Process and Outcome Evaluation of the NIAID DAIDS Biphasic Grant Award Mechanism (R21/R33) to Fund High-Risk, High-Reward, Product Oriented Research

Final Report

Prepared for:

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Division of Acquired Immunodeficiency Syndrome (DAIDS)
National Institutes of Health

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April 2014

Table of Contents

Acknowledgements

The authors of this report thank the many people who contributed to this study and to the conceptualization, design, and conduct of the *Process and Outcome Evaluation of the NIAID DAIDS Biphasic Grant Award Mechanism (R21/R33) to Fund High-Risk, High-Reward Product Oriented Research*. The evaluation could not have been completed without the cooperation and responsiveness of the Principal Investigators of the research projects funded by the AIDS Vaccine Research and Microbicide Innovation Programs and the four Program Directors from the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), the National Institute on Deafness and Other Communication Disorders (NIDCD), and the Division of Microbiology and Infectious Diseases at NIAID. We also thank the members of the Evaluation Advisory Group for their input on the evaluation design and discussion of some of the ideas expressed in this report; these members included Drs. James Corrigan and Tony Dickherber from NCI, Dr. Sarah Glavin from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Dr. Juliana Blome from the National Institute of General Medical Sciences (NIGMS), and Dr. Amanda Green from the National Institute of Nursing Research (NINR). Finally, and most importantly, we thank the members of the NIAID and NCI project team who worked closely with us on this evaluation, including Dr. Madelon Halula, Dr. Jim Turpin, Dr. Jon Warren, Dr. Kristen Porter, Robert Palmer, Brandie Taylor, and Liberty Walton from NIAID, and Dr. Margaret Ames, Dr. Karen Parker, Karl Poonai, and Dr. Judy Keen from NCI. Their guidance, thoughtful feedback, and support throughout this project were invaluable.

Executive Summary

Introduction

The National Institutes of Health (NIH) is interested in developing, implementing, and evaluating creative funding mechanisms that support the pursuit of innovative, novel, and potentially high-risk, high-reward research in the biomedical sciences. One approach for eliciting, funding, and managing "outside the box" research is through the use of the Phased Innovation Award (PIA) mechanism (R21/R33). Since 2006 The National Institute of Allergy and Infectious Disease's Division of Acquired Immunodeficiency Syndrome (NIAID DAIDS) has utilized the PIA mechanism to support investigator-initiated AIDS research at the early stages of concept genesis and evaluation. Two DAIDS initiatives utilized the PIA mechanism: The Phased Innovation Award Program for AIDS Vaccine Research (AVR) and the Microbicide Innovation Program (MIP). From FY 2006 -2011, NIAID DAIDS funded 27 AVR projects and 61 MIP projects. As the last of the research projects concludes, NIAID DAIDS commissioned the Madrillon Group Inc. to conduct a *Process and Outcome Evaluation of the NIAID DAIDS Biphasic Grant Award Mechanism to Fund High-Risk, High-Reward, Product Oriented Research* (the PIA Evaluation). The purposes of the PIA Evaluation are to examine the implementation and impact of the NIAID DAIDS PIA mechanism in order to inform the design of new initiatives within NIAID and to inform future applications of the PIA mechanism within NIH.

Evaluation Design and Methodology

Primary Evaluation Questions

1. ***Is the Phased Innovation Award mechanism an appropriate mechanism for desired microbicide and prophylactic vaccine research?***
2. ***Is the PIA mechanism a valuable component of the DAIDS research portfolio?***
3. ***What was the overall impact of the PIA mechanism-supported milestone-driven research?***

The PIA Evaluation utilized a mixed-methods, multiple case studies design employing both qualitative and quantitative data collection and analysis. The NIAID DAIDS AVR and the MIP initiatives served as the primary cases for the evaluation. These primary cases were supplemented by four secondary cases: NIAID's Division of Microbiology and Infectious Diseases' (DMID's) *Host-Targeted Interventions as Therapeutics for Infectious Diseases* program, the National Cancer Institute's (NCI's) *Innovative Molecular Analysis Technology* (IMAT) program, the National Institute on Deafness and Other Communications Disorders' (NIDCD's) *Accessible and Affordable Hearing Health Care* program, and the National Institute on Drug Abuse's (NIDA's) *Biological Data Integration* program, which permitted a deeper exploration of the issues involved in implementing the PIA mechanism through a cross-case analysis. The evaluation team formulated three broad evaluation questions shown in the textbox. Data collection methods included: archival data abstraction; an online survey of PIA-funded Principle Investigators (PIs); semi-structured in-person and telephone interviews with a sample of nine PIs having two or more funded grants in either or both of the AVR and MIP programs; bibliometric analyses; semi-structured interviews with the AVR and MIP Program Directors, DAIDS Program Officers, and federal staff members at the NIH Center for Scientific Review (CSR) and Grants Management Officers who worked with the funded AVR and MIP grants; and semi-structured interviews with the Program Directors of the four other research programs using the PIA mechanism.

Evaluation Findings

Major findings for each of the evaluation questions are summarized below.

Question 1: Is the Phased Innovation Award mechanism an appropriate mechanism for desired microbicide and prophylactic vaccine research?

- AVR and MIP Program Directors and DAIDS Program Officers reported that from their perspectives, the PIA mechanism is especially appropriate for scientific fields having a relatively narrow focus and a strong product development orientation, two characteristics that fit the microbicide research field. The AIDS vaccine research field shared this orientation in its goal of identifying potential new vaccine candidates, but also included a broader focus on understanding and identifying the underlying mechanisms by which these vaccine candidates would work.
- A review of AVR and MIP grant applications indicated that the vast majority of applicants submitted some preliminary data as part of their grant applications despite statements in the Funding Opportunity Announcements (FOAs) that such data was not required. Interviews with the AVR and MIP Program Directors and DAIDS Program Officers indicated that applicants who contacted them to discuss their ideas during the application process were counseled to include some preliminary data.
- The secondary case interviews with other Program Directors using the PIA mechanism indicated that the mechanism could also be useful in leading established research investigators into new research areas where they had not been previously active and creating new research partnerships involving disciplines that had not previously worked together in a newly emerging research field.
- In weighing the pros and cons of alternative grant mechanisms as a means of funding the AVR and MIP research programs, the two Program Directors agreed that use of the traditional R01 grant mechanism was not appropriate for either program for two reasons: (1) R01 grants encourage incremental science rather than innovative or high-risk approaches, particularly in their emphasis on the requirement that R01 applicants submit substantial preliminary data; and (2) innovative projects carry a level of financial risk for the funding agency. The typical R01 project is funded for five years, which in their view was too long to continue funding projects that had shown early on that they were unlikely to yield results.
- Both the AVR and the MIP programs sought to attract new early-stage investigators to their respective fields. A comparison of average success rates across the FY 2006-2011 period for early-stage investigators for the AVR and the MIP programs showed that new investigators in both NIAID DAIDS initiatives had higher success rates than new investigators for R21 grants across NIH.
- AVR and MIP Program Directors and DAIDS Program Officers agreed that the level of effort required to oversee PIA grants is greater than the effort required to manage R-series and P-series grants, and similar to that required for cooperative agreements. The additional effort included negotiating milestones and evaluating transition applications. However, the Program Directors and Program Officers agreed that the additional effort is very worthwhile.
- Online survey data indicated that AVR and MIP PIs almost universally (95%) reported clearly understanding the grant application process, the targeted scientific areas listed in the FOAs, the requirement for negotiated milestones, and the transition evaluation process.
- AVR and MIP PIs felt that the transition evaluation process was, for the most part, efficient. Less than one-third of PIs whose projects successfully transitioned reported delays that adversely affected their research; this proportion was higher among the AVR investigators.
- The research project teams on AVR and MIP grants were highly collaborative and involved multiple disciplines. This was especially evident for the MIP projects where a core group of 33 key personnel collaborated on seven different funded research projects.

Question 2: Is the PIA mechanism a valuable component of the DAIDS research portfolio?

- The AVR and MIP Program Directors and the DAIDS Program Officers agreed that the PIA mechanism was an effective tool in establishing and accelerating the product development pipeline.

- They also agreed that they would like to see the PIA mechanism retained at DAIDS. They argued that the mechanism has had a positive effect on divisional priorities at DAIDS by enabling DAIDS staff to respond quickly to emerging research opportunities (e.g., inclusion of nanotechnology as a targeted scientific area in MIP FOAs) while managing the risk inherent in high-risk, high-reward research.

Question 3: What was the overall impact of the PIA-supported milestone-driven research?

- The AVR and MIP Program Directors and DAIDS Program Officers agreed that the PIA mechanism had a major impact on the growth and pace of scientific development in the AIDS vaccine and microbicide research fields. Researchers funded by the two programs produced a variety of new tools, animal models, methodologies, and vaccine and microbicide candidates that are now being investigated in follow-on research. PIs indicated that many of these new approaches would never have been submitted as grant applications in the absence of the PIA mechanism because the investigators viewed them as unlikely to make it through the traditional R01 grant review process. This view was also shared by staff members from CSR.
- Of the 74 funded AVR and MIP PIs, a total of 48 (65%) obtained 143 new NIH grants; of the 143 subsequent NIH grants, 43 (30%) grants focused on AIDS vaccine and/or microbicide research. In addition, about 10% of these new grants were SBIR/STTR grants.
- Between 2007 and September 2013, AVR and MIP investigators generated a total of 262 new publications on their AVR and MIP research activities.
- Nearly three-quarters (74%) of the AVR and MIP PIs formed at least one new research partnership or collaboration through their research activities, and about 60% of these new collaborations brought together disciplines or groups that had traditionally not worked together in the past.

Conclusions

The PIA (R21/R33) grant mechanism was developed to encourage submission of innovative high-risk, high-reward research grant applications while providing a means of managing the financial risk inherent in these grants for NIH ICs by allowing the termination of projects that did not meet transition evaluation criteria by the conclusion of the initial two-year exploratory period. The PIA Evaluation has shown that NIAID DAIDS use of the PIA mechanism:

- Attracted innovative, high-risk, high-reward grant applications;
- Funded a higher percentage of new investigators than the average rate for all R21 grant programs across NIH during the FY 2006-2011 period;
- Enabled NIAID DAIDS program staff members to evaluate research progress and advance promising research projects to a developmental phase while terminating projects that did not meet evaluation criteria;
- Produced important new hypotheses, models, methods, tools, and promising candidates;
- Brought together new multidisciplinary research collaborations and partnerships; and
- Achieved AVR and MIP programmatic goals and objectives.

Through a mixed-methods, multiple case study evaluation design, the PIA implementation process at NIAID DAIDS and four other NIH sites showed that the types of challenges and decisions faced at NIAID DAIDS were common to other IC's experiences in applying the PIA mechanism. In reviewing the results, the evaluation team developed a PIA implementation model that provides a framework that other NIH program staff could consider in future applications of the PIA mechanism.

1. Background and Introduction

A persistent challenge facing publicly-funded research concerns how funding can be used to stimulate innovation and high-risk, high-reward research. In the United States (US), as in many other countries, publicly-funded research provides the bulk of the financial resources investigators will have to conduct research and pursue new ideas. Public funding for research relies upon the mechanism of peer review to identify and recommend research proposals for subsequent funding, but this reliance comes at a cost. As Laudel (2006, page 502) has noted, "from the perspective of the scientific community, peer review is a mechanism that leads to the funding of the most promising projects and avoids researchers leaving their area of competence. …In shepherding its research towards the mainstream [however] a scientific community restricts unorthodox perspectives, which have always been important for the progress of science." Several studies have shown that peer review tends to be risk averse, and biased against innovative, high-risk, high-reward research (e.g., Laudel, 2006; Heinze, 2008). Not only do proposals presenting novel approaches or hypotheses face a greater likelihood of rejection during peer review, but the experience of meeting this rejection can discourage researchers from pursuing these ideas in the future. Chubin and Hackett (1990), for example, reported that from one-third to one-half of the scientists they interviewed dropped the specific line of research in their rejected proposals.

From the funder's perspective, however, high-risk, high-reward research poses a dilemma. On the one hand, thinking "outside the box" has demonstrably led to many valuable scientific discoveries and products. Yet for every one of these successes, there have been many costly failures. From a scientific point of view these failures may be useful, for part of scientific progress involves identifying and ruling out "dead-ends" or "dry wells." From an administrative perspective, however, these projects represent expenditures of scarce financial resources, sometimes over many years, with no easy way to curtail projects that were floundering. Thus the dilemma is how to encourage and promote innovative, novel research while maintaining some degree of administrative control over the element of risk involved in funding it.

1.1 The Phased Innovation Award Mechanism

The National Institutes of Health (NIH) is interested in developing, implementing, and evaluating creative funding mechanisms that support the pursuit of research that is innovative, novel, and potentially high-risk, high-impact. The Phased Innovation Award (PIA) mechanism (R21/R33) was established in 1999 to support the NCI *Exploratory Technologies for the Molecular Analysis of Cancer* program, and has since been used to fund a variety of technology development and research programs at nine of the 27 NIH Institutes and Centers (ICs).

While there have been some slight variations in its structure, the mechanism typically includes the following elements (**See Exhibit 1.1**).

Exhibit 1.1. Structural Elements of the Phased Innovation Award (PIA) Mechanism

- The research initiative is funded through a Request for Applications (RFA) or Program Announcement (PA).
- Grant review is conducted by a Special Emphasis Panel (SEP) or by the Center for Scientific Review (CSR).
- Preliminary data are not required for the grant application.
- The R21 component provides funding for a maximum of two years and is limited to a total of $275,000 in direct costs, with no more than $200,000 in direct costs for any one year.
- The R33 component provides funding for a maximum of three years and is limited to $300,000 per year in direct costs.
- Total grant support may not exceed five years.
- Applicants and program staff negotiate a set of quantitative milestones for the R21 phase of the project prior to Notice of Award.
- Transition to the R33 phase is dependent upon three criteria: meeting negotiated milestones; continued relevance of the project to the current research portfolio; and availability of research funding.

A unique feature of the mechanism is the use of negotiated milestones as part of the review and transition process. Although the use of milestones as part of the decision to continue funding is not a new feature of research (it is, for example, often part of pharmaceutical research), it had not been used at NIH prior to the creation of the PIA mechanism. The purpose of the milestones is to assure that there is a clear and mutually agreed upon basis for judging the success of the R21 phase of the project, and a necessary condition for transitioning to the R33 phase. The project must also exhibit continued scientific relevance in terms of the funding Institute's research portfolio, and there must be sufficient research funds available to provide funding for the R33 phase. Continued scientific relevance becomes important when the significance of the research may have been eclipsed by changes in the field, even if the milestones have been met.

1.2 Applications of the Phased Innovation Award Mechanism at NIAID DAIDS

Since 2006 NIAID DAIDS has utilized the PIA mechanism to support investigator-initiated AIDS research at the early stages of concept genesis and evaluation, specifically high-risk, high-impact studies with potential to advance the field toward an efficacious AIDS vaccine and/or microbicide. Two DAIDS initiatives[1] utilized the PIA mechanism: the Phased Innovation Award Program for AIDS Vaccine Research (AVR), and the Microbicide Innovation Program (MIP). The PIA Evaluation will use these two primary cases to examine the implementation and impact of the PIA mechanism at DAIDS. The evaluation will also inform other NIAID components (and NIH ICs) about the implementation process, challenges, and potential effectives of conducting a phased innovation award program. A brief overview of the AVR and MIP research initiatives is presented below.

1.2.1 AIDS Vaccine Research (AVR)

The AIDS Vaccine Research (AVR) initiative began in 2006 with the release of Program Announcement (PA) PA-06-109. The AVR initiative was described as a "…continuation and modification of the Innovation Grant Program for AIDS Vaccine Research." The PA notes that "this program will support prophylactic vaccine research projects that are innovative, novel, may be high-risk, high-impact and that exhibit the potential to advance AIDS prophylactic vaccine design or evaluation." Research priority areas identified in the initial PA included: approaches to enhance HIV vaccine-induced immunologic memory; vaccine approaches that induce mucosal immunity; improving HIV vaccines by harnessing innate immunity and regulatory T cell responses; methods to enhance antigen presentation/processing; vaccine approaches that use adjuvants or immune-modulators to increase or improve immunogenicity

[1] Throughout this report, the word *initiative* is used to refer to a set of related Funding Opportunity Announcements (FOAs) and their associated research grants.

of HIV vaccines; mobilizing antigen presenting cells to vaccination sites; novel approaches in nucleic acid vaccination; recombinant vectors; and pseudovirion approaches. Three PAs funded a total of 27 AVR projects led by 24 Principal Investigators (PIs).

1.2.2 Microbicide Innovation Program (MIP)

The Microbicide Innovation Program (MIP) also began in 2006 with the release of the Request for Applications (RFA) RFA-AI-06-005. The stated purpose of the new initiative was to support novel and under-explored strategies in the field of topical microbicides. The RFA stated that the MIP would support research in four broad areas:

(1) Discovery and exploration of microbicides (singly or in combination) directed against HIV and/or STIs linked to HIV acquisition;

(2) Emerging technologies or models that contribute to new and/or more efficient mechanisms for (i) assessing microbicide safety, efficacy and acceptability, (ii) discovery and exploration of new microbicide candidates, (iii) formulation and delivery of microbicide products, and (iv) validation of surrogate markers for safety and/or efficacy;

(3) Prevention strategies incorporating vaginally, rectally, and/or penile applied microbicides; and

(4) Development of behavioral and social tools that address product acceptability, initiation, and potential for sustained use.

The MIP initiative funded 61 projects led by 52 PIs.

Exhibit 1.2 summarizes the Funding Opportunity Announcements (FOAs) by year for the two initiatives.

Exhibit 1.2. Summary of AVR and MIP Funding Opportunity Announcements (FOAs)

AIDS Vaccine Research (AVR)	Microbicide Innovation Program (MIP)
• PA-06-109 (Released 12/23/2005, Expired 5/2/2006) • PA-06-519 (Released 8/9/2006, Expired 5/8/2009) • PA-09-119 (Released 3/6/2009, Expired 1/8/2011)	• RFA-AI-06-005 (Released 11/22/2005, Expired 1/27/2006) • RFA-AI-06-042 (Released 9/12/2006, Expired 12/21/2006) • RFA-AI-07-034 (Released 08/17/2007, Expired 11/21/2007) • RFA-AI-08-016 (Released 4/16/2008, Expired 7/26/2008) • RFA-AI-09-021 (Released 4/15/2009, Expired 7/11/2009) • RFA-AI-10-011 (Released 4/20/2010, Expired 7/10/2010)

1.3 Organization of this Report

This report describes the design and methodology, findings, and conclusions and recommendations from the *Process and Outcome Evaluation of the NIAID DAIDS Biphasic Grant Award Mechanism (R21/R33) to Fund High-Risk, High-Reward, Product Oriented Researc*h (also called the PIA Evaluation). The evaluation employs a mixed-method, multiple case study approach to the application of the PIA mechanism. To compare and contrast important variations, the evaluation focuses intensively on the two primary cases, the NIAID DAIDS AVR and MIP initiatives. To provide a broader contextual perspective, the evaluation also examines four other applications of the R21/R33 mechanism implemented at NIAID's Division of Microbiology and Infectious Diseases (DMID), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute on Deafness and other Communication Disorders (NIDCD). These applications vary in terms of the nature of the scientific problem addressed, the goals and objectives, structure and management of the initiatives, and the results observed by program leaders. This review allows examination of how variations in these variables affect the perceived value of the PIA mechanism for each Institute.

The report is organized as follows. **Chapter 2** describes the purposes of the evaluation, considerations that shaped the design, evaluation questions, and data collection approaches and methods. **Chapter 3** focuses on the two primary cases (AVR and MIP) and presents qualitative and quantitative findings based on multiple data sources including archival data abstraction and new data collection. **Chapter 4** provides the results from the cross-case analyses of the four secondary cases and compares them with results from the primary cases. **Chapter 5** discusses the strengths and limitations of the process and outcome evaluation, lessons learned, conclusions, and recommendations for future applications of the PIA mechanism.

2. Process and Outcome Evaluation of the NIAID DAIDS Phased Innovation Award Mechanism

A process evaluation is intended to examine whether a program is functioning as planned, while an outcome evaluation is designed to learn whether a program has achieved its ultimate goals. Since both the functioning of the PIA mechanism as currently conceived, and whether it achieved its goals are of interest, NIAID DAIDS elected to implement both a process and outcome evaluation. This chapter presents an overview of the purpose and objectives of the PIA Evaluation, considerations shaping the evaluation design, evaluation questions and sub-questions, and the mixed-methods approach applied in the evaluation.

2.1 Purposes of the Process and Outcome Evaluation

The purposes of the process and outcome evaluation are to examine the implementation and impact of the NIAID DAIDS PIA mechanism in order to inform the design of new initiatives within NIAID DAIDS as well as to inform other NIAID and NIH components of the potential effectiveness and challenges of utilizing the PIA mechanism. To these ends, the evaluation will also assess feasible modifications that will enhance the structure and program implementation.

2.2 Considerations Shaping the Evaluation Design

A mixed-method, multiple case studies design employing both qualitative and quantitative data collection and analysis, was utilized for this evaluation. The case studies conducted included the NIAID DAIDS PIA initiative as a whole (AVR and MIP initiatives combined), the AVR and MIP initiatives separately, and the other selected R21/R33 programs at NIAID, NCI, NIDA, and NIDCD. Two major challenges influenced the shape of the evaluation design. First, the primary focus of the evaluation was the R21/R33 Phased Innovation Award mechanism as implemented in NIAID DAIDS rather than the AVR and MIP initiatives specifically. The intent of the evaluation was not to compare the two initiatives. The difficulty with this approach is that it is impossible to know in advance whether the results from each initiative would be sufficiently similar to warrant combining them. In fact, given that the nature and maturity of the science varies between the two initiatives, one would expect to find differences. Therefore data from the AVR and MIP initiatives were examined separately as well as together. The second challenge was the nine-month timeframe (July 2013-April 2014) targeted for completion of the evaluation. In order to complete data collection and analysis necessary to answer the evaluation questions and sub-questions, strict adherence to an ambitious timeline was necessary.

2.3 Evaluation Questions, Data Collection Approaches, and Methods

As shown in **Exhibit 2.1**, three primary and 14 secondary evaluation questions were developed for this evaluation. Data collection methods included: archival data abstraction; bibliometric analyses; an online survey of PIA PIs; semi-structured in-person and telephone interviews with a sample of nine PIs, AVR and MIP Program Directors, NIAID Program Officers, NIAID and CSR (Center for Scientific Review) Scientific Review Officers, NIAID Grants Management Officers; interviews with Program Directors of four other PIA initiatives at NIH; and an Expert Panel review of the findings. A crosswalk between the data collection approaches and the evaluation questions is shown in **Exhibit 2.1.**

Exhibit 2.1. Crosswalk of Primary and Secondary Evaluation Questions with Data Collection Approaches

No.	Secondary Evaluation Questions	Archival Data	Bibliometric Data	Web-Based Pi Survey	Selected PI Interviews	Interviews With Federal Staff	Expert Panel
Primary Question 1. Is the PIA mechanism an appropriate mechanism for desired microbicide and prophylactic vaccine research?							
1A	*Is the mechanism budget (i.e., dollar limits) appropriate to support the research?*	✓		✓		✓	✓
1B	*Is the administrative burden on program management worth the effort?*					✓	
1C	*Is the R21/R33 mechanism more appropriate than the R01?*			✓		✓	✓
1D	*Are there differences in the types of applications received through the PIA mechanism versus R01 that could be attributed to the type of mechanism or set-aside funding?*	✓		✓	✓	✓	✓
1E	*Was the transition from the first to the second phase made efficiently without gaps in funding?*			✓	✓	✓	
1F	*What are the demographic and professional characteristics of successful and unsuccessful PIA applicants?*	✓					
1G	*Does the PIA mechanism create networks across the research portfolio?*	✓	✓	✓	✓		
1H	*Was the Funding Opportunities Announcement effectively communicated?*			✓	✓	✓	
Primary Question 2. Is the PIA mechanism a valuable component of the DAIDS research portfolio?							
2A	*Does the PIA program satisfy the need to advance new products through the development pipeline?*		✓			✓	✓

No.	Secondary Evaluation Questions	Archival Data	Bibliometric Data	Web-Based Pi Survey	Selected PI Interviews	Interviews With Federal Staff	Expert Panel
2B	*What was the impact of the PIA program on Division priority-setting and pace to change research directions?*					✓	

Primary Question 3. What is the overall impact of the PIA mechanism-supported milestone-driven research?							
No.	**Secondary Evaluation Questions**	**Archival Data**	**Bibliometric Data**	**Web-Based Pi Survey**	**Selected PI Interviews**	**Interviews With Federal Staff**	**Expert Panel**
3A	*Was there an impact on the targeted research areas?*	✓	✓			✓	✓
3B	*Did the program increase the research capacity of the field?*	✓	✓			✓	✓
3C	*Has the developmental pathway been accelerated?*		✓			✓	✓
3D	*Did the research promote multidisciplinary research?*	✓	✓	✓	✓	✓	✓

2.3.1 Archival Data Abstraction

The primary source of archival data was NIH's Query/View/Report (QVR) system, a tool designed for viewing and retrieving detailed information about grant applications and awards, which integrates information from IMPAC II (database of information on extramural applications and awards), the NIH Data Warehouse (database of financial obligations), and the National Library of Medicine's PubMed. QVR is accessed through the eRA IMPAC II system. The NIH RePORTER (Research Portfolio Online Reporting Tools Expenditures and Results) Tools were used to a limited extent to extract comparison data such as the NIAID overall R21 success rate and the NIAID R01 success rate. To obtain data on success rates for R21s across NIH by investigator status (new and experienced investigators), the NIAID Project Director requested a special run from the Office of Extramural Research (OER) Division of Statistical Analysis and Reporting (DSAR) which is responsible for RePORTER. Also used were the three AVR PAs and six MIP RFAs as well as other program-related materials provided by NIAID. In addition, the search feature on the home page of the NIH Office of Extramural Research (OER) was used to locate FOAs for R21/R33 programs across NIH.

The first step in the data abstraction process was to create a list of AVR and MIP applicants, both funded and unfunded. Searches were performed in QVR on all 9 FOAs and the following information was abstracted: PI name; application (project) number; the RFA/PA in response to which the application was submitted; the program initiative (AVR or MIP); funding status (funded or not); and transition status (still in the R21 phase, stopped at R21 phase, or transitioned to R33 phase).

Data were entered into an Excel file and lists of funded and unfunded projects and applicants by initiative were generated and reviewed by NIAID program staff. A total of 298 AVR and MIP applications were submitted by182 unique PIs between FY 2006 and FY 2011. Of the 182 unique PIs, 74 received funding for at least one application while the other 108 PIs were unfunded. The 74 successful PIs received 88

project awards. These lists served as the foundation for the archival data abstraction, bibliometric analyses, PI survey, and the semi-structured interviews with the sample of nine multiple award PIs. Four types of archival data were abstracted: demographic and professional characteristics of PIA applicants; science content of funded projects; other grant funding history of both successful and unsuccessful applicants; and key personnel and collaborations of successful applicants. The process for each data abstraction activity is described below.

2.3.1.1 Demographic and Professional Characteristics of PIA Applicants

Data abstraction related to demographic and professional characteristics of PIA applicants were designed to answer the evaluation question **"***What are the demographic and professional characteristics of successful and unsuccessful R21/R33 applicants*?"A QVR search was performed on each of the 182 PI names (74 funded (successful) and 108 unfunded (unsuccessful) and the following information was abstracted: application number; initiative (AVR or MIP); degree (PhD, MD/DVM or both); year of degree; year of residency (for MDs); investigator stage (new or early stage); whether the project involved animal research; whether primates were used; whether preliminary studies were described in the application; whether data from preliminary studies were included in the application; institution type (academic, non-profit, for-profit); and QVR institution code (institution of higher education; research organization; independent hospital; education organization other than higher education; other health, human resources, environment/community service organization; or other). Data were entered into an Excel file for analysis.

2.3.1.2 Science Content of Funded Projects

Data abstraction related to science content involved developing two classification systems to characterize the scientific coverage of the AVR and MIP initiatives. The goal was to develop a set of categories that could provide a broad description of research areas addressed by each of the funded projects. These categories were designed to highlight the types of research funded by each of the two initiatives. The results of this classification exercise were intended to inform the following evaluation question: "*Was there an impact on targeted research areas?"*Development of the project classification system began with a review of the targeted research areas outlined in the Funding Opportunity Announcements (FOAs) for each initiative.

In the AVR initiative, there were three Program Announcements (PAs). Targeted research areas were outlined in the *Research Objectives* section of each PA and were similar across the three PAs. All relevant areas of investigation contributing to the development of an efficacious prophylactic HIV/AIDS vaccine were encouraged including: structural studies of HIV envelope proteins to aid immunogen design; strategies to induce broadly reactive neutralizing antibodies to primary isolates; approaches to enhance HIV vaccine-induced immunologic memory; vaccine approaches that induce mucosal immunity; improving HIV vaccines by harnessing innate immunity and regulatory t cell responses; methods to enhance antigen presentation/processing; vaccine approaches that use adjuvants or immuno-modulators to increase or improve immunogenicity of HIV vaccines; mobilizing antigen presenting cells to vaccination sites; novel approaches in nucleic acid vaccination; recombinant vectors; and pseudovirion approaches. One PA also included evaluations of nonhuman primate virus challenge models (using SIV or SHIV) as a research area. The classification system used for the evaluation was based on one proposed by the AVR Program Director in a November 2012 presentation, and consists of five categories derived from the targeted research areas. Based on a review of project titles, abstracts, specific aims, and NIH-assigned RCDC (Research, Condition, and Disease Categorization) key words (those with the highest weights), projects were classified into the following five categories:

- Env-based Immunogens
- Mechanisms of Viral Control
- Vector Design

- Adjuvants (mucosal and other)
- Functional Genomics

In the MIP initiative, there were six funding announcements. **Exhibit 2.2** provides a description of the six areas of science targeted across the RFAs.

Exhibit 2.2 Targeted Research Areas Listed in MIP RFAs

Targeted Research Area	Description
Basic and Preclinical Research	Advancement of microbicides through preclinical and basic research, leading to new opportunities for microbicide development.
Discovery and Exploration of Microbicides	Discovery and characterization of microbicides (singly or in combination) directed against HIV and/or STIs that potentially contribute to HIV transmission and acquisition. These STIs include, but are not limited to Herpes Simplex virus, *Trichomonas vaginalis*, *Treponena pallidum*, human Papillomavirus, *Haemophilus ducreyi*, *Neisseria gonorrhoeae*, *Chylamydia trachomatis* and Bacterial Vaginosis.
Emerging Technologies or Models	Emerging technologies or models that contribute to new and/or more efficient mechanisms for (i) assessing microbicide safety, efficacy and acceptability; (ii) discovery and characterization of new microbicide candidates; (iii) formulation and delivery of microbicide products; and, (iv) validation of surrogate markers for safety and/or efficacy.
Prevention Strategies	Complex prevention strategies incorporating application of vaginal, rectal and/or penile microbicides.
Development of Behavioral and Social Tools	Development of behavioral and social tools that address product acceptability, initiation, and potential for sustained use. Tools must be designed to integrate with microbicide preclinical development and allow iterative improvements in the product or strategy employed. Success of these tools will hinge on behavioral, cultural, and contextual factors (e.g., product characteristics, perceived risk of infection, partner cooperation, etc.).
Nanotechnology	Nanotechnology approaches for all areas of interest.

The following classification scheme was developed based on the six targeted research areas and a review of project titles, abstracts, and specific aims.

- Basic and preclinical research
- Discovery and exploration of microbicides
- Emerging technologies or models
- Prevention strategies
- Development of behavioral and social tools
- Nanotechnology

2.3.1.3 Other Grant Funding History

Data abstraction related to other NIH grant funding history focused on subsequent grants for both funded and unfunded AVR and MIP investigators. Utilizing a QVR search on each investigator's name and subsequent access to their QVR Person Info Section and relevant SNAPs, the grant histories for each AVR and MIP investigator from the date of his or her earliest unfunded or funded grant application through FY 2013[2] were reviewed. If an investigator had applied to but had not been funded under AVR or MIP, the grant number for the earliest AVR or MIP application and the Summary Statement Release date were recorded. This date was used as the baseline date for reviewing the subsequent grant history. Where an investigator had been funded under AVR or MIP, the Summary Statement Release date of the funded

[2]Data on subsequent grants were collected during September 2013.

grant was used as the baseline date. Using the Summary Statement Release date, it was first recorded whether the investigator had obtained any subsequent grants (yes/ no). For each subsequent *funded* grant, information was recorded on the Grant number, Grant title, RFA/PA/PAR number (or whether the grant was unsolicited), Council Date/Award date, Activity code, Primary Institute funding the grant, Primary Program Class Code (PCC), and whether the research was considered to be focused on the targeted research field (PCC of A22 or A24). The data permit analyses at two levels—the number (and proportion) of PIA applicants obtaining one or more subsequent grants, and the characteristics of those grants.

2.3.1.4 Key Personnel and Collaborations

Data abstraction related to key personnel and collaborations focused on two aspects of collaboration: collaborators within and across the funded projects' research teams, and co-authors on publications produced by the funded projects in order to address three broad questions:

1. *What patterns of organizational collaboration are evident among the PIs and collaborators of the AVR and MIP projects?*
2. *What patterns of organizational collaboration are evident among the co-authors of project publications?*
3. *To what extent do the authorships of project publications reflect multidisciplinarity?*

For all funded AVR and MIP applications the following information was abstracted: PI organization; Application (Project) number; RFA/PA number; Transition status (still in R21 phase; stopped at R21 phase; transitioned to R33 phase); Collaborator; Collaborator role; Collaborator organization; and Program (AVR or MIP).

PI names, funded application numbers, RFA numbers, and status were obtained from existing project files. The remaining information was abstracted from the grant applications and subsequent annual progress reports found in QVR. Collaborators are defined as Key and Senior Personnel. The key personnel/other significant contributor pages of the grant application were the initial source of collaborator names, organizations and roles on the project. The PI's organization was also collected from this page. Next the Personnel Reports and All Personnel Reports found in annual progress reports were reviewed and any additional collaborators (including collaborator organization and role on the project) were added to the database. Budget pages in the grant applications and progress reports were sometimes used to confirm a collaborator's role. Technicians, research assistants, graduate students, and laboratory managers were not considered to be key personnel and thus were not included. In cases where a collaborator had increasingly more responsible roles over the course of the project, the most senior role was recorded. Varying similar roles were grouped into one category (e.g. postdoctoral scholar, postdoctoral fellow. and other postdoctoral positions were coded as "post doc"). A number of collaborators were designated as "Faculty." Collaborators with roles having specific academic ranks such as Professor or Associate Professor were coded as Faculty. The names of both PI and collaborator organizations were collected and then recoded to one of the following categories: academic; government; hospital; industry; and nonprofit.

The data for the analysis of co-authorship on publications were produced using the list of unique articles from each funded research project generated by the bibliometric analysis as of mid-September 2013. For each article, the listing of co-authors and the corresponding author affiliations was abstracted. Reviewing these data, for each publication, the following data were generated: number of co-authors; number of academic departments among the co-authors; number of institutions or organizations among the co-authors; and whether any of the institutions/organizations were: non-academic public/private organizations, federal agencies, or located outside the US.

Multidisciplinarity was defined in two ways for the analyses: the involvement of distinct co-authors from two or more *departments*, and the involvement of distinct co-authors from two or more *institutions or organizations*. These definitions meant that to meet either definition of multidisciplinarity, a publication had to have two or more co-authors.

2.3.2 Bibliometrics

For the bibliometric analyses, publications attributed to each PIA grant were identified using the Scientific Publication Information Retrieval & Evaluation System (SPIRES). The primary function of SPIRES is to match NIH extramural research grants with scientific publications from the NLM PubMed system. Publications and projects are linked in SPIRES using the grant number, also referred to as the project number. While the project number is stored in the eRA database in a standard format, the format of the project number in the PubMed system cannot be predicted. Over the years, changes in formatting and reporting practices in PubMed has resulted in a variety of project number formats being associated with publication records. In addition, authors continue to report grant numbers in a wide variety of ways. Boyack and Jordan give an example of a grant that was listed 16 different ways in different publications in PubMed. For this reason, SPIRES assigns case match scores ranging from 1 to 5 to each project number match with 5 being an exact match. Each match case score describes the reliability of the match from the standpoint of which combination of project number elements have been identified. For the PIA projects, grants having different activity codes (R21 and R33) with the same organizational code and serial number are given a score of 3 even though the numbers represent phases of the same project. Therefore publications with case match scores of 3-5 were included. The numbers of publications produced by searching SPIRES should be considered conservative as not all publications acknowledge their funding sources and not all journals are included in PubMed. NLM estimates that for 2008-2011, approximately three quarters of publications acknowledged at least one funding source. For AVR and MIP projects with publications, the following data items were abstracted into an Excel file: project number; article title with secure hyperlink; article title without hyperlink; SPIRES Match score[3]; SPIRES Journal Impact Factor (JIF); 2012 *Journal Citation Report* (JCR) JIF; 2012 JCR 5-year JIF[4]; number of citations by articles in PubMed Central archives; authors; year/month grant was awarded; publication year; publication date; journal; volume and page numbers; RFA/PA; program; and transition status.

This search strategy yielded 274 publications for the 88 AVR and MIP projects combined. Publications which were credited to more than one project were counted more than once for project-level analyses. For publication-level analyses 262 unique publications were abstracted.

2.3.3 Survey of Principal Investigators

An online survey was developed and fielded to obtain input from funded AVR and MIP PIs. The survey questionnaire was developed in collaboration with NIAID staff members and programmed into SurveyGizmo. Since 65 PIs would be invited to participate in the survey, clearance from the Office of Management and Budget (OMB) was required. The questionnaire was pre-tested by NIAID, NCI, and Madrillon staff members to determine respondent burden. On August 29, 2013 the NIH Office of Human Subjects Research Protection (OHSRP) made a determination that the survey was exempt from Institutional Review Board (IRB) review. On September 5, notification of approval for the survey was received through the OMB/PRA (Paperwork Reduction Act) Fast Track mechanism.

[3] Publications abstracted from SPIRES appeared in 101 journals. For 75 of the 101 journals, the journal impact factor was missing from SPIRES. When consulted on the problem, SPIRES' staff reported a software glitch and provided a direct link to Journal Citation Reports® (JCR). Therefore JCR was used as the source of JIFs.

[4] Thompson Reuters Journal Citation Reports® was the source of the Journal Impact Factors and 5-Year Journal Impact Factors. An alternative approach to the use of the 5-Year Journal Impact Factors was to use the Crown index, which represents the ratio of the expected citation rate to the observed citation rate; however, time and cost considerations precluded the use of this approach.

The survey questionnaire contained 36 questions, some with multiple items. Topics covered in the survey included: adequacy of the research budget; adequacy of the grant timeframe; use of negotiated milestones; advantages and disadvantages of the R21/R33 mechanism; goals of the mechanism; communication about the FOAs; roles of the Program Officer; the transition process; obtaining new grants and other funding; and forming new collaborations.

Sixty-five PIs who received funding for a single PIA project constituted the survey sample. Nine PIs with multiple awards were excluded. The survey was launched on October 1, 2013 and closed on October 29, 2013. One of the early AVR PI's could not be located (the invitation email bounced). Therefore 64 PIs received the survey: 61 completed the survey for a response rate of 95%. Average response time for completing the survey was 20.2 minutes.

2.3.4 Interviews with a Sample of Principal Investigators

Nine PIs received more than one award: one PI had four AVR awards; six had two or more MIP awards; and two had one AVR and one MIP award. Since these PIs have a unique and valuable perspective and completing the survey for multiple awards would have been burdensome, semi-structured telephone interviews were conducted. The semi-structured interview protocol was finalized after the PI survey had been fielded and the results examined in order to follow-up on interesting findings and problem areas. The interview protocols were personalized to each PI based on grant program (AVR, MIP, both), number of awards (2-4) and number of grants transitioning to the R33 phase (0-3). PI interviews were conducted between December 2013 and January 2014 with a 100% response rate. The average length of an interview was 48 minutes.

2.3.5 Stakeholder Interviews with NIAID Program Officers, Grants Management Officers, and Scientific Review Officers

Since the PIA mechanism involves negotiating milestones and a transition process, it may place more of an administrative burden on program, review, and grants management staff than programs that use other grant mechanisms. To gain their perspectives on the mechanism, semi-structured interviews were conducted with MIP and AVR Program Officers, MIP and AVR Scientific Review Officers, and Grants Management Officers. Since the AVR program was funded through PAs, the applications were reviewed at the Center for Scientific Review (CSR). Therefore the AVR Scientific Review Officers were from CSR. All other staff members were from NIAID. The semi-structured interview protocols covered the following topics: career history at NIH, and then at NIAID or CSR; degree of involvement in the PIA initiative; experience with other R21/R33 initiatives as well as other grant mechanisms; administrative burden; the process for transition from R21 to R33; and suggestions for ways to improve the implementation of the PIA mechanism. Interviews were conducted in November and December, 2013. The average length of the interviews was 43 minutes for Program Officers, 18 minutes for Scientific Review Officers, and 12 minutes for Grants Management Officers. Of the 15 people invited for interviews, 14 participated for a response rate of 93%.

2.3.6 Interviews with AVR and MIP Program Directors

In-depth, face-to-face interviews were conducted with the AVR and MIP Program Directors. The average length of the interviews was two hours. The interview protocols inquired about career history, familiarity with other grant mechanisms, the PIA milestone negotiation process, the transition process, and administrative burden. Additional questions focused on the state of the science targeted by the PIA mechanism, the rationale for using the mechanism, the structure of the program, and the impact of the mechanism on AVR or MIP goals.

2.3.7 Case Studies of the Use of the PIA Mechanism at NIAID, NCI, NIDA, and NIDCD

In order to compare the implementation process of the PIA mechanism by NIAID DAIDS for the AVR and MIP initiatives, case studies of four additional PIA programs across NIH were performed. The four programs shown in **Exhibit 2.3** were selected in collaboration with NIAID staff based on features of the programs such as length of time in existence, dollar limits, and maximum years of funding available.

Exhibit 2.3. Selected Programs at NIH Using the PIA Mechanism

IC	Name of Program	FOA	Grant Mechanism	Dollar limits	R21 & R33 phases	Maximum Time For Project
NCI	Innovative Technologies for the Molecular Analysis of Cancer	PAR-01-104; PAR-99-100	R21/R33, R33	$100,000/ year	No limit	4 years
NIDA	Secondary Analyses for Substance Abuse Research	RFA-DA-09-020	R21/R33	$260,000/2 years	$240,000/ year for 2 years	4 years
NIDCD	Research on Hearing Health Care	RFA-DC-14-001; RFA-DC-12-003; RFA-DC-10-002	R21/R33	$275,000/2 years	$400,000/ year	5 years
NIAID	Host-Targeted Interventions as Therapeutics for Infectious Diseases	RFA-AI-11-032	R21/R33	$275,000/2 years	$300,000/ year	5 years

A semi-structured interview protocol was employed similar to the protocols used for the AVR and MIP Program Directors and tailored to each specific program. Topics covered included: career history at NIH and their IC; familiarity with other programs that used the PIA mechanism; the scope and size of their program; the nature of the science being targeted by the program; rationale for using the mechanism; goals of the program; the structure of the R21/R33 grants; reasons for the particular dollar and time limitations; their approach to transitioning to the R33 phase; whether grant reviews were conducted by CSR or an IC Special Emphasis Panel (SEP); challenges or problems with the structure; the milestone negotiation process; administrative burden; and the impact of the mechanism on program goals. Interviews were conducted with the four Program Directors between December 2013 and January 2014 with the length of the interviews ranging from 90 minutes to two hours.

3. Findings from the Process and Outcome Evaluation of the NIAID DAIDS Phased Innovation Award Mechanism

This chapter presents results from the process and outcome evaluation to examine the implementation and effects of the NIAID DAIDS Phased Innovation Award (PIA) mechanism. The results are presented in four sections. The first section (3.1) describes the nature of the scientific problems for which the PIA mechanism was used at NIAID DAIDS and examines the structure and implementation of the AIDS Vaccine Research (AVR) and Microbicide Innovation Program (MIP) initiatives. Section 3.2 presents the analysis of process evaluation findings focusing on the design and implementation of the PIA mechanism. Section 3.3 presents findings on program participation, including funded and unfunded applicants, new and established investigators, and project teams. The final section (3.4) presents findings on the effects of the PIA mechanism including how the mechanism is building research capacity within the AIDS vaccine and microbicide research fields.

Throughout this chapter, the focus is on the use of the PIA funding mechanism as applied in the AVR and MIP initiatives. The findings show, while there were broad similarities in how these two initiatives were structured and how they implemented the PIA mechanism, there were important differences as well. These differences resulted in different experiences with the mechanism, and led to several lessons learned about how it could be applied in future initiatives.

Data and discussions responsive to specific Evaluation Questions are indicated by a text box that identifies the questions(s) to which the data and findings correspond.

3.1 Nature of the Scientific Problems at DAIDS for which the Phased Innovation Award Mechanism Was Used

In general terms, research on the development of vaccines for AIDS can be described as primarily oriented toward basic research, whereas research on the development of topical microbicides is highly product oriented. This distinction has important implications for the degree to which the choice of the PIA mechanism provides a "good fit" as a funding tool for the AVR and MIP initiatives.

This discussion draws upon three sources of data: interviews with the AVR and MIP Program Directors, published literature, and archival data on the various funding announcements released for AIDS vaccine and microbicide research.

3.1.1 AIDS Vaccine Research

In the late 1980s, the policy community in the US began to awaken to the realization that HIV/AIDS was a serious and costly public health problem. Faced with growing public pressure to take action against HIV/AIDS, policy makers turned to the scientific community to seek quick solutions for the treatment and prevention of this disease. On the prevention side, this took the form of a search for a vaccine that could halt the spread of the disease while other researchers sought treatment options. At that time, there was considerable false optimism about the likelihood of successfully identifying an effective vaccine; some politicians were promising a vaccine within "three years."

Three years became five years, then ten, and even longer. The search has been characterized by many setbacks and disappointments. At the time the AVR initiative was launched in 2006, 35 candidate vaccines had been tested in more than 65 Phase I and Phase II clinical trials, and two Phase III clinical trials had been completed with a third in progress. This led the authors of one review to conclude that "…we are still years away from an effective HIV vaccine" (Girard et al., 2006). As the research community reflected on its past setbacks, they identified several factors that continued to challenge research, including the high genetic variability of the virus, the lack of knowledge of immune correlates of protection, the difficulty of generating broadly neutralizing antibodies, the absence of relevant and

predictive animal models, and the challenges of mounting multiple large-scale clinical trials in developing countries. These challenges underscored the need for additional basic research. Fundamental questions remained unanswered, such as how immune cells are mobilized to the site of infection, why broadly neutralizing antibodies are uncommon and how they can be elicited, and what are the correlates of vaccine-induced immune protection. New tools and animal models were needed as well. While much early research had focused on identifying and developing candidates for vaccines, it was recognized that additional basic research would be necessary to provide a better understanding of how and why earlier candidates had failed and what was needed to promote better candidates for the future (Fauci et al., 2008).

At this same time, a different challenge was emerging. NIH in general was entering a period of flat budgets following a five year interval which saw the NIH budget double. Dr. Anthony Fauci and his colleagues noted that the purchasing power of research dollars had decreased by more than 13% since 2003. This had particularly serious consequences for AIDS vaccine researchers who sought to work with nonhuman primate animal models.

3.1.1.1 AIDS Vaccine Research Initiatives at NIAID

The program history of the AVR initiative is illustrated below in **Exhibit 3.1**. At the recommendation of the AIDS Vaccine Research Committee, NIAID DAIDS created the *Innovation Grant Program (IGP) for Approaches in HIV Vaccine Research* with the release of PA-97-042 in 1997. This program solicited applications for research projects involving ***"…a high degree of innovation, risk, and novelty—as well as a clear promise of helping to improve vaccine design or evaluation—in the following three general areas: (1) the structure/ function of HIV envelope protein; (2) creation/improvement of animal models for vaccine evaluation and pathogenesis studies; and (3) mechanisms of directing antigen processing in vivo***." The program used the R21 mechanism, and provided up to two years of support at a maximum of $150,000 per year in direct costs. Over the course of the next nine years (through 2006), the IGP funded 292 awards.

In 2006, the IGP program was replaced by the AVR Phased Innovation Awards initiative which used the R21/R33 mechanism. The initiative was grounded in a clear scientific agenda that highly favored research on neutralizing antibodies.

In 2011, NIAID DAIDS replaced the AVR initiative with a new program called the *Innovations for HIV Vaccine Discovery Program* (IHVD) (RFA-AI-11-018). The IHVD Program replaced the earlier R21/R33 mechanism with a four-year modified R01 grant. The FOA strongly emphasized the importance of innovative applications that would support bold and transformative research, and relaxed the usual requirement for substantial preliminary data. The FOA was reissued in 2013 as RFA-AI-13-007.

Exhibit 3.1 Program History of the NIAID DAIDS AVR Initiative

3.1.2 The Microbicide Innovation Program

Topical microbicides "consist of products that attack cellular or viral targets and prevent infection of target cells or the replication of the virus, resulting in decreased virus transmission and acquisition on HIV" (Buckheit et al., 2010). This field is a fairly "young" research field, although research has been ongoing for nearly 20 years. As was the case for AIDS vaccine research, the search for topical microbicides has also been marred by many setbacks. In their review of the field, Friend and Kiser (2013) suggest that microbicide research has developed through three stages. The first research stage explored the feasibility of using broad spectrum detergents and polyanions to prevent transmission of HIV-1 vaginally. Research on this question continued through the mid-2000s, and showed that these products were either ineffective or actually increased transmission. A second stage of research focused on products that contained the antiretroviral tenofovir. Results from studies of products containing tenofovir showed that the use of gels provided partial protection when used prior to intercourse, but larger trials indicated that adherence to their appropriate use was unacceptably low.

Friend and Kiser identified a third stage of research which is currently in progress. This stage represents an attempt to reflect upon and learn from some of the earlier failures, and emphasizes the development of products women are willing to use, such as intra-vaginal rings and vaginal gels delivered by tablets or films. Important issues in this stage include product acceptability and investigations of combinations of topical microbicides.

One of the implications of the discouraging track record of past research on topical microbicides is that peer review panels grew increasingly skeptical about this research. As described by the MIP Program Director, prior to the creation of the MIP initiative, R01 grant applications on topical microbicides generally scored poorly in peer review due to concerns about feasibility... "***We had no proof of concept that a microbicide would work. We had one trial that was continuing and we did not know what it would show. We also had other trials that were failing. So naturally, peer review was saying 'Well, can you show that it works over here and hits a target?' There was doubt that this research would have any value…the enthusiasm goes down because there is that doubt…it's risky***." One consequence of reviewer skepticism was that at the time the MIP initiative began in 2006, the Program Director had only seven investigator-initiated research grants in his research portfolio (one R21, four R01s, and two Small Business Innovation Research [SBIR] grants).

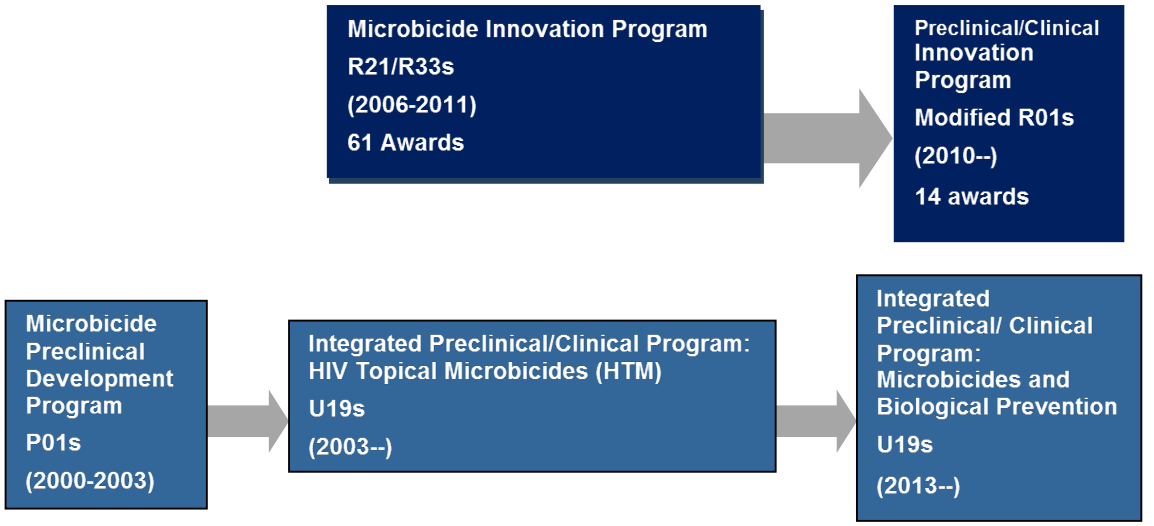
The topical microbicide research field is very product oriented, in contrast to the more basic science nature of AIDS vaccine research. One implication of this product orientation is that the creation of a sustainable developmental pipeline is especially important—it ensures that if candidate microbicides fail at later stages in the developmental process, there is an adequate supply of new candidates moving through earlier stages that are ready to take their place. At the time MIP began in 2006, this pipeline was largely empty, and one of the MIP Program Director's main goals for this new initiative was to build this pipeline and ensure that it was well-stocked at all stages. A second implication is that there has been considerable participation by researchers from private industry.

3.1.2.1 Microbicide Research at NIAID

The program history of the MIP initiative is shown in **Exhibit 3.2**. This shows that there were two separate tracks of solicited[5] grant programs that supported topical microbicide research. The MIP initiative was created in 2006; initial funding occurred in 2007. There were six cohorts of MIP projects; the last cohort was funded in 2011. There were a total of 61 MIP projects, led by 52 PIs. After the last funded cohort in 2011, the MIP initiative was ended.

[5]Solicited grants are those for which a specific Funding Opportunity Announcement (FOA) exists, contrasted with unsolicited grants (also called investigator-initiated grants) which do not respond to a given FOA.

Exhibit 3.2. Program History of the NIAID DAIDS MIP Initiative



A separate microbicide research program also operated during this period. This program began in 2000 as the Microbicide Preclinical Development Program (RFA-HD-00-018) which funded P01 project grants. In 2003, this program was renamed the Integrated Preclinical/ Clinical Program for HIV Topical Microbicides (IPCP-HTM), and the funding mechanism was changed to the U19 Cooperative Agreement mechanism. This program continued under several subsequent RFAs, most recently RFA-AI-12-003. When the MIP initiative began in 2006, there were 11 projects funded by the IPCP-HTM. In 2013, a second IPCP program called Microbicides and Biomedical Prevention (IPCP-MBP) began, also using the U19 mechanism. At the time of this report no projects have been funded under this program.

3.1.2.2 Scientific Goals of the Microbicide Innovation Program

As noted earlier, the MIP initiative was designed to stock the topical microbicide developmental pipeline with promising candidates. In particular, the initiative was intended to provide opportunities for submission of innovative and high-risk, high-reward approaches that would survive the risk-averse review process that had resulted in so few unsolicited topical microbicide applications in the past. The new initiative would support the development of: new and unique microbicide products, candidates, and strategies; novel approaches for modeling safety, efficacy, use, and acceptability of topical microbicides; and the integration of new technologies and methodologies into the topical microbicide pipeline. The MIP Program Director stated that "***the goal in MIP was to create a protected environment where we could create the microbicide pipeline, make a robust pipeline, and develop the new technologies, processes, and models that will support that pipeline and development in general***."

3.2 Structural Design and Implementation of NIAID DAIDS Phased Innovation Award Mechanism

This section examines the structural elements and implementation of the PIA mechanism in the AVR and MIP initiatives. **Exhibit 3.3** shows the structural elements of the two initiatives. The main differences occur in terms of the type of funding announcement, the number of opportunities to submit grant applications per year, the use of CSR peer review panels versus NIAID peer review panels, and the number of times per year that transition reviews took place.

Exhibit 3.3. Structural Elements of the AVR and MIP PIA Initiatives

Structural Element	AVR Initiative	MIP Initiative
Type of FOA	PA	RFA
Number of Grant Submission Periods per Year	3	1
Scientific Review	CSR	NIAID SEP
Duration and Funding Limits: R21 Phase	Two years maximum; $275,000 maximum in total direct costs with no more than $200,000 in any one year	Two years maximum; $275,000 maximum in total direct costs with no more than $200,000 in any one year
Duration and Funding Limits: R33 Phase	Three years maximum; $300,000 maximum in total direct costs per year	Three years maximum; $300,000 maximum in total direct costs per year
Number of Transition Review Periods per Year	3	1
Cross-Division versus Within-Division Program Management	Within Division (DAIDS)	Within Division (DAIDS

The findings reported in this section are drawn from the PI survey, PI interviews, and interviews with AVR and MIP Program Directors, NIAID Program Officers, Grants Management Officers, and Scientific Review Officers. The discussion follows the progression of program implementation and administration steps shown in **Exhibit 3.4**.

Exhibit 3.4. Program Implementation

3.2.1 Decision to Use the PIA Mechanism

For both the AVR and the MIP initiatives, the decision to use the PIA mechanism was made after careful deliberation and consultation with other individuals. In both cases, the Program Directors needed to develop a set of arguments that would persuade others within DAIDS, as well as the NIAID Council, which would provide the final approval. This was especially important since knowledge about the funding mechanism was not widely available.

The AVR Program Director weighed several factors in his decision-making process. Previous experience with R21 grants had persuaded him that there was a need for a rapid transition to developmental funding for projects that had successfully demonstrated 'proof of concept.' Additional factors considered were the possibility of future reductions in the NIH and NIAID research budgets, and his dissatisfaction with alternative funding mechanisms for the scientific goals he wanted to achieve. In particular, he wanted to create an opportunity to solicit and fund high-risk, high-reward research.

The reasons the MIP Program Director gave for selecting the PIA mechanism differed somewhat from those of the AVR Program Director. He noted that the topical microbicide research field needed innovative approaches, but he was aware that the types of applications he wanted to solicit might not be able to provide strong preliminary data. At the same time, however, he wanted to control the risk of funding an unsuccessful project by halting funding at the R21 stage. By building this level of control into

the funding process, he hoped to encourage reviewers to move innovative projects forward with higher priority scores.

Following approval of the use of the R21/R33 mechanism at DAIDS, NIAID convened a working group comprising representatives from DAIDS and other NIAID Divisions. This working group drafted a set of Standard Operating Procedures (SOP) that established broad procedures for conducting the milestone negotiation process and the transition evaluations.

3.2.1.1 Weighing the Pros and Cons of Alternative Grant Mechanisms

Evaluation Questions

1C. Is the R21/R33 mechanism more appropriate than the R01?

1D. Are there differences in the types of applications received through the PIA mechanism versus the R01 that could be attributed to the type of mechanism or set-aside funding?

The AVR and the MIP Program Directors and their Program Officers discussed some of the strengths and limitations of alternative grant mechanisms that might have been used in place of the R21/R33 mechanism. The major alternative funding mechanism was the R01 research project grant which provides from one to five years of project funding without a dollar limit, although proposals with annual budgets of more than $250,000 in direct costs must submit detailed budgets for each project year.

The AVR and MIP Program Directors and DAIDS Program Officers interviewed, were asked about whether there might be differences in the types of research ideas and approaches that might be packaged as an R01 grant versus an R21/R33 grant. Three inter-related themes emerged from the responses.

R01 applications are less likely to present ideas that are innovative and high-risk, high-reward. One interviewee stated that "***the R01 application is averse to risk by definition. R01 applications are aimed at incremental innovation.***" As discussed earlier, reviewers on scientific review groups tend to be highly conservative and therefore skeptical of innovative approaches or hypotheses.

The R21/R33 mechanism provides greater control over the risk associated with innovative research. One interviewee responded: "***the chief advantage of this program [the R21/R33] is that you can get reviewers to consider ideas that are more innovative since they feel that they are starting investigators off on a smaller budget and are only increasing the budget if the early stages of the project look promising***." While R01s can move projects from bench work to product development, they can be very costly (research costs can range from $500,000 to $1 million for five years of work). The R21/R33 incorporates a built-in mechanism (the negotiated milestones and the transition review) which allows unproductive work to be halted after a two year expenditure of around $275,000 in direct costs. Thus, both the reviewers and the Program Officers can feel more comfortable in funding innovative projects.

The R01 requires strong preliminary data, which may not exist for very new ideas and approaches. Technically, the FOAs for the AVR and the MIP initiatives indicated that preliminary data were not necessary. Both Program Directors mentioned this as a possible strength of the R21/R33 mechanism. One Program Director noted that "***no one had done an R01 without preliminary data. No one had such a program; it wasn't even on the radar screen. If investigators had to present preliminary data, we wouldn't get the innovative ideas we were looking for. This wouldn't have been a good match***." However, both Program Directors acknowledged that, in their contacts with applicants during the application phase, they advised applicants to include at least some preliminary data with their applications, and all but a few did so.

The nine PIs interviewed offered several perspectives on the differences between R01 and R21/R33 applications. One PI noted that the availability of the R21/R33 grant "…***allows a basic scientist like***

myself to test out ideas relatively early in an applied development program." A second PI offered this comment on the effect of the R21/R33 on the pace of his animal research: ***"the first two years of in vitro experiments, if successful, would allow us to collaborate with people more experienced with animal models for the R33 phase to conduct in vivo testing. The R01 would not allow us to move into animal models that quickly***." Echoing the perspective of program staff on the issue of preliminary data, a third PI said that "***for the R01, the bar is set very high. You have to have specific aims and preliminary data. To prepare the application, you have to have a really coherent story that people will buy with sufficient preliminary data, and that is difficult. The R21/R33 grant overcomes this problem***."

One investigator summarized some of these differences. ***"I think there are huge differences between the R21/R33 and the R01 because the R21/R33 allows you to stick your neck out to try to push things. You can say 'I have a new method and I have a hint that it's working. So in the first two years I'll develop this method, then in the last years I'm going to use this method to ask these really important questions.' Method development is really difficult with an R01 because it means you are trying to develop a method. If it works, that's great, but if it doesn't, the R01 money is wasted. So having checkpoints at two years allows you to write a different application. It allows applicants to be ambitious, push the envelope, argue against paradigms, and drive the field forward. A lot of the field is less ambitious than it should be but that is driven by the conservative nature of the R01 mechanism."***

The second funding mechanism considered was the use of the R21 mechanism alone. The R21 was originally introduced as an exploratory/developmental grant mechanism that provided limited funding for a two-year period during which an investigator could demonstrate a new idea or approach and collect preliminary data that could be used for a subsequent major grant, such as an R01, P01, U01, or U19 project grant. The problem with using the R21 grant mechanism alone was that when the initial funding ends, the investigator has to pursue a new grant. One of the PIs interviewed described the problem: "***One disadvantage of the R21 by itself is that by the time you get results for the R21, you have to apply for another grant which causes gaps in your research. Gaps are worse than telling investigators to hold off on pushing their research forward. The people with whom you have collaborated, who have special expertise, have to move on or sometimes you don't have the extra money to keep things crawling along until funding becomes available.***"

These responses suggest that the PIA mechanism is more appropriate than the R01 in instances where the nature of the research is innovative and high-risk/high-reward, preliminary data may not be much in evidence, building and maintaining a specialized research project team is important, and program staff members want to retain some degree of control over the degree of risk inherent in the proposals. Investigators are also receptive to the mechanism because it enables them to test the feasibility of ideas or approaches relatively quickly and relatively early in the developmental process. Closely related to this finding is the idea that if a new idea or approach can be shown to be feasible within an initial two-year period, the research can move forward to the next developmental stage without the gap that would be caused by the need to locate funding for a follow-on grant.

3.2.1.2 Perceived Advantages and Disadvantages of the PIA Mechanism

DAIDS program staff interviewees, multiple grant PI interviewees, and PI survey respondents described the perceived advantages and disadvantages of the PIA mechanism. **Exhibit 3.5** shows the similarities and differences in the perspectives of program staff and PIs.

Exhibit 3.5. Perceived Advantages and Disadvantages of the PIA Mechanism

AVR & MIP Program Directors	AVR & MIP Program Staff	Multiple Grant PI Interviewees	PI Survey Respondents
ADVANTAGES: ▪ Makes the research process more efficient ▪ Ability to support high-risk, high-reward innovative research ▪ Creates a safe harbor for this type of research via Special Emphasis Panels (MIP) ▪ Creates standing yearly mechanism to support prevention research	**ADVANTAGES:** ▪ Manages funding of innovative research, allowing only successful research to continue ▪ Terminates unsuccessful research early ▪ Unburdens reviewers from the constraints of previous research and risk when considering innovation ▪ Provides a faster pace through the product developmental pipeline	**ADVANTAGES:** ▪ Provides seed money for proof-of-concept evaluations for high-risk research ▪ For transitioning projects, it avoids gaps in funding and holds a productive team together ▪ Promotes collaborations between basic scientists and scientists working further up the pipeline ▪ R33 funding provides more funding per year than typical R01 ▪ Allows NIAID to fund more projects up front	**ADVANTAGES:** ▪ Scientific review by Special Emphasis Panel (MIP) ▪ Significantly increased funding in R33 phase ▪ Opportunity to negotiate milestones ▪ Encourages novel research that may be high-risk, high-reward ▪ Obtaining R33 funding without having to write a new application ▪ Multiple receipt dates (AVR) ▪ Did not require preliminary data
DISADVANTAGES: ▪ Time required of program staff to adequately oversee the program	**DISADVANTAGES:** ▪ Small budget and short time frame for initial R21 phase can hinder some types of research or the number of applicants ▪ Some reviewers find it difficult to give up funding control (for transition), handing it over to the program office ▪ Heavier workload for scientific review and program staff	**DISADVANTAGES:** ▪ The five-year structure and the uncertainty of transition means that you have to be very conservative in your approach to developing the product or technology ▪ Not being able to move funds from one year's budget to another as the science dictates	**DISADVANTAGES:** ▪ Too few funds/too little time for first phase (R21) ▪ Uncertainty about R33 transition ▪ Difficulties in working with milestones ▪ Predicting long-term research progress in advance

Looking across the three respondent categories, there are some similarities as well as differences. For example, program staff and multiple grant PIs agree that the PIA mechanism provides important seed funding to test the feasibility of new ideas and approaches in AIDS vaccine and topical microbicide research. The strongest perceived disadvantage from the program staff perspective is the time required to oversee the projects, particularly in terms of negotiating milestones and transition reviews. By contrast, the multiple grant PIs perceived the mechanism as a way of encouraging new project collaborations, minimizing gaps in funding between the exploratory and developmental phases, and allowing NIAID to fund more projects up front. The chief disadvantage mentioned by the multiple grant PIs was the uncertainty over transition from the R21 to the R33 phase.

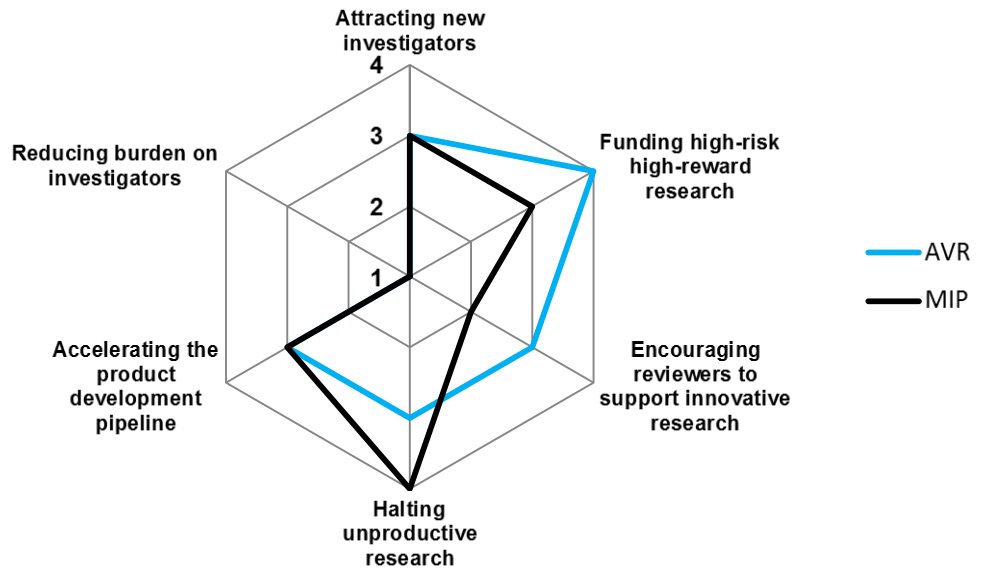
3.2.1.3 Goals of the AVR and MIP PIA Initiatives

The preceding discussion shows that the decision to utilize the PIA mechanism to fund the AVR and MIP initiatives followed a decision-making process that took into account the possible advantages and disadvantages of alternative grant mechanisms such as the R01 research project grant and the use of the R21 exploratory grant alone. The AVR Program Director consulted with a colleague from the NCI who was using the mechanism with NCI's IMAT program, while the MIP Program Director considered these

factors as well as a stated desire to control the degree of risk that reviewers and program staff might perceive in funding high-risk, high-reward research. Both also weighed the relative advantages and disadvantages that might arise from using the PIA mechanism.

The Program Directors also considered the various scientific and administrative goals they hoped to achieve through their initiatives. As a way of identifying and exploring the relative importance of various goals, they were asked to rate the relative importance of a list of goals the evaluators derived from discussions with members of the NIAID DAIDS staff collaborating on the evaluation. Based on group discussions, a list of six goals were identified:(1) attracting new investigators, (2) funding high-risk, high-reward research, (3) encouraging reviewers to support innovative research, (4) halting unproductive research, (5) accelerating the product development pipeline, and (6) reducing burden on investigators (by allowing them to submit their R21 and R33 applications as part of a single grant application). Program Directors were asked to rate each possible goal on a scale from one to three, where one represented "no importance," two represented "somewhat important," and three represented "very important." After rating all of the goals, the Program Directors were asked to identify the single most important goal from among the six. This was assigned a rating of four. The results are shown in **Exhibit 3.6.**

Exhibit 3.6. Relative Importance of Scientific and Administrative Goals for AVR and MIP R21/R33 Initiatives



The ratings are presented in the format of a radar chart—a graphic device that shows a profile across multiple dimensions that is measured on the same scale. The AVR profile (in aqua) shows that the most important goal for the AVR initiative is funding high-risk, high-reward research and the least important goal is reducing burden on the investigators; all other goals are considered 'very important.' The MIP profile (black) shows that the most important goal is halting unproductive research, while the least important goal is reducing burden on investigators, followed by encouraging reviewers to support innovative research. Other goals such as attracting new investigators, funding high-risk, high-reward research, and accelerating the product development pipeline, are considered as 'very important.'

3.2.2 Communicating the Funding Opportunities

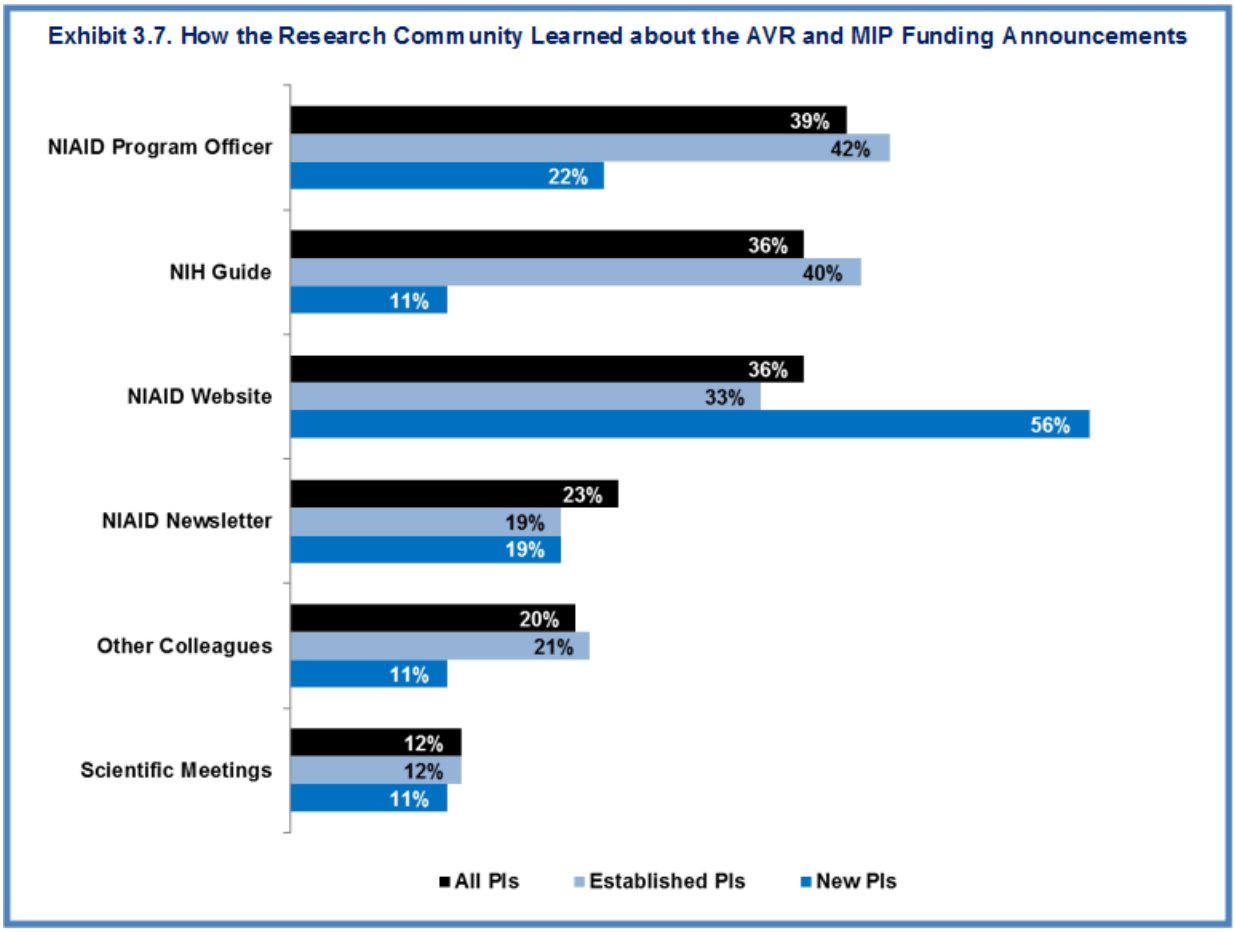
Evaluation Question

1H. Was the Funding Opportunities Announcement effectively communicated?

PI survey respondents identified specific information channel(s) through which they learned about AVR and MIP FOAs. The results are shown in **Exhibit 3.7**; note that survey respondents could (and did) choose more than one information channel.

The results underscore the importance of the Program Officer in the research process, as Program Officers were the most frequently endorsed source of information on the funding announcements. Because both initiatives hoped to attract new investigators into their respective fields, survey responses were compared in terms of established investigators versus new investigators (defined as investigators within ten years of their most recent research degree and who had not yet obtained an award for a major grant such as an R01). The findings show that PIs who are in the early stages of their research careers use information channels differently from those who are more established investigators. New investigators are more likely to rely heavily on the NIAID website, while established investigators are more likely to talk with Program Officers and use the NIH Guide more heavily.

Exhibit 3.7. How the Research Community Learned about the AVR and MIP Funding Announcements



Once a research investigator has learned about the existence of a funding opportunity, it is important that he or she clearly understands the application requirements. This is particularly true for applications that present new requirements. Evidence from the multiple grant PI interviewees and PI survey respondents

indicates that the funding announcements did clearly describe the requirements for the R21/R33 grant applications. As one PI who was funded by both initiatives stated, "***I thought the announcements were very well organized for both grant programs. The written funding announcement that was distributed and placed on the website was very good, and the Program Officers were very helpful at different stages to develop a plan.***" The PI survey included questions about specific elements of the program announcements. All respondents either strongly agreed or agreed that the application requirements were clearly explained and that priority target research areas were clearly identified. Almost as many respondents (95%) strongly agreed or agreed that the requirements for milestones were clearly explained. However, a slightly smaller percentage (79%) strongly agreed or agreed that criteria for R33 funding were clearly explained. These criteria included meeting the negotiated milestones, continued scientific relevance, and the availability of funds. Given that almost all respondents stated that they understood the milestone requirements and that the availability of funds is almost always a criterion in publicly-funded research, it is likely that the second criterion (continued scientific relevance) was somewhat more problematic. This is partially confirmed by the response of one multiple awards PI, who noted that "***I think it was clearly indicated what we needed to do in order to transition to the R33. As far as the parts that were not clear…there were obviously a lot more R21s than NIAID was capable of transitioning to the R33 phase. So you could successfully meet the milestones, but NIAID funding and other strategic directions came into play with the decision to transition…That's obviously a gray zone***."

3.2.3 The Application Process

The application process for the PIA R21/R33 mechanism involved many of the same challenges that applicants typically face in applying for other grants, with the additional consideration of the inclusion of milestones. Multiple award PIs were asked about the amount of time required to develop and prepare an R21/R33 application. Respondents were divided in their opinions; one noted that "***for the AVR, it wasn't much longer than a regular R21…for the MIP, it took a lot longer to develop the application. The Program Officer explained the reviewers' expectations for microbicide work, so we had to do a lot more preparation for that proposal to meet those expectations.***" Four respondents believed that the time required to prepare an R21/R33 grant application was a little longer than would be required to prepare an R01. Investigators with both AVR and MIP awards agreed that the MIP application took longer to prepare.

Program Officers at DAIDS were viewed by both the multiple award PIs and the survey respondents as an important and valuable source of help in constructing an application. One multiple award PI said "***we spoke with some of the leadership about the concept we had and what some of the goals of the project would be. We solicited their feedback and guidance on how we should put the project together***." One investigator who did not talk with a Program Officer wished he had: "***We didn't contact NIAID when writing our application. That might have been helpful. Sometimes you feel like you don't want to bother the Program Officers too much up front, because they have other applications on their plate. We were a little hesitant to call in the beginning. Now, if we have questions, we're a little more comfortable about calling and asking them.***"

Almost three-quarters (74%) of survey respondents reported that they contacted DAIDS Program Officers at least once while developing their applications. Investigators who applied for a MIP funding were much more likely to discuss their applications with Program Officers during the application phase than those applying for AVR funding (86% versus 47% of investigators). Established investigators were also more likely than new investigators to discuss their ideas with Program Officers (77% versus 56%). Those who did contact a Program Officer agreed that the contact helped them to develop a stronger application.

Two aspects of the process of developing the grant application that were challenging for some investigators were: (1) the development of milestones, and (2) the limits on funding and duration imposed by the use of the R21 and the R33 grant mechanism. These are discussed in further detail below.

3.2.3.1 Milestones and Their Impact on Applications

One of the more challenging aspects of the application process for investigators was the inclusion of milestones. In general, PIs surveyed understood the use of the milestones as they prepared their grant applications; almost all (89%) respondents strongly agreed or agreed that they had a "clear understanding of the use of milestones while writing my application." Multiple awards PIs shared this perspective about the use of milestones.

Six of the nine multiple award PIs interviewed said that they were familiar with the use of milestones from past work: ***"I have developed milestones for projects before in applications sponsored by private sector partners."*** Milestones are often incorporated into pharmaceutical research projects as well. None of the multiple award PIs stated that the inclusion of milestones as a requirement in the R21/R33 grants affected their decisions to apply. One PI commented that ***"I suppose the milestone requirement made me think more clearly, but it neither encouraged nor discouraged me one way or the other."*** Almost all (eight of nine) multiple award PIs held favorable views about the inclusion of a milestone requirement. As one PI said, "***the milestones allowed us to put some of the typical project management approaches to work—things like developing Gantt charts, identifying bottlenecks, and go/no go decision-making points. I think it helped us think through the project a little more.***" On the other hand, milestones did have an effect on how the application was packaged. "***I think it impacted the research for sure. Once you realize you must achieve particular milestones to be judged in a positive way, it will have a constraining effect. Is that good or bad? I think the R21/R33 program is designed to be translational, so it's hard to imagine a program like this without milestones. On the other hand a basic scientist like me is going to be more affected than somebody working on the translational end. It affected the work, but not in a way that made it less productive—it was just differently productive.***"

One potential problem that concerned some of the multiple awards PIs was the possibility that establishing milestones for two years might pose challenges if the investigator's research encountered problems, or if the direction of the scientific field changed over that time. One investigator decried the lack of flexibility in milestones and recommended that Program Officers allow for "***a better understanding of the flexibility that might be available regarding changing the direction of science if you run into problems…I think it works, but the milestones set rigid targets for where you need to be, and I don't think this mechanism allowed for a lot of flexibility in changing directions as the data would dictate like what occurs in a normal grant process.***"

PI survey results confirmed the finding that investigators generally held a positive view of the impact of milestones on their research. For example, 89% of PIs either strongly agreed or agreed that the milestones helped them focus their research during the R21 phase, and a similar percentage said the milestones helped them to be realistic about what they could accomplish in those first two years.

The one discordant finding was in responses to the question on whether milestones "discouraged innovative research during the R21 phase," with which about 36% of survey respondents either strongly agreed or agreed. New investigators did not differ from established investigators in their responses to this question.

3.2.3.2 Limits on Funding Levels and Grant Duration

Evaluation Question

1A. Is the mechanism budget (i.e., dollar limits) appropriate to support the research?

The second potential challenge applicants faced was the limits on funding and grant duration for the R21 and R33 grants. The limits imposed for each grant were those established by NIH. Thus, the R21 phase was limited to a total of $275,000 in direct costs for a maximum of two years, with no more than $200,000 in direct costs allowed in any one year. The R33 phase was limited to a total of $300,000 in

direct costs per year for a maximum of three years. It should be noted that this level is actually about $50,000 per year higher than the typical R01 grant ($250,000), although that funding level can be exceeded with approval. For those investigators whose grants may be slow in starting up, grantees could obtain a No-Cost Extension from their Program Officer. Here the focus is on whether these funding and duration limits affected what an applicant could propose in an application.

The PI survey data provide some general insights into this question. First, about 65% of respondents either strongly agreed or agreed with the statement "the $275,000 limit in the R21 phase limited the research that I would otherwise have proposed for the first two years of my grant." On further examination this percentage differed by initiative, with about 79% of the AVR respondents endorsing it and 59% of the MIP respondents. One interpretation of this difference is that the AVR projects were more likely than the MIP projects to involve animal studies (which tend to be expensive). There were no differences for new versus experienced investigators.

Further understanding of this issue was provided by the multiple award PIs. Five of nine PIs interviewed stated that they believed that the R21 budget was reasonable. As one investigator responded, "***Yes, it's reasonable. Would you like to have a little more money in the R21 phase? Sure. There are going to be some projects that won't be able to fit in under this budget, but then they have to go for a different mechanism.***" Another PI commented "***I think some of the mechanisms out there have some allowance for non-human primate work or humanized mice. There are some things you want to do that are very expensive…an allowance or a mechanism to explore specific things that may be more expensive would be great because the budget is very limited for that type of work.***" Two other investigators mentioned that they coped with inadequate R21 budgetary limits by using external funding to supplement their proposed budgets. "***We have done a little bit of subsidizing. Sometimes we get access to recycled money. For instance, we were able to get access to recycled animals without much cost to our lab or anyone else. People would send us tissue samples they already had that would also work for our projects. These are informal subsidies, but it really makes a difference to get things to work.***"

Program Officers appeared to recognize the limitations the R21 funding limits placed on the types of research that could be funded under the R21/R33 mechanism. One Program Officer commented that "***the amount of funding that you can provide in the first two years is limited. In many cases that hindered the research for investigators who wanted to conduct nonhuman primate immunogenicity studies. Those are very expensive, and could not be done to any great extent using an R21 mechanism.***" Another Program Officer suggested that the more limited dollar value of the R21 "***may limit the number of people who are willing to respond to the funding announcement because they don't want to do the amount of work necessary to write a grant for that limited amount compared with the amount awarded from an R01 grant.***" A third Program Officer expressed a more negative view concerning the limits of the R21 budget: "***The funding limit was the reason why we abandoned the mechanism, despite its other advantages. The kind of work we are interested in supporting relies heavily on the use of nonhuman primates, which is expensive. The dollar limit even in the R33 phase was no longer considered adequate. My understanding was that the dollar amounts adopted were the maximum limits permitted under the mechanism but we finally decided that it wasn't cutting the mustard. Investigators were completing experiments in their laboratories, but weren't able to publish because no one believes a four-animal experiment anymore.***"

3.2.4 The Grant Review Process

The AVR and the MIP initiatives followed two different approaches in terms of the grant review process. Because the AVR initiative used a PA mechanism, CSR conducted the application reviews. CSR assigned the applications to a standing peer review panel (the VACC). AVR staff members were enjoined from having any contact with the members of this panel. Although the AVR Program Director requested to

make a short presentation to the panel members on how to evaluate the proposed milestones, the request was denied.

By contrast, the MIP initiative used the RFA mechanism which allowed the formation of SEPs by NIAID. The MIP Program Director presented a short orientation to panel members describing the critical features of the R21/R33 mechanism, including the emphasis on innovation and high-risk, high-reward research, and the inclusion of milestones.

The AVR and MIP Program Directors described several issues with their respective review groups. Their perspectives are presented and supplemented with responses from two Scientific Review Officers who were interviewed.

3.2.4.1 Reviewers' Comfort with Innovative and High-Risk Research

One issue the AVR and MIP Program Directors anticipated was the lack of comfort some reviewers have with innovative, high-risk research. In practice, it often turns out that one or two reviewers in particular are resistant to giving innovative applications favorable priority scores. This was confirmed by two Scientific Review Officers interviewed for the evaluation (one from each of the two initiatives). They noted that reviewers on their panels struggled with the high-risk nature of some applications despite clear instructions from the chairperson of each panel. The MIP Program Director explained that "***the R21/R33 mechanism works enough like an R01 for some reviewers to treat it like that. We need to keep them focused on the need for and acceptability of high-risk, high-reward research.***"

3.2.4.2 Reviewers' Discomfort with Allowing Program Staff to Determine R33 Transition

A second issue concerned reviewers' opinions about the R21/R33 mechanism and combining two applications into a single application. Some reviewers held the opinion that program staff should make decisions on transitions to the R33 phase of a grant only after bringing it back to the peer review panel for a second review. Other reviewers felt that program staff could make those decisions without the panel, and that bringing projects in for a second review would be a waste of reviewers' time. The AVR Program Director estimated that the consensus for the VACC panel was about 60/40 in favor of letting the program make these decisions.

One factor that may have contributed to some reviewers' misgivings was that the R33 proposals were sometimes poorly conceptualized. The inclusion of both the R21 application and the R33 application in the same application package meant that the R21 portion could be very well designed while the R33 portion might be less developed. However, reviewers had to assign a single priority score for the applications as a pair. One Scientific Review Officer said "***reviewers had a very difficult time with the two-in-one scoring. Sometimes the applicants did not do a good job describing the second phase, which could make an application less likely to be funded***"; on the other hand, a different Scientific Review Officer commented that there were no issues with this process.

3.2.4.3 How Reviewers Addressed the Applicants' Milestones

A third major issue that arose from the scientific review process concerned the quality of reviewers' feedback on the proposed milestones. Applicants were instructed to include specific quantifiable milestones as part of their applications. Reviewers were supposed to review and comment on the adequacy of these milestones as part of their research critiques. All of the Scientific Review Officers agreed that the reviewers understood what the milestones were and how they were to be used as part of the transition review process. Some reviewers disagreed about the feasibility of establishing milestones for truly innovative research: ***"if you are doing something truly innovative, you cannot possibly write milestones.***" Nonetheless, peer review panel chairs clearly instructed reviewers on the need to review the milestones. The main issues reviewers encountered with milestones were determining whether they were clearly present in an application, and evaluating the quality of the milestones. Based on a review of the applications, it was not hard to understand the confusion about whether milestones were actually present,

as applicants did not always clearly position the milestones within the application. Some applicants created a specific section at the close of the research narrative where they stated their milestones. Others listed milestones separately under each Specific Aim within the narrative. In several instances, milestones were simply restatements of the Specific Aims.

Gauging the quality of the milestones proved a more challenging task than locating them. The AVR and MIP Program Directors expressed frustration with the feedback they received from review panels on applicants' milestones, particularly in the early application rounds. The chief problem was that the milestones lacked quantification. As the AVR Program Director said, "***I wanted the reviewers to make suggestions for how to correct them on the scientific and technical level."*** The MIP Program Director noted that the peer review feedback on the quality of the milestones was highly variable. "***The R21/R33 was a new concept and people didn't know what to do with the milestones. Most of the time they just said the milestones were okay. They didn't say a word about them.***" The MIP Program Director addressed this issue as part of the presentation made before each review group, and the Program Officers discussed milestones with prospective applicants when they called for advice. It was also noted that, as time passed, reviewers improved the quality of their assessments of the milestones.

3.2.5 Negotiating the Milestones

From the perspective of the AVR and MIP Program Directors, negotiated milestones provide some assurance that the project aims are reasonable and achievable within the two-year R21 phase. The negotiation process also allows program staff to have some input into the development of the project. One of the Program Officers commented that "***…the negotiated milestones allow us to assist and facilitate research during the product development stage, which is the most hazardous stage in terms of investment.***" Another Program Officer stated "***I think we should use milestones for everything because it helps our investigators be more focused and get their work done.***"

While the Program Officers strongly favored the negotiated milestones process, they also found it challenging in some instances. "***The only negative aspect for the program staff was the challenge of developing milestones that could be achieved in two years and that could truly gauge the feasibility of a study. Sometimes it took two years just to develop the reagents to pursue the hypothesis. And that truly did not assess whether the research was feasible or not. …Often what would happen is that the investigator would get a two-year R21 then not be able to achieve the milestones within those two years. Then they would ask for a one-year No-Cost Extension in which case they would have three years to address the milestones. At that point they would include milestones that tested the feasibility of their study.***"

The AVR and MIP initiatives used slightly different approaches in conducting the negotiation process.

AVR program staff members formed a committee that reviewed the application and the peer review panel's Summary Statement. This committee included members from other NIAID Divisions who had specific expertise in some aspect of the investigator's proposed research. The Program Officer assigned to oversee the project was required to draft a written summary of the milestones and their feasibility and limitations. This summary formed the basis for discussion within the committee, which then reached a consensus on issues such as: what questions or studies may be missing from the application, and how best to develop quantifiable indicators of success. At the conclusion of the preliminary meeting, the Program Officer drafted an agenda for the PI, which was also reviewed by the committee. The approved agenda was sent to the PI and a conference call scheduled. A written summary of the calls was maintained by the Program Officer. The final negotiated milestones were signed by the PI and the Program Director and filed with the Notice of Award.

The MIP process was somewhat more streamlined. The Program Director and one Program Officer divided the single round of applications. Each reviewed the assigned applications and Summary

Statements, drafted feedback, and emailed it to the PI. The investigator responded in writing, and an additional round of negotiation was held if necessary. The MIP Program Director wanted to construct a process that would leave clear documentation of the negotiation process. Most negotiations only required two rounds, although a small proportion required three. Occasionally a conference call was needed although he preferred to do the negotiations in writing.

PIs surveyed expressed highly favorable views about the milestone negotiation process. Overall, 97% of survey respondents strongly agreed or agreed that they had adequate input during the milestone negotiation process, and 69% described themselves as very satisfied and an additional 30% were satisfied with the negotiation process. There were no differences by initiative or for new versus established investigators. When asked about the degree to which PIs perceived their original milestones to have changed as a result of the negotiation process, about 28% either strongly agreed or agreed that their milestones had changed 'substantially' over their original applications. There were slight differences by initiative (32% for AVR PIs, 26% for MIP PIs, and 33% for new versus 27% for experienced investigators).

3.2.6 Transition Evaluation

As investigators neared the last few months of the second year of their projects, they submitted an Interim Progress Report which was discussed with the Program Officer. This discussion provided an overview of progress to date on the research project, and allowed the Program Officer and the PI an opportunity to decide whether the latter would be submitting a Request for Transition at the two year mark, or whether progress had been such that a No-Cost Extension might be warranted. This discussion also provided the Program Officer with some advance warning about the potential number of transition evaluations that would be likely by the two-year point.

To transition to the R33 phase, investigators had to submit a formal Request for Transition that stated the negotiated milestones and provide evidence that the investigator had successfully met or exceeded each milestone. There were three transition criteria: achieving the negotiated milestones, continuing scientific relevance, and the availability of funding.

Of the 27 AVR projects, 11(41%) transitioned to the R33 phase, 14(52%) stopped at the R21 phase, and two projects (7%) were still in progress (as of September 13, 2013 when the data abstraction concluded). The AVR PAs indicated that "a maximum of 50 percent (50%) of projects would transition to the R33 phase." The actual percentage of transitioning projects (41%) fell within this range.

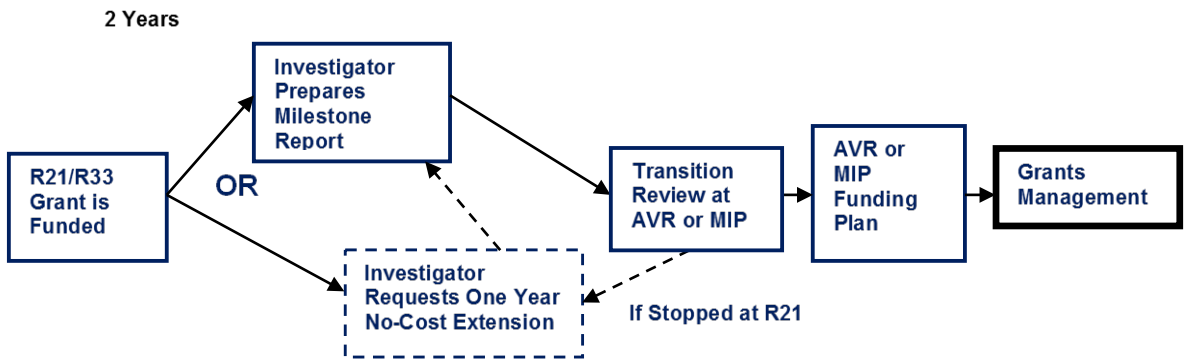
Of the 61 MIP projects 39(64%) transitioned to the R33 phase, 20(33%) stopped at the R21 phase, and two (1%) are still in progress. The initial MIP RFA (RFA-AI-06-005) estimated that no more than 25% of the R21 awards would transition to the R33 phase; however, by the second of the six RFAs, this estimate was revised upward to a maximum of 50%. The actual percentage (64%) exceeded this range, in large part because the MIP Program Director was successful in locating several additional funding sources.

3.2.6.1 Transition Evaluation Process

The process for conducting AVR and MIP transition evaluations was similar to that shown in **Exhibit 3.8**. Transition evaluations normally occurred two years following the date of award, but investigators who had started their projects late or were not prepared to demonstrate that they had met their milestones could obtain a No-Cost Extension (provided that there were funds remaining in the R21 grant). For the AVR initiative, the three annual application receipt dates meant that transition evaluations occurred three times per year. For the MIP initiative, the single annual application receipt date meant that the evaluations occurred only once per year. In order to ensure that these evaluations were not delayed due to late submissions by PIs, the Program Directors from each initiative prompted investigators in advance to remind them to prepare and submit the milestone reports. The AVR Program Director noted that "***most awardees are so busy they sometimes lose track in getting the research done in time to apply for the***

advanced support. As POs, we should call the investigator 3 or 4 months before their R33 application is due to remind them. When we do, they are surprised but say they can do it, or they say they had better come in for a No-Cost Extension, which is allowed."

Exhibit 3.8. Transition Review Process for AVR and MIP



While No-Cost Extensions could be advantageous for PIs, they could also lead to problems for Program Officers. One MIP Program Officer described the problem : "***…the budget planning process was based on the idea that at the end of Year Two, an investigator would demonstrate that he or she had met their milestones and either proceed to an R33 or be finished. In practice, almost everyone asked for a No-Cost Extension in Year Three. Since we were making initial awards to one cohort one year and another cohort the next year, and so on, occasionally we would have more than the expected number of people asking for milestone transitions. Occasionally we had twice as many people who were scheduled ask for a transition evaluation.***" This also meant that some investigators had additional time (although not funding) to complete their R21 exploratory work.

Both initiatives used teams of Program Officers to conduct programmatic transition evaluations. For the MIP initiative members of the evaluation team could include other Program Officers outside DAIDS who were interested in topical microbicides. Occasionally, they included representation from NIMH. MIP used the following process. "***We started with the issue of reminding applicants to submit on time. They would often ask us, 'What is a milestone report?' and we helped them with that. Then the milestone reports arrive, and you have 10 milestone reports of up to 10 pages each. You read the whole batch in less than a week, evaluate and rank each project, then meet for two hours with the team to rank them again, write it all up and put it to budget at a second meeting. This second meeting is in just a few days. We discuss where there is agreement and where there is disagreement, and then prepare a funding plan. This takes about 60 hours of my time.***" At the initial evaluation meeting, the MIP Program Director typically served as either the chief advocate or the chief detractor for each project. The team would then challenge him and debate the merits and weaknesses of each project. An interesting feature of this process is that it was not simply limited to the contents of the investigator's report. "***We can pull from everything we know, beyond what is just in front of us. This is more than what a review [panel] does, because we can pull from information beyond what's in the room.***"

The efficiency of the MIP transition evaluation process may have been possible in part because it was only necessary to conduct a single review per year. The AVR PAs permitted three application periods per year, thus beginning two years after the release of the first PA, there were three transition evaluation periods per year. The AVR Program Director stated that "***the timing of the transition has caused bottlenecks. We had three receipt dates in a year so we transitioned some investigators before others. The process had somewhat of a bias toward those investigators who submitted transition reports earlier in the fiscal year because the full pot of money was available then; as the year wore on, we'd spend down our money and near the end we could find that we didn't have enough to fund all of the***

investigators we wanted to transition. We tried to offset that by delaying some of the earlier transitions to see whether something more promising would come in during the next cycle…Anytime you can't transition right away when the research is done, there is a bottleneck."

3.2.6.2 Principal Investigators' Reactions to the Transition Evaluation Process

Evaluation Question

1E. Was the transition from the first to the second phase made efficiently without gaps in funding?

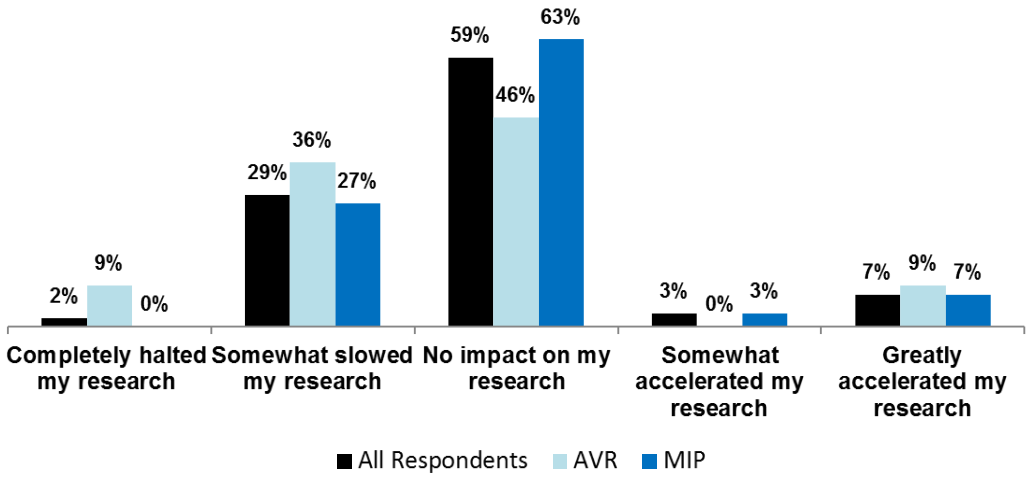
Interviews with the nine multiple award PIs provided additional contextual information on the transition evaluation process. In general, PIs were satisfied with the process, even when their grants were halted at the R21 phase. In some instances, PIs recognized that they were not going to meet their milestones and therefore did not submit milestone reports for consideration. Among those who did, the general consensus was that both the time interval required for transition evaluation and the process itself (including notification about the decision) were fairly efficient. As one PI noted, "***It was very specific. If you achieve the milestones then you have a chance for advancement; if you don't, you can't advance. But if you do meet your milestones, the program staff will rank your project based on program priorities and the top grants advance. I accepted that. That's the nature of the science."***

PI survey respondents expressed similar views. About 95% of respondents either strongly agreed or agreed that the transition process was efficient. However, among those who did not transition, about 59% believed that the reasons they did not transition were not clearly explained to them[6]. There were slight differences by initiative. About 67% of AVR respondents and 55% of MIP respondents, who did not transition did not think that the reasons had been clearly explained to them. There were no differences for the new versus experienced investigators.

PIs were also asked whether the transition time between the R21 and R33 phases had an adverse (or a positive) impact on their research. The results are shown in **Exhibit 3.9** which also shows the responses for investigators who transitioned to the R33 phase and who were funded by AVR or MIP. As this Exhibit shows, the majority of respondents (59%) reported no impact, and about 10% reported a positive impact. However, 31% of respondents did experience some impact or even a complete halt in their research. About 45% of AVR PIs and 27% of MIP PIs who transitioned reported an adverse impact on their research. This difference may be attributed to the higher proportion of animal studies among the AVR projects; almost all (93%) AVR projects involved animal research, and of those projects, about two-thirds (68%) involved nonhuman primates.

[6] This reflected the requirements set forth in the NIAID Standard Operating Procedures, which stipulated what could and what could not be reported about the evaluation process.

Exhibit 3.9. Impact of Transition Time on AVR and MIP Investigators' Research



3.2.7 Project Oversight and Management

In addition to providing advice and suggestions for PIs during the application development phase and negotiating milestones during the pre-award phase, DAIDS Program Officers oversaw the grant progress, annual progress reports, and communications initiated by either party during the course of the research. This section examines two aspects of that oversight from the perspectives of the PIs, focusing on communication (both frequency and perceived helpfulness), and project monitoring. This section also examines Program Officers' perceptions of the level of effort required to oversee R21/R33 projects compared with other types of projects.

3.2.7.1 Communication between Principal Investigators and Program Officers

Program Officers interviewed reported that the R21/R33 grant mechanism required a greater degree of communication with PIs over the course of each grant than other grant mechanisms. While this would be anticipated given the need to negotiate milestones and review transition materials, there seemed to be more contacts overall during the R21 and R33 phases. Several questions in the PI survey examined PIs' perspectives on the issue of communication, including the frequency and perceived helpfulness for both the R21 and R33 phases. The R21 phase includes data from all respondents while the R33 phase includes data only from those respondents who transitioned to the R33 phase.

About 90% of survey respondents reported that the amount of contact they had with Program Officers during the initial R21 phase was "appropriate." A similar percentage of respondents who had transitioned to the R33 phase also indicated that the amount of contact they had with their Program Officers during the R33 phase was "appropriate." Similar percentages of respondents (95% for the R21 phase and 96% for the R33 phase) either strongly agreed or agreed that communication with their Program Officer was helpful. In both phases, investigators were satisfied with the amount of contact provided by Program Officers and their helpfulness during contacts.

3.2.7.2 The Project Monitoring Function

Progress toward milestones was documented in the annual progress reports. Based on the PI survey, 84% of respondents found the process for reporting grant progress either very easy or somewhat easy. Almost all respondents (90%) either strongly agreed or agreed that the milestones were used to hold them closely accountable to progress on their grants, and 93% either strongly agreed or agreed that they were satisfied with their Program Officer's grant monitoring.

3.2.7.3 Administrative Level of Effort

Evaluation Question

1B. Is the administrative burden on program management worth the effort?

Analysis of responses from the AVR and MIP Program Directors, Program Officers, Scientific Review Officers, and Grants Management Officers, shows a general consensus that managing an initiative comprising R21/R33 grants does require as much or more administrative effort than other types of grants and contracts, although not prohibitively so. **Exhibit 3.10** summarizes respondent comments on this issue. Both AVR and MIP initiatives were conducted with existing staff and no additional resources were provided. The interviews with the Program Officers showed that staff members were strongly engaged with each initiative, and willingly put in the extra time and effort required at peak periods. In the MIP initiative, staff members from other NIAID Divisions and other NIH Institutes willingly participated in review meetings and discussions. One way to interpret this is that participation in the AVR and MIP PIA initiatives allowed staff members to become involved in the science of their investigators' research to a greater degree than mechanisms such as the traditional R01, and staff members found this engagement professionally rewarding.

Exhibit 3.10. Perspectives on the Administrative Effort Required to Manage R21/R33 Grants

AVR & MIP Program Directors	Program Officers	Scientific Review Officers	Grants Management Officers
▪ A much higher [level of effort] is required than for other programs, higher than R01s. For those who are transitioned it's every bit as much if not more than a standard R01. ▪ The effort is greater than an R01 at all points along the process. With a R01 grant, it gets reviewed, you fill out a checklist, review any JIT comments the specialist has, do another checklist once a year, read a progress report, and that's it. For the R21/R33, you do all that and negotiate milestones, review and manage the transition, and have ongoing communication with the investigator so he or she understands how to construct a transition report and plan for the R33 phase. This is significantly greater time.	▪ It takes more time to manage and monitor this mechanism than others due to the greater amount of time needed for reviews and discussions, milestone negotiation, and maintaining an increase in regular, ongoing communication with investigators over the life of the grant.	▪ It requires either the same amount or more effort because "you had to find two different types of reviewers...those who could assess the project in terms of its innovation, and those who were more product-oriented to review the R33 phase.	▪ The amount of effort is slightly greater than for other types of mechanisms, but not as complex as Cooperative Agreements, which can have 15 to 30 subcontractors on a single grant. The R21 involves a single institution or business, and the R33 may involve an institution and maybe four or five subcontractors.

Given that the AVR and MIP Program Directors and Program Officers perceive the R21/R33 mechanism as requiring a greater level of administrative effort than some other types of grant mechanisms, the question of whether this extra effort is worthwhile was further explored.

When asked whether the extra work engendered by the mechanism was worthwhile, Program Officers for both initiatives clearly supported it. Support was stronger from the MIP program staff members. One Program Officer said that "***I definitely think this mechanism was worth the effort. In my scientific opinion, too much microbicide research was hypothetical in the past, and it was not really grounded in a lot of true product development expertise. So I think the R21/R33 mechanism had a positive impact by moving product development thinking into the field."*** Another Program Officer added, ***"It is very worth it. The amount of extra work we have to do I consider negligible. The benefits far outweigh the little bit of extra work. If anything, negotiating milestones helps you become a better Program Officer."*** A third Program Officer emphasized the value of the mechanism in attracting innovative thinking. ***"I just think that we have to try everything we can think of. We've got to get people with novel ideas working. It's just so hard to do that. I think this mechanism made it easier for some people with novel ideas to apply. It also made it easier for the review panels to fund novel or new ideas. That's just the way to do it."*** One multiple award PI commented that "***If I was an NIH Director, I would push the use of the R21/R33. The biological biomedical field moves very quickly, and we cannot afford to stay for four or five years in an R01."***

3.3 Program Participation

Evaluation Question

1F. What are the demographic and professional characteristics of successful and unsuccessful PIA applicants?

This section focuses on program participation and examines the demographic and professional characteristics of funded and unfunded AVR and MIP applicants. The analysis of funded investigators and their projects includes the characteristics of the research project teams assembled by the PIs, size of the teams, number of organizations participating in the teams, and frequency of university-industry partnerships and participation of international universities. This section also examines the success rates for R21/R33 grants, comparing the combined success rates for the AVR and MIP initiatives over the years 2006-2011 with 2006-2011 success rates for R21 and R01 grants at NIAID. Success rates for new and experienced investigators in the two DAIDS R21/R33 initiatives are also compared with success rates for R21 grants for new versus experienced investigators across NIH.

3.3.1 Funded and Unfunded Applicants

For the AVR and MIP initiatives combined, there were a total of 298 grant applications submitted between FY 2006 and 2011, of which 88(30%) were funded. The 298 applications were submitted by 182 unique investigators, of whom 74(41%) received grant awards. The three PAs issued for the AVR initiative attracted a total of 128 applications (including resubmissions), of which 27(21%) were funded. The six rounds of RFAs for the MIP initiative had total of 170 applications (including resubmissions), of which 61(39%) were funded. Together and separately, both initiatives produced a higher funding success rate than NIAID R21s (18%) and R01s (17%) funded between FY 2006-2011.

Neither PI academic degree (PhD, MD, or MD/PhD), nor institutional type (academic, for-profit, or non-profit) differed for funded and unfunded AVR and MIP applicants. A slightly higher proportion of women than men were funded across both initiatives. New investigators are a group that both the AVR and MIP initiatives hoped to attract by suspending the usual requirement for preliminary data to accompany an application. Of the 40 new investigators who applied, 11(28%) were funded. This is considerably higher than the NIH R21 average (12%) for new investigators funded between FY 2006-2011. Of the 148 experienced investigators who applied, 65(44%) were funded.

3.3.2 Characteristics of Principal Investigators and Research Projects

Exhibit 3.11 shows demographic and professional characteristics of AVR and MIP PIs. In general, PIs in both initiatives are fairly similar. A slightly higher percentage of women were PIs for MIP projects (33%) than AVR projects (17%). Of the 11 new investigators funded by the two initiatives combined (15%), seven were funded by AVR (29%) and four were funded by MIP (8%). Neither academic degree nor institutional location differed for the two initiatives, although five PIs with MIP projects were employed with for-profit organizations and no AVR PIs were.

Exhibit 3.11. Demographic and Professional Characteristics of AVR and MIP PIs (n=74[1])

Characteristic	AVR (N=24) Frequency	AVR (N=24) Percentage	MIP (N=52) Frequency	MIP (N=52) Percentage
Female	4	17%	17	33%
Male	20	83%	35	67%
PhD	18	75%	39	75%
MD	3	13%	6	12%
MD/PhD	3	13%	7	13%
New Investigator	7	29%	4	8%
Experienced Investigator	17	61%	48	92%
Academic Institution	20	83%	40	77%
For Profit Organization	--	--	5	10%
Non-Profit Organization	4	17%	7	13%

[1]There are 74 unique investigators for AVR and MIP combined. However, 2 PIs received both AVR and MIP awards, resulting in n=24 for AVR and n=52 for MIP separately.

Several characteristics of the 88 research projects are shown in **Exhibit 3.12**.There are more than twice as many funded MIP projects as AVR projects despite the fact that there were more application receipt dates for AVR over the six-year period. A higher percentage of MIP proposals (80%) were funded on the first submission for MIP than for AVR (41%), which may be attributed to the higher degree of contact between applicants and Program Officers for the MIP initiative during the grant application process. As noted earlier, Program Officers discussed reviewers' expectations with applicants which many PIs described as helpful in assisting them to plan their applications. Despite the presence of clear statements in the PAs and RFAs de-emphasizing the need for preliminary data, all of the PIs who applied to either initiative included some data. Animal subjects were used extensively in projects for both initiatives although slightly more so for AVR. AVR projects were also more likely to include nonhuman primates as research subjects. A comparison of the use of nonhuman primates in projects that transitioned to the R33 phase for AVR and MIP showed that 60% of AVR transitioning projects involved nonhuman primate research while only 41% of transitioning MIP projects did. This greater reliance on nonhuman primates in AVR projects may partially explain the greater negative impact of delays in the transitioning process for AVR projects.

Exhibit 3.12. Characteristics of AVR and MIP Projects (n=88)

Characteristic	AVR (n=27) Frequency	AVR (n=27) Percentage	MIP (n=61) Frequency	MIP (n=61) Percentage
Proposal funded on first submission	11	41%	49	80%
Proposal resubmitted one or more times	16	59%	12	20%
Application contained Preliminary Data	26	96%	61	100%
Proposal involved animals	25	93%	51	84%
Proposal involved use of nonhuman primates	17	63%	30	49%
Project transitioned to R33 phase	11	41%	39	64%
Project stopped at R21 phase	14	52%	20	33%
Project still in progress in R21 phase	2	7%	2	3%

3.3.3 Research Project Teams

The composition of research project teams assembled for each funded project was defined as individuals whose project roles were described in the grant application as PI, co-PI, co-investigator, faculty, collaborators, and postdoctoral fellows, and lead investigator on a sub-contract.

AVR project teams ranged in size from 2 to 10 members, with an average of 5.0 team members. Team members included individuals from an average of 2.5 organizations. AVR project teams involved several types of partnerships, including university-industry partnerships (7%), university-non-profits (30%), and partnerships with international universities (19%). Seven (26%) of the 27 project teams involved individuals from only one institution.

MIP project teams ranged in size from 1 to 14 members, with an average of 5.9 team members. These teams included members from an average of 2.9 organizations. MIP project teams had a higher percentage of university-industry partnerships (25%) and pairings with international universities (20%). They had a similar percentage of university-non-profit partnerships (28%). Eight of the project teams involved members from only one institution (13%), which is a lower percentage than for the AVR project teams. The MIP project teams involved extensive collaboration among themselves; two team members participated on six separate projects and one individual participated on seven projects.

3.3.4 Success Rates for the DAIDS R21/R33 Grants

As noted earlier, a total of 88 AVR and MIP projects were funded out of a total of 298, yielding an overall success rate of 30%. **Exhibit 3.13** compares this rate for FY 2006-2011 for the two initiatives combined, the MIP initiative alone, the AVR initiative alone, and for NIAID R21 and R01 grants awarded over the same period[7] **Exhibit 3.13** shows that each of the two initiatives separately and combined enjoys a more favorable six-year success rate than NIAID R21 and R01 grants over the same six fiscal years. These rates support the idea that the R21/R33 mechanism has helped to build research capacity. This is especially true for the MIP initiative, which is important since there had been relatively few projects funded on topical microbicides during the years before the MIP initiative. In order to further examine whether the two initiatives were encouraging new investigators to submit applications in AIDS vaccine research or topical microbicide research funded and unfunded AVR and MIP applications were reviewed to identify applicants classified as new investigators (using the NIH definition). Data were also obtained on success rates for new versus established investigators for R21 grants across NIH as a whole through a

[7]These data were calculated by averaging the rates for the six years for NIAID R21 and R01 grants as reported in the NIH RePorter, Table #206.

special request from the NIH's Office of Extramural Research Division of Statistical Analysis and Reporting (DSAR). These data are shown in **Exhibit 3.14**.

Exhibit 3.13. Success Rates for AVR and MIP Projects Compared with NIAID R21 and R01 Grants for FY 2006-2011

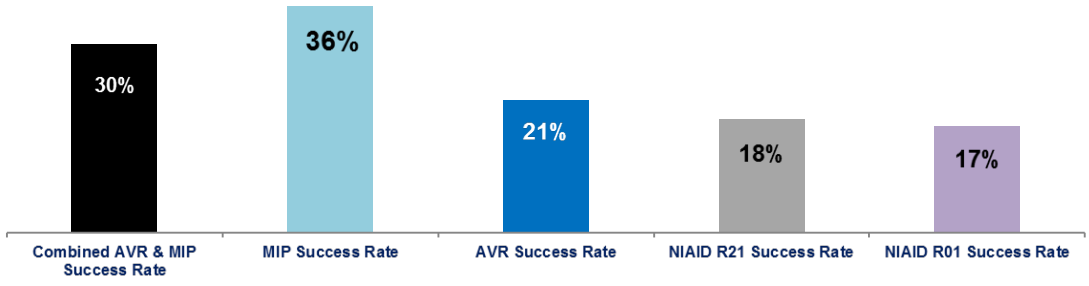
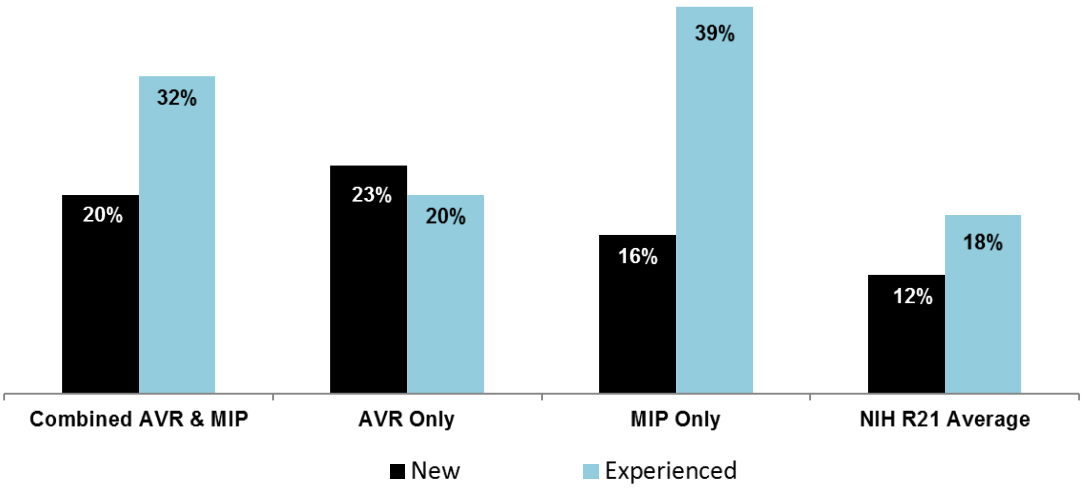


Exhibit 3.14. Success Rates for New versus Experienced Investigators, FY 2006-2011 AVR and MIP Combined, AVR, MIP, and NIH Combined



These rates show that for the two initiatives combined, and for each of the AVR and MIP initiatives alone, the six-year success rates for new investigators were slightly higher than the average success rate for R21 grants across NIH for new investigators. The six-year success rates for experienced investigators for the two initiatives were also higher than the averaged six-year success rate for NIH R21 grants experienced investigators. This was particularly true for MIP; however there were only four new investigators in that initiative.

3.4 Effects of the NIAID DAIDS Phased Innovation Award Mechanism

Research initiatives are frequently assessed in terms of outputs such as new publications and grants. This section addresses those outputs for the NIAID DAIDS PIA initiatives and also considers additional

outcomes that flow from those outputs, such as the development of new research collaborations and partnerships. Several aspects of collaborations are important, including the manner in which they contribute to building a research community, and their contributions to bringing together disciplines that have not traditionally worked together. The idea of multidisciplinarity is an important theme that emerges in the analysis of publications but is especially prominent in new collaborations. A second major outcome is the effects that the AVR and MIP initiatives are having on their targeted scientific fields. The discussion highlights some of the new technologies, models, and methods that the AVR and MIP initiatives have developed. An exciting aspect of these discoveries is that they are fueling new research projects and collaborations between investigators funded by the AVR and MIP initiatives.

3.4.1 Publications

Peer-reviewed research publications are a basic output stemming from the research process. NIH and other funding agencies use these data to track the productivity of a research project or investigator. The bibliometric analysis of articles produced by the AVR and MIP initiatives yielded an unduplicated count[8] of 262 articles published between 2007 and mid-September 2013 acknowledging AVR or MIP grants[9].

As of the latter date, 63 of the 88 projects (72%) had produced one or more peer-reviewed research articles for an average of 4.4 articles per project. Five projects produced 71 articles (27% of the total.) Not surprisingly, projects that had transitioned to the R33 phase published almost three-quarters of the articles (73%). A majority of these articles (70%) had been cited at least once. There were a total of 2,217 citations of the 262 articles, or an average of 11.5 citations per article. The five most frequently cited papers published by AVR and MIP investigators as of September 2013 are shown in **Exhibit 3.15:**

Exhibit 3.15. Five Most Frequently Cited Papers from PIA Projects

Authors	Year	Title of Paper	Journal	Number of Times Cited
Li et al.	**2009**	"Glycerol monolaurate prevents mucosal SIV transmission."	**Nature**	**133**
Goulder and Watkins	**2008**	"Impact of MHC Class 1 diversity on immune control of immunodeficiency virus replication."	**Nature Reviews Immunology**	**130**
Haase	**2010**	"Targeting early infection to prevent HIV-1 mucosal transmission."	**Nature**	**117**
Denton et al.	**2008**	"Antiretroviral pre-exposure prophylaxis prevents vaginal transmission of HIV-1 in humanized BLT mice."	**PLoS Medicine**	**84**
Saratianos et al.	**2009**	"Structure and function of HIV-1 reverse transcriptase: molecular mechanisms of polymerization and inhibition."	**Journal of Molecular Biology**	**65**

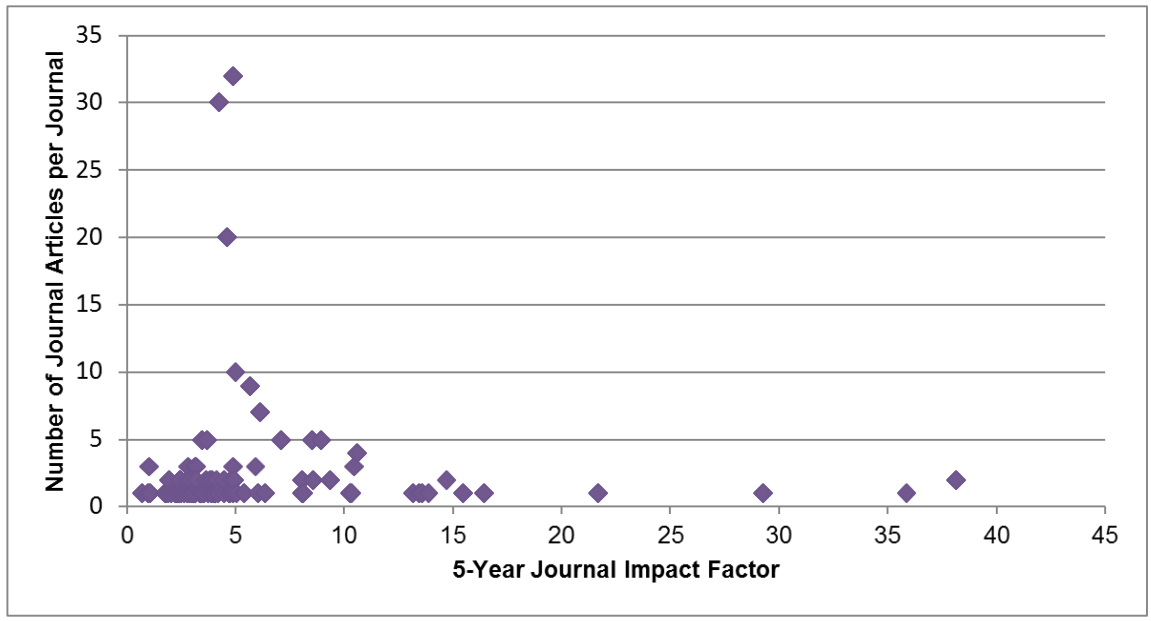
As part of the analysis of research publications, the evaluation team analyzed information on co-authors, including their organizational affiliation, and academic department. There were a total of 2,143 authors listed on the 262 articles. The unduplicated count of unique individuals was 1,114. The average number of co-authors per publication was 7.8 representing an average of 2.7 institutions or organizations and 3.7

[8] Some publications acknowledged more than one PIA grant. For grant-level analyses, these publications were counted for each grant. For publication-level analyses such as those included here, each publication was counted only once (unduplicated).
[9] Because some projects were funded later during the time interval examined, those projects had less time to generate publications counted in the total. For example, a project funded in 2010 would only have had three years to produce publications counted in the observational window, while a project that was funded in 2006 would have had seven years. Thus, projects funded in later years may have been under-counted in the publication count.

academic departments. In terms of publications, there was considerable multidisciplinarity among the co-authors.

The 5-year Journal Impact Factors (JIFs) were also examined for the journals in which the research articles appeared. The impact factor of a journal in a particular year is the number of citations received in the current year to articles published in the two preceding years divided by the number of articles published in the same two years. The measure applies to journals and not articles or investigators. JIFs were originally developed as a tool for librarians to aid them in identifying which journals were more important for the library to carry. Their use as an evaluation measure is based on an assumption that articles reporting on higher quality science are more likely to be published in the more prestigious journals, and therefore JIFs have sometimes been used as a proxy measure of the quality of the science in an article. Their use has also been extended by administrators and department chairs to assess faculty on the quality of their scientific work. This is a misleading use of the JIF, and there is currently public resistance by some researchers and faculty against this practice (San Francisco Declaration on Research Assessment, 2013). The data on five-year JIFs are reported with these cautions in mind. Almost all (96%) of the journals in which the 262 articles were published had a five-year JIF. As shown in **Exhibit 3.16**, their distribution was highly skewed (which is typical); about 66% of the articles appeared in journals with five-year JIFs of less than 5, another 27% appeared in journals with five-year JIFs of 5 to 15, and the remaining 3% appeared in journals with JIFs greater than 15.

Exhibit 3.16. Number of Journal Articles per Journal by 5-Year JIF



The journals in the top tier of five-year JIFs along with the numbers of article and five-year JIFs are shown in **Exhibit 3.17.**

Exhibit 3.17. Distribution of Journal Titles, Number of Articles per Journal, and Journal Citation Reports® (JCR) 5-Year Journal Impact Factor for the Top Tier

Journal Title	Number of Articles	JCR 5-Year Impact Factor
Nature	2	38.159
Advanced Drug Delivery Review	1	15.431
Annual Review of Pharmacology and Toxicology	1	21.644

Journal Title	Number of Articles	JCR 5-Year Impact Factor
JAMA	1	29.273
Nature Reviews Immunology	1	35.851
PLoS Medicine	1	16.426
Total number of articles in tier 1	7	-

SPIRES offers a report feature which includes creating a report of the top 20 (top 50, etc.) journals for all of NIH or a particular IC by year where top 20 is defined as the 20 journals having the greatest numbers of publications from grants funded by that IC. A report of the top 20 journals for NIAID for 2013 was prepared and cross-walked with the top 20 journals in terms of numbers of PIA publications. As shown in **Exhibit 3.18,** eleven of the journals are found in both the PIA and NIAID lists, indicating comparability in terms of journals in which scientific findings are published.

Exhibit 3.18. Journals Common to the Top 20 Journals by Number of Publications for PIA Projects (2006-2013) and the Top 20 Journals for NIAID Publications for 2013 Based on SPIRES Data

Journal	Top 20 Rank for PIA Publications 2006-2013	Number of PIA Publications	Top 20 Rank for NIAID Publications 2013	Number of NIAID Publications
Journal of Virology	1	32	2	482
PLoS One	2	30	1	725
Journal of Biological Chemistry	4	10	8	190
Journal of Immunology	5	9	3	398
AIDS	6	7	17	94
PLoS Pathogens	10	5	5	229
Vaccine	11	5	19	82
Proceedings of the National Academy of Sciences	12	4	4	275
Journal of Acquired Immune Deficiency	15	3	9	158
Journal of Infectious Diseases	17	3	7	197
Virology	20	3	14	100

3.4.2 New Research Grants

Evaluation Question

3A. Was there an impact on targeted research areas?

3B. Did the program increased the research capacity of the field?

Through September 30, 2013, 48 of the 74 AVR and MIP investigators (65%) obtained a total of 143 new NIH grants of all types. **Exhibit 3.19** shows the number of NIH grants by activity code for the two initiatives. Three sets of activity codes (grant mechanisms) are particularly important. First, one of the objectives of both initiatives was that investigators would move from their R21/R33 grants to R01s (R56 grants are combined with R01s.) As **Exhibit 3.19** shows, AVR and MIP investigators obtained 46 new R01 and R56 grants (32% of the total new grants). Second, investigators obtained 15 new R41, R43, and R44 grants funded under the STTR and SBIR programs which support development of new technologies; all but one of these grants were obtained by MIP investigators. Finally, there were a total of 21 new U19 grants, many of which were funded under the successor to the MIP initiative. Using movement into these

grant categories as one indicator of forward movement in the developmental process, almost half of the new grants (93 grants, or 65% of the total) show the desired forward progression.

Exhibit 3.19. New NIH Grants by Activity Code, AVR and MIP Initiatives

Activity Code	AVR	MIP	Total
DP2	--	1	1
K24	--	1	1
S10		2	2
T32	1	2	3
P01	5	6	11
P30	1	--	1
P50	--	2	2
R01	12	29	41
R03	--	2	2
R13	1	2	3
R21	13	16	29
R33	--	1	1
R41	--	1	1
R43	1	11	12
R44	--	2	2
R56	3	2	5
U01		4	4
U19	2	19	21
U54		1	1
TOTAL	39	104	143

Subsequent grant activity among investigators whose projects either transitioned to the R33 phase or stopped at the R21 phase is shown in **Exhibit 3.20**. Slightly more new grants were obtained by investigators whose projects had transitioned (80 versus 63). Investigators who had transitioned were more likely to obtain U19 grants than those from projects that stopped at the R21 phase, but were about equally as likely to obtain R01s, R56s, and the SBIR/STTR grants (R41, R43 and R44). Investigators on transitioned R21/R33 projects were more likely than those on projects that stopped at the R21 phase to be PIs on P01 grants.

Exhibit 3.20. Activity Codes for New NIH Grants by R21/R33 Transition Status

Activity code	Stopped at R21 phase	Transitioned to R33 phase	Total
DP2	--	1	1
K24	--	1	1
S10	1	1	2
T32	1	2	3
P01	3	8	11
P30	1	--	1
P50	--	2	2
R01	20	21	41
R03	--	2	2

Activity code	Stopped at R21 phase	Transitioned to R33 phase	Total
R13	2	1	3
R21	14	15	29
R33	1	--	1
R41	--	1	1
R43	6	6	12
R44	1	1	2
R56	2	3	5
U01	4	--	4
U19	6	15	21
U54	1	--	1
TOTAL	63	80	143

The evaluation team also investigated subsequent grants that remained in the AIDS vaccine or topical microbicide research fields. Whether a new grant remained in one of these two targeted research fields was determined using *Program Class Codes* (PCCs). These codes, created by each NIH IC, designate a scientific program, category of research, and Program Officer for administrative purposes. Targeted research was defined as applications/projects that carried a NIAID PCC for topical microbicides (A22C, A22E, and A22F) or AIDS vaccine research (A24A—A24R). This scheme may undercount the number of projects that addressed these two areas since a few other ICs may fund research projects on these topics using other PCCs. Applying this definition, 43 new NIH grants addressed either AIDS vaccine or topical microbicide research (30% of total new projects).

3.4.3 New Collaborations

Evaluation Question

1G. Does the PIA mechanism create networks across the research portfolio?

2A. Does the PIA program satisfy the need to advance new products through the developmental pipeline?

3D. Did the research promote multidisciplinary research?

New collaborations with other research investigators were one of the early and most important outcomes that arose from the AVR and MIP initiatives. According to the PI survey results, nearly three-quarters of PIs (74%) reported forming at least one new research collaboration through their R21/R33 activities. Almost three-fifths of the investigators stated that new collaborations brought together disciplines or sectors that had traditionally not worked together; this was observed to be much higher for MIP investigators (69%) than for AVR investigators (31%). New collaborations were most common with individuals in academia, but many respondents mentioned establishing new partnerships with private industry and non-profit organizations.

Interviews with the nine multiple award PIs provided additional detail about and insight into these collaborations. All nine PIs said that they established new collaborations or partnerships as a result of their R21/R33 research. Collaborations that began during the R21 phase were especially helpful in contributing to subsequent research project grants at NIH as the following example shows. ***"We started collaborating with clinicians who had conducted various trials using microbicides. The expertise they brought to us was huge. That ended up leading us to getting interested in applying for a second MIP grant. The new collaborator on our first grant was also key personnel on the second grant, and then ended up being the PI of the U19 application we just submitted. The U19 brought in a bunch of people. So the R21/R33 had a profound effect on getting collaborations going, and bringing people together to***

do a lot of good work." Another PI emphasized the value of collaborating with investigators at various points along the product development pipeline. ***"As part of the R21/R33 mechanism, you are taking a product from early development through animal studies and eventually to human testing. Although our product hasn't been tested in humans yet, we were able to meet clinicians who are collaborating with us today. So our R21/R33 was a very useful grant. We are working with three different groups that use the same technology we use but on different proteins. It was helpful to talk with them and think about these different areas."*** A third PI raised a different point. ***"In our second R21, groups we collaborated with were basically competitors who were working individually on different products for HIV prevention. This mechanism took those groups and brought them together. That is very different from most of our grant mechanisms.***"

Many of these collaborations began early during the research process. Some research collaborations began as early as the application development process. ***"For the grants that transitioned, the collaborative relationships started when we were developing the proposal. We thought about the work we wanted to do and identified collaborators. So they were involved with the whole project."*** Others occurred after the application had been awarded and the research had begun. ***"For our first grant, collaborations occurred during the R21 and R33 and beyond. For our second grant, they began during the R21 and extended somewhat beyond that. I'm still in contact with one collaborator and recently wrote a review article with him. Even though we don't work together on a specific research project [now], the collaboration was fruitful in a different way.***"

While four of the nine multiple award PIs reported that they subsequently obtained additional research funding through their collaborations, eight of the nine emphasized the importance of their non-financial contributions to research. ***"We gained the access to my collaborator's animal models and his added expertise. I had had no hands-on experience with animal models before. I have subsequently published a paper with this collaborator. I have also educated myself by reading his papers and asking him questions to learn how to think about animal model work more methodically. Having his expertise on hand is very useful.***"

As the previous example suggests, bringing together individuals from different disciplines can lead to benefits that outlast the specific project. One multiple award PI noted the value of the R21/R33 mechanism in setting up multidisciplinary collaborations. ***"It did set up some collaborations that are multidisciplinary. It also made us more able to communicate with people working in other fields. This happened even when it wasn't our own research. We could appreciate what other people were doing. The ability to pull together a multidisciplinary grant makes a scientist better able to judge multidisciplinary science. There is a carry-over benefit. Educating Principal Investigators may not be the benefit NIH is looking for, but it does have that effect.***"

A critical phase in the development of these collaborations comes when the original grant ends. It can be difficult to maintain collaborative relationships when the funding has run out. "***We formed collaborations that would not have formed otherwise. They are not necessarily all long-lived. If things don't work, then those collaborations can fall apart depending on the collaborator's location and interest level. You're trying to bring together basic scientists and translational scientists and their worlds are very different. They'll get together for the funding opportunity, but when the opportunity goes away there may be less motivation to stick together.***"

3.4.4 Impact on AIDS Vaccine and Topical Microbicide Research

There was widespread agreement among the Program Directors, Program Officers, and multiple award PIs that both the AVR and MIP initiatives have had a major impact on AIDS vaccine and topical microbicide research. It is difficult to measure this impact in a quantitative manner, but there are two types of qualitative evidence that support this assertion. The first set of data is the perspectives of the

three respondent groups, who can look across their fields from different vantage points. The second type of evidence is the variety of scientific advances that have emerged from both initiatives.

3.4.4.1 Perspectives of Program Directors, Program Officers, and Principal Investigators

Evaluation Questions

2A. Does the PIA program satisfy the need to advance new products through the development pipeline?

3C. Has the developmental pathway been accelerated?

The AVR and MIP Program Directors agree that the R21/R33 mechanism has had a major impact on the growth and pace of scientific development in their respective fields. The AVR Program Director noted that "***when it was proposed and initially implemented, I thought it was a perfect vehicle for funding research quickly. It ended research that was not working and promoted research that was. The impact on the [AIDS vaccine research] field would be that in a field where we are trying to create progress as quickly as possible, we are moving things along. It could mean that we reach a vaccine in five years instead of ten years, but we won't know that until it happens….There are many things contributing to this, but the funding mechanism is one of them."*** The MIP Program Director recalled his initial scientific goal of establishing and maintaining a 'robust' developmental pipeline of topical microbicides and stated that ***"[it's] very simple—without this funding mechanism, we would have no pipeline and most of the delivery systems and technologies we are using today to develop new molecules we would not have—plain and simple. If we hadn't started this in 2006, we would not have these things today. The impact of this program will still be felt in 2020 and beyond.***"

The DAIDS Program Officers elaborated on these themes. "***It allowed us to test a much larger number of ideas for the amount of money spent. A successful program results not only in ideas, not only in getting positive results, but also in getting negative results so that you can eliminate ideas. We have often been asked how we can gauge success. Success is not only projects moving on, but it is also projects and ideas that you can eliminate***." Another Program Officer offered an assessment of both initiatives: "***I think from the MIP standpoint, it's been very productive in terms of the research that has continued. They are still using the program and some of the investigators have moved into larger grants like P01s. For AVR, some of the investigators were successful in getting R01s. I can't remember a specific vaccine candidate that has come from a specific project that wasn't covered in some other fashion. …My general impression is that several projects are moving forward on the AVR side***."

The multiple award PIs also shared their views on how the PIA mechanism has benefitted AIDS vaccine and topical microbicide research. One respondent described its impact for AIDS vaccine research. ***"From my point of view, I know that without the R21/R33 program I and other investigators might never have initiated our projects because it is so daunting to obtain a regular R01 grant. In other words, I would always be a basic scientist forever, because I never would have had the opportunity to get drug discoveries in the clinical environment. Every basic scientist would love to have his discovery tested, but we don't have an introduction into that area. That's what the R21/R33 mechanism did for me. The mechanism allowed us to transform our basic science knowledge of drug discovery into the translational medicine area. This encourages basic scientists to do more drug discovery in our work."*** Another PI related that the MIP PIA "***…allowed us to do work we otherwise would not have been able to do. It brought my collaborator into the HIV/AIDS field who would otherwise not have entered it. It brought my lab into the microbicides field, which we would otherwise not have been in. It allowed us to generate some small molecules for which we filed as intellectual property and now have patents pending."*** A third PI described how the PIA initiative was contributing to accelerating the pace of science. ***"In our case we had three inhibitors. We identify targets and develop compounds. Usually it takes almost ten years to know whether or not a target was valid and can really block HIV transmission. The R21/R33 mechanism was really great because after two years we were able to***

identify the compounds and after five years we could determine whether we had obtained protection in an HIV transmission model. So, after five years we now have an answer. Usually it takes much longer because it requires two R01s to make the determination. In our research, two series of compounds were not successful in offering great protection against HIV transmission. However, our last series of compounds was very successful in offering great protection. So, we are really happy. Now we know it's worth pursuing the second generation of these compounds."

3.4.4.2 Scientific Advances

The AVR and MIP Program Directors identified several specific scientific advances stemming from their initiatives (see **Exhibit 3.21**). For both AVR and MIP initiatives, these accomplishments represented new models, new technologies, and new research directions.

Exhibit 3.21. Scientific Advances Attributed to AVR & MIP Initiatives

AVR	MIP
▪ Induction of mucosal immunity in nonhuman primates by secreted Hsp gp96-IG-SIV ▪ Capsid-incorporation of HIV antigens as a novel adenovirus HIV vaccine approach ▪ Targeting gp41 to elicit neutralizing antibodies ▪ Exploring in vitro and in vivo T-cell immunity to SIV with MHC-identical macaques	▪ Creation of a new science of perceptibility as a new way to examine acceptability of microbicides ▪ Creation of a new sheep safety model ▪ Integration of optimal tomography with novel tissue imaging mechanisms ▪ Introduction of nanotechnology into microbicide research ▪ The intra-vaginal pod ring ▪ Evaluation of hydroponics for microbicide research

4. Cross-Case Analysis of Multiple Case Studies (NIAID, NCI, NIDA, and NIDCD)

This chapter presents results from the cross-case analysis of four secondary case studies detailing how the PIA mechanism has been implemented in four other settings at NIH. The four cases represent applications of the mechanism with different scientific problems and call attention to variations in how the mechanism was structured and implemented. The cross-case analysis is not an evaluation of the secondary cases; rather, the analysis provides a broader context for consideration of how other PIA initiatives have approached and addressed several of the challenges the NIAID DAIDS AVR and MIP initiatives faced.

Based on interviews with the four Program Directors and archival data on the FOAs for the four initiatives, the cross-case analysis focuses on five general implementation issues:

1) Decision to use the R21/R33 funding mechanism
2) Structure of the R21/R33 mechanism
3) Grant review process
4) Milestone negotiation process
5) Transition review process

Because these are secondary cases, this chapter does not provide the same level of detail on the four cases as was provided for the AVR and MIP initiatives. The emphasis in this chapter is on the cross-case comparison of the secondary cases.

4.1 Selection and Characteristics of the Secondary Cases

Since the introduction of the NIH Phased Innovation Award mechanism in 1999, nine of the 27 NIH ICs have used it. To explore how it has been used at different Institutes, the evaluation team selected four cases that reflect different areas of biomedical research and technology development. The four cases are described below.

4.1.1 NIAID—Division of Microbiology and Infectious Diseases

NIAID's Division of Microbiology and Infectious Diseases (DMID) currently supports four initiatives that use the R21/R33 mechanism. This case provided an opportunity to examine R21/R33 implementation experiences and outcomes at a second Division within NIAID. This case focuses on one of the four initiatives, *Host-targeted Interventions as Therapeutics for Infectious Diseases (RFA-AI-11-032).* This is a new initiative that "…seeks to stimulate innovation in the discovery and development of therapeutics that target host-encoded functions required for infection, replication, spread and/or pathogenesis by one or more NIAID Category A, B, or C pathogens." The Program Director stated that this was a field of research that is very new, and the initiative is an attempt to lead researchers into this area. The RFA was new; it was posted in July 2011 and had an expiration date in December 2011.

The Division had had no prior experience with the R21/R33 mechanism before the release of this initiative. The Program Director learned about the R21/R33 mechanism through attending a workshop conducted by the MIP Program Director.

4.1.2 NCI—Innovations in Molecular Analysis Technologies for Cancer

The Innovations in Molecular Analysis Technologies for Cancer (IMAT) is the program that originally developed and launched the PIA mechanism in 1998 with an initiative called *Applications of Innovative Technologies for the Molecular Analysis of Cancer* (PAR-98-067). The evaluation team believed it was important to interview a Program Director from this program to obtain some insights into how the mechanism was originally developed and applied. The program has evolved considerably since its

inception. In 2008, program leaders chose to discontinue use of the PIA mechanism although they have continued to fund the programs through individual R21s and R33s.

When IMAT began in 1998, there had been several major advances in biomedical imaging technologies at the *in vitro* level (e.g., magnetic resonance imaging, nuclear medicine, computed tomography, ultrasound). At the same time, NCI had funded research that dramatically increased knowledge about cancer at the genetic and molecular level, and there was a need to develop new imaging technologies that could provide information at the cellular and molecular (*in vivo*) levels. IMAT was an effort to fund the developmental costs of new, high-risk, high reward approaches.

The IMAT program is large; at one point there were three inter-related streams of research funded through the initiative. A sense of the size and scope of this program is apparent from the number of grants it has funded. To date, the IMAT Program has funded a total of 327 R21 grants[10] and 179 R33 grants; of the latter, 72 were Phased Innovation Awards that had transitioned from the R21 developmental phase. IMAT involves Program Officers from all extramural NCI Divisions, but there is a strong centralized management process in place.

4.1.3 NIDA—Biological Data Integration

The biological basis of drug use, addiction, and its treatment has been a major research priority at NIDA for many years. Through research funding, many investigators constructed valuable databases that contained biological and psychosocial data on human and animal research subjects. Investigators and their institutions tended to view these databases as valuable resources and were reluctant to share them with others outside their immediate research networks. Efforts to share these data were also hindered by the lack of a common set of data definitions and conventions that would apply across institutions. In 2009, NIDA created an initiative called *Secondary Data Analyses for Substance Abuse Research* (RFA-DA-09-020). The purpose of the initiative was to provide interested investigators with exploratory funding that would enable them to reach out to other investigators who were interested in forming a partnership that might bring two or more biological databases together. By providing investigators with exploratory funding, NIDA hoped to break down some of the resistance to sharing and harmonizing these databases. During the first two years, investigators could establish collaborations, develop definitions that enabled them to link their datasets, and lay the ground work for research that could be pursued during the subsequent three years of the R33 phase.

The Program Director of this initiative was not familiar with the R21/R33 mechanism before being asked to lead this initiative, although NIDA has used it in the past and the present. The initiative involved program staff from several Divisions at NIDA. The Program Officers operated autonomously, and management of the initiative across the Divisions was a challenge. This was further complicated by the initiative's lack of a formal status as a program; according to the Program Director, it was viewed as simply a part of NIDA's larger data integration activities.

4.1.4 NIDCD—Accessible and Affordable Hearing Health Care

The fourth case also involved the development of a new research field. NIDCD previously funded basic and clinical research on hearing health care, but had never funded research on the hearing health care system as a whole. Health services research (and health systems research) are not new fields, but had not been pursued within the hearing health care field before this initiative. The PIA mechanism allowed NIDCD to provide funds to bring new disciplines together as partners and to develop the tools they would need during an exploratory phase to conduct health services research during the developmental phase.

[10] These 327 awards include 12 awards that had been recently approved as of 3/27/2014, but not yet formally awarded.

NIDCD is a small NIH Institute with 13 Program Officers. Its small size and budget meant that the Program Officers know most of their research investigators by name.

NIDCD used the PIA mechanism in 2009 with a pair of related initiatives aimed at improving hearing health care interventions. These initiatives had a very broad focus—applicants could address any of the Institute's seven mission areas. In retrospect, this broad focus was seen as part of the reason these two initiatives failed. For the current initiative, the decision was made to narrow the focus to one specific program area (access and affordability). The RFA has been reissued three times.

Exhibit 4.1 summarizes several characteristics of the four secondary cases and highlights their similarities and differences. All four cases used the RFA funding announcement, with the NCI IMAT program adopting this approach in 2005. Two of the four cases involved a single, one-time announcement, while the other two cases continued for several years, with multiple reissues of the RFA. In two cases, the scientific field was described as "emerging" while for the other two cases, a research field already existed. For three cases, the creation of new research partnerships was an important aim, while this was less true of the fourth case. Three of the cases had had institutional experience with the use of the R21/R33 mechanism in the past (and were continuing to use it in the present), while the fourth case was the original initiative for which the mechanism was developed.

Exhibit 4.1. Description of the Four Secondary Cases

Characteristic	Host-targeted Interventions as Therapeutics for Infectious disease	Innovative Molecular Analysis Technologies for Cancer	Secondary Data Analyses for Substance Abuse Research	Accessible and Affordable Hearing Health Care (Research on Hearing Health Care)
NIH Institute	NIAID-DMID	NCI	NIDA	NIDCD
Funding Opportunity Announcement(s)	▪ RFA ▪ Issued in 2011 ▪ Single announcement	▪ PAR, then RFA ▪ (R21/R33 stopped in 2008) ▪ Issued in 1998 ▪ Reissued several times	▪ RFA ▪ Issued in 2008 ▪ Single announcement	▪ RFA ▪ Issued in 2010 ▪ Reissued several times
Science Orientation	▪ Emerging new field ▪ New types of therapeutics for infectious diseases ▪ Product development ▪ New partnerships less important	▪ New applications ▪ Molecular and cellular analysis technologies ▪ Product development ▪ Creation of new research partnerships important	▪ New applications ▪ Informatics development ▪ Product development ▪ Creation of new research partnerships important	▪ Emerging new field ▪ Health services/systems research in hearing health care ▪ Applied research ▪ Creation of new research partnerships important
Prior Institutional Experience with R21/R33	Institutional experience with several R21/R33 initiatives in past and present	R21/R33 originated with this program in 1998	Institutional experience with several R21/R33 initiatives in past and present	Institutional experience with several R21/R33 initiatives in past and present
Scope of Program	Single Division	Multiple Divisions	Multiple Divisions	Single Division
Number of Funded Projects	12 funded projects	506 funded projects	9 funded projects	10 funded projects

4.2 Deciding to Use the PIA Mechanism

For each of the four cases, the decision to use the R21/R33 mechanism involved some consideration of alternative funding mechanisms and weighing scientific and administrative goals. The following two subsections discuss these two factors.

4.2.1 Consideration of Alternative Funding Mechanisms

Interviews with Program Directors revealed that they considered a variety of alternative funding mechanisms as approaches for funding their respective initiatives, but ultimately rejected these alternatives in favor of the R21/R33 mechanism. **Exhibit 4.2** summarizes the reasons these alternative mechanisms were rejected.

Exhibit 4.2. Reasons for Rejecting Alternative Funding Mechanisms

Mechanism	NIAID DMID	NCI IMAT	NIDA	NIDCD
R01	▪ Five years was too much money for high-risk early stage research ▪ Investigators at early stage unlikely to be able to provide strong preliminary data	▪ Not designed to promote high-risk technology development or encourage new research partnerships ▪ Did not provide sufficient control over funding if project failed	▪ Had small budget for this initiative, and the R21/R33 would allow funding more grants ▪ Did not provide sufficient control over funding if project failed	▪ Did issue a separate R01 announcement in tandem with this one ▪ R01 required greater degree of preparation and readiness than R21/R33
R21	---	▪ Gap in funding after R21 ended—needed to promote transition to developmental phase	▪ Considered *Cutting Edge Basic R21 Research Award (CEBRA)* but rejected it because it could take investigators two years to bring a merged dataset together then funding would end	--
R43/R44 (SBIR)	--	▪ Not designed for early-stage testing of ideas	--	▪ Good fit for technology-related research but this was designed to build a field
U01 Cooperative Agreements	▪ Provided too much PO oversight	--	--	--
Contract Vehicles	--	▪ Not attractive to academic research investigators (too little prestige)	--	--
NCRR P41 Technology Development Centers	--	▪ Too few funds to permit funding more than one or two per year	--	--

Exhibit 4.2 shows that the four Program Directors considered the use of R01 grants, but rejected this mechanism because the high-risk, innovative nature of the grant applications they hoped to attract traditionally did not do well in scientific reviews. They also noted that the five-year R01 did not provide a

sufficient degree of administrative control if a project failed during its first two years. Other grant mechanisms were also considered, including the *Cutting Edge Basic Research Award* (CEBRA), a type of R21 mechanism that explicitly targets novel, high-risk research for which there may be little or no preliminary data. CEBRA grants were aimed at experienced investigators or investigators with a proven research history in a field other than drug abuse research who wanted to test novel hypotheses or approaches that were not represented in NIDA's research portfolio. However, this mechanism was rejected because any investigator whose project succeeded would have to reapply for new funding after two years. Cooperative Agreements were considered in one case, but the Program Director indicated that this mechanism provides for more oversight and involvement by program staff than was desired.

These reasons are similar to those reported by the AVR and MIP Program Directors and NIAID DAIDS program staff members.

4.2.2 Scientific and Administrative Goals of the Four Initiatives

The decision to use the R21/R33 mechanism also involved consideration of the various scientific and administrative goals for each initiative. These differed somewhat by initiative as shown below in **Exhibit 4.3**.

Exhibit 4.3. Scientific and Administrative Goals of the Four Initiatives

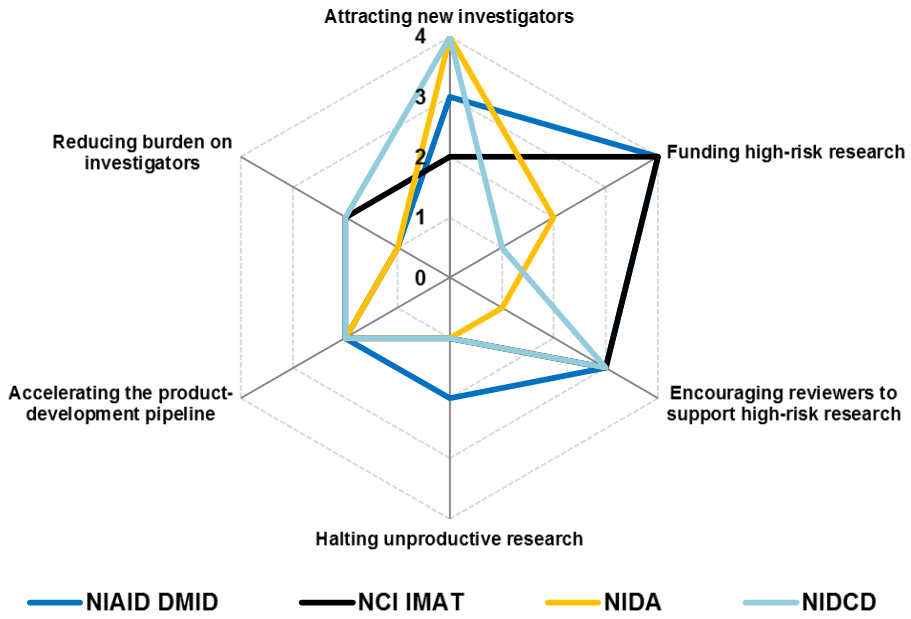


Exhibit 4.3 shows that two initiatives (NIDA and NIDCD) rated "attracting new investigators" as their most important scientific and administrative goal. This is consistent with their stated intentions of creating new research partnerships and building research fields. The other two initiatives (NIAID DMID and NCI IMAT) rated the goal of "funding high-risk research" as their most important goal. Both initiatives shared a product-development orientation. The goal of "halting unproductive research" is only minimally important for three of the four initiatives and only somewhat important for the fourth.

By comparison, "halting unproductive research" was the most important goal for MIP and "funding high risk research" was the most important goal for AVR. "Accelerating the product development pipeline" was less important for all four secondary cases than it was for both AVR and MIP.

4.3 Structure of the PIA Mechanism

With slight variation, the way each of the four initiatives structured their use of the PIA mechanism followed a similar pattern. Time periods for the R21 and R33 components of the grants were consistent with those established by NIH. Dollar limits for the R21 component were consistent with NIH regulations for three of the four initiatives, and less than this amount for one initiative. For two of the initiatives, the R33 dollar limits were consistent with NIH regulations; the AVR and MIP initiatives used similar levels. The other two initiatives, however, had higher dollar limits. At NCI IMAT, there was no formal budgetary limit, but budgets exceeding $500,000 per year required programmatic approval. For NIDCD, the dollar limit was closer to that of an R01.

Exhibit 4.4. Structure of the PIA Mechanism for the Four Initiatives

Structural Elements	NIAID DMID	NCI IMAT	NIDA	NIDCD
Funding Announcement Mechanism	RFA	PAR (1999-2004) RFA (2005-)	RFA	RFA
Number of Application Receipt Dates Per Year	One	Three	One	Two
Grant Review	SEP	CSR/SEP	SEP	SEP
R21 Component	NTE two years, and $275,000 in direct costs, with no more than $200,000 allowed in any one year	NTE two years and $100,000 in direct costs per year (later raised to $125,000 per year)	NTE two years and $260,000 in direct costs, with no more than $200,000 in any one year	NTE two years and $275,000 in direct costs, with no more than $150,000 in any one year
R33 Component	NTE three years, and $300,000 in direct costs per year Total project NTE five years	NTE three years No budgetary limit but large budgets over $500,000 per year require approval Total project NTE four years	NTE three years and $240,000 in direct costs per year Total project NTE four years	NTE four years and $1.5 million in direct costs, with no more than $400,000 in any one year (later reduced to $375,000 in any one year) Total project NTE five years
Transition Reviews	Transition applications reviewed as a group once yearly	Transition applications reviewed as received	Transition applications reviewed different ways in different Divisions	Transition applications reviewed as received
Percentage of R21s anticipated to transition to R33	50%	No estimate	50%-70%	100% if meet milestones
Transition decision finality	No appeals	Investigator could appeal if R21 did not transition	No appeals	No appeals

Two of the four initiatives capped the total duration of both phases at four years, a shorter interval than that used by the AVR and MIP initiatives. Only one Program Director offered an explanation for this four year limit. At NCI IMAT, for example, the Program Director explained that there was a strong emphasis on obtaining preliminary results within the first year of the project; most of those projects in fact did so, with only 10% going into a second year. Those projects tended to be ones in which there was a change in research staff, or some type of equipment failure.

4.4 Grant Review Process

Three of the four initiatives used RFA funding announcements from their inception. The fourth initiative (NCI IMAT) began by using a PAR announcement, but changed to a RFA announcement around 2005. Use of the RFA announcement allowed the initiatives to conduct the grant review process using Special Emphasis Panels rather than through CSR. As Chapter 3 showed, the Special Emphasis Panels offered an important advantage in that the Program Director could provide an orientation to the reviewers prior to the start of the review process. This orientation allowed the Program Director to emphasize the high-risk orientation of the initiative, downplay the importance of preliminary data, and explain the review of milestones. Chapter 3 also documented that even with this orientation, the peer review panels struggled with the innovative nature of the applications and their assessment of the milestones.

Interviews with Program Directors from the secondary cases showed that these issues were also encountered. For example, one Program Director noted that ***"a lot of work went into identifying and training good reviewers. I felt good about how most of the technical reviews went regarding getting the right people in to review particular applications. We established a good cadre of reviewers in technology development areas"***. The Program Directors did take advantage of the opportunity to address Special Emphasis Panels prior to the start of the reviews; however, this did not always help. One Program Director reported that an earlier R21/R33 initiative was not renewed, in part because the review community "…***found it really, really hard to understand what we wanted to do. Instead of viewing the R21 phase as the preliminary pilot phase, they wanted more proven work. They couldn't understand the phase structure of the program."*** However, this same Program Director noted that "…***since this current initiative is a brand new one for our Institute, it may have been easier for the reviewers to understand what we are trying to do. The first R21/R33 was Institute-wide so anyone could apply. The current one is targeted to a specific program area, which is a more effective way to use the mechanism.***"

Only one Program Director mentioned any possible drawbacks from using Special Emphasis Panels for the grant review process. The Program Director noted that it could be more difficult to recruit reviewers for those panels because participation is viewed by some academic researchers as less "prestigious" than participation in a CSR peer review panel.

A final response addressed the recent reduction in the page limit for research narratives in grant applications (reduced from 20 to 12 pages). For one initiative, program staff advised applicants to spend more space on describing the R21 portion of the application, and less on the R33 phase. The Program Director used the pre-review orientation to alert reviewers that investigators had been told to spend less time on the R33 portion of the application, but noted that it was hard to persuade reviewers to accept that.

4.5 Milestone Negotiation Process

Program Directors for the four initiatives encountered problems similar to those reported by the AVR and MIP Program Directors regarding the milestone negotiation process. Problems included: the quality of the feedback on investigators' proposed milestones from the review group; the learning curve the Program Officers experienced in working with investigators to create milestones that were quantitative, well-defined, and objective; and creating a process for negotiating the milestones.

The four Program Directors agreed that the general process of negotiating milestones was challenging and time-consuming; one Program Director estimated that it took 3-4 hours per award to negotiate a set of project milestones. Program Directors also commented on the variable quality of review group feedback on investigators' proposed milestones, but noted that they had to rely on the reviewers' comments in the Summary Statements and could not freely tell applicants the specific milestones they would like to see investigators adopt.

Learning as a group to conduct the milestone negotiation process was challenging for Program Officers who often were not initially familiar with milestones and how to formulate them. The process was generally the same across the four initiatives, and involved reviewing the project's Summary Sheet, contacting the investigator to share the feedback and initiate a discussion about how to improve the milestones, and repeating this communication process until a final consensus could be reached on the milestones. At this point, the final milestones would be communicated to Grants Management to become part of the Notice of Award. Overseeing the process would be more or less complex as more Program Officers or Divisions were involved. NIDCD was situated at the least complex end of this continuum because the initiative was small and the Program Director served as the Program Officer for all of the grants. For the NIAID DMID initiative, 3-4 Program Officers and the Program Director participated in the milestone negotiation process. This initiative was unusual in that the investigator and his/her Institutional Grants Management Officer took part in the negotiations as a means of preventing subsequent disputes over the milestones.

The two initiatives that included Program Officers from multiple Divisions differed substantially in how they were able to learn from the milestone negotiation process over time. For NCI IMAT, Program Officers within a Division met as a group to conduct the negotiations, and the Program Director attended as many of these sessions as possible. It was clear that some Program Officers were more skilled at formulating milestones, and often these individuals would teach the others how to do it. Since this initiative continued for more than eight years, the Program Officers as a group improved their ability to negotiate milestones, and this transferred to teaching PIs how to formulate milestones during their application development phase. In this way, the quality of proposed milestones improved over time as well. By contrast, there was almost no communication between Program Officers in different Divisions for the NIDA initiative and Program Officers negotiated milestones with their investigators without oversight.

The AVR and MIP milestone negotiation processes more closely resembled the IMAT model, with multiple Program Officers and Program Directors participating in the negotiation process. There was a high degree of discussion among the Program Officers and Program Directors for these initiatives, and a similar type of group learning process occurred, with Program Officers gaining increased skill and knowledge about milestones over time. Like the IMAT initiative, the AVR and MIP Program Officers passed their learning along to investigators who contacted them during the application development phase.

4.6 Transition Evaluation Process

Managing the transition evaluation process was a challenge for all four initiatives and they addressed this challenge in several ways. NIDCD and NCI IMAT both had multiple annual receipt dates (two and three per year, respectively). They evaluated the two-year transition applications as they arrived (first-in, first-out). Since investigators sometimes requested (and received) No-Cost Extensions, the actual arrival of transition review applications could be "off-schedule." The first-in, first-out evaluation process meant that Program Officers' workload could be spread more evenly across the year. On the other hand, investigators would experience the same problem described earlier in the AVR initiative, where transition funding was already spent on earlier projects.

The NCI IMAT case was further complicated by the fact that Program Officers from five NCI Divisions were involved. The Program Director took an active role in meeting with the Program Officers on a regular basis and helping them develop a common process. The Program Director also participated in many of the transition evaluation meetings and encouraged Program Officers to share ideas and procedures for conducting evaluations efficiently. This was critical since the IMAT used the R21/R33 mechanism over an eight-year period and funded 92 projects during that time (almost 12 projects per year on average).

NIAID DMID is adopting a transition evaluation process similar to that used by MIP. This initiative had a single application receipt date, and in theory, their investigators would be on the same schedule. This is likely to change as some investigators obtain No-Cost Extensions and therefore move to the following year's schedule. NIAID DMID's first transition evaluation process is scheduled to take place in 2014, and will evaluate the available transition applications in a single group (batch). For investigators, the batch approach means that all transition funding decisions will be made at the same time, rather than throughout the year. For the Program Officers, however, the batch approach will require a significant investment of time and effort concentrated into a short interval of time. This may be workable where the number of funded grants in the initiative is relatively small, as is the case with the host-targeted interventions initiative (12 funded projects); however, it may be more problematic when the initiative contains a larger number of projects, or, as is also true at NIAID DMID, there are multiple initiatives that began at the same time.

The NIAID DMID case is unique for a second reason. The Program Director established a written set of Standard Operating Procedures (SOP) modeled on the earlier NIAID SOP to govern the management process for the host-targeted interventions initiatives and the other three currently active ones. This SOP creates a two-tiered review process that requires that the transition evaluation process to be completed within a four week period. The first tier consists of a transition evaluation committee comprised of the Program Director and assigned and unassigned Program Officers. Participation on the committee differs slightly for initiatives managed within a single DMID branch versus those involving multiple DMID branches. Additional staff from within DMID may also participate at the Program Director's discretion. The transition evaluation committee evaluates each transition application and ranks it into one of three categories (Yes, Maybe, No). When all applications have been evaluated, discussed and ranked, a second committee, comprised of the members of the evaluation committee and additional NIAID staff members, meets to consider the overall summary and generate a final ranking of the applications by consensus. The Program Director prepares and submits a funding plan to Grants Management based on the final consensus. The first trial of this process will take place later in 2014, at which time the impact on staff time will be observed.

In contrast to the first-in, first-out and batch approaches discussed above, the NIDA initiative did not establish a clear process, and left the transition evaluation up to the Program Officers. The Program Director noted that there was no communication about conducting transition evaluations across the three Divisions involved with the initiative.

5. Conclusions and Recommendations

The NIAID DAIDS PIA Evaluation was designed to answer three broad questions about the implementation of and outcomes from DAIDS use of the NIH PIA R21/R33 mechanism:

1) *Is the PIA mechanism an appropriate mechanism for desired microbicide and prophylactic vaccine research?*

2) *Is the NIH PIA mechanism a valuable component of the DAIDS research portfolio? and*

3) *What is the overall impact of the PIA-supported milestone-driven research?*

An unusual and occasionally challenging feature of this evaluation is that it examines the use of a specific funding mechanism (the NIH PIA R21/R33 mechanism) rather than the two DAIDS initiatives that used it. Direct comparisons between the AVR and MIP initiatives were not the focus of the evaluation. Such comparisons would not be worthwhile in any event, since the two research fields differ in terms of their stage of development, size of research portfolio at DAIDS, and other considerations. This led the evaluation team to choose a case study design, in which the AVR and MIP initiatives represent different examples of the application of the PIA mechanism. In order to compare and contrast the experiences at DAIDS with the experiences of other NIH Institutes applying the PIA mechanism, the evaluation team conducted four additional secondary case studies. These included initiatives from a different Division at NIAID (DMID), and from three other Institutes, (NCI, NIDA, and NIDCD).

This chapter covers three areas: strengths and limitations of the evaluation; conclusions from the intensive case analysis of the AVR and MIP initiatives and the cross-case analysis of the four secondary cases; and recommendations for the future use of the NIH PIA R21/R33 mechanism. The strengths and limitations of the evaluation are discussed in Section 5.1. The conclusions from the evaluation are presented in Sections 5.2-5.4. Recommendations are provided in Section 5.5.

5.1 Strengths and Limitations of the NIAID DAIDS PIA Evaluation

As is true for all program evaluation studies (and research, as well), the NIAID DAIDS PIA Evaluation had several strengths and limitations as shown in **Exhibit 5.1** and discussed below.

Exhibit 5.1. Strengths and Limitations of the Evaluation

Strength or Limitation	Description
STRENGTHS	▪ First evaluation ever conducted of the NIH Phased Innovation Award (R21/R33) ▪ Multiple case study design allows generalization beyond NIAID DAIDS ▪ Provides a detailed analysis of the implementation process for the NIH PIA mechanism ▪ Use of multiple sources of qualitative and quantitative data allows triangulation across sources
LIMITATIONS	▪ Does not address the effectiveness of the evaluation ▪ Insufficient time has passed to observe long-term impacts (e.g., increased commercialization) ▪ Partial reliance on self-report data

5.1.1 Strengths

This evaluation is the first formal evaluation of the NIH PIA mechanism[11]. The PIA mechanism was first used at NCI in 1999 and has been used at NIAID since 2006. Over that period, the use of the PIA

[11] There was an abbreviated report concerning the use of the R21/R33 mechanism at NCI (Couch, 2004); however, this PowerPoint presentation does not describe the scope or methods of the evaluation.

mechanism has not been evaluated, despite its use for more than 25 initiatives at nine NIH Institutes. In that sense, this evaluation of the PIA mechanism at DAIDS is groundbreaking.

The multiple case study design used in this evaluation allows the results from to be generalized beyond NIAID DAIDS. The primary focus in this evaluation was the use of the NIH PIA mechanism at NIAID DAIDS in two initiatives. Had the evaluation examined only these two applications of the NIH PIA mechanism, it would have been possible to investigate how the mechanism was applied in these two cases and how that implementation affected the results obtained by those two initiatives. By including the secondary case studies, however, the evaluation could examine whether there were also differences in implementation outside DAIDS and whether those differences affected the experiences of other Institutes. This inclusion of outside perspectives makes the evaluation results useful to a wider audience that includes but extends beyond NIAID DAIDS.

The inclusion of a strong process orientation in the evaluation enabled the creation of a detailed analysis of the implementation of the NIH PIA mechanism at DAIDS and elsewhere. The initial seven-stage implementation model presented in **Chapter 3** provided a structure for consideration of the challenges encountered in implementing this mechanism. The results from the evaluation provide a useful guide for Program Officers considering the use of the NIH PIA mechanism.

The use of multiple quantitative and qualitative data sources permitted effective triangulation of findings across types and sources of data. The evaluation drew upon data from archival sources, bibliometrics, interview, and survey data. Data from multiple sources made it possible to use interview and archival data to expand upon survey findings, and survey findings to provide greater generalization for interview and archival data. This provided a more nuanced perspective on findings than would have been possible with any single source of data.

5.1.2 Limitations

There were also limitations of the evaluation as discussed below.

The evaluation does not directly address the effectiveness of the NIH PIA mechanism. The purposes of the evaluation were to examine the implementation of the PIA mechanism at DAIDS and determine whether the mechanism met the goals established for the AVR and MIP initiatives. The effectiveness of a program, mechanism, intervention or other evaluand implies a direct comparison with an alternative (the counterfactual). In commissioning this evaluation, DAIDS program staff members were very clear that they did not wish to compare the AVR and the MIP initiatives with each other. Such a comparison would not have been warranted, because the science underlying each initiative differed in important ways and any differences in the accomplishments of the two initiatives would have been strongly affected by the scientific challenges investigators in each field were facing. Instead, DAIDS program staff were interested in examining how well this funding mechanism (new to NIAID at that time) had succeeded in achieving various outcomes, such as stimulating new research publications, generating new research, promoting greater multidisciplinarity within the research communities, and encouraging new collaborations and partnerships.

Given that the AVR and MIP initiatives were not the focus of comparison, the evaluation team discussed with DAIDS program staff various possibilities based on different grant mechanisms. The NIH PIA mechanism had not been used before at DAIDS, and it was considered of interest within NIH precisely because no other mechanism existed that was comparable. The evaluation team considered possible alternative grant mechanisms such as R01s, R21s, and even SBIR grants (R43 & R44). R01s were ruled out as comparators because they do not typically attract the kind of high-risk, high-reward grant applications that were the focus for the NIH PIA mechanism. Both the R21s and the R43 SBIR grants were ruled out because they do not provide unbroken funding for successful projects (investigators need to apply for a new grant after completing the first one, unlike the R21/R33 hybrid). In addition, R43

grants usually require projects to be more developed than those that would be appropriate for the NIH PIA.

These reasons made the case study design attractive. Case studies are especially useful for situations where it may be difficult to distinguish between the intervention and its context. The evaluation team chose a multiple case study evaluation design that would look closely at the process of implementing the NIH PIA mechanism in the two cases at DAIDS and the outcomes that resulted from its use. The addition of the four secondary cases allowed for a comparison of implementation experiences in other settings besides DAIDS, thereby providing a means of demonstrating whether the challenges and issues DAIDS faced in applying the mechanism were unique to DAIDS, or more commonly experienced by others in different organizational settings. With this approach, it would be possible to say that users of the NIH PIA mechanism might anticipate the occurrence of certain decisions and issues and might also expect to see certain types of outcomes as a result of its use. It would not be possible to conclude that the NIH PIA mechanism is more effective than other alternative grant mechanisms, but in the absence of suitable alternative comparators, this is nonetheless an important conclusion.

Insufficient time has passed to observe long-term impacts. A second limitation is one that frequently arises in evaluations of research programs: the timing of the evaluation precludes any opportunities to examine long-term impacts. In terms of a product-development pipeline, a long-term impact would be taking a basic science discovery through preclinical and clinical research stages all the way to commercialization and utilization in the clinical care setting. This is often a lengthy process, and the oldest projects in the AVR and MIP portfolios are currently only seven years old. To observe whether any of the discoveries arising from AVR or MIP research projects actually makes it to routine use in the clinical setting would require ten years or more. As an example, the NCI IMAT project can claim several important science advances, but that program began fifteen years ago. While it is not possible to observe those kinds of clinical applications here, it is possible to highlight the development of new and promising research tools, methodologies, and animal models that have occurred through DAIDS PIA funding and which might well not have occurred at all in its absence.

The evaluation relies in part on self-report data. The evaluation relies on self-report information collected through interviews with NIAID and NIH program staff and an online survey of PIs. It is true that the data collected from interviews with key staff and the PI survey face all the limitations and potential biases associated with self-report data generally. This is unavoidable, since there were no other sources for the information elicited through these data collection approaches. An important step taken to reduce the possible impact of these potential biases was use of the analytic strategy of triangulation. That is, whenever possible, the evaluation team compared information from multiple sources and placed greater emphasis on findings that could be corroborated in this manner.

5.2 Conclusions

The evaluation addressed three broad evaluation questions and several sub-questions. Conclusions for each of the three evaluation questions are discussed below. Exhibits showing conclusions for the sub-questions related to each of the three overarching questions are presented in their corresponding sections.

5.2.1 Evaluation Question #1: *Is the NIH PIA mechanism an appropriate mechanism for desired microbicide and prophylactic vaccine research?*

Answering this question depends on how one defines an “appropriate” mechanism. In theory, any existing funding mechanism could be used to fund research for a given scientific field, from the R03 small grant to the larger R01s, P-series project grants, and the U-series Cooperative Agreement mechanisms. In order to provide a clear answer to this evaluation question, it is first necessary to unpack the meanings carried by the term “appropriate.” On further analysis, the term “appropriate” and the initial question subsume three subsidiary questions:

(1) *Did the structure of the NIH Phased Innovation Award mechanism provide a good fit for the specific challenges and goals DAIDS program staff faced in establishing the AVR and MIP research initiatives?*

(2) *Did NIAID DAIDS implement the NIH PIA mechanism in a way that enabled DAIDS program staff to meet their scientific and administrative goals?*

(3) *Were the challenges and issues faced by DAIDS program staff unique to the DAIDS implementation process, or similar to those experienced by other NIH Institutes that have applied the NIH PIA mechanism?*

Conclusions associated with each of these three overarching questions are discussed below.

5.2.1.1 Did the structure of the NIH Phased Innovation Award mechanism provide a good fit for the specific challenges and goals DAIDS program staff faced in establishing the AVR and MIP research initiatives?

Assessing whether the structure of the NIH PIA mechanism provided a good fit for the AVR and MIP research initiatives encompasses four evaluation sub-questions as shown below in **Exhibit 5.2**.

Exhibit 5.2. Summary of Conclusions—Appropriateness of the Mechanism for Microbicide and Prophylactic Vaccine Research

Evaluation Question #1: Is the PIA mechanism an appropriate mechanism for desired microbicide and prophylactic vaccine research?		
No.	**Evaluation Sub-Question**	**Conclusions**
1A	Is the mechanism budget (dollar limits) appropriate to support the research?	▪ Applications of the PIA mechanism have used existing dollar and time limits for R21 and R33 grants. ▪ The dollar limits are adequate for research other than animal studies. ▪ For animal studies, especially those using nonhuman primates, existing dollar limits on R21s are problematic. ▪ R21 dollar limits have sometimes restricted the types of research projects investigators would propose using the PIA mechanism.
1C	Is the PIA mechanism more appropriate than the R01?	▪ R01s are viewed as more appropriate for incremental, traditional research projects and less appropriate for innovative projects. ▪ The PIA mechanism is viewed as clearly appropriate for innovative, high-risk research.
1D	Are there differences in the types of applications received through the PIA mechanism versus the R01 that could be attributed to the type of mechanism or set-aside funding?	▪ R01s typically require strong preliminary data that support the feasibility of a proposed project. ▪ Preliminary data are often very limited or unavailable for innovative, "out-of-the-box" ideas and approaches. ▪ The PIA mechanism does not require preliminary data to the same extent as R01s and is therefore viewed as more receptive to novel, high-risk ideas and projects.
1F	What are the demographic and professional characteristics of successful and unsuccessful PIA applicants?	▪ There were a total of 298 applications submitted for the AVR and MIP initiatives between 2006 and 2011, of which 88 (29.5%) were funded. ▪ Neither PI academic degree nor institutional affiliation differed for funded versus unfunded applicants. ▪ PIs for both AVR and MIP were fairly similar. ▪ A total of 11 New Investigators were funded for both initiatives. Average success rates for New Investigators were higher for both initiatives than average success rates for R21 grants across NIH during the same six-year time period.

In interview responses, AVR and MIP Program Directors and Program Officers believed that the PIA mechanism is especially appropriate for scientific fields that are relatively narrowly focused and have a strong product-development orientation. These characteristics closely fit the microbicide research field. The AIDS vaccine research field focused on the identification of potential candidate vaccines, but had a broader emphasis as well on understanding the fundamental mechanisms that would describe how these candidates would work. Thus there was also a basic research component to the AVR initiative.

AVR and MIP Program Directors described similar scientific and administrative goals but differed slightly in the relative importance they attached to various goals. The MIP Program Director, for example, rated "halting unproductive research" as the most important goal, while the AVR Program Director ranked "funding high-risk, high-reward research" as most critical. Both rated "attracting new investigators" and "accelerating the product development pipeline" as very important, and neither considered the reduction of burden on investigators by permitting them to combine applications for two grants in the same proposal as particularly important.

Both Program Directors weighed the pros and cons of alternative grant mechanisms, focusing particularly on the R01 grant mechanism. They agreed that the R01 grant was not an appropriate choice for either initiative for two reasons. First, they believed that R01s addressed incremental science rather than innovative or high-risk approaches. They were concerned that the importance R01 applications place on substantial preliminary data was not appropriate when investigators were asked to generate new ideas for approaches, models, or hypotheses that had not previously been tested. They also said that the financial risk that innovative proposals posed to NIH needs to be managed. The typical R01 is funded for five years, which in their view was too long to continue funding for projects that had shown early on that they were dead-ends or otherwise unlikely to be productive. The PIA mechanism seemed ideal as a means of encouraging innovative, high-risk research proposals while allowing a means to "pull the plug" on projects that could not quickly demonstrate "proof of concept" within a two-year period.

In crafting the FOAs for the two initiatives, the Program Directors and their program staff incorporated the existing dollar limits and timeframes for R21 and R33 grants *circa* 2006. In retrospect, they had some concerns about the adequacy of the R21 budgetary limits for their scientific fields, which rely heavily on animal research (especially nonhuman primates). Dollar limits for the R33 phase were perceived as adequate. Assessing the adequacy of the timeframes for both grants proved more challenging, particularly for the initial R21 exploratory phase. Many investigators encountered initial delays in start-up that led to unexpended funds at the time of transition review (two years post-award). The Program Directors acknowledged that many investigators in each initiative received No-Cost Extensions in lieu of submitting their transition review applications. Thus, it may have taken some investigators more than two years to demonstrate that they had achieved their milestones.

A final consideration in assessing the "goodness of fit" of the PIA mechanism for the AVR and MIP initiatives concerned the types of research investigators and projects attracted to each initiative. One administrative goal was to attract new investigators to both research fields. The results indicate that this in fact did occur. Average success rates for New and Established Investigators for each initiative were compared with average success rates for New and Established Investigators for NIH R21 grants across all Institutes over the same six-year period. This comparison showed that New and Established Investigators in both DAIDS initiatives had higher success rates than New and Established Investigators for R21 grants across NIH.

These findings support a conclusion that the structure of the NIH PIA mechanism provided a good fit for both the AVR and MIP initiatives.

5.2.1.2 Did NIAID DAIDS implement the NIH PIA mechanism in a way that enabled DAIDS program staff to meet their scientific and administrative goals?

Determining whether DAIDS successfully implemented the NIH PIA mechanisms for the AVR and MIP initiatives encompassed four of the evaluation sub-questions, as shown below in **Exhibit 5.3**.

Exhibit 5.3. Summary of Conclusions—Program Implementation

Evaluation Question #1: Is the PIA mechanism an appropriate mechanism for desired microbicide and prophylactic vaccine research?		
No.	**Evaluation Sub-Question**	**Conclusions**
1B	Is the administrative burden on program management worth the effort?	▪ Program Directors and Program Officers agreed that the level of effort required to oversee PIA initiatives is greater than that required for R-series and P-series grants, and similar to that required for cooperative agreements. ▪ The sources of this additional level of effort were negotiating milestones and reviewing transition applications. ▪ Program Directors and Program Officers agreed that the additional effort is very worthwhile.
1E	Was the transition from the first to the second phase made efficiently without gaps in funding?	▪ Most projects and investigators that did transition felt that the transition process was efficient and without gaps in funding. ▪ About 31% of PI survey respondents indicated that delays in funding adversely affected their research; this proportion was higher among AVR investigators. ▪ About 59% of those who did not transition believed that the reasons they had not transitioned were not clearly explained to them.
1G	Does the PIA mechanism create networks across the research portfolio?	▪ Research project teams included an average of 5 key personnel for AVR and 6 key personnel for MIP. ▪ There was a strong degree of collaboration on MIP projects; 33 key personnel worked on as many as 6 or 7 different MIP research projects.
1H	Was the Funding Opportunities Announcement effectively communicated?	▪ Online survey data indicated that PIs clearly understood the application, milestone and transition review features and targeted scientific areas for AVR and MIP FOAs.

Results from the analysis of the AVR and MIP cases show that DAIDS program staff members were able to implement the NIH PIA mechanism in a manner that enabled them to meet their scientific and administrative goals for both initiatives. The MIP Program Director was particularly pleased with the overall experience and results for that initiative. The AVR Program Director was generally pleased as well, acknowledging, however, that the decision to use the PA type of FOA created additional problems for the AVR program staff, particularly at the grant review and transition review steps of the implementation process.

The results confirmed that for each case, the respective FOAs clearly conveyed the range of scientific areas targeted for research under each initiative, the dollar limits and time intervals for funding, the requirements for milestones, and the nature of the transition review process. Both sets of FOAs encouraged investigators to contact program staff to discuss their proposals during the planning stage, and about three-quarters of funded PIs indicated that they did so at least once while preparing their applications. PIs gave program staff high marks in terms of assisting them with planning the scope of their applications. New Investigators, however, were less likely to seek assistance than Experienced Investigators; according to the interviews, some New Investigators felt that they did not want to 'bother' program staff.

The grant review stage of the implementation process was the first stage where clear differences emerged in the experiences of the AVR and MIP Program Directors. The grant review process for AVR was conducted through CSR using a standing peer review panel (designated VACC). Under CSR rules, program staff members are not permitted to have any contact or communication with the reviewers. CSR staff members are charged with providing an explanation of the terms of the PA and the nature of the initiative. By contrast, the MIP (using the RFA) employed SEPs for grant reviews, and MIP program staff members were allowed to address the reviewers prior to the start of the review. That initial orientation enabled the MIP Program Director to emphasize the innovative, high-risk nature of the MIP initiative, de-emphasize the importance of preliminary data, and explain the milestones and the transition review process. It also helped the MIP Program Director to cultivate those reviewers who seemed to "get" the purpose of the PIA mechanism and work to retain them over successive reviews.

The milestone negotiation process was handled in a similar fashion by both initiatives. In both cases, program staff members noted that it was challenging in part because the milestones represented a novel way to think about research progress and because developing milestones that were well-designed, objective, and quantitative was often a complex process. There was an evident learning curve associated with the negotiation process. For both initiatives, there was clear frustration with the lack of adequate input from the reviewers, particularly in the earlier years of each initiative. MIP reviewers who served on multiple peer review panels appeared to improve their skill at providing useful critiques on proposed milestones, and as program staff grew more skilled in working with investigators to negotiate milestones, they were able to transfer this type of assistance to investigators who were applying for MIP grants.

Using the PA funding announcement also created problems for the AVR initiative during the transition review step. The PA announcement provided three application receipt dates per year, rather than the single date for the MIP RFAs. For AVR, this meant that there were three groups of projects that would be due for transition review two years post-award. On the other hand, the AVR project portfolio was substantially smaller than the MIP project portfolio. In addition, some investigators requested No-Cost Extensions rather than face review on their milestones at their scheduled time. This resulted in a piling up of transition reviews in later years of the AVR initiative; one Program Officer commented that for one scheduled review, there were about twice as many review applications to evaluate as had been scheduled because of the No-Cost Extensions.

The secondary case studies enabled the evaluation team to observe that there were two approaches to organizing reviews: "batch," when all applications scheduled for a review at approximately the same time were grouped together and reviewed; and "first-in, first-out," where each application was reviewed as received. Both AVR and MIP initiatives used the batch model; however, for AVR, there were three batches per year rather than one for MIP. Both review models tended to be somewhat biased toward investigators who submitted their transition review applications earlier in the fiscal year before all funding decisions had been made. The single review per year for MIP meant that this issue was diminished for that initiative. For the AVR initiative, however, there could be delays in making funding decisions on promising earlier applicants because program staff members wanted to see whether later projects might offer a closer fit to the current research portfolio. This was also confirmed by the PI survey data, which showed that a larger proportion of AVR investigators reported that the transition time had adversely affected their research.

Program staff members for the two initiatives acknowledged that the level of administrative effort required to manage the NIH PIA mechanism was higher than that required for R- and P-series grants and most U-series cooperative agreements. However, there was a strong conviction by all concerned that the extra effort was worthwhile given the types of results obtained for both initiatives.

Overall, these findings indicate that DAIDS program staff members implemented the NIH PIA mechanism in a manner that enabled them to meet their scientific and administrative goals for the AVR

and MIP initiatives. Reflecting on their experience with the PIA mechanism, the AVR program staff members strongly agreed that the mechanism worked well, but that it should not be used with Program Announcements.

5.2.1.3 Were the challenges and issues faced by DAIDS program staff unique to the DAIDS implementation process, or similar to those experienced by other NIH Institutes that have applied it?

The cross-case analyses of the four secondary cases support the conclusion that the types of issues and challenges experienced in the AVR and MIP initiatives were similar at the other NIAID Division and NIH Institutes using the PIA mechanism. The cross-case analysis explored five issues: the decision to employ the mechanism; how it was structured; experiences with the grant review process; the milestone negotiation process; and the transition review process. The four Program Directors' experiences with these issues were generally similar to those expressed by the AVR and MIP Program Directors, Program Officers, and PIs.

The four Program Directors described a similar process for deciding to use the NIH PIA mechanism, involving consideration of the nature of the scientific field or problem, the scientific and administrative goals of the initiative, the strengths and limitations of alternative funding mechanisms (notably the R01), and in some cases, consultation with other NIH staff who have had some experience with the mechanism. Program Directors view the PIA mechanism as particularly useful for fields or problems that involve the development of new technologies or fields of research activity.

The four initiatives structured the PIA mechanism in a similar manner, generally following the dollar limits and time intervals established by NIH for R21 and R33 grants. Like the AVR and MIP Program Directors, the four Program Directors interviewed for the case studies acknowledged that the grant amounts could limit research, particularly during the initial two years for projects involving animal models.

The grant review process posed a challenge for the four initiatives in that reviewers often had difficulty understanding the phased nature of the PIA mechanism and accepting the high-risk nature of some proposed projects. Three of the four initiatives used Special Emphasis Panels for the review process and the Program Directors explicitly mentioned conducting pre-review orientations with reviewers as had the MIP Program Director. Part of this orientation focused on the review of milestones, which proved as problematic for these reviewers as they had for AVR and MIP reviewers.

All four Program Directors acknowledged that the milestone negotiation process was time-consuming, and emphasized the importance of working with their Program Officers to improve their skills at negotiating milestones with PIs. The Program Directors also mentioned the value of working with PIs during the application development phase to improve their ability to propose better milestones.

The four initiatives adopted one of two approaches to managing the transition review process (a third approach that let every Program Officer develop their own procedures was not recommended. Program Directors whose initiatives involved multiple application receipt dates over the course of a year used a first-in, first-out approach in which transition applications were reviewed as received. This reduced the workload for Program Officers at any one time but did spread the transition review process across the year. In the batch approach, transition applications were grouped together and reviewed once per year. This concentrated the work associated with reviewing transition documents into a single period of time (e.g., one week), and seemed to work well where the number of applications was relatively small. Both approaches had implications for the PIs involved. The first-in, first-out approach meant that PIs who submitted their transition materials earlier in the fiscal year would be reviewed at a time when more funding was available, while those submitting later might find that funds had already been committed.

5.3 Evaluation Question #2: *Is the PIA mechanism a valuable component of the DAIDS research portfolio?*

This evaluation question included two sub-questions, summarized in **Exhibit 5.4**. A meaningful answer to this question depends on how one defines a "valuable component." Discussions with NIAID DAIDS program staff suggested that this question involves consideration of three aspects of the term "valuable." Under what circumstances would the NIH PIA mechanism be a desirable mechanism to use; does it accelerate the development of new methods, models, hypotheses, and products from a preclinical to clinical phase; and has it had an effect on decision-making at DAIDS?

Exhibit 5.4. Summary of Conclusions—Value of the PIA Mechanism

Evaluation Question #2: Is the PIA mechanism a valuable component of the DAIDS research portfolio?		
No.	**Evaluation-Sub-Question**	**Conclusions**
2A	Does the PIA program satisfy the need to advance new products through the development pipeline?	▪ Program Directors and Program Officers agreed that the PIA mechanism accelerates the product development pipeline. ▪ The PIA mechanism provides a means of funding preclinical ideas and moving them closer to clinical testing.
2B	What was the impact of the PIA program Division priority-setting and pace to change research directions?	▪ The PIA mechanism was responsive to new developments in the targeted research fields. ▪ The two central features of the PIA mechanism have now been integrated into a new innovation R01 as of 2011.

Results from the analyses of the AVR and MIP primary cases and the cross-case analyses indicate that there is a general consensus about the types of circumstances that are favorable to the use of the NIH PIA mechanism. Based on the findings, the NIH PIA mechanism should be considered when:

- There is a clear need to seek research proposals that are innovative, high-risk, and high-reward in nature;
- The scientific field is somewhat narrow in focus;
- There is a need to lead existing researchers into a new research area they have not been investigating;
- There is a need to encourage new research partnerships and collaborations; and
- There is a strong product-orientation, or a clearly envisaged scientific endpoint.

If one or more of these conditions applies for a proposed application of the PIA mechanism, it should be considered.

The AVR and MIP Program Directors agree that the NIH PIA mechanism appears to accelerate the product development pipeline. They acknowledged that it is difficult to say whether similar progress could have been achieved by using a different funding mechanism, although they noted that the projects funded under both initiatives would very likely not have been funded as R01 grants given their high-risk nature. This view was also endorsed by the Program Directors interviewed for the secondary case studies.

The AVR and MIP program staff also strongly agreed that the PIA mechanism should be retained at DAIDS. Use of the PIA mechanism has had an effect on divisional priorities at DAIDS. One strand of evidence lies in changes made to successive MIP RFAs, which included new areas of targeted research (e.g., nanotechnology). The strongest evidence lies in the creation two years ago of a new "Innovation R01" mechanism at DAIDS. Like the NIH PIA mechanism, this new mechanism focused on innovative research, and relaxed the usual requirement for strong preliminary data. It also incorporated the two hallmarks of the PIA mechanism: the use of negotiated milestones, and the two-year transition review.

5.4 Evaluation Question #3: *What is the overall impact of the PIA mechanism-supported milestone-driven research?*

This evaluation question includes four sub-questions that address four types of research outcomes (targeted research areas, research capacity, developmental pathways, and multidisciplinary research). The PIA evaluation examined two types of research outputs (new publications and new research grants) as well as outcomes including the number of new grants that focused on AIDS vaccine and microbicide research, the development of new partnerships and collaborations, scientific advances, and multidisciplinary research. Conclusions for the sub-questions related to this broader question are summarized in **Exhibit 5.5**.

Exhibit 5.5. Summary of Conclusions—Impact of PIA-Supported Research

Evaluation Question #3: What is the overall impact of the PIA-supported milestone-driven research?		
No.	**Evaluation Sub-Question**	**Conclusions**
3A	Was there an impact on targeted research areas?	▪ A total of 48 of the 74 AVR and MIP PIs obtained new NIH grants; there were a total of 143 new NIH grants. ▪ 43 of the 143 grants (30%) carried NIAID Program Class Codes that assigned them to either AIDS vaccine or microbicide research. ▪ AVR and MIP investigators obtained 36 new R01 or R56 grants (25% of total) and there were 14 new SBIR/STTR grants as well. ▪ Investigators whose projects had transitioned were slightly more likely to obtain new NIH grants than those whose projects stopped at the R21 phase.
3B	Did the program increase the research capacity of the field?	▪ Almost three-quarters (74%) of survey respondents reported forming at least one new research partnership or collaboration. ▪ About three-fifths of these new collaborations involved disciplines or sectors that had not previously worked together; this was much higher for MIP investigators.
3C	Has the developmental pathway been accelerated?	▪ The AVR and MIP Program Directors agreed that the PIA mechanism has had a major impact on the growth and pace of scientific development in their respective fields. ▪ The two initiatives have produced a variety of new tools, animal models, vaccine approaches, and methodologies that are being applied in some of the new NIH grants mentioned above. ▪ PI interviews indicated that many of these new approaches would never have been proposed if the PIA mechanism had not been in place because they were viewed as unlikely to make it through the traditional R01 review.
3D	Did the research promote multidisciplinary research?	▪ Evidence for multidisciplinarity is apparent from the composition of the project research teams, co-authors on publications, and formation of new partnerships and collaborations.

Both the AVR and MIP initiatives were highly successful in producing new publications, generating new research in general and in the targeted scientific fields, promoting greater multidisciplinary research, and encouraging the formation of new partnerships and research collaborations. AVR and MIP researchers produced a total of 262 new publications on their research activities between 2007 and September 2013. Almost three-quarters of projects published at least one research article, and about 70% of these articles had been cited at least once. On average, each published article was cited about 11.5 times. AVR and MIP investigators obtained a total of 143 new NIH grants of all types; more than half (54%) represented R01, P01, U01, U19, or U54 awards. A total of 43 new awards (30%) in AIDS vaccine or microbicide research were funded at NIAID.

Nearly three-fourths of PIs reported forming at least one new research partnership or collaboration through their AVR or MIP research activities, and about 60% of these new research relationships brought

together disciplines or groups that had traditionally not worked together. Multidisciplinarity was evident in terms of publication co-authorships, new research grants, and new partnerships.

AVR and MIP Program Directors and program staff agree that the NIH PIA mechanism has had a major impact on the growth and pace of scientific developments in both research fields. Among the major strengths of the mechanism interviewees reported were the innovative nature of the research and the fact that it allowed for initial testing of a larger number of ideas. In some cases, these ideas have turned into successful ongoing projects; in others, the ideas proved unproductive. As one Program Officer noted, success in front-line research fields is not only a matter of successful discoveries that move forward, but of identifying approaches and lines of research that can be eliminated. The NIH PIA mechanism has provided a structure that makes both objectives easier to achieve.

5.5 Recommendations for Future Applications of the NIH PIA Mechanism

The PIA Evaluation has shown that when properly used and implemented, the NIH PIA mechanism provides a funding and grant management structure that:

(1) Attracts innovative, high-risk, high-reward grant applications;

(2) Encourages participation by New Investigators and by multidisciplinary research teams;

(3) Encourages scientific reviewers to feel greater comfort in recommending high-risk projects for funding; and

(4) Provides program staff members with the means to advance projects that can demonstrate proof of concept within a reasonable period of time while allowing them to terminate projects that do not.

In reviewing the results from the interviews with AVR and MIP program staff and Program Directors for the four secondary cases profiled, the evaluation team developed a PIA implementation model, shown in **Exhibit 5.6**). The model shows that the implementation process follows a series of eight steps. Each step is associated with particular decisions that need to be made and challenges that need to be faced in implementing the PIA mechanism. The model provides a useful framework that other program staff members who might wish to adopt the NIH PIA mechanism could consider in future applications. It also furnishes a way of organizing a series of recommendations the evaluation team formulated based on this implementation process.

Exhibit 5.6. Recommendations for Future Use of the NIH PIA Mechanism

PIA Implementation Process	Key Challenges & Decisions	Recommendations From The Evaluation
Decision to use the NIH PIA mechanism	Nature of scientific field Scientific and administrative goals Consideration of alternative funding mechanisms	Use the NIH PIA mechanism when: ▪ There is a need for innovative, high-risk research; ▪ The scientific field is either highly product-oriented, or there is a clear scientific endpoint envisioned; ▪ There is a need to entertain multiple smaller-scale projects rather than larger R01-type initiatives; ▪ There is a need to lead an established research community into a new research area, or to encourage partnerships with other research communities.

PIA Implementation Process	Key Challenges & Decisions	Recommendations From The Evaluation
Crafting the Funding Opportunity Announcement	▪ Type of FOA ▪ Dollar limits for R21 and R33 phases ▪ Duration of R21 and R33 phases	▪ Do not use the NIH PIA mechanism with PA-type FOAs. ▪ Do not establish more than two application receipt dates per year. ▪ For fields in which research with nonhuman primates is common, increase the dollar limit for the exploratory R21 phase.
Communicating the Funding Opportunity Announcement	▪ Outreach to research community ▪ Use of multiple communication channels	Consider holding several conference call Q&A sessions during the application phase in order to encourage New Investigators to seek assistance from program staff.
Grant Application Process	Coaching prospective applicants	Provide written examples of acceptable milestones that applicants can download.
Grant Review Process	Orienting peer review panelists	Conduct an orientation briefing for SEP reviewers describing the initiative, types of research sought, and importance of milestones.
Milestone Negotiations	▪ Establishing internal procedures for the milestone negotiation process ▪ Training Program Officers to negotiate milestones	▪ Create written procedures for conducting the milestone negotiation process. ▪ Orient program staff to the development and use of milestones.
Transition Review	▪ Establishing written procedures for transition review ▪ First-in, first-out versus batch reviews	▪ Establish written procedures for the transition review process. ▪ Choice of first-in, first-out versus batch approaches for conducting reviews should be based in part on the amount of available funding for transitioning projects.
Project Oversight and Management	Adopting a sound management structure for the initiative	▪ Initiatives that use the NIA PIA grant mechanism should have a clear programmatic identity. ▪ For initiatives that involve program staff from multiple Branches or Divisions, ensure that milestone negotiations and transition reviews are conducted in the same way across different units.

Decision to use the NIH PIA mechanism. The evaluation found that Program Directors for the various initiatives were quite clear about when the NIH PIA mechanism should be used. They agreed that the mechanism should be used when a scientific field has reached a stage at which there is a need for new ideas and innovative, high-risk projects. The most appropriate fields in which to apply the mechanism are those with a strong product orientation (technology development), or those in which there is a clear scientific endpoint envisioned. For fields without a product orientation, the field should be narrow in focus, rather than broad. The PIA grant mechanism is also suitable for use when there is a need to lead an established research community into a new research area, or when there is a desire to encourage new research partnerships and collaborations with other research fields that have not traditionally worked together. A final consideration concerns the size of the research budget, and whether a field would benefit from funding many smaller-scale exploratory projects versus a smaller number of larger-scale projects.

Crafting the Funding Opportunity Announcement. There was strong agreement among Program Directors that the PIA mechanism should be used with RFAs rather than PAs. The main reason underlying this recommendation was the desirability of conducting the grant review process through SEPs rather than through standing review groups (CSR). Program Directors also emphasized the importance of briefing peer review panelists at the beginning of the review process. Because the number of receipt application dates will affect the number of batches of transition reviews that will need to be conducted

two years later, it is also advisable to keep the number of application receipt dates to a minimum. Another consideration concerns the dollar limits for the R21 exploratory phase. The existing dollar limit NIH uses for R21 grants has not kept pace with the rising costs of animal research, particularly for projects using nonhuman primate subjects. If the initiative for which the NIH PIA mechanism is contemplated involves such projects, thought should be given to increasing the dollar limit for the initial R21 phase.

***Communicating the FOA*.** The evaluation showed that PIs believed that DAIDS had communicated the AVR and MIP FOAs effectively and clearly. There were, however, differences in how New Investigators learned about the FOAs, and a smaller percentage of New Investigators contacted and received assistance from DAIDS program staff during the application review process. Interview data suggested that some New Investigators were hesitant to contact program staff because they feared that these staff members were too busy with other work. One way to reach out to less experienced investigators would be to hold several group conference calls during the application process to explain the nature of the initiative, the targeted scientific issues, the application process, and the milestones and transition review. Another way that has been used by some of the secondary initiatives is to post written examples of acceptable milestones to assist investigators in developing milestones.

Grant Review Process. Most Program Directors interviewed for the evaluation conducted orientation briefings with the SEP reviewers prior to the start of the grant review. Many of the reviewers were unfamiliar with the use of milestones and had a difficult time providing adequate critiques. Reviewers invited to participate in SEP reviews might benefit from receiving a packet of the same types of examples of acceptable and unacceptable milestones prior to the review itself.

Milestone Negotiations. Some of the initiatives examined in the evaluation involved Program Officers from two or more branches within a single Division, or even two or more Divisions. In these instances, maintaining standard procedures across multiple organizational units is an important management function. An aid in maintaining standard procedures is to draft written internal procedures for conducting the milestone negotiation process. One element of these procedures should include training for Program Officers on how to develop and negotiate milestones; this training could include the same materials used for investigators and reviewers.

Transition Review. One critical decision to make in establishing an internal process for conducting transition reviews is whether to conduct the reviews on a first-in, first-out basis or on a batch basis. Factors affecting this decision include the number of transition reviews to be conducted each year, the availability of funds for transitioning projects, and the use of No-Cost Extensions with projects that would otherwise be due for a transition review. A critical issue to consider is whether applications received earlier in the fiscal year are likely to be delayed in funding in order to conserve funding for those received later in the fiscal year.

Project Oversight and Management. It is important that initiatives that use the NIH PIA mechanism have a clear programmatic identity. For the one secondary initiative where this was lacking, there were a number of administrative problems encountered that stemmed from the absence of strong initiative oversight. By contrast, one initiative that involved Program Officers from five different divisions had strong central management. The Program Director met with Program Officers from each division and encouraged them to develop standardized processes and procedures. That initiative continued for seven years.

5.6 Conclusion

Funding innovative, high-risk research involves meeting three inter-related challenges. First, research investigators must be persuaded to submit new ideas and high-risk proposals. Second, scientific reviewers used to conservative, incremental scientific progress must be encouraged to take a chance on new ideas, methods, and approaches for which preliminary data may be limited or lacking. Finally, program staff

must feel that they can manage the risk posed by these proposals in a manner that enables them to curtail unproductive research while providing adequate resources to develop promising approaches. One means by which these challenges can be met is through the use of the Phased Innovation Award (PIA) mechanism. At NIAID DAIDS, program staff used the PIA mechanism to fund two initiatives—AVR and MIP. This evaluation showed that the NIH PIA mechanism provided an appropriate mechanism for supporting microbicide and prophylactic vaccine research, and that program staff strongly support maintaining this mechanism as part of the DAIDS research portfolio. The evaluation also showed that the PIA mechanism attracted new investigators, stimulated research productivity in terms of peer-reviewed research publications and new NIH grants, increased research in AIDS vaccine and microbicide research, and led to new multidisciplinary research partnerships and collaborations. Based on the results from the PIA Evaluation, the evaluation team created an implementation model for future applications of the NIH Phased Innovation Award mechanism.

References

1. Boyack, K.W. and Jordan, P. (2011). Metrics associated with NIH funding: A high-level view. *Journal of the American Medical Informatics Association,* 18: 423-431.

2. Buckheit, R.W. Jr., Watson, K.M., Morrow, K.M., and Ham, A.S. (2010). Development of topical microbicides to prevent the sexual transmission of HIV. *Antiviral Research,* 85: 142-158.

3. Chubin, D.E. and Hackett, E.J. (1990). *Peerless Science: Peer Review and U.S. Science Policy.* Albany: State University of New York Press.

4. Couch, J. (2004). The R21/33 Grant Mechanism: What Works, What Doesn't. PowerPoint presentation before the National Cancer Institute STEP, February 3, 2004.

5. Fauci, A.S., Johnston, M.I., Dieffenbach, C.W., Burton, D.R., Hammer, S.M., Hoxie, J.A., Martin, M., Overbaugh, J., Watkins, D.I., Mahmoud, A., and Greene, W.C. (2008). HIV vaccine research: The way forward. *Science,* 321: 530-532.

6. Friend, D.R. and Kiser, P.F. (2013). Assessment of topical microbicides to prevent HIV-1 transmission: Concepts, testing, lessons learned. *Antiviral Research*, 99: 391-400.

7. Girard, M.P., Osmanov, S.K., and Kieny, M.P. (2006). A review of vaccine research and development: The human immunodeficiency virus (HIV). *Vaccine,* 24: 4062-4081.

8. Heinze, T. (2008). How to sponsor ground-breaking research: A comparison of funding schemes. *Science and Public Policy,* 35: 302-318.

9. Laudel, G. (2006). The art of getting funded: How scientists adapt to their funding conditions. *Science and Public Policy,* 33: 489-504.

10. _____ (2013). San Francisco Declaration: Putting science into the assessment of research. *Microbe,* 8: 478-481.

Appendix. Customer Satisfaction Survey

OMB Number: 0925-0668
Expiration Date: 1/31/2016

DIVISION OF AIDS (DAIDS), NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID), PHASED INNOVATION AWARD PROGRAM CUSTOMER SATISFACTION SURVEY

The Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID) has utilized the biphasic R21/R33 grant mechanism to support AIDS Vaccine Research and the Microbicide Innovation Program. Survey respondents are Principal Investigators (PIs) who received AIDS Vaccine Research (AVR) or Microbicide Innovations Program (MIP) phased innovation awards from FY 2006 through FY 2012.

The purpose of the survey is twofold:

- To determine grantees' overall satisfaction with the Phased Innovation Award R21/R33 grant funding mechanism; and
- To obtain information regarding key aspects of the funding mechanism that is particularly helpful or challenging.

Your answers to this survey will provide valuable information for the future of this program. The survey is voluntary, and results will only be reported in the aggregate.

Informed Consent Form

Identification of Project

DIVISION OF AIDS, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
PHASED INNOVATION AWARD PROGRAM CUSTOMER SATISFACTION SURVEY

Statement of Age of Subject

I state that I am at least 18 years of age, in good physical health, and wish to participate in research being conducted by the Division of AIDS of the National Institute of Allergy and Infectious Diseases, Rockville, MD 20852.

Purpose

The purpose of this research is to assess grantees' overall satisfaction with the Phased Innovation Award R21/R33 grant funding mechanism and obtain information regarding key aspects of the funding mechanism that were particularly helpful or challenging.

Procedures

Participants will be asked to access a web-based questionnaire and complete the questionnaire by a specific date. The total time involved, including instructions, will be no more than 20 minutes.

Confidentiality

All information collected in this study will be kept secure to the extent permitted by law. I understand that the data I provide will be grouped with data that others provide for the purpose of reporting and presentation, and that my name will not be used.

Risks

I understand that the risks of my participation are expected to be minimal in nature.

Benefits, Freedom to Withdraw, & Ability to Ask Questions

I understand that this study is not designed to help me personally but that the investigators hope to learn about the grantees overall satisfaction with the Phased Innovation Award Program. The survey population will include Principal Investigators who received Phased Innovation awards. I am free to ask questions or withdraw from participation at any time and without penalty.

Contact Information of Investigators

Name: Madelon Halula, PhD
Office: Division of AIDS, National Institute of Allergy and Infectious Diseases
Telephone: 301-402-2636
Email: mhalula@niaid.nih.gov

Agreement to Consent

- ☐ **I have read the information about this study, and I agree to participate in this survey.**
- ☐ **I have read the information about this study, and I do not wish to participate in this survey at this time.**

SECTION 1: FUNDING ANNOUNCEMENT

1. How did you first hear about the R21/R33 funding announcement? (Please check all that apply.)

   - ☐ NIH Guide
   - ☐ NIAID Program Officer
   - ☐ NIAID Newsletter
   - ☐ NIAID Website or other NIAID resource
   - ☐ Colleague
   - ☐ Scientific meeting
   - ☐ Other (Please specify) _____

SECTION 2: APPLICATION PROCESS

2. Did you contact the DAIDS Program Officer while developing your R21/R33 application?

   - ☐ Yes. (If yes, have questions 3(a) and 3(b) appear)
   - ☐ No (If no, skip to question 4)

   2(a) How did you contact the Program Officer while developing your application? (Please check all that apply)

   - ☐ Email
   - ☐ Phone
   - ☐ In person meeting
   - ☐ Other (Please specify) _____

   2(b) My communications with the Program Officer during the application phase helped me to develop a stronger application than I would have otherwise.

   - ☐ Strongly Agree
   - ☐ Agree
   - ☐ Disagree
   - ☐ Strongly Disagree

SECTION 3: MILESTONES REQUIREMENT

3. Please rate your level of agreement with the following statements: (Please fill in one for each row.)

	Strongly Agree	Agree	Disagree	Strongly Disagree
I had a clear understanding of the use of milestones while writing my application.				
The milestones in my awarded application changed significantly from those in my initial application.				
The amount of input that I had in establishing the milestones for my awarded application was appropriate.				

4. How satisfied were you with the process used to set milestones in the awarded application?

   - ☐ Very satisfied
   - ☐ Somewhat satisfied
   - ☐ Somewhat dissatisfied
   - ☐ Very dissatisfied

5. How would you improve the process used to set milestones? (*free text response*)

SECTION 4: MILESTONES EFFECT ON RESEARCH

6. Please rate your level of agreement with the following statements: (Please fill in one for each row.)

	Strongly Agree	Agree	Disagree	Strongly Disagree
The milestones helped focus my research during the R21 phase.				
The milestones discouraged innovative research during the R21 phase.				
Having milestones helped me to be realistic about what I could accomplish during the R21 phase.				
The milestones helped me move my research forward to completion.				

SECTION 5: R21 BUDGET/GRANT PERIOD

7. Please rate your level of agreement with the following statements: (Please fill in one for each row.)

	Strongly Agree	Agree	Disagree	Strongly Disagree
The $275,000 dollar limit in the R21 phase limited the research that I would have otherwise proposed in the first two years of an R01 grant.				
The milestones in my awarded grant were too ambitious for the R21 budget.				
Two years for the R21 phase was sufficient time to meet the milestones necessary to be eligible to transition to the R33 phase.				

SECTION 6: TRANSITION PROCESS

8. Did you transition from the R21 award and receive R33 funding?

   - ☐ Yes (*have all of the questions for transitioners appear*)
   - ☐ No, I am still in the R21 Phase (*skip to question 14)*
   - ☐ No (*have all questions for nontransitioners appear*)

9. The reasons why I did not receive R33 funding were clearly explained to me. (*nontransitioners only*)

- ☐ Strongly Agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly Disagree

10. The transition process from R21 funding to R33 funding was efficient. (*transitioners only*)

- ☐ Strongly Agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly Disagree (*if they answer disagree or strongly disagree, have question 11(a) appear*)

10(a) From your experience, what was inefficient about the transition process from R21 funding to R33 funding? (*free response text*)

11. How could the transition process be improved? (*free response text*) (*transitioners only*)

12. How did the transition time between R21 and R33 funding affect the progress of your research? (*transitioners only*) (Please check only one.)

- ☐ Completely halted my research
- ☐ Somewhat slowed my research
- ☐ No impact on my research
- ☐ Somewhat increased the speed of my research
- ☐ Greatly increased the speed of my research

SECTION 7: R33 BUDGET GRANT PERIOD (*transitioners only*)

13. Three years for the R33 phase was sufficient time to expand proof-of-concept to the preclinical or clinical trial stage.

- ☐ Strongly Agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly Disagree

SECTION 8: PROGRAM OFFICER MANAGEMENT AND MONITORING

14. Expected research progress during the R21 phase was closely tied to milestones.

- ☐ Strongly Agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly Disagree

15. The process to report on grant progress based on the milestones was:

- ☐ Very easy
- ☐ Somewhat easy
- ☐ Somewhat difficult
- ☐ Very difficult (*If they respond somewhat difficult or very difficult have 16(a) appear)*

16(a) From your experience, what made it difficult for you to report on grant progress based on the milestones? (*free text response*)

16. The milestones were used to hold me closely accountable on my grant progress.

- ☐ Strongly Agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly Disagree

17. I was satisfied with the NIAID Project Officer's progress monitoring.

- ☐ Strongly Agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly Disagree

18. During the R21 phase, frequency of communication with my Project Officer was:

- ☐ Too frequent
- ☐ Appropriate
- ☐ Not frequent enough

19. Communication with my Project Officer during the R21 phase was helpful.

- ☐ Strongly Agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly Disagree

20. During the R33 phase, frequency of communication with my Project Officer was: (*transitioners only*)

- ☐ Too frequent
- ☐ Appropriate
- ☐ Not frequent enough

21. Communication with my Project Officer during the R33 phase was helpful. (*transitioners only*)

- ☐ Strongly Agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly Disagree

SECTION 9: CHARACTERISTICS OF THE R21/R33 FUNDING MECHANISM

22. Below are some characteristics of the R21/R33 funding mechanism. Please indicate which characteristics you thought were advantageous when you decided to apply for R21/R33 funding. (Check one column for each row)

Characteristics of the R21/R33 mechanism	Did you consider this characteristic to be an advantage of the R21/R33 mechanism? Yes	Did you consider this characteristic to be an advantage of the R21/R33 mechanism? No
Encouraged innovative, novel research that may be high risk/high impact		
Required a single application submission and evaluation of the R21 and R33		
Required inclusion of quantifiable milestones		
Opportunity to negotiate milestones prior to award		
Opportunity to continue funding in R33 phase without submitting a new application		
Did not require preliminary data		
Availability of multiple application receipt dates		
Other (Please specify)		
Other (Please specify)		

23. Please list below any aspects of the R21/R33 program that you felt were disadvantageous when deciding to apply. (*free text response*)

24. Please rate your level of agreement with the following statements:
(Please fill in one for each row.)

	Strongly Agree	**Agree**	**Disagree**	**Strongly Disagree**
The R21/R33 mechanism is a useful method to attract more (or new) investigators to the field (AIDS Vaccine Research/Microbicide Innovation).				
The R21/R33 mechanism is a useful way to support high risk or novel approach in the field (AIDS Vaccine Research/Microbicide Innovation).				

SECTION 10: COLLABORATIONS

25. Has a new collaboration or partnership resulted from your R21/R33 application or award?

- ☐ Yes (*If yes, have questions 27 to 31 appear*)
- ☐ No (*Skip to question 32*)

26. In what area was this collaboration(s)? (Please check all that apply.)

- ☐ Academia
- ☐ Private Industry
- ☐ Non-Profit
- ☐ Federal Government
- ☐ State or Local Government
- ☐ Other (Please specify) _____

27. Does this collaboration(s) bring together disciplines or sectors that traditionally do not work together?

- ☐ Yes
- ☐ No

28. When did this collaboration(s) occur? (Please check all that apply.)

- ☐ During R21 Phase
- ☐ During R33 Phase
- ☐ Beyond R21/R33 funding

29. Has this collaboration(s) resulted in a direct financial contribution to your research?

- ☐ Yes
- ☐ No

29 (a) If yes, was the estimated dollar amount:

- ☐ Less than $500K
- ☐ Between $500K and $1M
- ☐ Greater than $1M

30. Has this collaboration(s) contributed in non-financial ways to your research?

- ☐ Yes (*If Yes, please explain*) (*free text response*)
- ☐ No

30 (a) If yes, please explain:

SECTION 11: OTHER FUNDING

31. Based on your research progress during the R21/R33 award, did you apply for **other NIH funding** (aside from the R21/R33) to continue the line of research of your R21/R33 application?

- ☐ Yes (*If yes, have question 32(a) and 32(b) appear*)
- ☐ No

31(a) The other NIH funding that I applied for was: (Please check all that apply.)

- ☐ In response to a Funding Opportunity Announcement (FOA)
- ☐ Investigator Initiated

31(b) Please list the type(s) of other NIH awards you applied for and complete the following table. (One row per funding request or application; list multiple awards of the same mechanism as R01-1, R01-2, etc.)

	NIH Award Type (e.g. R01, U19)	Did you receive this funding?	Did you receive this funding?	How were the funds distributed to you?
Award 1	_____	☐ R21 ☐ R33 ☐ After R21/R33	☐ Yes ☐ No	☐ Directly to me ☐ As part of a larger award ☐ N/A
Award 2				
Award 3				
Award 4				
Award 5				

32. Based on your research progress during the R21/R33 award, did you apply for or receive **other, non-NIH funding** to continue the line of research of your R21/R33 application?

    - ☐ Yes
    - ☐ No

SECTION 12: CONCLUDING COMMENTS

33. Please describe any challenges or barriers that you experienced with the R21/R33 program. (*free text response*)

34. Please list any recommendations you have to improve the design, management, and/or administration of the R21/R33 program. (*free text response*)

35. Please tell us anything else you think is important to know about your experience with the R21/R33 funding mechanism and process. (*free text response*)

Please click **Save and Close** to complete the survey at another time, or **Submit. (***If Submit is selected, the following will appear).*

THANK YOU!

Thank you for taking the time to complete this survey.
Please close your browser window to exit this survey.