DUAL USE RESEARCH OF CONCERN (DURC) MANUAL

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HEALTH SECURITY
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Introduction

This Dual Use Research of Concern (DURC) manual was developed by local & international experts in collaboration with Health Security Partners, USA. It is intended to serve as an informational guide for life scientists working with potentially infectious materials in research and biomedical laboratories in order to improve health and wellbeing in both human and veterinary domains and to implement the Global Health Security Agenda in Pakistan.

Ultimately this manual seeks to promote the discussion of DURC within the research and biomedical laboratories whether human or animal. Health Security Partners and the authors hope that the content will be useful to thousands of dedicated life scientists supporting the people, animals, plants, and environment of Pakistan in the spirit of One Health and the Global Health Security Agenda. Each of the 10 sections in this manual focuses on understanding and identifying Dual Use Research (DUR) and DURC and developing risk mitigation strategies by and for those working in research and biomedical laboratories across the country.

The preparation of the manual was a collaboration between Health Security Partners and Dr. Shamsul Arfin Qasmi from Fazaia Ruth Pfau Medical College, Karachi, Sindh, Pakistan. This manual was developed with the support of national and international scientists working in the fields of Biorisk Management and Global Health Security. In particular, Samreen Sarwar, of Health Security Partners, spearheaded the initial concept and vision for the project. We also wish to thank Dr. Erin Sorrell, of the Elizabeth R. Griffin Program at Georgetown University, for her review of the manual.

The manual served as a mechanism for organizing several DURC workshops throughout Pakistan and served as a tool for the dissemination of knowledge of DURC and its importance.

Although the first edition of the written manual is designed to help the Pakistani laboratory community strengthen responsible research, the manual is a "living document" to allow for revisions as technology and best practices change.

The manual covers a broad range of topics including, biorisk management, the Fink Report, key responsibilities of stakeholders, code of conduct, and gain of function research. As such it will remain an asset for all human and veterinary research facilities and biomedical laboratories.

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History of Program

This training manual was developed to support the implementation of DURC workshops in Pakistan as part of the larger project, "A DURC Training Initiative in Pakistan." The project was conceived during the development phase of the 2015 Health Security Futures Fellowship. In the first phase, a nationwide survey was conducted to assess the level of awareness and attitudes of postgraduate students towards DURC. In the second phase, this manual was developed to address the gaps and challenges identified by the survey. This manual has been used in training life sciences researchers on DURC across Pakistan and is intended to be used in the future so that researchers are able to take proper measures to mitigate the risks inherent to DURC.

Acknowledgements

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- Samreen Sarwar, Technical Advisor, Health Security Partners, USA
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About Health Security Partners

Health Security Partners is an international nonprofit organization dedicated to building local capacity to improve health security around the world. Health Security Partners develops and delivers programs that advance individuals' careers, institutions' capacities, and societies' ability to prevent, detect, and respond to infectious diseases. Their mission is to realize a better health security future for all. In Pakistan, Health Security Partners is actively engaged with local partners in government, university, and private institutions to support activities that address public health challenges.

Objectives of the Manual

The objectives of this manual are to help readers:

- Understand the importance of responsible conduct of life sciences research
- Understand the concept of DURC
- Identify DURC and take proper action when the research has dual use potential
- Compare & contrast DUR and DURC, with examples of DUR that has the potential to be DURC
- Explain what happens when DURC is identified, including the process of review, decision making, and communicating
- Apply DURC review process to real world scenarios
- Define actions to be taken when DURC is reported
- Recognize current initiatives and challenges for DURC management in Pakistan

Section I: Biorisk Management

Background Information and AMP Model

Before we begin discussing DUR and DURC it is important to review the key components of biorisk management in life science laboratories.[1] Laboratories that handle hazardous biological materials must implement safety and security procedures that protect those working inside the laboratory and in the outside environment and prevent misuse. Effective biorisk management system incorporates biosafety and biosecurity best practices, establishes a culture of safety and security in the laboratory, allows biosafety and biosecurity to become part of the daily routine of all laboratory personnel, and improves the overall level of working conditions with the aim of good laboratory management.

Key terms[2]

Biosafety

Containment principles and practices implemented to prevent the unintentional exposure to biological agents and toxins, or their accidental release.

Biosecurity

Protection, control, and accountability for biological agents and toxins within laboratories to prevent loss, theft, misuse, diversion, unauthorized access, or intentional unauthorized release.

Biorisk

The combination of the probability of harm occurring and the severity of the harm due to a biological agent or toxin.

Biorisk assessment

This is the foundation for biorisk management and is performed to determine the necessary level of protection and risk control measures in a laboratory. Biosafety regulations in many countries require biorisk assessment during the authorization process for laboratories. Biorisk assessment is a major element of the fourth's edition of the World Health Organization's Laboratory Biosafety Manual[3] and the basis for the biorisk management standard ISO 35001:2019.[4]

The AMP Model

The AMP Model[1] identifies 3 key components of a biorisk management system:

- Assessment
- Mitigation
- Performance

Assessment

Assessment is a process used to identify the risks related to pathogens and toxins and to assess the likelihood and consequences of an exposure event in the context of already existing controls, and to determine if the risks are acceptable or not.[5]

Mitigation

Mitigation activities and control activities are placed in a laboratory to decrease or remove the risks associated with living agents and toxins. These may include but are not limited to implementing measures

such as use of PPE, administrative controls, engineering controls, and substitution and/or elimination. Mitigation should be determined based on the risk assessment and should target the most unacceptable risks.[1]

Performance

Performance involves having a system to address key issues by recording, calculating, and assessing actions of the organization and the related outcomes in order to reduce the incidence of biorisks and improve biorisk management.[1]

Biosafety and Biosecurity in Pakistan

The Pakistan Biosafety Rules[6] and National Biosafety Guidelines[7] were released in 2005 by the Pakistan Environmental Protection Agency. The National Biosafety Guidelines faced implementation challenges as a result of devolution under the 18th amendment. The guidelines focused on biorisk management in genetic manipulations and enforced implementation of risk assessment and mitigation protocols by establishing a 3-tier system.[7]

- Institutional Biosafety Committee: Assists an institution's researchers who conduct field research
- Technical Advisory Committee: Reviews applications for the use, sale, and import of genetically modified organisms in Pakistan
- National Biosafety Committee: Oversees tasks related to final approval of genetically modified organisms and provides guidance to other stakeholders

The National Biosafety Guidelines 2005[7] do not address biorisk management in health and life sciences research laboratories. Currently, health and life sciences facilities use either the World Health Organization's Laboratory Biosafety Manual[3] or Centers for Disease Control and Prevention's Biosafety in Microbiological and Biomedical Laboratories guidelines[8] on biosafety. National Biosafety and Biosecurity Guidelines for healthcare systems and research laboratories are in development, in Pakistan, to address these gaps.

Significant advances have been made in Pakistan for the improvement of biosafety and biosecurity both by the government and other stakeholders, including nonprofit organizations. For example, the government released the National Laboratory Biosafety and Biosecurity Policy in early 2019.[9] However, DURC remains a neglected topic and needs urgent consideration to increase awareness of the issue among scientists.

Responsible Research

The US National Healthcare Group's Responsible Conduct of Research encourages researchers to establish a research culture that demonstrates best practices in their daily activities and in situations that challenge individual's values and integrity.[10,11]

This research culture promotes:

- Honest reporting of research findings
- Effective utilization of resources to avoid waste
- Following the rules and regulations set by the authorities
- Responsible communication of research data
- Respect for study subjects (animals, humans, and the environment)

Figure 1. Components of Responsible Conduct of Research (RCR)[10]

There are 8 key areas to consider while enforcing responsible conduct of research, as shown in Figure 1. In addition to holding the researchers accountable, the Responsible Conduct of Research also places responsibilities on institutions such as, promoting awareness of legislation, standards, and policies to the researchers; encouraging cooperation between researchers and partners; establishment of good management practices and guidance; training and education of all research staff; and effective supervision and a safe research environment. The Responsible Conduct of Research is linked to DURC because the issues relevant to DURC can only be addressed by recognizing responsibilities of different research stakeholders.

Section II: Introduction to DUR and DURC

Advances in life science and biotechnology have led to considerable progress in the prevention, diagnosis, and treatment of diseases. Basic research in the life sciences has resulted in a better understanding of host-pathogen interactions, pathogen evolution, and improved and targeted therapies and vaccines. The same advances can be directly or indirectly misused for biowarfare or bioterrorism and pose a dual use dilemma. These advances present new challenges in the field of bioethics and of equitable access to life sciences research and have been the subject of several studies.[12]

The 1990s and early 2000s marked an era of escalating concerns about bioterrorism. Following a 2001 event of bioterrorism, in which letters containing *Bacillus anthracis* spores were mailed to US senators, several controversial research findings with dual use potential were reported and further escalated fears about the possibilities of bioterrorism.[13] In 2004 the US National Research Council convened a committee, chaired by Dr. Gerald Fink, to study the threats posed by damaging applications of biotechnology. The committee published a report, "Biotechnology Research in an Age of Terrorism," which became known as the Fink Report.[14] The Fink Report contained several recommendations, 1 of which was the establishment of a federal advisory committee to provide guidance and leadership regarding DUR. Following the recommendation, the US National Science Advisory Board for Biosecurity (NSABB) was established in 2005.

What is Dual Use?

Let's discuss some of the definitions and usage for DUR and DURC.

Definitions

DUR is research that is carried out for legitimate reasons and produces knowledge, information, technology, and/or products that could be used for both good and bad purposes.[15]

The World Health Organization defines DURC as life sciences research that is intended for benefit, but which might easily be misapplied to do harm.[16]

The European Commission-Trade website[17] defines DUR as, "Dual use items shall mean items, including software and technology, which can be used for both civil and military purposes, and shall include all goods and materials which can be used for both non-explosive uses and assisting in any way in the manufacture of nuclear weapons or other nuclear explosive devices." This definition highlights concerns around dual use which arose during the Cold War and continue today; dual use in the context of nuclear weapons is also referenced in the Nuclear Non-Proliferation Treaty.[18]

In a 2007 report, "Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for minimizing the potential misuse of research information,"[19] the NSABB defines 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."

Developments in biotechnology can be used legally for human improvement but can also be abused for biological warfare. Therefore, DURC is a matter of relevance and importance to all life sciences researchers. All researchers have a role in upholding high standards and the responsible conduct of research. When a researcher identifies potential DURC the project must undergo a review process to determine the specific

concern. The key to reviewing potential DURC is documentation and justification of conclusions and decisions.[11]

DURC in Pakistan

In an era of heightened fear of bioterrorism, Pakistan has taken steps to address biosecurity issues. It ratified the Biological and Toxin Weapons Convention in 1972. Article IV of the Biological and Toxin Weapons Convention directs Pakistan to maintain control of dual use sensitive technologies. Some governmental institutions have already taken the initiative to address DURC. The Pakistan Academy of Sciences and the Department of Biotechnology at Quaid-i-Azam University, Islamabad have been pioneers in dual use education in life sciences in Pakistan. These organizations implemented a survey on DURC awareness in Pakistan and based on the resulting gap analysis, arranged 2 interactive workshops on DURC. Quaid-i-Azam University also added a course on bioethics and dual use education to their curriculum.[20]

The Pakistan Biological Safety Association, a non-profit organization established in 2008, has taken substantial steps to improve biosafety and biosecurity and has initiated formal DURC training in Pakistan.[21] Many international partners are helping Pakistan raise awareness and building capability of life science researchers in understanding and managing DURC. Health Security Partners conducted a nationwide survey on DURC awareness and attitudes among postgraduate students[22] and conducted a series of workshops in different regions of Pakistan. This manual was developed as a part of that project.

Compare and contrast DUR and DURC

Example

DUR

Any life science research that has dual use potential e.g., molecular cloning to produce interferons and interleukins for therapeutic purposes.

DURC

De novo synthesis of polio virus from chemically synthesized oligonucleotides in 2001 by Dr. Eckard Wimmer of the State University of New York at Stony Brook.[23, 24]

Exercise

Compare DUR and DURC by writing down the differences between them.

DUR	DURC

Section III: Research in an Age of Terrorism

Commonly known in the scientific community as the Fink Report, "Biotechnology Research in an Age of Terrorism" presents the findings and recommendations of a US National Research Council committee's work.[14] The report was developed to help protect the community of life sciences researchers against the potential misuse of biological materials and information, while maintaining scientific enquiry and communication to the maximum extent possible. The committee, led by Dr. Gerald Fink, proposed a system that would use a number of stages for experiments and their results to be reviewed. The system relies on a mix of self-governance by the scientific community and expansion of existing regulatory processes.

The Fink Report focused on 2 main areas of risk:

1. Dangerous materials that might be stolen from laboratories
2. Results of research that could be misused

In the view of some policymakers, publication of DUR can be helpful to terrorist groups or individuals with nefarious purposes and intentions.

The committee worked on methods to overcome and minimize the threats of research leading to biological warfare and bioterrorism without halting the progress of life sciences research.

Recommendations from the Fink Report

Although the Fink Report is a US-based report, its recommendations were designed for both local and international adoption. Therefore, the recommendations can be applied to any institution in any country.

1. Educating the Scientific Community

The committee recommended that national and international professional societies and institutions create programs to educate scientists about the nature of the dual-use dilemma in biotechnology and their responsibilities for mitigating risks.

2. Review of Plans for Experiments

It was recommended that the US Department of Health and Human Services enhance the existing system of evaluating experiments that involve recombinant or synthetic nucleic acid molecules by creating system of review that provides advice, guidance, and leadership for 7 categories of experiments ("experiments of concern") with microbial agents that carry concerns about the potential for misuse. The Fink Report also emphasized that organizations expand the role of existing Institutional Biosafety Committees (IBCs) to act as the first formal line of review for research proposals with dual use concerns or establish separate Institutional Review Committees or Entities (IRCs/IREs) for DURC oversight.[15] The report demanded capacity building, increased awareness, and understanding of the DURC issue by the members of IBCs.

3. Publication Stage Review

The committee recommended relying on self-governance by scientists and scientific journals to review publications for potential DURC and national security risks.

Publication of research results provides the widest dissemination, including to those who would misuse the information. It's thus important to think carefully about what kind of review procedures may be put in place at the time of publishing to offer an extra layer of protection.

4. Creation of a National Science Advisory Board for Biosecurity

It was recommended that the US Department of Health and Human Services create the NSABB to provide information and direction with governance for the suggested structure of evaluation and oversight of DURC. The NSABB is composed of experts in security and law enforcement and representatives from federal funding agencies and life science research organizations.

NSABB has the following responsibilities:

- Develop criteria for identifying DURC
- Develop guidelines for the oversight of DUR
- Provide recommendations for a code of conduct regarding DURC
- Provide recommendations for training and education programs for all researchers
- Advise on national policies regarding DURC
- Advise on national policies for research communication
- Develop guidelines for review of research proposals by IBCs
- Advise, guidance and review by IBCs on these specific experiments
- Support research institutions with additional advice if a project is not approved by IBCs and submitted to NSABB for reconsideration
- Help to develop strategies for coordinated international oversight of DURC
- Address other issues as directed by the Secretary of Health and Human Services

5. Improve communication between security, law enforcement, and life science organizations

The scientific, national security, and law enforcement communities should improve their communication and should work closely to provide relevant information and advice to each other. Law enforcement agencies need the help of scientists to work effectively in events of bioterrorism and to stay updated with the latest technologies. An advisory board of scientists and clinicians with relevant expertise should be established to provide technical help to national security and law enforcement agencies.

6. Review Physical Containment and Personnel Issues

Addressing any gaps in physical containment and untrained personnel can augment issues related to biosecurity and DURC because these factors have an important influence on how research is conducted.

7. Coordinate International Oversight

International oversight is indispensable for many reasons which includes, but is not limited to, the availability of the same information to researchers in different parts of the world. Technologies with dual use potential are being developed around the world, therefore international consensus and consistent guidelines are critical.

Experiments of Concern: 7 Categories

The Fink Report identified 7 categories of experiments which the committee believed encompass the types of activities or discoveries that should require review and discussion by informed members of the scientific and medical community before they are undertaken or, if carried out, before they are published in full detail.[14] These include experiments that:

1. Render a vaccine (human or animal) to a pathogen ineffective
2. Confer antibiotic resistance to a pathogen (human, animal, or plant) that decreases the effectiveness of a countermeasure

3. Increase the virulence of a pathogen (human, animal, or plant)
4. Increase the transmissibility of a pathogen (within or between species)
5. Increase the host range or tropism of a pathogen (human, animal, or plant)
6. Enable evasion of diagnostic or detection capabilities
7. Demonstrate weaponization of a pathogen

Any experiment which falls under 1 of these categories of experiments has high potential to be characterized as DURC, however DURC is not limited to these 7 categories. Therefore, identification of DURC needs a much deeper understanding of the issue.

The 7 Categories of Experiments Explained

To elaborate, examples of each class of experiment are discussed below to aid understanding.[25]

1. Render a vaccine (human or animal) to a pathogen ineffective

Rationale: Resistance to infection in the form of immunity is the main host defense, so disrupting vaccine-induced immunity could be harmful to public health, agriculture land, plants, and wildlife.

Example: Inserting an immunosuppressive messenger molecule (cytokine) into the genome of a virus can make the antiviral immune defense ineffective.

2. Confer antibiotic resistance to a pathogen (human, animal, or plant) that decreases the effectiveness of a countermeasure

Rationale: This could be used to navigate the defense system and increase host susceptibility to a pathogen allowing it to spread on a scale that could be epidemic due to the lack of available treatments or countermeasures.

Example: Imparting vibramycin (a brand name doxycycline antibiotic) resistance to *Vibrio vulnificus* (a cause of life-threatening wound infections), or by extending antibiotic resistance to important plant pathogens, for example the *Ralstonia sloanacearum* bacterium (on the USDA list of pathogens with a high-potential to cause fatal disease) has been found to be resistant to rifampicin.

Standard microbial strain selection methods in laboratories with antibiotics that use a host-vector system are not likely to be designated as DURC because these experiments don't normally pose a significant threat to public health and safety with broad potential consequences (these methods select transformed bacteria, in which antibiotic resistant gene is introduced along with the gene of interest for screening purposes).

3. Increase the virulence of a pathogen (human, animal, or plant)

Rationale: Increased virulence can lead to enhanced pathological effects of a pathogen or toxin, could raise the probability of ailment, and decrease the ability to manage the illness including rendering existing therapeutic agents ineffective.

Example: Identification of virulence factors by screening with genome wide or knockout methods for gene recognition.

4. Increase the transmissibility of a pathogen (within or between species)

Rationale: This could aid in the malicious use of a pathogen or toxin by increasing its transmissibility.

Examples: Changing genetic factors of a pathogen for intensification of transmissibility or modifying the method of transmission to increase the ease and efficiency of disease transmission.

5. Increase the host range or tropism of a pathogen (human, animal, or plant)

Rationale: This will jeopardize a host population that is not normally vulnerable to that agent or toxin. The prophylactic and therapeutic measures for the new and susceptible host population may be inadequate, which can result in uncontrolled spread of disease.

Examples: Converting non-zoonotic pathogens into zoonotic pathogens or changing the tropism of pathogens (viruses). Development of animal or plant models for infectious diseases could change the tropism or host range of a pathogen and increase the number of susceptible hosts.

6. Enable evasion of diagnostic or detection capabilities

Rationale: Any procedure which can decrease the ability to detect, manage, or provide prophylaxis for an illness (human, animal, or plant) caused by pathogens or toxins can result in a substantial negative effect on public health and increased economic burden.

Examples: Manipulating a pathogen to remove key target molecules used in diagnostics or altering a pathogen's antigen profile to evade immunoassay detection.

7. Demonstrate weaponization of a pathogen

Rationale: Host population immunity to new and novel agents or reconstituted and eradicated pathogens may not be in place and there may not be proper diagnosis, prevention and management available for these agents.

Examples: Creating improved delivery mechanisms for extinct and emerging pathogens. Full constitution of a microbial agent using whole exclusive sequences of genes or blends of sequences that are not present in nature. Reconstitution of an agent that can no longer be found in nature, for example the pandemic influenza virus of 1918.[26]

Following a critical review, experiments or studies dealing with knock outs, complement types, mutants, reassortments and clones of viruses having infectious molecular characteristics similar to naturally occurring pathogens, may be designated as DURC on a case-to-case basis.

Examples of Potential DURC

In 2001, Dr. Eckard Wimmer assembled the synthetic poliovirus using its sequence found on the internet. Poliovirus synthesis in itself is not of high concern since it is not classified as a select agent and is readily available for experimentation. The research served, however, as a proof of principle that other pathogenic viruses could be synthesized using the same method.[23,24]

In 2005, the virus (H1N1 influenza A) that caused the 1918 influenza (Spanish flu) pandemic was reconstructed by a group of scientists. The reconstruction could help scientists understand the reasons for the deadly nature of the virus and prepare the world for outbreaks in the future. At the same time, its misuse and threat of escape into the environment highlighted the dual use concerns of this research (24).

Case Study

Following is an example of potential DURC and the review that it underwent prior to publication in 2005. Lawrence Wein and Yifan Liu of Stanford University published a paper on the effects of an intentional discharge of botulinum toxin into 1 milk-producing company.[27] They resolved that with enough toxin, rapid distribution of and consumption of milk could result in poisoning hundreds of thousands of individuals. They also established that timely and precise in-process testing has the capacity to identify the hazard, while only increasing the cost of product by less than 1 cent per gallon.

Reasons for Concern?

- Considered a road map for terrorism

- Gave dosing requirements
- Gave total deaths upon the use of various quantities
- Identified the step in processing to undertake the attack

After considerable review, the numbers in the original paper were found to be drastically overestimated. Even the most conservative estimate resulted in only 99% inactivation of the target biological agent. The actual numbers were wildly different as after 1 second of the lowest acceptable temperature for pasteurization, 99.99% of the protein was inactivated resulting in no threat as DURC.[28]

Security Sensitive Agents

All pathogens and toxins cannot be regulated. Countries have to decide which pathogens and toxins are of highest priority for security and thus should be regulated. Designated agents are classified as Select Agents in the US[29] or Security Sensitive Biological Agents in Australia[30] or other designations elsewhere in the world.

Although there are many similarities, pathogens identified in this group differ by country.

The lists are derived using following 3 principles:

1. Intelligence
2. Impact
3. Feasibility of misuse

Many factors come into play when considering the classification of pathogens and toxins as security sensitive. Considerations include characteristics of pathogen or toxin with regard to its impact on human and/or animal health including virulence, pathogenicity, transmissibility, and available countermeasures. Economic impacts of an outbreak are considered as is any expressed or inferred interest or intent from criminal or terrorist groups to use such pathogens or toxins for acts of bioterrorism. Also relevant is how practicable it is to misuse the agent, as well as factors such as the convenience of availability, simplicity of manufacturing, and dissemination.

Section IV: Identification of DURC

US government policies[31,32] of 2012 and 2014 outlined the steps for identification of DURC:

- The application to an IBC for a proposed research project will ask a principal investigator to show whether the research involves any of the 15 select agents and whether the project falls under 1 of the 7 categories of experiments for DURC described in Section III.
- If the research includes 1 or more of the 15 select agents and/or involves 1 or more of the 7 categories of experiments, the IBC will forward the application and protocol for review to the IRC/IRE.
- If the IRC/IRE determines that the project does meet 1 of the above criteria, the IRC/IRE must then determine whether the research is to be designated as DURC.

The policy for the oversight of DURC focuses on 15 select agents and the 7 categories of experiments; however, DURC identification and designation extends above and beyond these parameters and needs a broader review.

DURC designation criteria should also take into account the following additional 2 factors:

1. Scope of the potential threat (broad consequences)
2. Immediacy of the potential threat (direct misapplication)

DURC Risk Assessment, Management, and Communication

There is no legislative framework available in Pakistan for institutional review of research proposals on DURC grounds in research institutions. However, the "United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern"[32] can be used as a guide for institutional review and formation of institutional DURC policy in Pakistan. In the US, DURC oversight is limited to research that uses the 15 select agents, falls under the seven categories of experiments, and is funded by the US Government; Pakistan, however, has the opportunity to apply DURC policy far more broadly. In the US policy example, a framework for institutional review requires the establishment of an IRC/IRE. This committee can be a new committee, an IBC, part of an IBC, or an existing review entity at an institution.

In Pakistan, awareness raising and capacity building of the institutional biosafety committees (IBCs) for the institutional review and oversight of DURC is a more practical and sustainable approach. The members of the review committee should have knowledge of policies in place and risk assessment and management strategies, for biosafety, biosecurity and DURC. At least 1 member of the committee should have in-depth knowledge of standard operating procedures, policies in place, and the institution's commitments. The committee should be involved in a continuing dialogue with the principal investigator during the risk assessment and risk mitigation planning.

IRC/IRE/IBC should undertake the following steps in the DURC review process:

1. Verification that the research involves 1 or more of the security sensitive agents
2. Review the principal investigator's risk assessment: whether the research produces results, is intended to produce results, or is reasonably anticipated to produce results that falls under 1 of the 7 categories of experiments
3. Identify DURC, review the principal investigator's risk-benefit assessment
4. Based on the risk-benefit assessment, decide on whether the project should proceed, and draft a risk mitigation and communication plan
5. Review the implementation and suitability of risk mitigation plans

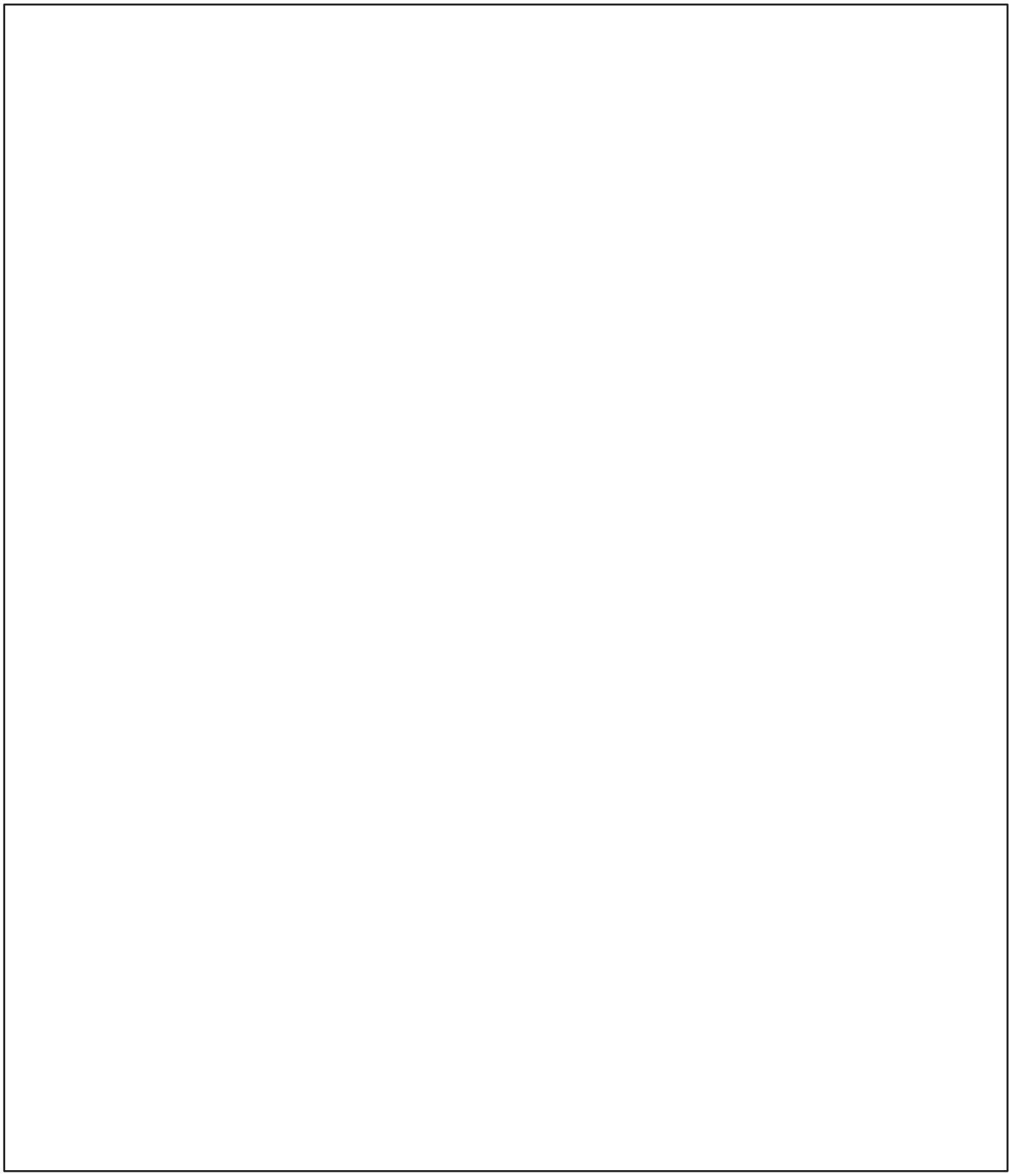
A risk mitigation plan should be made using the findings of the risk assessment. One or more of the following strategies can be used to address the risks identified.

- Ensure the adequacy of biosafety and biosecurity measures
- Evaluate applicability of existing countermeasures such as drugs, public health practices, pesticides, or devices used for diagnosis, detection, mitigation, prevention and treatment
- Develop a proper risk communication plan
- Training and education on DURC
- Develop a plan for monitoring DURC
- Restricting certain experiments of DURC

Key Points

- If the study is believed to be DURC, a risk mitigation plan needs to be developed, reviewed, and approved by the institution, government, or funding organization.
- A risk mitigation plan indicates specific measures to reduce the identified risks and addresses whether current biosafety and biosecurity programs are satisfactory. It also evaluates the applicability of the present countermeasures, education and training of the research staff, the plan for monitoring how the study is conducted, and the plan for responsible communication of the research findings.
- The IRC/IRE/IBC will evaluate and review the DURC protocols and risk mitigation strategies annually or as needed and modify the plans as needed. When the IRC/IRE/IBC has been engaged in the review of a protocol, no research activities may begin until the approval of the IRC/IRE/IBC and other review committees have been received.
- Principal investigators are required to notify the IRC/IRE/IBC immediately of any changes in the research or any unexpected results that might involve 1 of the 7 categories of experimentation.

Exercise: Draw a Scheme for the Identification of DURC



Key Responsibilities of Stakeholders

Addressing dual use concerns of a research proposal is the responsibility of multiple stakeholders including but not limited to researchers, principal investigators, institutions, funding agencies, journal editors and the government. It has implications for a wide range of sectors including the security community, media, and civil society.[31]

Researchers and principal investigators have a key role in helping mitigate DURC-related risks.[32] Their responsibilities span all stages of a research project from conceptualization, proposal development, institutional approval, funding approval, ongoing research, analysis of results, and communication through publication or otherwise. Review of research proposals for DURC implications should start as soon as the idea is conceptualized.[32] The later a researcher realizes the dual use potential of the research, the more difficult it becomes to mitigate it.

Researchers and principal investigators have the following responsibilities regarding DURC:

- Know responsibilities as a researcher
- Identify security sensitive agents
- Able to list the 7 categories of experiments that are included in DURC
- Understand that DURC is not limited to the 7 experiments of concern
- Identify potential DURC in their own research and institution
- Conduct biosafety and biosecurity risk assessments
- Conduct risk-benefit assessments
- Work with their specific review committees to identify potential DURC and mitigate identified risks
- Properly document decisions regarding DURC with proper justification
- Hold themselves personally accountable for their own research

It is important that every institution involved in life sciences research has 2 systems in place:

1. DURC oversight policy
2. An IRC/IRE or IBC

A DURC oversight policy will help guide researchers working with security sensitive pathogens and toxins in research projects which could be used for dual purposes.

The local oversight provided by institutions may consist of the following:

- Education and training
- Initial evaluation for DURC by the researcher
- Periodic assessment of dual use potential by the researchers and IRC/IRE or IBC

The IRC/IRE or IBC will be a group of professionals that will help each researcher ascertain whether their research can be classified as DURC, decide whether the institution will allow the research, and make relevant recommendations on how to proceed if it is DURC. The IRC/IRE or IBC will conduct a review of the risk assessment and management plan by analyzing the biosecurity risks related to the pathogen in use, research techniques planned, and anticipated results. It will also help develop a responsible plan of risk mitigation, including research communication to the scientific community and to the public (if needed).

Funding agencies should aim to reduce potential DURC risks by developing policies and procedures for DURC review. Funding agencies should demand an initial assessment of the proposal on DURC grounds and approval by the institution after IBC review. The funding agency must also perform periodic reviews for DURC projects.

Journals should have a standard operating procedure for handling manuscripts with DURC. Publication is the last stage of a research project and mitigation at this step can be of limited effectiveness. However, journal editors can request authors to provide additional information on the institutional review conducted, risks-benefit assessment of sharing research findings, and can seek external expert review to make final decisions regarding publication of the results.

It is important for governments to make their own national policy for managing DURC to best fit the research environment within the country. A national approach is indispensable to harmonize and effectively implement DURC policy across the country.

Section V: DURC Awareness and Oversight

It is widely recognized that while scientific discoveries may have important applications for the betterment of society, some advances could also pose a threat to humanity. However, governance of research for dual-use potential should not hamper useful research and the growth of the bioeconomy.[35]

Judicial Work of the Government

In order to protect and preserve agriculture, people, and the environment, the government of Pakistan is determined to introduce bio-friendly legislation. In 2020, a code of conduct for life scientists was published by the Pakistan National Institute of Health that focuses on integrity and responsible conduct of research while taking into consideration the various roles of stakeholders in addressing dual use issues.[36] There are a number of laws related to biosecurity in Pakistan, however, a specific DURC policy for federal and institutional oversight does not yet exist. Important legislation relevant to biosecurity issues[20] are noted below:

- Pakistan's Environmental Protection Act, 1997 (PEPA 1997)
- Anti-Terrorism Act, 1997 (ATA 1997)
- Pakistan Export Control Act, 2004 (PECA 2004)
- Pakistan Export Control List, 2005, 2011 (PECL 2005, 2011)
- Biosafety Rules, 2005 (BR 2005)
- National Biosafety Guidelines, 2005 (NBG 2005)
- National Counter Terrorism Authority Act, 2013 (NTCAA 2013)
- Counter Terrorism Legislations, 2015 (CTL 2015)

Executive Work of the Government

Pakistan is a party to many international agreements that are linked to biosafety and biosecurity.[20] In addition, Pakistan is also taking part in a number of local biosecurity and biosafety initiatives that includes the following:

- National Point of Contact to the Global Conventions and Treaties
- Biological and Toxin Weapons Convention (BTWC)
- Draft of Legislation for Implementation of the BTWC
- UN Security Council Resolution 1540 (UNSCR 1540)
- World Trade Organization (WTO)
- Sanitary and Phytosanitary (SPS) Agreement
- Cartagena Protocol on Biosafety to the Convention of Biological Diversity (CBD)
- National Core Group of Life Sciences (NCGLS)
- Pakistan Biological Safety Association (PBSA)
- Strategic Export Control Division (SECDIV)
- Inter-Agency Working Group (Task Force) MOFA
- National Biosafety Center (NBC)
- National Bioethics Committee (NBC)
- COMSTECH International Committee on Bioethics (CICB)
- National Commission on Biotechnology

Exercise

What is DURC to you?

This exercise will help the user to evaluate their knowledge and comprehension of DURC. After completing this exercise, the user should review the preceding sections of the manual and additional DURC resources to gain a better understanding of the subject.

1. What is your concept of DURC? Explain 3 key points.

2. Have you thought of DURC as a real-world problem?

3. Is DURC applicable to One Health? If yes, how?

4. Is DURC governance a part of the Global Health Security Agenda?

5. What are international obligations regarding DURC?

6. What are national concerns regarding DURC?

NOTE: The Global Health Security Agenda is a collaborative effort of nations, international organizations and civil society to enhance progress towards full implementation of global health security frameworks and to promote global health security as an international priority.

Section VI: Possible Actions and Outcomes

Risk-Benefit Assessment

Identify risks and benefits in the research example given to you.

Risks	Benefits

What to do about DURC?

Key Points

When DURC is identified by researcher and institutional committees, the following measures[34,37] may be employed to mitigate risk and potentially allow the research project to go forward.

Enhance Aspects of Biorisk Management Performance

- Institutions must have a functional biorisk management system.
- Biosafety and biosecurity risk assessments must be conducted periodically.
- Enhanced biosafety and biosecurity measures should be applied.
- The research or study can be discontinued.
- Seeking of grant funding for the proposed research project can be postponed.
- The pathogen of choice may be changed to a less virulent strain or subtype.
- The efficacy of existing countermeasures against agents, toxins, or technologies should be evaluated.
- Targeted training of the staff involved in the research project should be conducted.

Modification in partnership

- Researchers should be chosen for the study after background checks and education on DURC.

Alteration in research communications

- Select information of the study, such as methods or findings with dual use concern, can be limited to selected parties (e.g., on a need-to-know basis etc.).
- Manuscripts can be modified by providing additional information about benefits of the study, biosafety and biosecurity measures taken during the study, and dual use concerns of the study and by withholding specific information, such as certain methods.
- Submission of the article can be postponed to a point at which the research doesn't pose the same degree of risk.
- Presentations at conferences can be modified.

Section VII: Overview of DURC Survey

Introduction

Dual use complexity of life sciences research poses a dilemma for researchers. Preventing the misuse of facilities, equipment, agents, and scientific knowledge for bioterrorism or biowarfare demands a web of prevention in multiple scientific disciplines. The concept of responsible conduct of research is not equally appreciated among all countries. This difference significantly threatens global biosecurity and needs special attention and deeper insights.

Methods

A cross sectional study was conducted to evaluate the level of awareness and attitudes of Masters of Philosophy (18 years of education) and Doctor of Philosophy students (19 years of education and above) towards DURC at 32 universities in 4 provinces, federal area, and the Azad Jammu and Kashmir regions of Pakistan.[22]

Results

Across the geographic regions targeted, 933 students responded (Table 1). Most of the respondents (58%) had never heard of DURC, while 19% had heard of the term, but were unsure of its meaning. In response to a question on the responsibility of evaluation of research projects on DURC grounds, many students indicated that universities (61%) and researchers (18%) should evaluate research projects on DURC grounds. Few indicated that government (9%) should evaluate research for DURC. Some (10%) were unsure, while 1% did not think that the evaluation was necessary. Almost half (46%) of the students indicated that they would prefer to learn about DURC in workshops. Fewer students supported learning about DURC online (5%) or as part of the course curriculum (6%). A small minority (3%) showed no interest in learning about DURC. The other important findings of this survey are summarized in Table 2.

Outcome

The survey results identified substantial knowledge gaps and are valuable for addressing awareness and training needs in Pakistan.

Conclusion

The awareness of DURC among researchers across Pakistan is limited. It is important to note that the respondents, although not formally educated about DURC, were quite aware of its potential impact and associated ethics.

Table 1. Survey of advanced degree students' awareness about DURC (N = 933)

Question: Were you previously aware of the term "Dual Use Research of Concern"?			
Degree Program	No (%)	Yes (%)	Yes, unsure of meaning (%)
MPhil (n = 730)	45.1	18.6	14.5
PhD (n = 203)	13.0	4.7	4.1
Total	58.1	23.3	18.6

Table 2. Key questions and percentage of positive responses from the survey

Questions	Yes (%)
Do you feel an obligation to report research misuse?	68.6
Do you believe there should be a section of your thesis/dissertation that describes the dual use potential of your research?	75.7
Before publishing your research, do you think it should be evaluated by the experts (IRB, journal editors, peer reviewers, etc.) for potential DURC?	54.1
As a scientist, do you think all research should be published for the sake of science, regardless of any biosecurity or DURC potential?	50.0
Do you think researchers performing DURC should be certified?	87.5
Do you think DUR concerns should be given greater attention at the government level?	89.7
Do you think the principal investigator / research supervisor should train laboratory staff and students about (DUR) before starting a new research project?	94.1
Would you be willing to publish your work with a limited protocol if your research is designated as DURC?	69.1
Should DURC be considered when results are communicated outside of journal publication such as poster and oral presentations?	95.0

Section VIII: Responsible Communication

Communication Decisions

The content, timing, and extent of distribution are crucial factors to consider when communicating research with dual use potential.[34]

Content

Depending upon findings of the risk-benefit assessment about communication of results, researchers should consider how to best communicate the contents of their research. Communication strategies may include providing additional information, such as details on dual use potential of the research, and/or limiting access to information, such as omitting materials and methods.

Timing

Risk can also be managed by controlling the timing of communication of research findings. Risk-benefit assessments may suggest immediate or delayed communication depending upon the potential consequences of released information.

Distribution

Distribution of the findings is also a crucial component of communicating research findings. The distribution can be limited to those with prior background checks and legal permissions or made accessible to everyone depending upon the risk-benefit assessment.

Audience

Communication plans differ depending upon the type of audience. The scientific community has a better understanding of science and can estimate the pros and cons of research. The public, however, may under or over-estimate the findings of the research and therefore require clear, plain language to describe the research and its findings in order to avoid confusion or overreaction.

Communication Methods

Communication methods need to be considered when communicating research findings. Besides publishing results, scientific presentations and other formal and informal means of communication should be considered for risk-benefit assessment when communicating research with dual use potential.

Exercise

Outline your research communication plan for the scenario provided.

Section IX: Gain of Function Research

Gain of function research can be broadly defined as experiments resulting in a mutation that confers a new or enhanced activity to an agent, usually by altering the gene and protein function.[38]

The main concern regarding gain of function research is centered on a specific subset of studies that can result in generation of potential pandemic pathogens (PPPs) by raising the transmission rate and/or pathogenicity of an organism. This subset of gain of function research has raised biosafety and biosecurity concerns, in part because of the potential for misuse.

When performed by accountable researchers, gain of function research aims to expand the understanding of the biological agent's pathogenesis, potential effect on humans (host-pathogen interactions), and ability to cause global spread of disease (pandemics). It is important to note that not all GOF studies involve PPPs. The main theme of these studies is to improve information on public health and emergency preparedness measures, and to develop medicinal countermeasures. Apart from these very significant potential benefits, gain of function research also has the potential for accidental release or intentional misuse.

Section X: Code of Conduct for DURC

Codes of conduct are in place to govern professional behavior in most professions, including the life sciences. These codes define appropriate behaviors. They are helpful in increasing biosafety and biosecurity mindfulness and preventing the misapplication of research in the life sciences. The adherence to a code of conduct can help all the participants in life science research. In many ways a codes of conduct boost ethical considerations and hold scientists accountable. However, it is questionable whether they can prevent those willing to do damage with results. The National Institute of Health, Islamabad, Pakistan published a national code of conduct for life scientists to define responsibilities of all stakeholders involved in life sciences research.[36] Institutional codes of conduct should also be developed to define the organizational framework, clear lines of institutional responsibilities, behavior expectations, reporting and implementation tools, and training requirements for those subject to the code.

Developing a code of conduct increases awareness and adherence to biosafety and biosecurity protocols and responsible conduct of research. In this regard many professional societies have codes of conduct which reflect and express acceptable behavior. DURC, because of the critical nature of the potential manipulation of pathogens, needs the strongest code of conduct.

Keeping in mind the importance of a code of conduct for DURC, stakeholders must recognize the need to develop a code of conduct, customize the code to their specific research area, and understand the essential or core responsibilities of those undertaking the research.

Institutional policy makers should include its employees in the development process, especially those involved in the potential DUR and thus subject to the code of conduct being created. Institutions should educate all relevant employees on the institutional code of conduct during annual ethics meetings and integrate it into research training.

A code of conduct will be helpful for the following stakeholders:

- Life scientists
- Technicians, students, and others involved in life sciences research process
- Research institutions
- Research leadership
- Professional societies and associations for the life sciences
- Scientific industries
- Journal editors, reviewers, and publishers
- Funding agencies
- Government

Code of Conduct for Biosecurity and DURC

A national code of conduct serves as a model that institutions may adopt and tailor to their specific needs. The Pakistani government has issued a national code of conduct for responsible life science research[36] but a distinct code of conduct for biosecurity and DURC could considerably strengthen all stakeholders' responsibilities in this area. The Dutch government developed a national code of conduct for biosecurity for their life scientists that can be used as an example in Pakistan.[39]

Following are the key elements of the Dutch code of conduct[39] for biosecurity and DURC:

1. Raising awareness and DURC training for all research personnel
2. Institutional policies and procedures for identification, review and oversight of DURC
3. Accountability and oversight, including reporting systems
4. Securing internal and external communication
5. Access control for security of sensitive materials and information
6. Shipment and ransport

The development of a similar code of conduct for Pakistani scientists will help galvanize individual's responsibilities towards biosecurity and DURC.

Key Messages

- DURC is relevant to all researchers in the life sciences and beyond.
- All persons involved in research must educate themselves on DURC and responsible research.
- Research projects must undergo review in order to ascertain whether there are DURC issues.
- A review or determination of DURC does not necessarily result in cessation of the project; it can continue with adequate mitigation measures and oversight.
- The key aspects of reviewing potential DURC are:
    - Documentation of decision-making process
    - Justification of decisions and conclusions
- Gain of function research projects should be reviewed for DURC potential.

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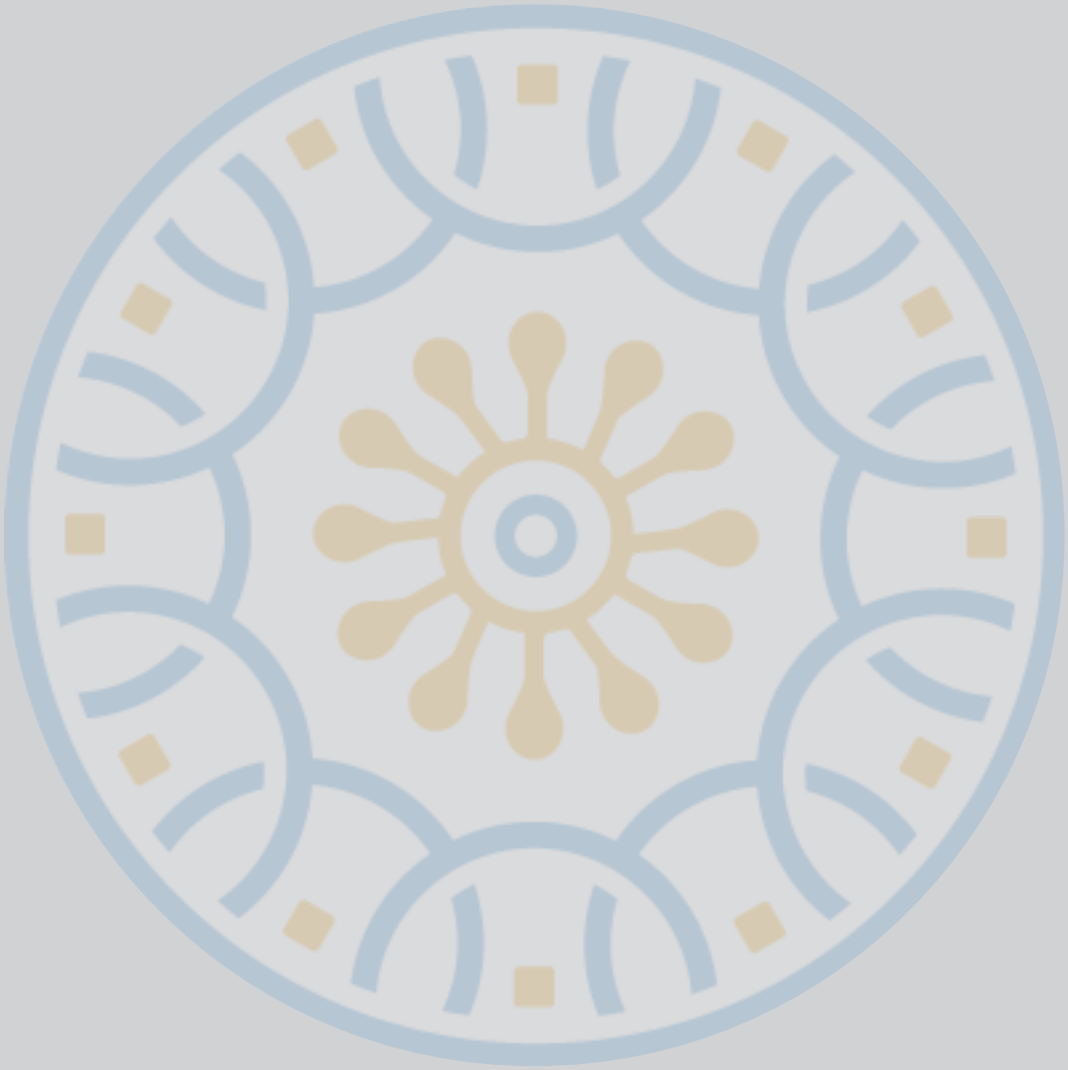

This training manual aims to increase awareness and understanding of Dual Use Research of Concern among researchers and to enable them to apply this knowledge to their research from the conception of an idea through to publication.