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The role and value of a community and stakeholder engagement strategy for the establishment of a Controlled Human Malaria Infection Study (CHMIS) for *P. vivax* in Bangkok, Thailand.

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The role and value of a community and stakeholder engagement strategy for the establishment of a Controlled Human Malaria Infection Study (CHMIS) for *P. vivax* in Bangkok, Thailand.

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B.S. Biology,
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Abstract

The role and value of a community and stakeholder engagement strategy for the establishment of a Controlled Human Malaria Infection Study (CHMIS) for *P. vivax* in Bangkok, Thailand.

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Abstract

South East Asia carries 83% of the global burden of Plasmodium Vivax (*P.vivax*) malaria[1], and has increasing development of multi-drug resistant *P.vivax* [1],[2]. Standard control measures have proven unsuccessful at combating *P.vivax*, leading the Mahidol Oxford Tropical Medicine Research Unit (MORU) in conjunction with Mahidol University to propose and receive funding to conduct a Controlled Human Malaria Infection Study (CHMIS) to test vaccines, identify correlates of protection and test novel drugs for *P.vivax* malaria. Due to its study design CHIMS creates a multitude of ethical and regulatory challenges [3],[4].

This thesis was a qualitative case study to examine the role and potential value of a community and stakeholder engagement strategy for the establishment of a *P.vivax* CHMIS by the Mahidol Oxford Tropical Medicine Research Unit (MORU) in Bangkok Thailand. The aim of the study was to examine: 1.) the unique challenges that arose during the planning and creation of a CSE strategy for a *P.vivax* CHIMS, 2.) how CSE was used to address these challenge; and 3.) the value of utilizing CSE in the development of CHIMS for *P.vivax*. Seven in-depth interviews and nine informal interviews were conducted with MORU and Mahidol staff, along with a focus group discussion with global ethical researchers and Thai ethics committee members. Additional data were collected through field observations and literature reviews. Data analysis was conducted using grounded theory and qualitative analysis methods of memo writing, analytic code creation, clustering, and freewriting. Findings showed that a *P.vivax* CHIMS had unique societal, social and ethical challenges compared to other clinical trial studies and that community and stakeholder engagement functioned as a "de –risking" mechanism for the *P.vivax* CHIMS in Bangkok, Thailand.

[1] World Health Organization. (2018). "World malaria report 2018." Retrieved February, 2018 from https://apps.who.int/iris/bitstream/handle/10665/275867/9789241565653-eng.pdf?ua=1

[2] CDC (2018) "Malaria: Frequently Asked Questions" Retrieved from: https://www.cdc.gov/malaria/about/faqs.html

[3] Gordon, S. B., Chinula, L., Chilima, B., Mwapasa, V., Dadabhai, S., Mlombe, Y., & Malawi Research Ethics Workshop 2018 Participants (2018). A Malawi guideline for research study participant remuneration. *Wellcome open research*, *3*, 141. doi:10.12688/wellcomeopenres.14668.2

[4] Lavery, J. V. (2018). Building an evidence base for stakeholder engagement. *Science*, *361*(6402), 554-556.

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CONTENTS

PURPOSE:

Malaria is the leading cause of death and disease in many countries. In 2017, there were an estimated 435,000 malaria-related deaths and 219 million cases of malaria globally (WHO, 2018; CDC, 2018). There are five known species of malaria parasite which can infect humans and hundreds of mosquito species that can act as a vector of malaria. Sub Saharan Africa carries 92% of the global burden of malaria, primarily caused by Plasmodium Falciparum (*P. Falciparum*) parasite and transmitted by female Anopheles mosquitoes, yet outside of sub-Saharan Africa the Plasmodium vivax *(P. vivax)* parasite is responsible for half of all malaria infections, and in areas where *P. falciparum* is controlled *P. vivax* quickly becomes the dominant malaria species (WHO, 2017, 2018). South East Asia has over 2.2 billion people at risk for malaria and carries 83% of the global burden of *P. Vivax* (WHO, 2018). In the countries comprising the Greater Mekong Subregion (GMS) of South East Asia, Cambodia, China, Laos, Myanmar, Thailand, and Vietnam, the development of multi-drug resistant *P. vivax* malaria is steadily increasing (WHO, 2017; CDC, 2018). The challenges faced in the GMS have resulted in global recognition that there is an urgent need to create new solutions to assist in the fight for malaria elimination in the countries of the GMS in South East Asia (Howes, 2016; WHO, 2018).

The Mahidol Oxford Tropical Medicine Research Unit (MORU) in conjunction with Mahidol University in Bangkok, Thailand proposed and received funding from the Wellcome Trust to conduct a series of Controlled Human Malaria Infection Studies (CHMIS) to test vaccines, identify correlates of protection, and test novel drugs for *P. vivax* malaria in Bangkok, Thailand. A CHMIS is a deliberate infection of a healthy volunteer with a controlled dose of malaria parasites to study immune responses, aspects of microbial infection, identify correlates of protection, and quickly test the efficacy of vaccines or novel drugs (Spring, 2015; Hodgson,

2015; Wellcome, 2018). Utilizing a CHIMS design offers an immediate opportunity for researchers to gain novel and essential information for the development of vaccines, which on average take 10-15 years to produce using common vaccine development strategies (Wellcome, 2018). The deliberate infection of volunteers with malaria in a CHIMS creates a multitude of unique ethical and regulatory challenges and complex considerations including intricate political, economic, cultural and social interactions which arise when conducting a human infection study which drastically affects the success of the program (Gordon, 2018 Lavery, 2018). Considerations such as public perception of the research and social acceptance of the study play critical roles in the effective implementation, recruitment of study subjects, and success of the program. Extensive literature has been published discussing common ethical considerations and challenges that arise when conducting a CHMIS, yet there is limited information on how to anticipate and mediate these challenges.

Community and stakeholder engagement (CSE) has been gaining attention and interest as a potential mechanism to mediate ethical, cultural, political, and implementation issues that arise in public health programs. (Lavery, 2018). This mounting interest in CSE has been met with sparse evidence on best practices for CSE in public health programs, limited information on how to adequately evaluate CSE and what or how it contributes to the success of public health programs or CHIMS (Lavery, 2018).

Purpose Statement: The purpose of this study is to examine the role and potential value of a community and stakeholder engagement strategy for the establishment of Controlled Human Malaria Infection Study (CHMIS) for *P. vivax* by the Mahidol Oxford Tropical Medicine Research Unit (MORU) in Bangkok Thailand.

OBJECTIVES:

Specifically, this thesis aims to examine: 1.) the unique challenges that arose during the planning and creations of a CSE strategy for a *P. vivax* CHIMS; 2.) how CSE was used to address these challenges; and 3.) the value of utilizing CSE in the development of CHIMS for *P. vivax*.

CONTEXT:

Section 1: Malaria

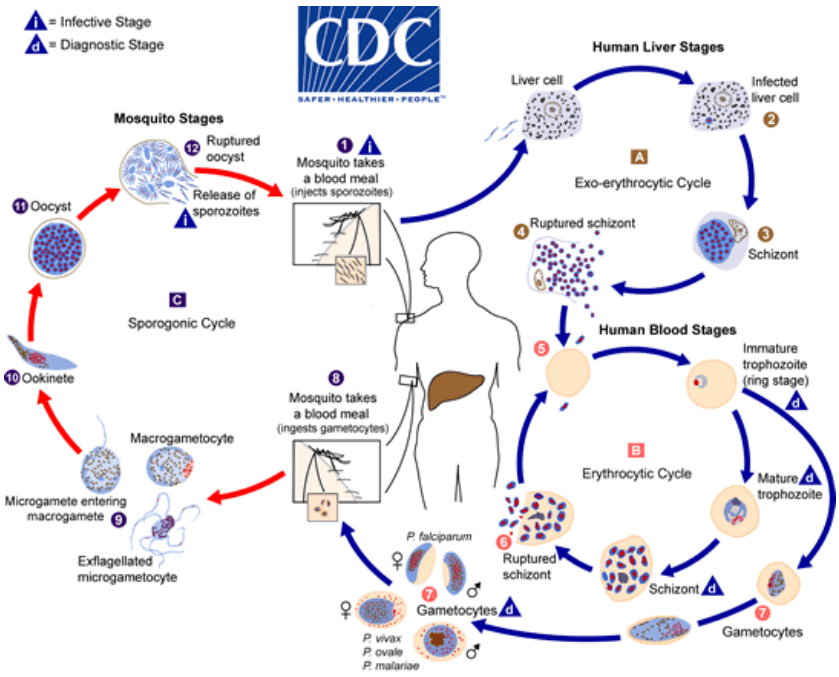
Malaria is a complex and life-threatening disease caused by the Plasmodium parasite. Five parasite species cause malaria in humans, and two of these species, *P. falciparum* and *P. vivax*, pose the greatest threat to humans (WHO, 2018). The complicated and human- dependent life cycle of Plasmodium parasites has hindered elimination efforts for hundreds of years (Lucchi,2019). Though significant progress has been made on *P. falciparium* elimination efforts in Sub Saharan Africa, the life cycle and biology of *P.vivax* have made it uniquely challenging to detect, treat, and eradicate in areas such as South East Asia where it is the dominant species (Lucchi,2019; Mendis, 2001; WHO, 2018). Unique attributes of *P. vivax* such as asymptomatic infection, ability to evade detection, relapse, and insecticide resistance have contributed to the development and spread of multi-drug resistant malaria parasites within the GMS of South East Asia (Howes, 2016; Steinhardt, 2018; WHO, 2018). The looming threat of antimalarial drug resistance spreading outside the GMS has created a robust push for the elimination of malaria in South East Asia (WHO, 2018). There is a need for a vaccine or novel drugs to combat specifically *P. vivax* malaria in the GMS. To understand the complexity of *P. vivax* malaria and

the need for the development of a vaccine it is important to understand how *P. vivax* fits into the context of malaria today.

Malaria infection:

Malaria is a disease caused by the Plasmodium parasite, which replicates and matures in the gut of the female *Anopheles* mosquito. Once fully mature it travels to the salivary glands of the infected mosquito. When a Plasmodium infected female *Anopheles* mosquito bites a human to take a blood meal to nourish her developing eggs, she injects the Plasmodium parasite into the human's bloodstream (CDC, 2018; Lucchi, 2019). The sporozoites, as they are called at this stage of their lifecycle, quickly travel to the new host's liver where they begin to multiply and replicate in the liver cells in what is known as the "the liver stage." Once the Plasmodium parasites have exponentially replicated in the liver cells, they rupture out of the liver cells to infect and to replicate in red blood cells (RBC) in the "blood stage" of infection. During the blood stage of infection, the Plasmodium parasites cause a multitude of chemical interactions interfering with the structure of the cell walls of RBC, causing them to burst and release large numbers of parasites into the bloodstream, which infect more RBCs and propagate the infection. The presence of parasites in the bloodstream causes the widely known and documented symptoms of malaria: high fevers, shaking, chills, and flu-like illness (CDC, 2018; Lucchi, 2019). During the blood stage of infection, parasites with the ability to sexually replicate, gametocytes, are freely circulating in the human bloodstream at high levels. If another female anopheles mosquito were to bite the infected individual, the mosquito would ingest gametocytes, and the Plasmodium parasite would start its sexual lifecycle within the mosquito's gut to carry on the transmission cycle of malaria. (CDC, 2018, Lucchi, 2019)

Figure 1: The Malaria Life Cycle



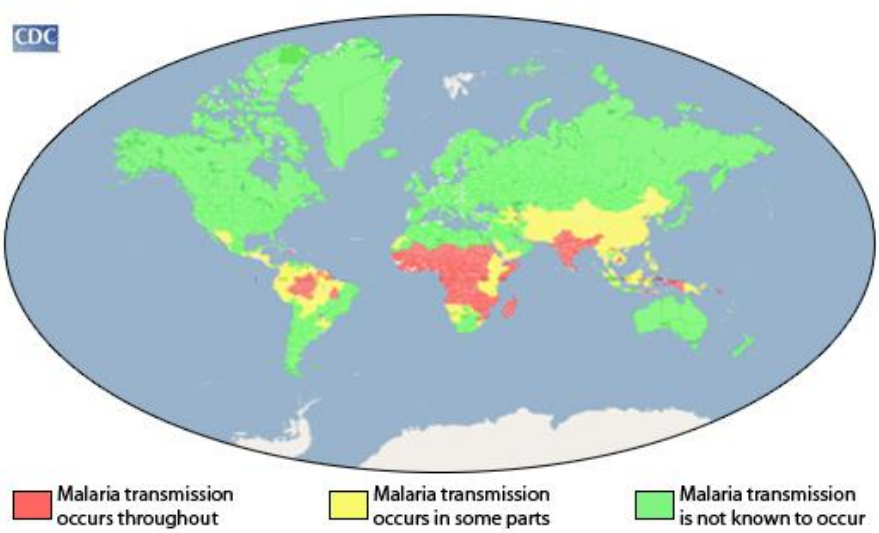
https://www.cdc.gov/malaria/about/biology/index.html

Malaria Transmission

The transmission of malaria is contingent on the presence of three factors: Humans, Anopheles mosquitos and Plasmodium parasites. Because Plasmodium parasites require an "invertebrate" host to complete half of their life cycle and a human host for the other half of its life cycle, both of these factors must be present for Plasmodium to complete its lifecycle and survive (CDC, 2018). The intimate and dependent lifecycle of malaria on these three factors is reflected in the global distribution of malaria where Anopheles mosquitoes and Plasmodium parasite can thrive. Anopheles' mosquitoes survival is directly tied to rainfall, heat, and presence of brackish bodies of water for the mosquito to lay their eggs (CDC, 2018). As a result, climate is a critical determining factor in malaria transmission and persistence of malaria in tropical and

subtropical areas of the world where transmission often coincides with “rainy seasons” (CDC, 2018).

Figure 2: Malaria Transmission



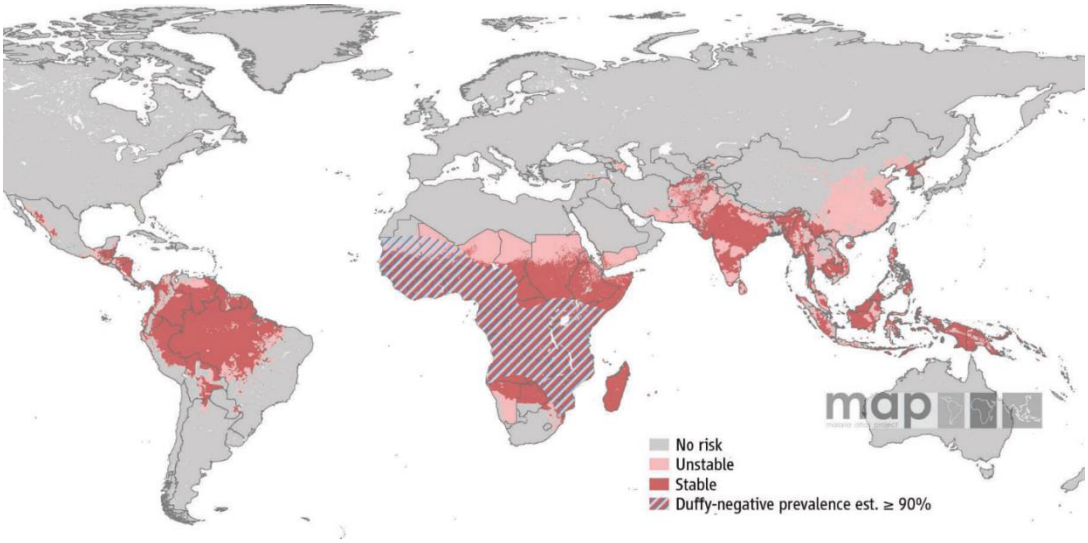
Malaria globally

Nearly half of the human population live in an area at risk of malaria transmission, with 91 countries and territories reporting active malaria transmission (CDC, 2018). In 2017, 92% of all malaria cases were in the WHO African Region, followed by 5% in the WHO South-East Asia Region and 2% occurring in the WHO Eastern Mediterranean Region (WHO, 2018). Globally there are five species of Plasmodium parasites known to infect and cause disease in humans: *P. falciparum, P. vivax, P. ovale*, and *P. malaria* and *P. knowlesi* each with unique biology, epidemiology of infection and sickness (WHO, 2019;CDC, 2018). *P. knowlesi* is a zoonotic strain of malaria predominant in Malaysia which primarily causes illness in monkeys but has been linked to sporadic yet severe cases of malaria in humans. Yet evidence does not

show that it can pass from humans to mosquitos and survive (WHO, 2018; CDC, 2018; Cowman, 2016). Globally, *P. falciparum* is the most prevalent malaria parasite accounting for 99.7% of all estimated malaria cases in WHO Africa Region in 2017 and the majority of global malaria deaths (WHO, 2018; Howes, 2016). Due to the severity of disease and the extreme morbidity and mortality caused by the *P. flaciparium*, the majority of malaria research and funding has been focused on the prevention, treatment, and control of *P. falciparium*, often ignoring other Plasmodium species. Nevertheless, contrary to historically held beliefs of the nonvirulence of *P. vivax*, recent developments have shown that *P. vivax* is associated with severe and fatal outcomes resulting in significant issues for some of the world's most densely populated and impoverished regions (Howes, 2016).

Section 2: *P. vivax* Malaria

Figure 3: Distribution of *P.vivax* globally.



Lucchi, 2019.

"*P. vivax* is a major cause of illness across large parts of the world, and it is increasingly argued that deaths, due to this parasite, have been underestimated" (Niang, 2014). Recent developments have shown that *P. vivax* is the most widespread human malaria with an estimated 2.5 billion people at risk for infection, with 2.2 billion of them residing in Asia and the Pacific (WARN, 2019; Howes, 2016; Niang, 2014). Outside of sub-Saharan Africa *P. vivax* is responsible for nearly half of all malaria infections and severe and fatal outcomes (WHO, 2017). *P.vivax* infections affect people of all ages and remain a significant cause of childhood illness in the tropics (WHO, 2017; CDC, 2018). Repeated *P. vivax* infections throughout childhood and adult life have damaging effects on personal well-being, growth, development, and economic performance of individuals, families, communities, and nations (Mendis, 2001). The estimated direct cost of *P. vivax* illness, treatment, and premature death is about US$12 billion yearly (CDC, 2018). There has been growing recognition that there is a need to understand the epidemiology, biology, infection, and etiology of *P. vivax* to develop better control measures (Howes, 2016). Past control efforts have fallen short of eliminating *P. vivax* due to its unique biology, which confers on the species the ability to survive and replicate in conditions that may be adverse to the transmission of the *P. falciripium* (Mendis, 2001). These abilities include the formation of asymptomatic infections, the ability to evade detection, recurring infections/relapses, resistance to standard vectors control measures, and the development of drug, and insecticide resistance.

Asymptomatic infection

The most common type of *P. vivax* infection is asymptomatic with only a small proportion of blood-stage *P .vivax* infections triggering any symptoms. As a result, few asymptomatic individuals receive medical attention or treatment for malaria (Howes, 2016;

Steinhardt, 2018). Studies from the Peruvian Amazon have demonstrated that only a quarter of individuals who tested positive for *P.vivax* by Polymerase Chain Reaction (PCR), a highly specific test used to identify DNA, exhibited any symptoms. And, if symptoms do occur they are often similar or almost identical to that of *P. falciripum* infections resulting in frequent, misdiagnosis and incorrect treatment (Howes, 2016; Martin, 2018). In the absence of correct treatment, asymptomatic individuals continue to carry low to high-grade parasite infections for months or years furthering endemic transmission of P. *vivax* to their communities (Martin, 2018). Studies have shown that up to 97% of *P. vivax* infections are submicroscopic, unable to be seen by a common light microscope, and require advanced diagnostic technology for detection, resulting in issues with detection and treatment of *P. vivax* in areas without access to advanced technologies (Howes, 2016).

Evading detection

Current strategies and technologies used for malaria detection were primarily developed for *P. falciparum,* which has distinctly different epidemiology of infection and biology than *P. vivax* infections. As a result, current diagnostic strategies are insufficient for detection of *P. vivax* infections. For example, *P. vivax* infections occur at lower gametocyte densities than *P. falciparum* infections because routine light microscopy and rapid diagnostic tests require high parasitemia counts for a positive result, *P. vivax* infections are often missed when these methods are employed (Martin, 2018; Howes, 2016). Detection of *P. vivax* requires higher sensitivity diagnostics, such PCR or extremely sensitive RDTS to show positive infections, which are not readily available or feasible for use in the field (Howes, 2016*).* In addition to deficiencies in diagnostic technology for *P. vivax,* individuals infected with *P .vivax* are infectious and able to transmit *P. vivax* sooner than the standard ten days associated with *P. falciparum* infection,

rendering early 'detect-and-treat' efforts to limit transmission of *P. vivax* ineffective (Martin, 2018). The non-transferrable testing, detecting, containment and treatment strategies used for *P. falciripium* are proving ineffective in the fight against *P. vivax*. Research into effective control measures must be developed if there is any hope for *P. vivax* elimination (Martin, 2018; Howes, 2016).

Relapse

Unlike *P. falciparum*, which mounts a full blood stage infection after the liver stage, *P. vivax* can stay sequestered in the liver for weeks, months or years as hypnozoites and reemerge to cause a "relapse" (Mueller, 2015; CDC, 2018). The amount of time *P. vivax* hypnotizes, sequesters and incubates in the liver before causing a relapse is variable and differs by strain, region, and geography (Howes, 2016). Temperate and subtropical "strains" of *P. vivax* exhibit long incubation periods, with a long delay between primary infection and relapse, while tropical strains are characterized by short incubation and short relapse intervals (Howes, 2016). In South- East Asia and Oceania, *P. vivax* is in the short latency form, where relapses occur approximately every three weeks after treatment with antimalarial (artesunate, quinine) and 6-7 weeks after treatment with antimalaria (Mepacrine, Chloroquine, Mefloquine, or Piperaquine) (Howes, 2016).

The activation of hypnozoites results in new blood stage infections and clinical attacks in individuals who were treated and cleared of prior malaria infections furthering the transmission of *P. vivax* in communities that had been presumed to be clear of the parasite (Howes, 2016). Little is known about what triggers the activation of dormant hypnozoites, but leading hypotheses suggest that relapse may be triggered by systemic febrile illness. Febrile illness is

associated with immunological responses when the host is bitten by another mosquito, or that the relapse mechanism is an adaptive trait of the parasite to "sequester and hibernate" during conditions inhospitable to the Anopheles mosquito (Howes, 2016; Bassat, 2016).

Primaquine is the only available treatment or "radical cure" which can eliminate hypnozoites sequestered in the body. However, Primaquine is often not prescribed because of the prevalence of the enzyme disorder glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is one of the most common enzyme disorder in human beings and at highest prevalence in persons of African, Asian and Mediterranean descent (Chu, 2016). G6PD deficiency is a genetic metabolic abnormality caused by a deficiency in the G6PD enzyme, which is critical for the functioning of red blood cells. If a person with G6PD receives Primaquine, it can cause life-threatening acute hemolytic anemia and death (Nagalla, 2019). Lack of testing capabilities for G6PD results in Primaquine rarely being prescribed to *P. vivax* infected individuals if G6PD status in not verifiable, allowing for *P. vivax* to stay sequestered in an unknown number of individuals (Chu, 2016; Bassat, 2016).

Vector lifecycle:

There are 71 species of anopheline mosquitoes with the potential ability to transmit *P. vivax*. Many of these primarily feed on animals rather than humans as opposed to *P. falciripium* mosquitoes whose lifecycle is more closely tied with humans and their environment (Bassat, 2016). Standard vector control measures used for malaria such as IRS and ITN 's were created for *P. falciripium* mosquitoes that primarily inhabit and rest indoors, and as a result *P. vivax* carrying mosquitoes rarely come into contact with IRS and ITN's in human dwellings (Bassat, 2016, Malaria course, 2018). ITNs and IRS have been highly effective in reducing *P. falciparum*

malaria, but have proven less effective at controlling the transmission of *P.vivax* (Bassat, 2016). A small number of studies have shown that *P. vivax* gametocytes are transmitted more efficiently to some anopheline mosquito vectors than *P. falciparum*, allowing for transmission of *P. vivax* to mosquitos at lower parasite densities (Bassat, 2016). These distinct differences in the *P.vivax* vector lifecycle, environment preference, and biology have caused decades of vector control based strategies for *P. falcirparium* to be less successful at controlling *P. vivax* (Bassat, 2016).

Insecticide and drug resistance

"*The WHO Global report on insecticide resistance in malaria vectors: 2010–2016"* showed that resistance to the four commonly used insecticide classes, pyrethroids, organochlorines, carbamates, and organophosphates, is widespread in all major malaria vectors across the WHO regions of Africa, the Americas, South-East Asia, the Eastern Mediterranean, and the Western Pacific (WHO, 2018). In South East Asia, there is significant resistance to carbamates, organochlorines used in IRS. And resistance to pyrethroids, currently the only insecticide used on ITN's, have been detected in high levels in Sub Saharan Africa and South East Asia limiting the impact of vector control measures (WHO,2018).

In some countries in Southeast Asia *P. vivax* is resistant to chloroquine, primaquine and artemisinin therapies, which have been integral to the success of malaria elimination efforts. (White, 2011; Mehlotra, 2009; WHO, 2018). Many countries in South East Asia, specifically the Greater Mekong Sub region (Cambodia, China, the Lao People's Democratic Republic, Myanmar, Thailand, and Vietnam) have had to abandon the use of chloroquine treatment because it is no longer effective against *P. vivax* (WARN, 2019). "The development of resistance to drugs poses one of the greatest threats to malaria control and results in increased malaria morbidity and mortality due to malaria" (CDC, 2018).

56% of all malaria cases in South East Asia are attributed to *P. vivax* , and Southeast Asia carries 83% of the global burden of *P.vivax* (Howes, 2016; WHO, 2018 & 2015). The prevalence of all five species of malaria in the South East Asia GMS and the development multidrug-resistant *P. vivax* has pushed the GMS to create a drastic malaria elimination strategy to reduce the burden of malaria in their region (Howes, 2016; WHO,2018 & 2015). "The *Strategy for malaria elimination in the Greater Mekong Subregion (2015–2030)"* aims to achieve malaria elimination by focusing on two main development categories. The first category is expanding research for innovation for improved delivery of services, by developing novel tools and approaches to existing and new challenges by focusing on actions to facilitate the rapid uptake of new tools, interventions, and strategies (WHO, 2015). The second development category focuses on strengthening the enabling environment of health system policies for the delivery of services to meet the needs of mobile migrant populations and cross border regional collaboration (WHO, 2015).

Growing global recognition of the threat of drug-resistant malaria has highlighted the critical need for the scientific community to maintain a pipeline of new drugs and potential vaccine candidates (Spring, 2015). The WHO Global Plan For Artemisia Resistance states that "(t)he availability of an effective vaccine that provides protection and prevents transmission would be a valuable tool in efforts to eliminate *P. vivax*." Understanding that malaria control has been historically aimed principally at *P. falciparum* without regard to *P. vivax,* any program aiming for elimination of malaria transmission will need to adopt strategies and interventions that are effective against *P. vivax*. Without a way to drive out *P.vivax* transmission, there is little chance of eradicating malaria (Howes, 2016).

BACKGROUND AND SIGNIFICANCE:

The apparent need for the timely development of a *P. vivax* vaccine has become glaringly evident as research begins to show the widespread global distribution of *P. vivax*, the significant difficulties currently faced in elimination efforts, combined with the rapid development of multidrug-resistant malaria in the GMS. These factors highlight the urgent need for a vaccine for *P. vivax*. Yet strategies to create a vaccine are riddled with complications and feasibility challenges. The standard option of utilizing common research techniques prior to conducting large scale clinical trials that test vaccine efficacy may not serve as a viable solution due to time constraints, varying population responses to vaccines, and lack of information on potential correlates of immunity for vaccine development.

Section 1: Considerations for the feasibility of large scale vaccine trials for the development of a vaccine for *P. vivax*

Genetic and geographic responses

Vaccine trial results are highly variable in different global regions, and sometimes promising results from high-income settings have not been replicated in low and middle-income countries (LMIC) (Gordon, 2017). This variability in vaccine efficacy is due to a variety of differing epidemiological factors such as: naturally acquired immunity, dietary factors, intestinal microbiota, infectious disease history, co-infections, immune status, environmental factors, and host-pathogen relationships (Gordon, 2017). Mounting evidence has shown that vaccine efficacy varies significantly for vector-borne diseases such as malaria because of variability in host immune response to the pathogen and the vaccine. This unique host-pathogen interaction means that vaccines can only be appropriately tested in the targeted settings where the diseases occur

(Gordon, 2017). Variations in allele frequencies of functional variants different geographic ancestries influence individuals' and populations' genetic predispositions to disease, and the efficacy of vaccines and drugs within those population (Darr, 2005; Gordon, 2017). Different populations have polymorphisms, or variations in gene expression that play a critical role in the pathogenesis of infection and natural immunity development. These variations can lead to heterogeneity in immune responses to vaccines and influence how populations respond to medicines. Given its unique epidemiology it is critical that a vaccine for *P.vivax* malaria be tested and developed with the population it is intended to be used for (Darr, 2005; Poland, 2008).

Insufficient animal models and correlates of protection:

Research has shown that animal models can be especially unreliable for human-specific infectious organisms such as *P.vivax,* yet vaccine candidates must perform well in animal testing to make it to the first round of clinical trials (Wellcome, 2018). Though animal models have provided fundamental insights into malaria immunity, they cannot reproduce the human condition or immune responses that would be expected in populations in malaria-endemic areas (Day, 2018). They often produce discordant or inaccurate results when used to predict vaccine candidates for human-specific diseases (Day, 2018). The lack of an adequate animal model for *P. vivax* has led to a lack of information about humoral or cellular immune correlates of protection for *P. vivax*. Extensive research would need to be done to investigate potential immune response correlates before development of a vaccine could even begin (Spring, 2014) With only a single blood-stage vaccine candidate for *P.vivax* having been evaluated in any depth, very little is known the about what the potential vaccine candidates may be (Tham, 2017). Based on experiences with *P. falciparum* vaccine research, which has already progressed through the

large-scale testing of panels of antigens, successful phase III trials, and licensing. *P. vivax* research is still in early preclinical development and has a long way to go before there are even potential vaccine candidates to begin testing (Tham, 2017). *P. falciparum* research has shown there will need to be a much broader search of potential vaccine candidates to begin to gain a deeper understanding of what high potential, high priority targets are before any advances in the development of a vaccine for *P. vivax* can begin (Tham, 2017).

Time

Antimalarial vaccine development requires a significant investment of time and resources in antigen selection, development, and manufacturing. Vaccine efficacy trials require recruitment of many subjects and follow-ups for each subject, significant financial investments for infrastructure, training of medical and biological staff, contingency planning for affordable provision of tested products if success is demonstrated and considerations for how transmission and exposure would vary within time it would take to develop, test and implement the vaccine into large scale use (Gordon, 2018). On average, it takes 10-15 years to develop and test a vaccine in a clinical trial and prove its effectiveness, and up to an additional 17 years for the widespread adoption of the intervention into medical practice. In the variable 30 years it could take to develop a vaccine for *P. vivax*, the parasite could mutate and render the vaccine ineffective (Gordon, 2018; Lavery, 2007, p.8).

Where P.vivax *vaccine development is now*

Only two P. *vivax* antigens having been tested as vaccine targets. There are significant gaps in knowledge about mechanisms of immunity and correlates of protection for *P. vivax* malaria (Tham, 2017). The current inability to maintain *P. vivax* in long-term culture limits the

functional approaches that can be used to develop and understand the immune function and evaluate antigen candidates for *P.vivax* (Tham, 2017). The infancy of *P. vivax* research and limitations on long-term culturing and testing of candidates have left few options to address the need for the development of a vaccine for *P. Vivax* by 2030.

Alternate methods and studies for vaccine development, antigen testing, and selection for *P. vivax* malaria vaccine do exist. Because there are few correlates of immunity known for *P. vivax* and a limited number of vaccine candidates in development, a Controlled Human Malaria Infection Study (CHMIS) could allow for the rapid analysis and evaluation of potential antigens and vaccine products in well-controlled early-phase proof-of-concept clinical studies (Wellcome, 2018).

Section 2: Utilizing A Controlled Human Malaria Infection Study (CHMIS) Design in Bangkok, Thailand

A CHMIS is the deliberate infection of volunteers with a controlled dose of malaria parasites either through mosquito bites or direct injection of the parasite itself. After volunteers are infected, they are monitored under direct medical supervision for evidence of infection and treated if symptoms appear. Volunteers are treated for complete clearance of malaria parasites after the study (Gordon, 2017; Stanisic, 2018). CHMIS provide a cost-effective and expeditious way to provide reliable, accurate answers for the efficacy of drug and vaccine candidates (Spring, 2018). CHIMS can help researchers monitor and understand immune responses, gather highly detailed information about immune correlates, study aspects of microbial infection and gather more information regarding immune responses to novel drugs (Spring 2015; Hodgson, 2015; Wellcome, 2018). Findings from CHMIS can help deselect intervention candidates,

accelerate the process of developing a vaccine by testing for safety and efficacy more quickly than large scale population trials can (Wellcome, 2018; Hodgson, 2015).

Utilizing a CHIMS for *P. vivax* would be an expeditious way to study which correlates of protection are most viable for *P. vivax*, test efficacy of potential vaccine candidates, and determine which vaccines are most feasible and research-worthy. CHIMS can address the inability to culture *P. vivax*, common discordant and variable results which occur when vaccines are tested in different populations and can eliminate the potential for conflicting results often rendered from animal models (Spring, 2015; Hodgson, 2015; Wellcome, 2018).

The ability for a CHIMS design to expedite vaccine development and mediate the concerns highlighted above was integral in the decision of Mahidol University and Mahidol Oxford Tropical Medicine Research Unit (MORU) in Bangkok, Thailand to propose the use of a CHMIS strategy as an exploratory and informative alternative to a 10-15 years of experimental research before conducting large scale vaccine trials for the development of a vaccine for *P. vivax* (Day,2018). The goal of MORU and Mahidol University's CHMIS for *P. vivax* is to begin to understand correlates of protection and to test current vaccines and drugs in development on semi-immune and *P. vivax* naive patients. The study aims to fill the current gap in research regarding *P.vivax* mechanisms of infection, viable vaccines and alternative drug treatment in response to expanding drug-resistant *P. vivax* (Day,2018).

The MORU CHMIS programs aims explicitly to:

1. Identify and characterize correlates of protection in the populations at risk in both *P. vivax* naïve and semi-immune populations.

2. Test the efficacy of pre-erythrocytic, blood stage and transmission blocking of *P.vivax* vaccine candidates in the target populations of naïve and semi-immune individuals.
3. Test the efficacy of novel drugs under development for anti-hypnozoite activity.

MORU in conjunction with the Mahidol University Faculty of Tropical Medicine (FTM) and The Wellcome Thailand Asia and Africa Programme has proposed and secured funding to conduct a CHMIS strategy for *P. vivax*. Together these two institutions possess the medical infrastructure, clinical expertise, biological capabilities, ethical review protocols, and governmental support to conduct a *P. vivax* CHIMS in Thailand. With the world-renowned Mahidol Faculty of Tropical Medicine entomology department and their experience with breeding vivax infected mosquitoes, they possess the biological and laboratory capabilities to create the infected mosquito populations necessary for the study. The Vivax Research Unit lead by Mahidol Faculty of Tropical Medicine has supplied infected mosquitos to several other *P.vivax* CHMIS studies worldwide and understands the necessary components of conducting a *P.vivax* CHMIS (Day, 2018). The Wellcome Thailand Asia and Africa Programme have ample experience, resources, and support to offer Mahidol Faculty of Tropical Medicine and MORU in conducting human infection malaria studies (Day, 2018).

As the planning for the studies began, the MORU Bioethics and Engagement Department was responsible for creating a community and stakeholder engagement strategy to assess and address the social and ethical issues associated with conducting a *P. vivax* CHIMS in Thailand. CHMIS involve a culmination of vast and complex interactions, ethical considerations and stakeholder perceptions which can make or break the success of the trial. The growing recognition that community and stakeholder engagement can improve the performance and success of programs by offering ways to navigate complex social, economic, cultural, political

and ethical issues highlights the need to understand and investigate unique considerations and challenges that arise when conducting CHIMs in low and middle-income countries (Lavery, 2018)

Section 3: Considerations for CHIMS

Origins of Human infection studies:

The first reported human infection trial was conducted by Edward Jenner in 1796 when he infected a 9-year-old boy with Cowpox to test his theory that immunity to smallpox could be generated by inoculating with a small amount of related cowpox (CDC, 2016). Though he was correct, his strategy of infecting a child without consent or awareness of the situation violated many of the human rights guidelines used in any clinical trials today.

Throughout history, human infection studies have been conducted on various diseases with erratic levels of efficacy and morality. Trials conducted in the early 20th century by researchers and scientist in the United States took advantage of vulnerable populations in society including children in orphanages, institutions for disabled children and adults and prisons to examine courses of infection for various diseases (Hic-Vac, 2018). Individuals in these groups were often targeted because they were perceived to lack the freedom, or capacity to make informed choices or refuse participation (Hic-Vac, 2018). In 1958, students at the Willowbrook State School in Staten Island, New York, an institution for mentally disabled children, were deliberately infected with Hepatitis to study the disease further and develop a vaccine (Hic-Vac, 2018). In 1944-1946, Prison inmates of Statesville Penitentiary in Illinois were used to test the safety of novel anti-malaria drugs, after being deliberately infected with malaria through the bites

of infected mosquitos (Miller, 2013). Other countries were also used to conduct human infection trials due to what was considered more lax ethical regulations than the United States.

In the 1940s a team led by Jon Cutler conducted experiments on unknowing Guatemala citizens. With an agreement with the Guatemalan and United States government, doctors deliberately infected 1,300 people with sexually transmitted infections without their knowledge, to test penicillin as a treatment (Walter, 2012). These now blatantly unethical applications of human infection and human experimentation affect and color people's perceptions of what controlled human infection trials are and what the ethical requirements are for them today. Acknowledging the dark history of human testing in the examples listed above, including the Nazi Eugenic experiments during World War II, begins to shed light on the deep distrust created when doctors purposely infect patients with a disease to study it, rather than treating and helping patients. The long history of ethically suspect human infection trials greatly influences the perception of what CHMIS are today.

Malaria infection studies:

In 1986 the US Army, Navy, and National Institutes of Health (NIH) completed the first documented CHIMS in which they were able to safely infect volunteers with *P. falciparum* from Anopheles mosquitoes and study the course of infection, proving the efficacy of CHIMS design (Spring, 2014). Since then, malaria has become one of the most successful and established human infection study models, with over 1,000 volunteers infected over the past 30 years and no serious adverse events or hospitalizations recorded related to the studies (Epstein et al., 2007; Spring, 2014; Kraft, 2018). CHIMS were used in the development of the *P. falciparum* vaccine as "well-controlled early-phase proof-of-concept clinical studies" which allowed researchers to

identify only the most promising candidates that confirmed immunity against *P. falciparum* infection and move them forward in development (Gordon, 2017). Though there have been many successful completions of CHIMS in the past, conducting a CHIMS for *P. vivax* in Bangkok, Thailand is complicated for many reasons. The unique biology of *P. vivax* requires sufficient infrastructure to complete the trial, capable medical staff and scientists to conduct the trail, a responsive ethics and regulatory frameworks to address the vast ethical complexities of the trial and consideration for how the intricate interactions of public perception, cultural views of disease and infection will shape the outcome of the study (Gordon, 2017).

Infrastructure- and capacity of medical and scientific communities.

CHMIS require facilities to conduct safe microbiology including substantial laboratory and clinical facilities, the careful recruitment of subjects, staff with clinical expertise to execute the protocol and, intensive monitoring and close governance of the trial (Gordon, 2017). Lack of medical organization and support are determining factors for why most LMIC are unable to conduct CHMIS (Gordon, 2017). Having appropriate clinical facilities, laboratory diagnostics, clinical governance and expertise with the ability to monitor and support adverse events if they occur, such as intensive care units with experienced nurses, doctors and technicians to run those units are imperative for a CHMIS (Gordon, 2017). Careful recruitment and screening of volunteers is also critical for the development of CHMIS for *P.vivax* specifically the awareness of the prevalence of Glucose-6-phosphate dehydrogenase (G6PD) deficiency in Thailand. G6PD can cause acute hemolytic anemia in individuals if they are given primaquine to treat malaria (Luzzatto, 2014; GARD, 2019).

Though Thailand is considered a low to middle-income country (LMIC) it was the first LMIC to ever successfully conduct and complete a human infection study contrary to common

belief that human infection trials could not be conducted in LMIC due to the complex technical, clinical, ethical and regulatory issues associated with them (Spring, 2014; World Bank, 2018; Gordon, 2017). In 2012, MORU completed a human infection trial with *Shigella sonnei* which led to the evaluation of Shigella vaccine candidates and proof of Thailand's capacity to conduct a trial of this complexity and magnitude (Bodhidatta, 2012). Since the establishment of the Armed Forces Research Institute of Medical Sciences [AFRIMS] in 1977 in Bangkok, Thailand, Thai and US army doctors have worked collaboratively with the Ministry of Public Health (MoPH), other Thai academic institutions, and the pharmaceutical industry to develop and conduct vaccine efficacy trials for Japanese Encephalitis, Hepatitis A (HepA), dengue, and to develop protocol for a *P. vivax* CHMIS (Ratto-Kim,2018). The experience with vaccine research and development in Thailand has mitigated or limited concerns about the necessary capacity to conduct a *P. vivax* CHMIS in Bangkok, Thailand.

Ethical complexities:

Today human infection trials are rigorously regulated, organized, controlled and reviewed to limit harm, coercion, and violations of individual's rights and autonomy (Hic-Vac, 2018). Modern CHIMS studies undergo detailed independent review and oversight and have been described as "entirely unrelated to the unacceptable and unregulated infectious challenges carried out in the past" (Gordon, 2017). The strict international standards of ethics developed over the past 40 years have allowed for the successful completion of various controlled human infection trails, significantly contributing to public and global health by creating necessary and instrumental developments in vaccine research (Roestenberg, 2016). Over 22,000 volunteers have participated in well-regulated controlled human infection studies to date, in which the pathogenesis, clinical features, microbiology, and the immune response to more than 15

pathogens of public health importance have been examined for diseases including Typhoid & Parathyroid, Influenza, Shigella, E.coli, Norovirus, Dengue, Mycobacteria, Cholera and respiratory syncytial virus (RSV) (Gordon, 2017). The most notable success of a human infection trial model was the development of the new typhoid conjugate vaccine Vi-TT (Vi-tetanus toxoid conjugate vaccine) (Welcome, 2018). Although there have been numerous successful vaccine developments from controlled human infection, studies the past atrocities of human experimentation and historically lax ethical requirements raise anxieties and concerns regarding the ethics, and regulatory frameworks used when conducting CHIMS today.

Ethics and regulatory framework/ considerations

Serious analysis and reflection regarding the potential for coercion, participant confusion regarding informed consent and what regulatory framework will be used or developed to monitor the trial are common ethical considerations for CHIMS (Hodgson, 2015). Ethical considerations such as opportunities for collaborative partnership, the feasibility of the study, making sure there is protection for vulnerable populations and minimizing risks and enhancing benefits for participants are critical when planning any type of research, but are paramount for CHIMS (Lavery, 2007, p.6). Acknowledging the high social value of CHIMs is considered sufficient to justify the risk participants are exposed to in the study, it in and of itself may not be the main motivation for individuals participation in the study (Lavery, 2007, p. 11). Research has shown monetary motivations are often a primary determining factor for volunteer participation in CHIMS studies in Kenya (Njue, 2018). The motivation to receive compensation for participation by individuals of low socioeconomic status raises the prospect that they may be unduly influenced into participation in the study (Kraft, 2018). Arriving at a consensus for adequate or appropriate compensation for reimbursement of time, expenses, opportunity costs

and contribution to the study can be is a fine balance between incentivized research, and lack of appropriate compensation for negative impacts (Gordon, 2017). To mediate concerns of exploitation or coercion due to compensation "It is recommended that CHMI studies are based on a deep understanding of the local community's perceptions based on prior experience and previous engagement, and from a position of established mutual trust" (Gordon, 2017). Because informed consent has been recognized as a principal of ethical research for more than a century, addressing differing cultural norms, language differences, social traditions, and practices surrounding informed consent between sponsor organizations and host countries can make the process of informed consent complex, particularly in developing countries. (Lavery, 2007). Because local and cultural traditions play a role in what is deemed adequate remuneration and sufficient informed consent for participation, often gaining the appropriate international standards of fully informed consent can lead to points of contention and confusion (Hodgson, 2015).

Cultural concepts of infection widely influence understanding and individual autonomy when gaining informed consent, creating accessible information which fosters full understanding of what the study entails can be difficult. To achieve the standard of international informed consent information must be made accessible and understandable to participants. To create accessible information for the population in which the study is being conducted in study teams must consider cultural norms, practices, and communities understanding of infection to ensure that information presented respectful and understandable (Hodgson, 2015). Because means of information delivery, learning, understanding and obtaining consent vary in different countries, Western ideas can remain foreign, and the standard requirements of informed consent may appear misplaced and inappropriate (Hodgson, 2015; Gordon 2017). Consensus on appropriate

compensation, cultural norms surrounding consent and the inherent controversy entangled with doctors purposely infecting volunteers with malaria are salient concerns and issues which must be deliberated and considered when conducting a CHIMS (Hodgson, 2015; Gordon 2017).

Public perception of Human infection with malaria.

Human infection studies are inherently controversial; when researchers and doctors are infecting individuals with a disease rather than curing it, it conflicts with societal norms and expectations of the medical field. CHIMS can trigger memories of historical atrocities with human experimentation influencing public perception and understanding of what a CHMIS is and how it will be conducted (Gordon, 2017; Hodgson, 2015). "The underlying anxieties caused by CHIMS are likely to be similar in many regions, but the means to address these concerns should be locally determined in advance of study design, using regionally appropriate programs of community engagement, consultation and education (Gordon, 2017). To obtain ethical and regulatory approvals for CHIMS it important for MORU to engage in detailed discussions with key stakeholders to increase understanding and acceptance of the CHIMS. Discussion would allow for valuable feedback to guide the study design, increase approvals and mitigate serious concerns with the study (Hodgson, 2015). CHIMS trials differ significantly from other standard clinical trials in the flipped power dynamic of researchers and participants. CHIMS are completely dependent on participants willing to volunteer for the study for "altruist reasons" rather than reasons that benefit them as individuals. Because of this public perception and support of the study play a large role in the obtaining the required number of participants to complete the study and success of the study.

The need for Community engagement to address concerns

"The growing recognition that community and stakeholder engagement can improve the performance and success of programs by offering ways to navigate complex social, economic, cultural, political and ethical issues is well founded" (Lavery, 2018). Yet, developing a community and stakeholder engagement strategy for a CHIMS is uncharted territory. There is limited evidence about the effectiveness of community engagement for public health programs (Lavery, 2018), and limited published accounts addressing participants' understanding and perspectives of CHIMS (Hodgson, 2015). Currently there is limited guidance about what CSE approaches would be most effective in a *P. vivax* CHIMS or what a strategy for community engagement would could offer a *P.vivax* CHIMS (Lavery, 2010). Though there is a significant amount of literature on the ethical considerations for challenge trials, there is still limited literature explicitly addressing concrete strategies or methods to mediate the common challenges that arise when conducting a CHMIS. There is a need to understand what role community and stakeholder engagement would play in CHIMS and the value an engagement strategy would have for the implementation of the *P. vivax* CHIMS in Thailand.

This thesis is a qualitative case study of the development of a CSE strategy for the MORU and Mahidol University *P. vivax* CHMIS. This case study is an opportunity to investigate the purpose, function, and utility of developing a CSE strategy for CHMIS and to explore the value that developing a community and stakeholder engagement strategy can offer CHIMS. This case study aims to: (1) understand the unique challenges that arise during the planning and implementation of a *P. vivax* CHIMS; (2) To investigate and discuss how CSE was used to address the challenges that arose, and (3) to describe the value of CSE in the development of CHIMS for *P. vivax*.

METHODS:

Study Design:

A qualitative case study was conducted using grounded theory to investigate and understand the role of and value of a community and stakeholder engagement (CSE) strategy for a CHIMS at MORU in Bangkok, Thailand. Because community engagement strategies in CHIMs studies are highly contextual, under-researched and contain complex multivariate conditions, using a qualitative case study allowed for the multi-faceted complexity of CSE and CHIMS to be addressed. Qualitative cases studies are effective for observing the social phenomenon in their "raw form" allowing researchers to observe and consider cases and conditions under which processes or phenomena may emerge and vary (Charmaz, 2006; Glaser, Strauass, 1967). Utilizing a qualitative case study allowed for data to be "constructed through observations, interactions and any material which could be gathered about the topic and setting" allowing for the creation of a highly detailed picture of empirical events and experiences (Charmaz, 2006)

Data Collection:

The case study was conducted in collaboration with the MORU Bioethics and engagement unit before and during the preliminary stages of planning and development of the CSE strategy. Over course of eight weeks data were collected through observations, interactions, interviews, literature review, focus group discussions, informal interviews, events, and experiences (Charmaz,2016). Seven In-depth interviews (n=7) were conducted with researchers and staff of the Mahidol University Vivax unit (n=2), Clinical trial staff and support staff (n=2), MORU Bioethics and Engagement Department CHIM CSE strategy team (n=2) and Wellcome Vietnam CSE CHIMS planning team lead (n=1). Nine informal interviews (n=9) were

conducted with experts within MORU, including a unit director (n=1), Primary Investigator for the CHIMS project (n=1), MORU Malaria lab researchers (n=2), MORU field researchers (n=2) and Bioethics and Engagement Department team members (n=3). A focus group panel discussion was held with over 20 global ethics researchers and Thai Ethics Committees members to discuss the ethical implications and consideration for a CHIMS project in Bangkok, Thailand. Review of relevant academic literature and document analysis was conducted on publications, information, and pamphlets regarding CHIMs studies and community engagement. Observations were conducted of staff meetings, strategy development meetings and interactions of field staff working rural in Thai villages.

Data Analysis:

In keeping with grounded theory methodology, analysis was conducted in tandem with data collection (Charmaz, 2006). As data were collected, they were analyzed through the construction of analytic codes and categories which arose from previous data collections and document analysis. Analysis methods utilized were memo writing, clustering, and freewriting. Memo writing allowed for clarification and formulation of conceptual categories of challenges for *P.vivax* trials, social acceptability of the studies and an outline for the stakeholder analysis. Clustering tactics were used to visualize and conceptualization which themes and ideas were interconnected and under what conditions that connections were relevant (Charmaz, 2006). Bi-weekly freewriting was conducted, in which observations and interactions were documented as freewriting entries and were analyzed for patterns and repetition of themes. In-depth interviews were recorded and summarized and were compared to other data at each stage of analysis. This constant comparison allowed for the revision of research questions and objectives at various stages of data collection and analysis (Charmaz, 2006).

IRB Approval:

The Emory University Institutional Review Board (IRB) determined that this project did not meet the U.S. regulatory definition of "human subjects research" and therefore waived the requirement for IRB approval. Interviews and data collected were part of a program planning exercise at MORU and therefore no IRB review was required by the MORU IRB.

FINDINGS:

Section 1: Challenges for *P.vivax* CHIMS

The development of the CSE strategy for CHIMS at MORU confronted three main inter-related challenges: fear of infection; social acceptance of the study; and lack agreement regarding what CSE was within the CSE planning team.

"Fear of "infection" or participation in the study

The "fear of infection" was a pervasive theme in all discussions surrounding CHIMS. "Fear of infection" was commonly discussed in relation to prospective participants' fear of physical discomfort which would occur during the malaria infection component of the CHIMS, and as a potential reason individuals would be discouraged from volunteering for the study.

> *"People will be scared and not want to help. But we need to remind them frequently of the benefit for humanity for participating"*- MORU CHIMS CSE planning team member

There was variability in the discussions regarding how "participants" would react to this perceived "fear of infection" based on their experiences with malaria in the past. For example, the team hypothesized that the fear of infection or the fear of dying from malaria would vary

significantly for "semi-immune volunteers", individuals who had had malaria before in their lives vs. malaria naïve volunteers, individuals who had never had malaria before. The community engagement team saw the "fear of infection" as a prospective inhibiting factor for recruitment of volunteers because of how past experiences with malaria infection could significantly effect potential participants' perceptions of risk associated with the study. Fear of infection also came up in discussions about family members or friends of participants and how their attitudes, experiences or perceptions of infection with malaria could discourage potential participants from volunteering for the study. As one CSE strategy member pointed out

"Our recruiters need to be great explainers; they need to be able to assure and ease their fears (study participants). This will be critical for minimizing the concern and fear people will have after they leave the consent process. We don't want [them] to go home and start talking to their Aunt, cousin or whoever and get scared by what their family says. We need them to feel like they can trust us"- Social and Economic Scientist on MORU CSE planning committee

The fear of infection was also discussed relating to the long term implications of a *P. vivax* infection including the potential for relapse in study participants. Members of the ethics committee stakeholder forum discussed the potential for relapse as a significant and unnecessary risk for participants. The fear of the long term consequences of *P. vivax* infection and the controversial nature of purposefully causing those adverse effects in study participants was consistently brought up in discussion with various groups of stakeholders.

"Why do we need to infect people? There just seems to be a problem with creating people (purposely infecting participants) to conduct this research instead of selecting for them" – Stakeholder forum participant

Within the CSE planning team for CHIMS, there was consensus on the need for "fear of infection" to be "downsized and minimized" for the study to occur. The methods and ideas for how to minimize this fear of infection varied significantly between many of the interviews and discussions, but the acknowledgment of the need to reduce the fear of infection was discussed as integral for the success of the study and was consistent throughout interviews, discussion, focus groups, literature and conversation regarding CHIMS.

Social acceptance of the study

The social acceptance of the CHIMS program are highly dependent on the perceptions and attitudes of potential participants and other groups of stakeholders.

"Challenge studies (human infection trials) often do not directly benefit the individual medically, although there may be an indirect benefit from health screening and medical care. Rather, the benefit is at a societal level through scientific innovation and improved public health"

*(*Njue, 2018)

The lack of direct individual benefit for participants in CHIMS, and the dependence on the recruitment of healthy volunteers for CHIMS to be successful places CHIMS in a unique "power dynamic" situation that is not apparent in other clinical trials. Often clinical trials offer some prospect of direct benefit to participants in the form of consistent healthcare during the study, access to experimental drugs with direct lifesaving benefits or opportunities to gain information or access to resources with direct health benefits that are not publically available at the time. However, in CHIMs, there is a shift from participants' dependence on research for access to drugs, treatments or interventions to researchers' dependence on participants to volunteer for a study that has no direct benefit to them.

"We (researchers) need them (participants) more than they need us. In fact, they don't need us at all".- MORU CHIMS CSE planning team member

This shift in "power dynamics" led MORU to recognize the extreme importance and dependence on a positive societal view of CHIMS. 'Social acceptability' or 'social acceptance of the study' was a pervasive topic in interviews, conversations and the review of the literature as a critical component for the successful implementation of CHIMS. 'Social acceptability' was described in various ways from public and community's perception, trust and understanding of the research, or depictions of potential challenges with CHIMS such as the spread of misinformation and rumors due to lack of information, fear, distrust, and cultural stigmas. These challenges were conceptualized as threats or issues with the social acceptance of the program by the participants, communities, the government, and the greater public.

Figure 4: Themes Surrounding Social Acceptance of the *P.vivax* CHIMS studies at MORU

Various ideas were proposed on how to increase social acceptance of the study such as increasing "awareness" by conducting knowledge sharing about the study or working on "trust building" within communities to create more social acceptance in the study.

"This is a controversial study, but there are people in Thailand who will support it and finding them and having them support will be important. Some people will have objections, and you will need people's support if something goes wrong. We need Thai support"- Stakeholder Forum Participant

Social acceptability of the study was used as a catch-all phrase for addressing individuals' concerns and perceived challenges for the study. Social acceptability was often brought up in tandem with community engagement or public outreach activities. The universal acknowledgment and understanding within the organization of MORU and Mahidol University that increasing social acceptance of the study was going to be an integral component for the success of the program led to the third challenge, which specifically related to developing the Community and Stakeholder engagement strategy for CHIMS

Agreement within the team on what CSE was

Another challenge for the CHIMS was agreement on what the purpose of CSE was and the goal of the CSE strategy. The multidisciplinary makeup of the CSE planning team led to a high degree of variability on what team members thought CSE was, what concerns it could address in the program and what a successful outcome of CSE strategy would be.

Table 1: Ideas of the purpose of CSE for CHIMS organized by job title for the respondent.

Job title	**When asked what CSE could do for CHMIS at MORU in Bangkok, Thailand.**	**What should the focus of a CSE strategy be?**
Social scientist (n=2)	• To remind the greater public of the social benefit to society of this study • Addressing concerns and fears of the public and figuring out ways to "combat fears with positive messaging." • Maintaining a constant presence in the community	• Public focused • Addresses cultural stigmas

Clinical trials staff: (n=1)	• Mitigate the fears and concerns of participants about being infected with malaria. • A communications strategy • Situation and feasibility analysis for the study • Ensure staff are trained and able to complete the trail • Ensure participants are given all the necessary information and they sufficiently understand it to be able to consent to participate in the study.	• Participant-focused • Project feasibility. • Training skills development for clinical staff
MORU Researches Vivax Unit Field researchers/ scientists(n=3)	• Address the negative stigma associated with research in Thailand • Calming fears of infection in the public • Make communities "feel confident they can trust us." • Build credibility that MORU and Mahidol can be trusted.	• Public focused • Building trust in the community and for the organization
Bioethics Engagement team (n=3)	• Share knowledge with the greater public. • Limit misinformation and gossip. • Appropriate branding of the project to limit fear of infection • Social media • Internal support from all staff at MORU • Make sure the project is welcomed and accepted by communities • Ensure participants and participants' families and communities feel like they were not taken advantage of.	• Public facing • Information sharing • media intensive • Increasing social acceptability of the study

Responses varied significantly regarding what the purpose of CSE was based on what individuals on the planning team thought was the most significant challenge or concern facing them in the study. The variability in responses was influenced by a 'positional perspective', or what team members saw as the major threat for the success of the study, based on the differing positions they held at MORU, or what aspect or phase of the study they were working on. For example, clinical trial staff members thought that the community engagement strategy should be participant and clinically focused. Because their primary concerns were to ensure information was adequate and sufficient for participants and informed consent. They saw CSE as a way to

use communication to mitigate the fears of infection in participants, conduct feasibility studies to ensure that the trial could be conducted in their current facilities and to ensure that clinical staff was adequately trained.

In comparison, the scientists and field researchers working in the Mahidol Malaria Vivax unit saw a community engagement strategy as a means to engage with the public to build credibility and trust for the organization and in the research study. The MRVU researchers' primary concerns were the public perception and "negative stigma" of research and how that paired with the fear of infection to lead communities to not trust MORU or Mahidol as an organization. Their ideas for CSE were to be more public focused on helping mediate issues with negative "publicity" that could arise and hinder the recruitment of participants. The interpretation of what a CSE strategy was meant to address was highly variable based on the lens from which it was being viewed. Career position or job assignment at MORU colored what team members saw as major concerns for the study based on their experiences and affected what they saw as the priority concerns for the study.

The high variability of concerns led to little consistency or agreement on what CSE was or what it could contribute to the program, which resulted in a lack of clarity or agreement on the purpose of CSE and what the goals or priorities of the CSE strategy should be. The variety of concerns and priorities for the study was a barrier in strategy creation because deliberation to achieve agreement of the goal of CSE limited the team's ability to implement CSE.

<u>Section 2: How challenges were addressed with CSE</u>

Utilizing a stakeholder analysis to remedy a lack of clarity on the goal of CSE

The planning team used community and stakeholder engagement to identify the major concerns for individuals and groups of stakeholders by conducting a stakeholder analysis to inform the goal and development of the CHIMS CSE strategy.

Initially, groups of stakeholders were identified by reviewing literature specific to human infection trials and identifying unique stakeholder groups. This information was cross-referenced with expert opinions and consultations with various MORU staff members of the Bioethics and Engagement Department team members to develop "unique stakeholder groups" which the CSE team would target for the CHIMS study. Groups identified were:

1. Participants
2. Potential participants, families, and friends
3. Key national and local stakeholders
4. Public (Greater Thailand- not direct friends or families of participants)
5. MORU and Mahidol University colleagues, staff, faculty and scientific research community
6. Regulatory and ethics committees
7. CHIMS planning team – all levels.

After groups of stakeholders were identified, a forecasting of stakeholder interests and analysis of concerns was conducted. Information on stakeholder's fears, concerns and interests were gathered from literature about human infection trials. Interviews with individuals from various stakeholder groups and conversations with MORU colleagues who had extensive experience working with specific stakeholder groups were conducted. Initial findings were used to create a "stakeholder interests and considerations document" which was circulated to the planning team and acted as a guide to focus the discussion on the goal for a CSE strategy. The "stakeholder interests and considerations" document illuminated the relevant interests of

stakeholder groups that could be addressed with CSE. This improved the conceptual clarity on the purpose and a functional definition of CSE for the CHIMS at MORU.

Limiting fear of infection and increasing social acceptance

Identification of fear of infection and the direct link to social acceptance of the study was incorporated in the CSE strategy by planning to hire a Thai public relations specialist and spokesperson who could communicate to the greater Thai public the safety and social utility of the project. This public relations specialist would help create and demonstrate trust in the organization to limit stigma and distrust associated with research identified in the greater public stakeholder group. The creation of an interactive website with information about the study would allow for concerns, questions, and feedback to be posted, acting as an information link about the study for potential participants, their families and friends, as well as the greater public. The website aimed to give out correct information and limit "misinformation" and rumors that could circulate regarding the study. One CHIMS CSE planning team member stated that for the study to succeed

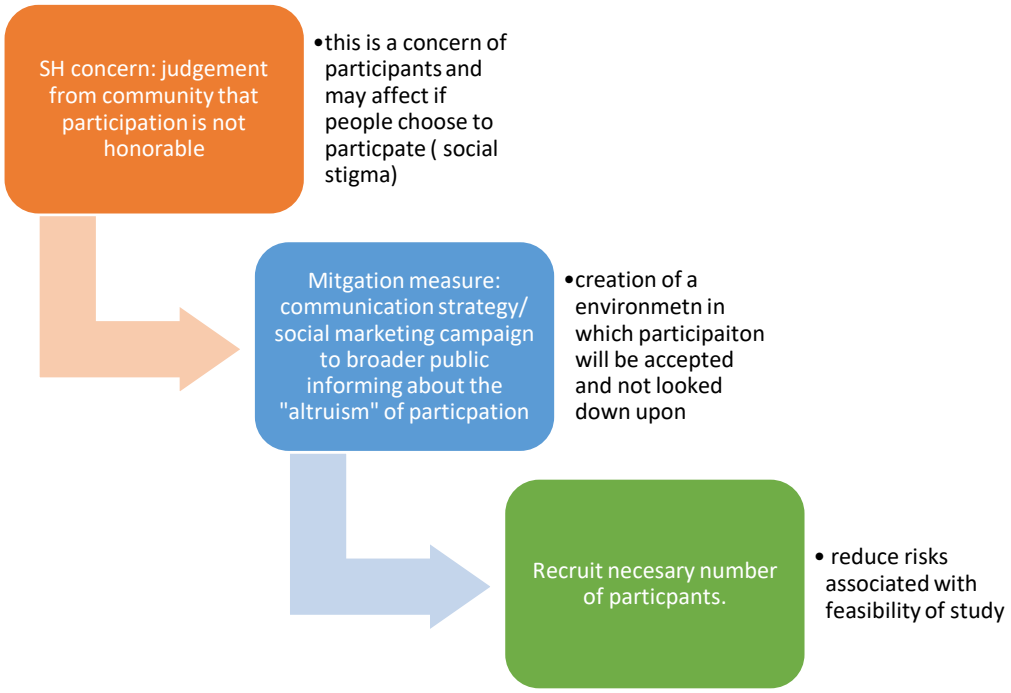
"...we need to assess their (stakeholder) values and to come to know what our biggest 'enemy' or challenge will be for this study and figure out a way to beat it."- MORU CHIMS CSE planning team member

To address the need to understand stakeholder interests further an open forum was proposed so that input and information could be collected from stakeholders to create a more in-depth understanding of the barriers, concerns and fears associated with CHIMS and allow for open discussion about CHIMS to calm the fear surrounding the study.

Section 3: Using CSE to De-Risk the Project

The utilization of stakeholder engagement allowed for the CSE team to conduct formative research to understand concerns, problems, issues, and fears about CHIMS. Acknowledging and addressing the interests of stakeholders in a strategy allowed the MORU CSE team to reduce the inherent risks associated with CHIMS studies and foster the success of the program. "De-risking" the CHIMS was never explicitly stated as the rational or reasoning behind the incorporation of CSE into CHIMS, but it became clear through interviews conducted that a major value of CSE in CHIMs is its ability to investigate, discover, address and create methods to mediate issues and concerns that arise in the complex interactions of controlled human infection studies. The process of developing a CSE strategy for CHIMS acted as a de-risking mechanism for the project. By conducting CSE, the MORU CSE team was able to gain a deeper understanding of the risks associated with CHIMS for *P.vivax* and were able to create a strategy which addressed these risks. By addressing these potential issues with study feasibility, social acceptance, and participant recruitment, the MORU CSE team created an environment in which the program could succeed.

Figure 5: Example of how CSE allowed the planning team to address the social acceptance of CHIMs and increase recruitment.



Due to CHIMs' dependence on voluntary healthy subjects, the success of the program is intimately tied to social perceptions and judgment of participation in the study. Addressing the social stigma of research and societal judgment for participation in research could impact recruitment of subjects who are willing to undergo infection with malaria for minimal personal benefit and marginal monetary compensation. Using community engagement with this group of stakeholders allowed for a better understanding of what would make participation in the study easier, or more enticing. Accessing and using insights from stakeholders allowed for adjustments to be made to the study, such as changing compensation for participants or the living situations for volunteers while participating in the study. Public outreach programs could change the social perception surrounding research, elevating it to more "honorable" choice assisting in alleviating the current negative view. Implementing insights about how to make the study easier for

participants and their families, removes the risk of not having enough participants to conduct the study, the negative social view of research and produces an environment in which the program has a higher chance of success. Acknowledging and addressing the interests of stakeholders in a strategy allowed for the MORU CSE team to reduce the inherent risks associated with CHIMS studies and foster the success of the program.

LIMITATIONS:

This qualitative case study had several limitations. The first limitation was the limited literature published on CSE in CHMIS, which left little guidance on creating interview guides and interview questions. Lack of information and clarity on CSE meant many of the conversations and discussion held were loosely structured exploratory discussions rather than specific and focused adhering to a detailed guide. Limited understanding of CSE also created high variability in answers and conversations. Another limiting factor was the information was gathered from a small convenience sample. The use of convenience sample may have impacted the breadth of ideas and opinions represented in the findings and the small sample size utilized for this study resulted in in these findings being highly program and organization specific to a CHIMS at MORU. Despite these limitations, the information collected is sufficient to understand of the value and role of CSE for a *P.vivax* CHIMS at MORU.

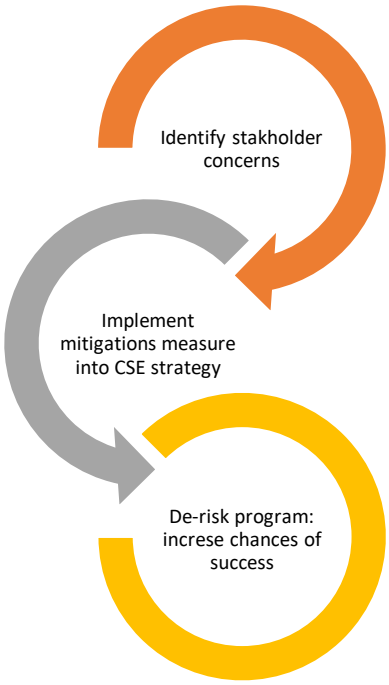
DISCUSSION:

What is de-risking?

The Project Management Institute's A *Guide to the Project Management Body of Knowledge (PMBOK® Guide*) describes a Project risk as "…*an uncertain event or condition that,*

if occurs, has a positive or a negative effect on at least one project objective, such as time, cost, scope, or quality. A risk may have one or more cause and, if it occurs, one or more impact." (Patanakul, 2008). Risks are intrinsic to programs and are often listed as determining factors for the success of programs. "Because risks have impacts on project objectives, project teams have to be aware of those risks and action plans should be developed in response to the risks." (Patanakul, 2008) The idea of collecting information and conducting research to guide the planning of a program prior to the implementation of a program is far from a novel concept in public health. Formative research, situation analysis, barrier analysis, KAP surveys, are only a few methods on an extensive list of tools used to identify risks associated with programs. Researching risks, barriers, and challenges through the application of formative research, or qualitative and quantatative methods to provide information for research to plan and develop effective and meaningful health interventions and programs is not new knowledge, it is simply good planning (Gittelsohm et al, 2006).

The understanding that formative research can increase a programs' chances of success and is critical for the development of effective health interventions has been demonstrated and documented by Gittelsohm et al, Higgins et al., Usdin et al, in social marketing strategies, behavioral interventions and many more. The use of formative research to gather information and evidence to inform message development, assess gaps in knowledge, determine appropriate channels of communication, understand local health and illness concepts, and rapport building are all factors which contribute to the successful implementation of public health programs (Gittelsohm et al, 2006; Higgins et al.,1996; Usdin et al, 2003)



However, the idea of applying a process of CSE to discover, address and mediate risks, is not commonly discussed as the integral value of CSE. The idea of mitigating risks by engaging with communities is prevalent in preventative ethics to create ethical research. Engaging with communities in the early stages of the planning process when important ethical decisions are being made is critical and vital for minimizing exploitation and risks associated with research for participants as well as increasing the potential for studies to have a lasting impact (Lavery, 2010). When CSE is framed in the idea of ensuring the scientific validity of a study, it becomes apparent that CSE is a way to contribute to the feasibility of a study. For CHIMS the ability for CSE to mitigate risks associated with the program, given the volatile social, political and cultural environment surrounding the study, was critical for the study to be implemented without severe negative repercussions.

Challenges with the terminology of "de-risking."

Focusing on the value of CSE for CHIMS as a process to de-risk the program makes CSE appear as if it is only a planning and risk mitigation tool. Depicting the value of CSE simply as a tool to mediate risks can be problematic and further complicate the already convoluted misconceptions around what CSE is. As illustrated in my findings above and the literature discussing CSE there is a lack of clarity and evidence on what exactly CSE is in public health

programs and more specifically there is little evidence or evaluation of the value of CSE of public health programs.

Labeling CSE simply as a de-risking mechanism for the program may only reaffirm the "tendency to think narrowly about CSE, or to emphasize or exaggerate some aspects relative to others" (Lavery, 2018). The inclination of CSE strategies to rely "heavily on mechanisms such as community advisory boards," or "emphasize communications and various strategies for developing and delivering key messages, to educate host communities about the goals and merits of the science program", might simply pigeon-hole the uses and purpose of CSE in global health programs and CHIMS (Lavery, 2018) . Because of the past predisposition in public health to focus on outcomes of CSE rather than mechanisms which create those outcomes, it is important that when discussing the value of CSE as an avenue to "de-risk programs" to refrain from simply viewing it as an outcome. It is critical to understand the mechanism which yields the outcome of "de-risking", in this case the process of listening and understanding concerns is the mechanism which allows CSE to mediate risks and concerns. Recognizing that identifying a risk by only asking stakeholders their concerns and then internally, without stakeholder consultations, create ways to mediate the identified risk only further entrenches the outcome based problematic view held regarding engagement. The value of CSE as risk mitigation mechanism arises when conducting authentic and meaningful engagement with communities and does not focuses solely on the outcome but the continual process of engagement as the actual mechanism that allows for risks to be mediated.

<u>The relational component of CSE</u>

Viewing CSE through the narrow lens of de-risking ignores a critical and vital component of what is thought to make CSE successful at identifying and mitigating risks in a program. As described by King Et al. (2014) the relational component or "the human infrastructure of CSE is the web of relationships between researchers and the community of stakeholders in a given global health research project and is the foundation of meaningful engagement" (King, 2014). The creation of relationships between researchers and the stakeholder communities involved in the research is what allows for risks and concerns to come to light during a study. The context of those relationships is what allows for the implementation of strategies to mitigate risks to be successful (Lavery, 2018). Mechanisms of risk mediation such as targeted messages or focus groups in and of themselves are not what mediates a risk it is the actions of listening, engaging with and creating relationships of trust with stakeholders that allows for the mitigation of risks to take place.

The value of CSE's ability to mediate risks is in the process of engaging with stakeholder and the process of listening to their concerns and interests. It is not in the act of gathering the information to identify risks for a program. The process of engaging with all relevant stakeholder continuously throughout the planning, design, implementation, and evaluation of the trial it what allows for the risks or concerns brought to light during engagement activities to be acknowledged, addressed and communicated.

Moving Forward.

This case study demonstrated the value and role of CSE in CHIMS studies. This value is found in the in the facilitation of researchers' discovery of risks and challenges associated with the study, and to create ways to reconcile identified risks and increase the studies chances of success.

Acknowledging the value of CSE outcomes to 'de-risk' the study was a novel finding for CHIMS. Nevertheless, there are potential challenges and dangers with viewing the value of CSE as a mechanism to 'de-risk' CHIMS.

Current lack of clarity and consensus on how CSE is conceptualized in public health and the greater global health community combined with the urge to standardize procedures of CSE divert the focus of CSE from the integral components which yield meaningful engagement to only the desired outcome of the successful implementation of the program. For CSE programs and strategies to be successful, a more in-depth interrogation of the essential components which allow for CSE to yield the benefits of de-risking programs or creating more ethical research would yield benefits. Merely stating the outcome does not allow researchers to scale and implement successful CSE programs in different contexts. A stronger program planning structure in conjunction with CSE planning done in tandem may result in teams that inform, and adapt to change based on the concerns and interests identified with stakeholders. The co-planning between program planners, protocol writers, primary investigators, funders and CSE teams is essential for the programs to reduce its risk through the utilization of CSE.

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