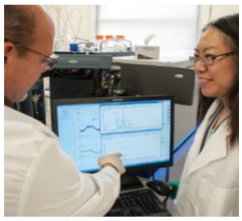
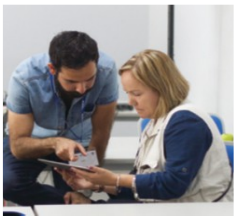
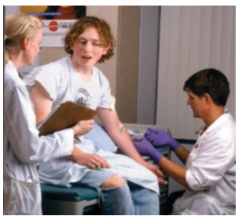
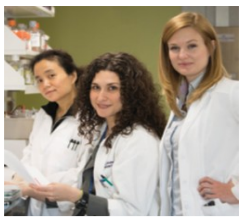
A Primer for the Design and Conduct of Clinical Trials for Vector Interventions

May 7-8, 2018
Meeting Report









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Executive Summary

On May 7-8, 2018, the National Institute of Allergy and Infectious Diseases (NIAID) held a two-day workshop to discuss the development of clinical trials for vector control interventions. The intended outcomes of the workshop were to: 1) better understand how to develop rigorously designed, multidisciplinary clinical trials for vector interventions; 2) enable multidisciplinary collaborations; and 3) improve capacity of investigators to develop competitive applications for NIAID clinical trial funding opportunities.

Attendees included investigators involved in vector control product development, experts from industry, representatives from regulatory agencies, other funders of vector control research, and NIAID staff. The first day included presentations and discussions on planning a field study, understanding regulatory requirements, and reviewing case studies. On the second day, participants worked in break-out groups to develop sample outlines of a hypothetical clinical study for an assigned vector intervention. Discussions included the identification of various challenges, gaps, and recommendations for designing and implementing vector control intervention trials.

Meeting Summary

Opening Remarks

Dr. Emily Erbelding, Director of the Division of Microbiology and Infectious Diseases (DMID) in NIAID, opened the workshop by contextualizing the importance of vector control research. She noted that a recent CDC report indicated that infectious diseases transmitted by vectors like mosquitos, fleas, and ticks more than doubled in the US between 2004 – and 2018 (https://www.cdc.gov/ncezid/dvbd/vital-signs/index.html). Dr. Adriana Costero-Saint Denis, Vector Biology Program Officer in DMID's Parasitology and International Programs Branch, stated that the purpose of the workshop was to discuss the development and planning of clinical trials for vector interventions that aim to generate evidence for decisionmakers.

Keynote: The Need for Clinical Trials of Vector Interventions

Dr. Anne Wilson of Durham University emphasized the public health importance of vector control by highlighting that 80% of the world's population is at risk of contracting at least one vector-borne disease. She provided examples of vector control successes as well as challenges to their sustained effectiveness and to the development of new tools. Dr. Wilson outlined two pathways for WHO prequalification of vector control products: 1) a product in a class with an existing WHO policy recommendation can proceed to prequalification; 2) a product in a class without a WHO policy recommendation requires a Vector Control Advisory Group (VCAG) review, a recommendation by the Strategic and Technical Advisory Group (STAG) or Malaria Policy Advisory Committee (MPAC), and a WHO policy recommendation to proceed to

prequalification. For products that are first-in-class, the VCAG requires at least two randomized-controlled trials in different settings with epidemiological outcomes. Dr. Wilson also highlighted that there is a lack of evidence on the efficacy of vector control tools; therefore, there is a need to invest in rigorously designed field studies. In the discussion that followed, it was noted that it is important to distinguish between efficacy (whether a tool works), effectiveness (whether it reduces disease), and compliance (whether people use it correctly).

Session I. Generating Evidence for Decision Makers

Speaker Presentations:

1. New Tools for Vector Control: A Regional Perspective –

   Dr. Haroldo Bezerra of the Pan American Health Organization (PAHO) outlined the goals of the Public Health Entomology and Vector Control Program at PAHO, which include strengthening the application of entomology in vector control, implementing Integrated Vector Management (IVM), and establishing a surveillance and management system for insecticide resistance. He also provided examples of current pilot studies of novel techniques in the Americas, including several studies of *Wolbachia* and gene drive methods.

2. Observational Studies for Vector Interventions –

   Dr. Ben Beard of the Centers for Disease Control and Prevention (CDC) illustrated the utility of observational studies in assessing the effectiveness of new vector control tools. He defined an observational study as observing the effect of exposure on the study subjects without assigning the exposure to the participants. He reviewed the strengths and weaknesses of different types of observation study designs, including case-control studies, cohort studies, cross-sectional studies, and other controlled designs.

3. Clinical Trial Designs to Address Different Questions/Settings –

   Dr. Immo Kleinschmidt of the London School of Hygiene and Tropical Medicine made the case that clustered randomized controlled trials (cRCTs) are the best way to evaluate vector control interventions. He reviewed several examples of cRCTs and noted that it is important to consider the community setting when designing a trial.

Panel Discussion:

A panel of ten experts, five from disease-endemic countries and five representing major funders, took questions from participants on study design, the regulatory environment, country-specific context, and vector-specific considerations. Key takeaways were:

- There is a need for funders and regulatory decisionmakers to establish standards for the minimum level of protective benefit required for an intervention to be viable.

- In terms of efficacy versus effectiveness, it was suggested that local program officials typically care more about effectiveness (i.e. reduction of disease).
- The VCAG process is seen by some as overly rigorous and inflexible. The requirement for two randomized controlled trials in different settings was discussed as being too onerous, particularly during an outbreak when an intervention is needed urgently.
- It was suggested that including entomological data in a study design can help explain conflicting results for the same intervention in different settings.
- There is a consensus that the evidence base for vector control interventions needs to be expanded, but there are varying viewpoints on how much evidence is needed and how to obtain it.

Session II. Planning a Field Study

Speaker Presentations:

1. Risk Assessment –

   Dr. Fred Gould of North Carolina State University reviewed the three components of risk assessment – risk analysis, risk characterization, and risk management – and illustrated the importance of appropriate risk consideration when designing a clinical trial.

2. Bioethics/Community Engagement –

   Dr. James Lavery of Emory University discussed that while community and stakeholder engagement (CSE) is recognized by funders and as a valuable part of research programming, the limited evidence base for CSE is hurting its funding allocations. He suggested that research funders can improve the evidence base for CSE by: 1) encouraging better reporting and scrutinizing already funded CSE strategies; 2) recognizing the asymmetry in evidence required for CSE compared to other aspects of research programs; 3) recognizing CSE as a critical part of program performance; and 4) experimenting with flexibility in protocols and budgets that adapt to stakeholder insights and studying the implications on program performance.

3. Field Site Selection –

   Dr. Thomas Scott of the University of California-Davis explained that there are few published guidelines on site selection for vector control trials. He outlined various site selection criteria, including presence of the vector, sufficient incidence of the disease, and adequate local political and regulatory support.

4. Challenges and Successes –

Dr. Simon Warner of Oxitec, a company that develops insect control technology, described the company's OX513A gene drive technology. Oxitec injects male *Aedes* mosquitos with the self-limiting gene OX513A. The males then mate with wild female *Aedes* and pass the gene to their offspring. The males die within days, and the offspring do not survive to adulthood. Oxitec has conducted successful field trials of this technology in Brazil, Panama, and the Cayman Islands.

Dr. Stephen Dobson of MosquitoMate described the use of *Wolbachia* to suppress mosquito populations. *Wolbachia* is a bacterium found in insect species that is inherited and interferes with sexual reproduction. *Wolbachia* can be used in two different strategies: population replacement and population suppression. In population replacement, *Wolbachia*-infected females are released into an area to interfere with virus transmission. In suppression, infected males are released with the goal of reducing the mosquito population.

Discussion:

- Participants noted the need to expand the evidence base for CSE but acknowledged that some things worth doing are not easily measurable or quantifiable.
- Layering is an important strategy in designing an intervention trial. Layering refers to determining the most appropriate time for various aspects of a project. In gene drive, for example, community engagement is critical at the outset because without community support an intervention may not move forward.
- Participants noted that sometimes it is impossible to predict whether a site will have sufficient incidence rates during the site selection phase. In those cases, selecting multiple sites can mitigate risk. Multiple sites may also be required to assess an intervention in different contexts.

Session III. Regulatory Requirements

Speaker Presentations:

1. Environmental Protection Agency (EPA): Vector Control Pesticides –

   Dr. Susan Jennings of the EPA described the EPA's pesticide registration process. Pesticide registration data requirements depend on which category the pesticide falls into – conventional chemical pesticides, biopesticides, or antimicrobial pesticides. There are also different types of registrations beyond commercial use such as experimental use permits (EUP). Dr. Jennings noted that a current challenge for regulators is determining how to categorize and register new interventions such as *Wolbachia* and gene drive methods which do not fall neatly under existing categories. Dr. Jennings also noted the importance of risk assessment and risk management in the evaluation of a pesticide.

2. Food and Drug Administration (FDA): New Animal Drugs and Vector Control –

Dr. Heather Lombardi of the FDA explained various vector control methods that target animals, including drugs directly administered to livestock to reduce transmission and genetic engineering of animals to reduce disease or transmission. She stated that new animal drugs are regulated under the United States Federal Food, Drug, and Cosmetics Act (FD&C Act). The Act defines a new animal drug as "any drug intended for use for animals other than man." She explained that in the 2017 "Guidance for Industry 236" document, the FDA clarified that mosquito-related products that function as pesticides for population control are not drugs and are therefore regulated by the EPA. Mosquito-related products for lowering viral loads or preventing disease transmission are drugs and are regulated by the FDA. Dr. Lombardi outlined the steps involved in reviewing/approving new animal drugs. She recommended that sponsors involve the FDA early in product development, especially for novel products which pose a regulatory challenge.

3. NIAID Funding Opportunities for Clinical Research and Resources

Dr. Greg Deye of NIAID's Division of Microbiology and Infectious Diseases reviewed the definition and aspects of a clinical trial according to NIH. He explained that the defining components of clinical trials are that participants are prospectively assigned to an intervention and that the intervention is evaluated for biomedical or behavioral outcomes. A study with only an entomological endpoint would not be considered a clinical trial. Dr. Deye outlined NIH funding mechanisms for clinical trials and provided links to further resources and funding announcements.

Session IV. Putting It All Together: Case Studies

Investigators involved in planning or executing ongoing vector control intervention trials presented their trial designs, planning considerations, challenges and lessons learned. The presenters included:

- Dr. Mauro Teixeira of Universidade Federal de Minas Gerais, who is planning a Phase III parallel-design, cluster-randomized trial to evaluate OX513A genetically engineered mosquitos to reduce the burden of arboviruses in Brazil.
- Dr. Mark Mulligan of Emory University's NIAID-funded Vaccine and Treatment Evaluation Unit (VTEU), who gave an overview of the vaccine discovery and development process.
- Dr. Katie Anders of Monash University and Dr. Nicholas Jewell of the University of California-Berkley, who described the Applying *Wolbachia* to Eliminate Dengue (AWED) trial in Indonesia that showed *Wolbachia*-infected mosquito deployments reduced incidence of Dengue in the study population.

Presentations were followed by a discussion of general trial issues as well as issues specific to the case studies. A major discussion point was the need to better explain conflicting results from

trials of the same intervention, particularly to decisionmakers who may misinterpret discrepant results. There are varying environmental, ecological, and social factors that may cause different results for the same intervention in different settings. It was suggested that modeling could be useful in explaining and anticipating variability in results from different settings.

Session V. Team-Based Exercise and Next Steps

Participants were organized into 10 groups focused on a specific vector species (*Aedes, Anopheles, Culex, Sabethes, Ixodes, Lutzomyia, Glossina, Xenopsylla, Simulium, and Triatoma*) and vector control intervention. Each group designed a mock clinical trial to test their intervention and presented it the larger group.

Challenges & Gaps

During the meeting, participants noted various challenges and gaps for designing and implementing clinical trials for vector control, including the following:

- New tools are needed to control vector-borne diseases.
- There is insufficient evidence on the effectiveness of many vector control interventions, particularly for *Aedes*. More evidence is needed, but there is no consensus on how much or what type of evidence is needed.
- Vector-borne disease control programs are often under-resourced and cannot support proper surveillance to monitor the effectiveness of the interventions.
- New methods are needed to monitor the efficacy or effectiveness of a vector control intervention where the disease is declining but is still endemic, and where there is potential for resurgence when public health interventions end.

Appendix 1: Agenda

DAY 1: 5/7/2018	**Knowledge Base Presentations**	
7:15 – 8:15am	Registration	
8:15 – 8:30am	Welcome	Emily Erbelding, NIAID
	Purpose/Format/Expectations	Adriana Costero-Saint Denis, NIAID
8:30 – 9:00am	Keynote: The Need for Clinical Trials of Vector Interventions	Anne Wilson, Durham University
	Generating Evidence (data) For Decision-Makers, Thomas Scott, Chair	
9:00 – 9:20am	New Tools for Vector Control: A Regional Perspective	Haroldo Bezerra, Pan American Health Organization
9:20 – 9:40am	Observational Studies for Vector Interventions	Ben Beard, CDC
9:40 – 10:00am	Clinical Trial Designs to Address Different Questions/Settings	Immo Kleinschmidt, London School of Hygiene and Tropical Medicine
10:00 – 10:15am	BREAK	
10:15 – 11:20am	Panel Discussion: Generating Evidence, Gaps and Challenges Participants: *Kate Kolaczinski, The Global Fund to Fight AIDS, TB and Malaria* *Haroldo Bezerra, Pan American Health Organization* *Immo Kleinschmidt, Vector Control Advisory Group* *Steven Kern, Bill and Melinda Gates Foundation* *Jennifer Armistead, US Agency for International Development* *Amy Morrison, Peru* *Mauro Teixeira, Brazil* *Ulrike Fillinger, Kenya* *Seydou Doumbia, Mali*	
	Planning a Field Study, Ulrike Fillinger, Chair	
11:20 – 11:40am	Risk Assessment	Fred Gould, North Carolina State University
11:40 – 12:00pm	Bioethics/Community Engagement	James Lavery, Emory University
12:00 – 1:00pm	LUNCH	
1:00 – 1:20pm	Field Site Selection	Thomas Scott, University of California, Davis
1:20 – 2:00pm	Challenges and Successes	Simon Warner, Oxitec Stephen Dobson, MosquitoMate

	Regulatory Requirements, Steve Huang, Chair	
2:00 – 2:15pm	Environmental Protection Agency (EPA)	Susan Jennings, EPA
2:15 – 2:30pm	Food and Drug Administration (FDA)	Heather Lombardi, FDA
2:30 – 3:00pm	NIAID Funding Opportunities for Clinical Research and Resources	Gregory Deye, NIAID
3:00 – 3:30pm	BREAK	
	Putting It All Together - Case Studies, Gregory Deye, Chair	
3:30 – 4:00pm	Vector Population Suppression	Mauro Teixeira, Universidade Federal de Minas Gerais Mark Mulligan, VTEU
4:00 – 4:30pm	Vector Population Replacement	Katie Anders, Monash University Nicholas Jewell, University of California, Berkley
4:30 – 5:00pm	Discussion	
5:00 – 5:30pm	Conclusions for Day 1 and Preparation for Day 2	
DAY 2: 5/8/2018	**Breakout Groups**	
9:00 - 9:15am	Instructions for Day 2	Adriana Costero-Saint Denis, NIAID Gregory Deye, NIAID
9:15 – 11:45am	***Team-Based Exercise*** Team Aedes Team Anopheles Team Culex Team Sabethes Team Ixodes Team Lutzomyia Team Glossina Team Xenopsylla Team Simulium Team Triatoma	
11:45 – 12:45pm	LUNCH	
12:45 – 2:45pm	Report Back from Each Team and Discussion (12 minutes per team)	
2:45 – 3:00pm	Next Steps	Adriana Costero-Saint Denis, NIAID Gregory Deye, NIAID
3:00pm	ADJOURN	

Appendix 2: Participants

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Appendix 3: Relevant Publications

Background Documents on Trials for Vectors:

1. Evidence-based vector control? Improving the quality of vector control trials. (2015)
2. Randomized controlled trials and changing public health practice (2017)
3. Guidance Framework for Testing of Genetically Modified Mosquitoes. (2014)
4. How to design Vector Control efficacy trials (WHO) (2017)
5. Framework for rapid assessment and adoption of new vector control tools. (2014)
6. Design of epidemiological trials for vector control products (WHO). (2017)
7. Assessing the effects of interventions for *Aedes aegypti* control: systematic review and meta-analysis of cluster randomized controlled trials (2017)
8. Quantifying the epidemiological impact of vector control on dengue. (2016)
9. Considerations in the design of clinical trials to test novel entomological approaches to dengue control. (2012)
10. Cluster Randomized Test-Negative Design (CR-TND) Trials: A Novel and Efficient Method to Assess the Efficacy of Community Level Dengue Interventions. (2018)
11. Parachute use to prevent death and major trauma related to gravitational challenge: systemic review of randomized controlled trials. (2003)

Related Articles of Interest:

1. Broadening the application of evolutionarily based genetic pest management. (2007)
2. Terms of reference for the external evaluation group on New Technologies for controlling *Aedes* spp (PAHO). (2017)
3. A critical assessment of vector control for dengue prevention. (2015)

Vector Control Approaches:

1. Insecticide-treated bed nets and curtains for preventing malaria (review). (2004)
2. Female Adult *Aedes albopictus* Suppression by *Wolbachia*-Infected Male Mosquitoes. (2016)
3. Male mosquitoes as vehicles for insecticide. (2015)
4. Oxitec's Vector Control Solution. (2016)
5. House screening with insecticide-treated netting provides sustained reductions in domestic populations of *Aedes aegypti* in Merida, Mexico. (2018)
6. Efficacy of *Aedes aegypti* control by indoor Ultra Low Volume (ULV) insecticide spraying in Iquitos, Peru. (2018)
7. Impact of autocidal gravid ovitraps on Chikungunya virus incidence in *Aedes aegypti* (Diptera: Culicidae) in Areas with and without traps. (2016)
8. Design and testing of novel lethal ovitrap to reduce populations of Aedes mosquitoes: community-based participatory research between industry, academia, and communities in Peru and Thailand. (2016)
9. Modification of arthropod vector competence via symbiotic bacteria. (1993)

Clinical Trial Examples:

1. Efficacy of topical mosquito repellent (picaridin) plus long-lasting insecticidal nets versus long-lasting insecticidal nets alone for control of malaria: cluster-randomized controlled trial.
2. Efficacy of indoor residual spraying with dichlorodiphenyltrichloroethane against malaria in Gambian communities with high usage of long-lasting insecticidal mosquito nets: a cluster-randomized controlled trial.
3. Indoor residual spraying in combination with insecticide-treated nets compared to insecticide-treated nets alone for protection against malaria: a cluster-randomized trial in Tanzania.

4. Effectiveness of residual acaricides to prevent Lyme Disease and other tick-borne diseases in humans.
5. Camino Verde (The Green Way): evidence-based community mobilization for dengue control in Nicaragua and Mexico: feasibility study and study protocol for a randomized controlled trial.
6. Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomized controlled, two-by-two fact. (2018)
7. Study protocol for cluster randomized controlled factorial design trial to assess the effectiveness and feasibility of reactive focal mass drug administration and vector control to reduce malaria transmission in the low endemic setting of Namibia. (2017)
8. Reduced incidence of Chikungunya virus infection in communities with ongoing *Aedes aegypti* mosquito trap intervention studies – Salinas and Guayama, Puerto Rico, November 2015-February 2016. (2016)
9. The additional benefit of residual spraying and insecticide-treated curtains for dengue control over current best practice in Cuba: evaluation of disease incidence in a cluster randomized trial in a low burden setting with intensive routine control. (2017)
10. Mitigating diseases transmitted by *Aedes* mosquitoes: a cluster randomized trial of permethrin-impregnated school uniforms. (2017)
11. The AWED trial (Applying *Wolbachia* to Eliminate Dengue) to assess the efficacy of Wolbachia-infected mosquito deployment to reduce dengue incidence in Yogyakarta, Indonesia: study protocol for a cluster randomized controlled trial. (in press, 2018)

Bioethics:

1. Ethical, social, and cultural considerations for site selection for research with genetically modified mosquitoes (2008)
2. Informed consent in field trials of gene-drive mosquitoes (2017)
3. Community engagement and the human infrastructure of global health research (2014)
4. What makes community engagement effective? Lessons from the Eliminate Dengue program in Queensland, Australia (2015)

Field Site Selection:

1. Criteria for identifying and evaluating candidate sites for open-field trials of genetically engineered mosquitoes (2014)

Risk Assessment/Management:

1. Expert risk perceptions and the social amplification of risk: a case study in invasive tree pests and diseases (2017)
2. Maintaining quality of candidate strains of transgenic mosquitoes for studies in containment facilities in disease endemic countries (2018)
3. Understanding Risk: Informing Decisions in a Democratic Society (1996)

Appendix 4: Resources

U. S. REGULATORY AGENCY INFORMATION

Modernizing the Regulatory System for Biotechnology Products: Final Version of the 2017 Update to the Coordinated Framework for the Regulation of Biotechnology: 2017_coordinated_framework_update

Food and Drug Administration (FDA)

- Regulation of Mosquito-Related Products (GFI #236) (January 2017)
- Regulation of Intentionally Altered Genomic DNA in Animals (GFI #187) (January 2017)

Environmental Protection Agency (EPA)

Registration Issues

- https://www.epa.gov/ingredients-used-pesticide-products https://www.epa.gov/pesticide-registration/registration-requirements-and-guidance https://www.epa.gov/pesticide-registration
- Pesticide Registration Manual: Chapter 12 - Applying for an Experimental Use Permit (EUP)

Pesticides and Biotechnology:

- https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/epas-regulation-biotechnology-use-pest-management
- https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/modernizing-regulatory-system-biotechnology-products

Environmental Assessment Explained

- EPA: Testing Requirements to Assess Risks to Human Health and the Environment
- FDA CVM Environmental Impact Consideration
- EFSA: Guidance on the environmental risk assessment of genetically modified animals

NIAID Clinical Resources

Guidance for Investigators:

- Clinical Trial Research at NIH: https://www.niaid.nih.gov/grants-contracts/clinical-trial-research
- Investigator-initiated Clinical Trials resources: https://www.niaid.nih.gov/grants-contracts/investigator-initiated-clinical-trial-resources

Clinical Resources:

- Vaccine and Treatment Evaluation Units: https://www.niaid.nih.gov/research/vaccine-treatment-evaluation-units-intro
- Infectious Diseases Clinical Research Consortium: https://www.niaid.nih.gov/research/idcrc
- Resources for Investigators: https://www.niaid.nih.gov/research/microbiology-and-infectious-diseases-resources

Pan-American Health Organization

- http://www.who.int/neglected_diseases/vector_ecology/resources/WHO_HTM_NTD_VEM_2017.03/en/
- https://www.who.int/neglected_diseases/vector_ecology/resources/WHO_HTM_NTD_VEM_2017.05/en/