratory staff has already received extensive biosafety, biosecurity, and incident response training required to work with select agents. They also received initial DURC training before the research with *F. tularensis* began. Additional training sessions are planned that will focus in detail on the specific mitigations measures that must followed by the laboratory to comply with the risk mitigation plan. All laboratory staff are also required to take institutional DURC Policy refresher training on an annual basis.

Finally, the IRE asks Dr. Jameson to provide them with project updates every six months along with a report of how the mitigation measures are being implemented. Mr. Middleton, as the University's ICDUR, prepares to submit the draft risk mitigation plan for Dr. Jameson's research to his federal funding agency.

For Discussion:

Question 28: How long after the ICDUR's submission of a draft risk mitigation plan does the funding agency have to finalize and approve the plan?

Three weeks after submitting the draft risk mitigation plan, Mr. Middleton receives notification from Dr. Jameson's federal funding agency that the plan has been approved. The funding agency determined the measures to be taken by the university were appropriate. Dr. Jameson is informed of the funding agency's decision and is told that, since his other institutional approvals (i.e. IBC, IACUC) are in order, he can now begin his work with virulent strains.

For Discussion:

Question 29: After funding agency approval of the risk mitigation plan, what should the IRE require so that they may stay abreast of his research?