1. PURPOSE

1.1 The purpose of this policy is to, first, ensure that Dual Use Research of Concern ("DURC"), including research involving Pathogens with Pandemic Potential ("PPP"), does not occur at Van Andel Institute ("VAI"). Second, this policy outlines how purely computational approaches to DURC (i.e., *in silico* research not subject to the "United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential" but for which the U.S. Government ***encourages*** institutional oversight) are to be identified, assessed, and mitigated if approved. This policy is designed to ensure compliance with federal regulations and promote responsible *in silico* dual use research practices that balance scientific advancement with the protection of national security and public safety.

2. APPLICABILITY

2.1 This policy applies to all research activities conducted at VAI that may potentially involve or use:

2.1.1 A Select Agent or Toxin, per 7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73 (for convenience, Appendix A to this policy provides a list of said agents and toxins; note, however, the U.S. Government maintains the most current and authoritative list, including exceptions based on threshold amounts, pathogenicity of certain strains, etc.), OR

2.1.2 A Risk Group 3 or Risk Group 4 pathogen listed in Appendix B of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules ("NIH Guidelines") (for convenience, Appendix A to this policy provides a list of said Risk Group 3 and 4 pathogens; note, however, the U.S. Government maintains the most current and authoritative list, including exceptions based on threshold amounts, pathogenicity of certain strains, etc.), OR

2.1.3 Any naturally occurring, bioengineered, or synthesized component of any biological agent or toxin listed in 2.1.1 or 2.1.2 capable of causing: death, disease, or other biological malfunction in a human, an animal, a plant, or another living organism; deterioration of food, water, equipment, supplies, or material of any kind; or deleterious alteration of the environment (i.e., a "Component").

3. POLICY STATEMENT

3.1 VAI will at all times comply with the United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential ("DURC/PEPP Policy").

3.2 Research requiring the on-site use of a Federal Select Agent or Toxin, or a Risk Group 3 or 4 pathogen listed in the NIH Guidelines, or a Component thereof, is not permitted at VAI unless:

3.2.1 The Federal government has explicitly identified an exception in the Select Agents and Toxins List or the NIH Guidelines (e.g., research uses amounts below established thresholds or a non-pathogenic strain), AND

3.2.2 The experimental outcomes specified in Sections 3.3.1 through 3.3.9 cannot be Reasonably Anticipated, AND

3.2.3 VAI's Manager of Environmental Health and Safety (or their designee) has approved such research.

3.3 Strictly *in silico* research involving a Federal Select Agent or Toxin, or a Risk Group 3 or 4 pathogen listed in the NIH Guidelines, or a Component thereof, is permitted without VAI's prior approval, provided none of the following experimental outcomes can be Reasonably Anticipated:

3.3.1 Increase transmissibility of a pathogen within or between host species.

3.3.2 Increase the virulence of a pathogen or convey virulence to a non-pathogen.

3.3.3 Increase the toxicity of a known toxin or produce a novel toxin.

3.3.4 Increase the stability of a pathogen or toxin in the environment, or increase the ability to disseminate a pathogen or toxin.

3.3.5 Alter the host range or tropism of a pathogen or toxin.

3.3.6 Decrease the ability for a human or veterinary pathogen or toxin to be detected using standard diagnostic or analytical methods.

3.3.7 Increase resistance of a pathogen or toxin to clinical and/or veterinary prophylactic or therapeutic interventions.

3.3.8 Alter a human or veterinary pathogen or toxin to disrupt the effectiveness of preexisting immunity, via immunization or natural Infection, against the pathogen or toxin.

3.3.9 Enhance the susceptibility of a host population to a pathogen or toxin.

3.4 Strictly *in silico* research involving a Select Agent or Toxin, a Risk Group 3 or 4 pathogen listed in the NIH Guidelines, or a Component thereof, requires prior approval from VAI's Vice President for Research Protections and Support if any of the experimental outcomes listed in 3.3.1 through 3.3.9 can be reasonably anticipated.

4. DEFINITIONS

DUAL USE RESEARCH. Research conducted for legitimate purposes that generates knowledge, information, technologies, and/or products that could be utilized for benevolent or harmful purposes.

DUAL USE RESEARCH OF CONCERN ("DURC"). Life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be misapplied to do harm with no, or only minor, modification to pose a significant threat with potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security.

IN SILICO RESEARCH. Scientific experiments or studies conducted or produced by means of computer modelling, simulation, and the like, including the use of artificial intelligence.

LIFE SCIENCES. The study or use of living organisms, viruses, or their products, including all disciplines, methodologies, and applications of biology (including, but not limited to: biotechnology, genomics, proteomics, bioinformatics, and pharmaceutical and biomedical research and techniques).

PATHOGEN WITH PANDEMIC POTENTIAL ("PPP"). A pathogen that is likely capable of wide and uncontrollable spread in a human population and would likely cause moderate to severe disease and/or mortality in humans.

PATHOGEN WITH ENHANCED PANDEMIC POTENTIAL ("PEPP"). A type of pathogen with pandemic potential ("PPP") resulting from experiments that enhance a pathogen's transmissibility or virulence, or disrupt the effectiveness of pre-existing immunity, regardless of its progenitor agent, such that it may pose a significant threat to public health, the capacity of health systems to function, or national security. Wild-type pathogens that are circulating in or have been recovered from nature are not PEPPs but may be considered PPPs because of their pandemic potential.

PRINCIPAL INVESTIGATOR ("PI"). A senior/key person responsible for proposing, designing, conducting or reporting on research and development activities.

REASONABLY ANTICIPATED. An assessment of an outcome such that, generally, individuals with scientific expertise relevant to the research in question would expect this outcome to occur with a non-trivial likelihood. It does not require high confidence that the outcome will definitely occur but excludes experiments in which experts would anticipate the outcome to be technically possible, but highly unlikely.

RISK ASSESSMENT. A systematic process of identifying and evaluating potential risks associated with DURC, including risks related to security, biosafety, public health, and ethical considerations.

RISK MITIGATION PLAN. A plan developed to manage and reduce the potential risks associated with DURC, which may include modifications to research methodologies, containment measures, communication strategies, and oversight mechanisms.

5. PERFORMANCE MATERIALS – N/A

6. HIGH LEVEL PROCEDURES

6.1 Initial Identification and Notification

Principal Investigators are responsible for ensuring that research requiring the on-site use of a Select Agent or Toxin, or a Risk Group 3 or 4 pathogen listed in the NIH Guidelines, or a Component thereof, does not occur in their labs.

PIs are responsible for immediately notifying the Vice President for Research Protections and Support ("VPRPS") of any plans to engage in *in silico* research that (a) involves an agent or toxin identified in Section 2, or a Component thereof, and (b) can be reasonably anticipated to result in one or more of the experimental outcomes identified in Section 3.3.

The PI's notification must identify which agents or toxins listed in Section 2 or Component thereof will be involved in their planned research, which experimental outcome(s) identified in Section 3.3 can be reasonably anticipated, and how their planned research may result in the identified experimental outcome(s).

PIs may not initiate *in silico* research subject to the prior approval requirements of this policy without first receiving said approval.

6.2 Policy Determination

The VPRPS will review the proposed research to determine if it falls within the scope of this policy, consulting with VAI's Institutional Biosafety Committee, Export Controls Committee, and others as needed.

6.3 Risk Assessment

If the VPRPS determines that the research in question is subject to the prior approval requirements of this policy, the VPRPS in consultation with other experts as needed will evaluate the potential benefits and risks of the research, the potential for misuse, the likelihood of harmful applications, and the potential magnitude of harm. When available, the VPRPS will use appropriately modified federal guidelines and risk assessment frameworks to guide their evaluation.

The VPRPS will endeavor to provide the PI with a written notice within 60 days of receiving the initial notification, informing them of whether the proposed *in silico* research may proceed and, if so, under what conditions.

6.4 Risk Mitigation

If the VPRPS determines that the research in question may proceed, the VPRPS will work with the PI and IBC to develop and implement a Risk Mitigation Plan that is informed by the VPRPS's assessment of risks and anticipated benefits. Mitigation strategies may include but are not limited to modifications to research protocols, increased security protocols (e.g., an export control technology control plan), collaboration with relevant government agencies, and plans that ensure the responsible sharing and communication of research results and datasets related to the biological agents and toxins involved in the research.

PIs must provide their written acceptance and agreement to follow the Risk Mitigation Plan before research subject to the Risk Mitigation Plan may commence and all subsequent research must be conducted in accordance with the approved plan.

6.5 Communication and Reporting

PIs must communicate the findings of *in silico* research approved under this policy in a responsible manner and in compliance with the approved Risk Mitigation Plan.

6.6 Monitoring and Reporting

PIs conducting approved *in silico* research must submit annual reports to the VPRPS, outlining project progress, any changes in risk assessment, and updates on risk mitigation measures no later than 30 days after the end of each project year.

If, during the course of the research, new information or developments suggest an increased risk, the PI must promptly notify the VPRPS. The VPRPS will re-evaluate the risk assessment and collaborate with the PI to implement additional risk mitigation measures if necessary.

6.7 Non-Compliance

PIs are responsible for complying with this policy and any approved Risk Mitigation Plans, reporting any deviations, and promptly informing the VPRPS of any new information or developments that could impact the assessment of risks associated with their research.

Non-compliance with this policy or an approved Risk Mitigation Plan may result in suspension or termination of the research project, disciplinary action up to and including termination, or other appropriate institutional responses.

6.8 Education and Training

PIs will ensure that laboratory personnel (i.e., those under the supervision of laboratory leadership, including graduate students, postdoctoral fellows, research technicians, laboratory staff, and visiting scientists) receive training on the requirements of any approved Risk Mitigation Plans.

7. REFERENCES

7.1 Select Agents and Toxins

7.2 NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

7.3 United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential

8. HISTORY

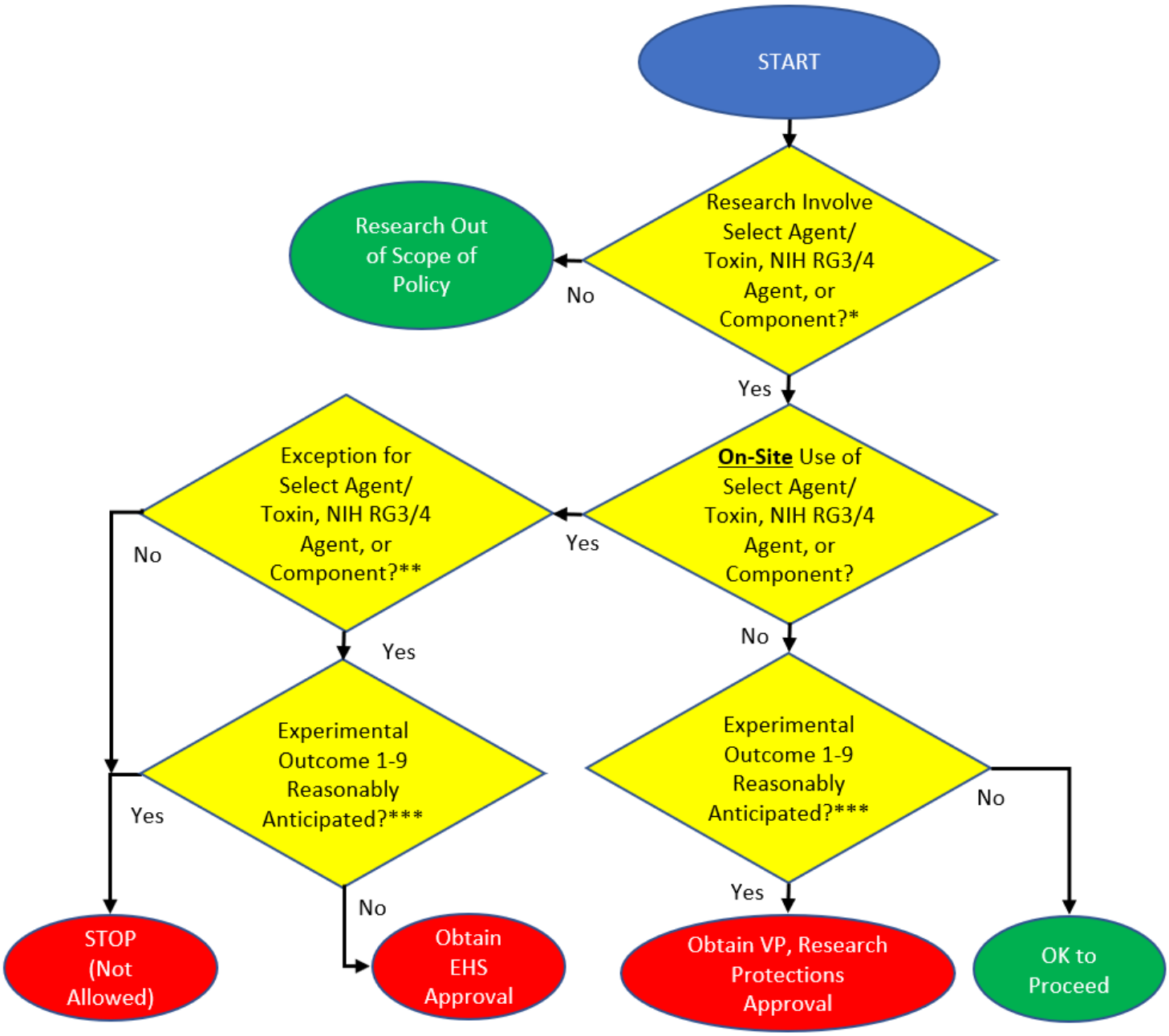
Original January 13, 2025

Appendix A: Select Agents and Toxins and Risk Group 3 and Risk Group 4 Pathogens from the NIH Guidelines (as of 11/21/2024)

1. Abrin
2. Absetterov virus
3. African horse sickness virus
4. African swine fever virus
5. Avian influenza highly pathogenic strains, H5N1 strains within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1)
6. Bacillus anthracis
7. Bacillus anthracis Pasteur strain
8. Bacillus cereus Biovar anthracis
9. Bartonella
10. Botulinum neurotoxin producing species of Clostridium
11. Botulinum neurotoxins
12. Brucella abortus
13. Brucella melitensis
14. Brucella suis
15. Burkholderia mallei
16. Burkholderia pseudomallei
17. Central European encephalitis virus
18. Chapare virus
19. Chikungunya virus
20. Classical swine fever virus
21. Coccidioides immitis
22. Coniothyrium glycines (formerly Phoma glycinicola and Pyrenochaeta glycines)
23. Conotoxins (Short, paralytic alpha conotoxins containing the following amino acid sequence $X_1CCX_2PACGX_3X_4X_5X_6CX_7$)
24. Coxiella burnetii
25. Crimean-Congo haemorrhagic fever virus
26. Diacetoxyscirpenol
27. Eastern Equine Encephalitis virus
28. Ebola virus
29. Flexal
30. Foot-and-mouth disease virus
31. Francisella tularensis
32. Goat pox virus
33. Guanarito virus
34. Hanta virus including Hantaan virus
35. Hanzalova virus
36. Hendra virus (Equine Morbillivirus)
37. Herpesvirus simiae (Herpes B virus or Monkey B virus)
38. Histoplasma capsulatum
39. Histoplasma capsulatum var. duboisii
40. Human immunodeficiency virus (HIV) types 1 and 2
41. Human T cell lymphotropic virus (HTLV) types 1 and 2
42. Hypr virus
43. Influenza viruses 1918-1919 H1N1 (1918 H1N1), human H2N2 (1957-1968), Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 Influenza virus)
44. Japanese encephalitis virus
45. Junín virus
46. Kumlinge virus
47. Kyasanur Forest disease virus
48. Lassa virus
49. Lujo virus
50. Lumpy skin disease virus
51. Lymphocytic choriomeningitis virus (LCMV) (neurotrophic strains)
52. Machupo virus
53. Marburg virus
54. Middle East Respiratory Syndrome coronavirus (MERS-CoV)

55. Monkeypox virus
56. Mycobacterium bovis (except BCG strain)
57. Mycobacterium tuberculosis
58. Mycoplasma capricolum
59. Mycoplasma mycoides
60. Newcastle disease virus
61. Nipah virus
62. Omsk hemorrhagic fever virus
63. Orientia tsutsugamushi (was R. tsutsugamushi)
64. Pasteurella multocida type B -"buffalo" and other virulent strains
65. Peronosclerospora philippinensis (P. sacchari)
66. Peste des petits ruminants virus
67. Ralstonia solanacearum
68. Rathayibacter toxicus
69. Ricin
70. Rickettsia akari, R. australis, R. canada, R. conorii, R. prowazekii, R. rickettsia, R. siberica, R. typhi (R. mooseri)
71. Rift Valley fever virus
72. Rinderpest virus
73. Russian spring-summer encephalitis virus
74. Sabia virus
75. SARS-associated coronavirus (SARS-CoV)
76. SARS-CoV/SARS-CoV-2 chimeric viruses resulting from any deliberate manipulation of SARS-CoV-2 to incorporate nucleic acids coding for SARS-CoV virulence factors
77. Saxitoxin
78. Sclerophthora rayssiae
79. Semliki Forest virus
80. Sheep pox virus
81. Simian immunodeficiency virus (SIV)
82. Staphylococcal enterotoxins (subtypes A,B,C,D,E)
83. Swine vesicular disease virus
84. Synchytrium endobioticum
85. T-2 toxin
86. Tetrodotoxin
87. Tick-borne encephalitis complex (flavi) viruses: Far Eastern subtype
88. Tick-borne encephalitis complex (flavi) viruses: Siberian subtype
89. Transmissible spongiform encephalopathies (TSE) agents (Creutzfeldt-Jacob disease and kuru agents)
90. Variola major virus (Smallpox virus)
91. Variola minor virus (Alastrim)
92. Venezuelan equine encephalitis virus
93. Xanthomonas oryzae
94. Yellow fever virus
95. Yersinia pestis

Appendix B: Policy Decision Tree



* See Appendix A.
** See EHS for guidance on exceptions.
*** See Section 3.3 of policy.