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Zika Virus and Transgenic Mosquitoes: Potentials of a Public Health Tool

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ABSTRACT

With transgenic mosquitoes now being deployed as a major solution to the pandemic Zika virus disease, more curious questions have arisen about this public health technology. This essay reviews the philosophical considerations that presaged the development, by WHO, of the genetically modified mosquitoes. It focuses more specifically on the inter-disciplinary approach in formulating the clinical trials process. While it is still early to determine the full merits of this health intervention tool, it is nonetheless timely to examine the rich vein of form that constitutes the clinical trial protocol. I argue that the steps it suggests should be a gold standard for all clinical trial procedures including those that use human subjects and those with both direct and indirect environmental implications. Also, the early signs portend that its application could indeed be widespread. For instance, malaria and dengue fever were the original targets, but now the development of transgenic mosquito technology is deemed a potent option in the fight against Zika virus disease. In addition, this clinical trial protocol has remarkably gone beyond the four pillars of principlism to recognize the possibility that a new technology (such as GMM), can have the potential to simultaneously impact human individuals, the community and the ecosystem in tandem. In “Guidance framework for testing of genetically modified mosquito,” the WHO has set an example that calls for emulation. With the right awareness, biomedical researchers, scholars, policy makers, and students stand to benefit immensely from this reformulated approach.

Keywords: African Philosophy, Bioethics, Dengue Fever, Ecocentrism, Environmental Ethics, Genetically Modified Mosquitoes, Holism, Malaria, WHO, Zika Virus.

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1.0 Introduction

The world was gripped. Somber alarm bells were tolled. Zika virus disease pandemic was exploding rapidly. This public health furrow, though known for decades, seemed to have caught health workers and policy makers off-guard. Once more, the human ingenuity was tasked to search for answers. What an opportune time to reexamine one of the deployed solutions – transgenic mosquitoes – in terms of the thinking prior to the development of this technology and the many potentials it might bode.

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This essay reviews the philosophical considerations that presaged the development of genetically modified mosquitoes which was meant to fight malaria and dengue fever-carrying mosquitoes. It focuses on the inter-disciplinary approach in formulating the clinical trials process. While it's still early to determine its full merits, nevertheless, its rich vein of form makes it a model for other clinical trial protocols. For instance, malaria and dengue fever were its original targets, but now the development of transgenic mosquitoes is part of the fight against Zika virus disease.

In sum, a well-developed clinical trial protocol that is burning on all elements may be hard to find, but it doesn't have to. In *Guidance Framework for Testing of Genetically Modified Mosquitoes*² (hence forth called GMM guideline or GMM framework), the WHO has set an example that is easily replicable. If modern clinical trial process were looking for a responsible model, the GMM framework is it. This GMM framework could be a paragon of responsible clinical trials protocol. The steps it suggests should be standard practice for *all* clinical trial protocols including those that use human subjects and those that potentially have both direct and indirect ecological implications.

This analysis is intentionally structured to concentrate only on the relevant parts of GMM framework, to sharply contrast it with another clinical trial example: the 1996 Trovan experimentation in Nigeria.³

Also, the GMM approach apparently boosts two important issues. One, ecocentrism – a widely shared philosophical perspective in African thought and, holism or interconnectedness and the intrinsic value of the biosphere in ranked order of being. Two, by calling to mind the intimate connection between environmental and human health, the GMM paradigm hits at the heart of a long-nursed objective that calls for the reunification of bioethics (here via clinical trials) with its estranged sibling, environmental ethics. In the African philosophical context where holism reigns, it comes as no surprise that these two broad issues have merged into what I will refer as bio-eco-communalism (BEC).⁴

2.0 Background

Zika virus is a mosquito-borne *flavivirus* that was first identified in Uganda in 1947 in monkeys through a network that monitored yellow fever. The virus is spread to people primarily through the bite of an infected mosquito (*Aedes aegypti* and *Aedes albopictus*). It was later identified in humans in 1952 in Uganda and Tanzania. Outbreaks of Zika virus disease have occurred in Africa, the Americas, Asia and the Pacific between the 1960s and 1980s accompanied by mild illness (American Public Health Association). Per the CDC, the first large outbreak of disease caused by Zika infection was reported in Micronesia in 2007. Before 2007, at least 14 cases of Zika had been documented. Because the symptoms of Zika are like those of many other diseases, many cases may not have been recognized. However, Zika virus infection during pregnancy can cause a serious defect called microcephaly (shrinking of baby head). In July 2015 Brazil reported an association between Zika virus infection and Guillain-Barré syndrome (WHO).

² Sponsored by the World Health Organization, *The 2014 WHO Guidance Framework for Testing of Genetically Modified Mosquitoes* compendium is the product of the meeting of the minds of some of the best experts in the field (with expertise in molecular biology, medical entomology, ecological, legal, ethical, social and cultural areas). However, not all aspects of this dense report will pertain to my discussion, hence I will be referencing only the parts that are relevant. I am indebted, and I pay special tribute to Paul B. Thompson a member of the think tank which formulated the report, and who made the report available to me early as it was still receiving reviews and comments prior to its publication.

³ This was a case of the experimental drug Trovan, an antibiotic. Its development coincided with concurrent outbreaks of cerebro-spinal and bacterial meningitis, measles, and cholera that were affecting some pediatric patients at a northern Nigerian city. Pfizer dispatched a research team to a local hospital providing treatment and quickly recruited over 100 kids among the long lines of people seeking care and administered the trial drug to determine its effectiveness. The drug had never been tested on children. An investigative report later blamed the drug trial for a catalogue of effects ranging from adverse drug reaction, adverse events, to serious adverse events including the death of 11 children; several more suffer (ongoing) permanent disabilities such as brain damage, paralysis, muteness, slurred speech, and blindness. A series of law suits by the victims and the Nigerian government (filed in the U.S. under the Alien Tort Claims Act) commenced in 2001 but aborted by the U.S. Supreme Court in the fall of 2010. Pfizer had struck a \$75-million out-of-court settlement for claims related to the experiment.

⁴ I credit Tangwa's (2004) ingeniousness in smithing the original term 'eco-biocommunalism.' There he fuses eco-ethics, environmental ethics, developmental ethics, medical ethics, and bioethics under one label. The nomenclature I formulate here though related, is however different.

Zika virus disease is merely piling on the pre-existing scourges of malaria and dengue fever. To put that in perspective, here are some statistics. Per WHO's 2013 figures, an estimated 3.4 billion people in 97 countries were at risk of malaria, of whom 1.2 billion were at high risk. In comparison, there were an estimated 207 million cases of malaria in 2012; and an estimated 627,000 deaths (482,000 children under five years of age – 1,300 children every day, or one child almost every minute); 90% of the total number of malaria-related deaths occurred in Africa.

Between 2000 and 2012, the scale-up of interventions helped to reduce malaria incidence rates by 25% globally, and by 31% in the WHO African Region. The global malaria mortality rate was reduced by 42% during the same period, while the decrease in the WHO African Region was 49% (WHO Factsheet). Despite the seeming progress, the abatement, though a remarkable suppression, seems to hold down the scourge only momentarily, while the scourge continued to gulp more funding resources. The WHO estimates that US\$ 5.1 billion is needed every year for this purpose. In 2012, the global total of international and domestic funding for malaria was US\$ 2.5 billion – less than half of what is needed (WHO Factsheet).

On its part, dengue is reportedly the most common mosquito-borne viral disease of humans that in recent years has become a major international public health concern. Globally, 2.5 billion people live in areas where dengue viruses can be transmitted. The geographical spread has led to the global resurgence of epidemic dengue fever and emergence of dengue hemorrhagic fever in the past 25 years with the development of hyperendemicity in many urban centers of the tropics. Dengue ranks as one of the most important mosquito-borne viral disease in the world. In the last 50 years, incidence has increased 30-fold. Up to 50 million infections occur annually with about 500,000 cases of dengue hemorrhagic fever and 22,000 deaths mainly occurring among children (WHO).

Malaria, dengue and Zika are vector-borne diseases – diseases that are transmitted via a carrier. Mosquitoes are the agents of transportation that convey pathogens for these diseases into the host cells (for example, humans).

It is against this backdrop; and owing to the intensified practice of transnational biomedical research (particularly the outsourcing of clinical trials from the Global North to the Global South); plus, the considerable controversy about the ethics of research, that the GMM framework crafting could not have been better. The expectation is to show how ethical principles and community engagement, not profit motives, should guide actions in determining how the cultural milieus of patient-subjects and residents of research sites must be engaged, respected, adequately compensated, and if possible, made to benefit from research outcomes. The urgent desire for further and continuing retooling of international guidelines or codes of research ethics and the considerable stakes involved also make the GMM framework most timely. Approaches such as this, have long been recognized to underpin, “claims that, in addition to the direct benefits for individuals within the study, benefits should include the linkage of otherwise unavailable health care to research projects, provision of proven treatments following completion of trials, as well as community empowerment” (Benatar, 2004).

Also, there is a semblance of sorts between the GMM framework and a working paper that emerged in the early 1990s from a symposium on ethics and public health which examined the challenges of trans-cultural clinical malaria research in the developing world. While highlighting the need that such investigative collaboration requires a unique bridging of cultural differences with respect to human subject investigation, the setting addressed other germane issues. They include the difficulties of informed consent in different cultural settings; whether there is any role for community involvement; whether drug and vaccine trials not approved in an industrialized country are ever defensible if performed in an industrializing country; potential conflicting priorities between investigators; and, issues regarding conflict resolution (Barry & Molyneux, 1992).

Though commendable, the tackling of these issues doesn't match the full-throated manner the GMM report articulated all the substantive and procedural aspects of the issues involved. Moreover, while the

symposium analysis asks, for instance, whether there is a role for community involvement, the GMM framework provides its cogency; pointing out the flaws in the mainstream informed consent process. Altogether, the comprehensive footnotes and illuminating cross-references reflect the consummate knowledge of the multidisciplinary areas experts in the GMM project represent.

3.0 The GMM model

The GMM effort is a preventionist precautionary strategy that is built on attacking mosquito vectors *ab initio* and thus, the most effective way to reduce transmission of diseases in endemic areas. Moreover, the more prevalent method of relying on insecticides for vector control increases, rather than diminishes, increases the risk that mosquitoes will develop resistance (WHO GMM, p. xi).

Irked by the menacingly high death tolls despite control efforts amidst depleting funding resources, the new WHO guidance framework aimed to perfect a mechanism with the aid of molecular biology to develop genetically modified mosquitoes as an efficient public health tool to halt the transmission of malaria and dengue fever. Due to its innovative, potent and more cost-effective approach, it is adjudged to trump other comparable methods such as radiation- and chemo-sterilization. Nonetheless, and specifically for reasons not to leave anything to chance, the multidisciplinary think tank behind this guideline insisted on the need for “thorough, thoughtful and transparent preparation for, and conduct of field trials of the GMM technology” (WHO GMM, p. xi). The GMM method hints at providing a reliable model for all countries to emulate.

The mechanics of the technology works when lab-hatched genetically modified mosquitoes are, ... made sterile and thus unable to pass the genetic modification on to future generations through mating. In other cases, the GMM are meant to mate and introduce the effect briefly into the local mosquito population, but the modification will gradually be diluted out by crossing with local mosquitoes over a number of generations until it is lost” (WHO GMM, p. xi).

But, in any novel method, some unknown outcomes could mean the possibility that this could take on a different trajectory outside of its intended purpose, potentially engendering grave ethical, environmental, social and other concerns. Considering this, the team fine-tuned implementation strategies for the testing of the modified vectors. The result was the following two-tenet agreements:

- Field testing must begin with release of sterile or otherwise self-limiting modified male mosquitoes in order to gain experience with the technology under circumstances where its effects can be reversed by halting releases.
- Testing of modified mosquitoes incorporating gene drive must begin under physical confinement. No genetically-modified mosquitoes designed to replicate and spread the modification to wild-type mosquitoes [should be] tested outside of the laboratory (WHO GMM, p. xi).

This guarantee is a confidence-booster and fosters quality and consistency in the processes for testing and regulating new genetic technologies. It promises to also provide a platform for “comparability of results and credibility of conclusions in addressing the requirements for decision-making by countries interested in potential use of these technologies as public health tools for control of [other] vector-borne diseases” (WHO GMM, p. xv).

Intense calls for ethics and public engagement in public health research is a claim that is often made, and the GMM guideline underscores its importance to the hilt:

Public dialog and outreach are important for realizing research goals, especially in the development of new technologies. Sincere and well-developed engagement can help to direct technical goals, reduce the chance of a misunderstanding of the science needed to meet the goals, and improve the performance of the research project in both technical and social contexts. Although engagement activities may overlap with regulatory requirements, researchers should not assume

that regulatory compliance also implies that ethical and engagement responsibilities have been adequately addressed. Respect for communities should be an overarching ethical goal in GMM trials (WHO GMM, p. xv).

So crucial and integral are ethics and engagement efforts that it is urged they be initiated early and at intervals throughout the study (and even after). Rightly noted, the role of ethics and engagement becomes crystal clear in the way that tensions are doused between scientists who are absorbed in the quest to realize the envisioned results of their research, and some in the public who view them as lacking in moral sensibility or fellow-feeling. Primed to be a 4-phased trial, the GMM report recommends that engagement activities be introduced during Phases 1 and 2,⁵ to ensure that the goals and methods of the project are well defined and communicated to meet genuine stakeholder needs.

Field researchers stand to benefit when community engagement activities are expanded in Phase 3 specifically because they address ethical responsibilities beyond the formal permissions required at the individual level (informed consent/assent) and the governmental level (regulatory compliance). If it hasn't been made apparent already, meaningful engagement with the community, among other related actions, smoothens the path to obtaining authorization to conduct study. "The concept of 'community authorization' entails providing those living in the trial site with methods to give or withhold agreement for trial activities, and to identify elements they believe to be important for the research to continue. During field testing, scientists also should expect to interact with third parties who express interest in the activity and its outcomes, both to ensure that the project is well understood and to avail the project team of information and insights that such interested parties might provide" (WHO GMM, p. 59). With tenacity and goodwill, by Phase 4, all stake holders would have gained deep appreciation of the research procedure to the point that the responsibilities for implementing the technologies being tested and interacting with affected individuals likely will shift to the relevant local, regional or national public health authorities.

Thus, the scope of ethical responsibilities and community engagement becomes the overarching goal in projects like the GMM project. My suggestion for engaging the community early on for greater understanding of purpose and successful project undertaking is supported by the idea that it would afford trial studies the opportunity to become aware of a laundry list of important issues likely to affect the study. For instance, Olin, J. et al. (2006) identified factors that either motivate individuals to volunteer for a vaccine trial or disincentivize them to participate, along with preparedness of the larger community for trials. "Personal concerns for health and for the impact of the epidemic on families and country were common motivations for participation. The danger of an experimental vaccine and the stigma of a positive HIV antibody test as the result of vaccination are major concerns and disincentives. The health, educational, and local non-governmental sectors are identified as having important roles to play in assuring [community] preparedness for trials" (p. 530).

The larger philosophical point that the GMM proposal precisely advocates is that ethics of engagement aims to identify and recognize the interests of stakeholders and their legitimate entitlements, rights, other types of claims and obligations, including what actions or activities that are necessary by the principle of respect for communities hosting the trials. As such, it brings into focus, such ethical issues as: how these rights and interests should be recognized in a decision for trials to proceed; how researchers can strike an ethically robust balance between the interests and rights of individuals, the collective interests of the host communities and the properly mandated activities of their public institutions; and,

⁵ I would rather suggest that considerations for ethics and engagement activities should commence at the planning stage (long before Phase 1). The advantage of this early application is to test the waters, meet with third party (outside) groups and individuals, and gauge the strategies in order to tweak any areas that might need improvements. It is at this stage that the GMM acknowledgment makes complete sense: "Engagement and involvement with the communities hosting the GMM trials must be guided by detailed knowledge of the local community, its institutions and common practices. Finding out what kinds of concerns the community might have, any past engagements around science that went badly, or determining what the community wants/expects in terms of engagement or consent [and assent] will be important," p. 70.

determining the appropriate role for communication and engagement with media, civil society organizations and others that take an interest in the research (WHO GMM report, p. 60).

Even on an individual level, the impact of ordinary word of mouth is not underrated particularly in how it can effectively disseminate a widely-shared impression of research goals, intended applications and methods, including within village, sub-urban, or city settings. Such broad representations of science can have the beneficial effect of expanding opportunities to obtain key informants, participants and partners. But if the community does not buy into it, the opposite effect will likely result: widespread misrepresentation, suspicion, distrust and even outright blackmail and antagonism against the scientific research project.

The GMM ethics and community engagement approach, like some of the concepts I have discussed in this study, also suggest a concentric relational web in a typical clinical trial procedure: from the core human research subjects, to their friends, families, and the larger community. The outer spectrum recognizes individuals who do not typically fall within the definition of human subjects but who might be affected by the conduct of research, either because they reside near the research project site, or that their daily activities and/or livelihood, including economic interests, could be affected by the research activities.

On the other hand, people living farther off from the trial site and are unlikely to be physically affected by the trial activities themselves, might still stake a very strong interest in the conduct or outcome of research simply because their interests overlap with those of their friends and relatives at the trial site. For instance, people who are under certain health conditions (and/or their friends and family) would likely have an obvious interest in the outcome of research or clinical trials, even if they are not involved with that specific trial. Such groups are likely to be strongly supportive of research intended to improve their condition.

Similarly, people who care about causes such as protecting vulnerable groups or endangered species are likely to take an interest in a wide range of research activities, and may as well be supportive of certain research goals or procedures. Although the nature of responsibilities to such individuals or groups is quite different from those of the research subjects and communities hosting the trial, an effective plan for engaging a wide scale of such interested parties can be critical to the success of research, especially for projects that can possibly draw a significant public media attention or monitoring from civil society organizations. In this way, the onus of ethical responsibilities by researchers can be quite encompassing and even complicated, and meeting these responsibilities requires an adequate preparation which can go a long way to smoothen rough edges by addressing the full range of stakeholder interests.⁶

Ordinarily, these are not the sorts of circumstances or communication activities standard research budgets accommodate as far as most scientific studies are conceived and conducted. However, it would be conceded that many scientists often view their work as having value and a social purpose, and this may be especially so for those conducting research on public health and disease control. But as the GMM guidelines attest, the problem is that scientists are often not very transparent. Also, scientists do not always articulate the purpose of their research explicitly, or discuss its value with others. The GMM guidelines seek to make explicit the value and social purpose of the scientific research project and initiate a broader reflection that serves several key functions and interests (WHO GMM, p. 66).

Ziman, J. (1998) makes that ethical burden more explicit thus, “As their products become more tightly

⁶ The GMM report provides a long list of such interested parties which include, persons associated with global or regional public health and international development organizations such as, governments; scientists and members of scientific organizations with disciplinary or inter-disciplinary links to research activities associated with field testing activities, including sciences dedicated to public health and infectious disease. Others are, persons and organizations engaged in competing approaches to control of infectious diseases; environmental and human rights activists. There is the added point to draw from the experience of GM crops to illustrate “the need also to consider possibilities for longer range economic, spiritual or cultural effects” scientific trials can have, and in what ways. Also, refer to p. 67 and 70.

woven into the social fabric, scientists are having to perform new roles in which ethical considerations can no longer be swept aside” (p. 5396). This beam of thought is likewise reflected in Elliot’s (2011) discussion of “Ethics for Experts” or ‘ethics of expertise,’ EOE. There, he develops a set of guidelines to assist researchers in sharing their study plans and findings; a move that will in turn assist the citizens, activists and policy makers as well to enable them to better understand the societal ramifications of the research they do.

Also, there is a lack of appetite in developing EOE for researchers even as the complexity involved in disseminating scientific findings to the public demands it. More so, the “scientists’ social responsibilities in general (not to mention their specific responsibilities for disseminating information) have received less analysis than ethical issues internal to scientific practice (e.g., management of data, relationship among researchers, treatment of human and animal researcher subjects)” (p. 135).

Thus far, there are enough grounds to be persuaded by the argument about the saliency of ethics and community authorization/engagement. But, that merely prepares the ground for other ethical requirements (for instance, the ethical principles in the Belmont Report) which are expressed in the informed consent/assent process). One of the major shortcomings of principlism is the lack of recognition that all research, directly or otherwise, do affect the larger communities and not just the individual study subjects (in fact, in most non-Western cultures, every research, just like all social activities, is considered to have either a direct or indirect effect on the community and/or environment). Likewise, the GMM guidelines have highlighted the apparent implications particularly the effects of the trials will largely be at the community level as well as on the environment.

4.0 GMM and biodiversity

I turn to the GMM recommendations as they emphasize the connection between human and environmental health. It is with delight that I encounter this factual rarity (particularly in Western literature) that fuses human health and environmental health. To be fair, pioneers of the larger bioethics project built their vision on that unity of purpose before the field witnessed the current splinterization. But more importantly, it is a widely shared philosophical perspective, for instance, in Africa which recognizes the holism or interconnectedness and the intrinsic value of the biosphere in ranked order of being.

My point here is simply to give readers a picture of some of the reasons a research team on a clinical trials mission might find the prospect of considering the safety of the environment appealing and as an integral part of their work. In certain clinical trial cases (e.g., the GMM trial) the connection is obvious, in others (e.g., the Trovan trials), it might be subliminal. Here, the GMM guideline gets at the point by way of *biosafety*. By biosafety, the guidelines highlight the connection and hence proffer plans to address the safe use of technologies “through the management of risks to the environment and to human health posed by the application of the new technology” (WHO GMM, p. 33).

The design of this public health intervention tool seriously considers the need to target the pathogens in a way that does not harm either environmental or human health (plus, health of non-human animals too). This is in addition to other set targets that risks be set primarily against improving human health; and that the overarching ethical goal should be to respond to obligations to individuals being asked to participate as human research subjects and/or to communities being asked to host trials.

The key word here is risk, how to avoid it if possible, or limit it as much as possible, and manage it to acceptable levels, if a hazard results. This, according the GMM report, is done through the compound phrase, ‘risk analysis,’ which when teased out gives rise to risk concern, risk assessment, risk management and risk communication. It explicates risk concern to mean alertness to and reason to worry about issues pertaining to both technology and social values, and in both cases supported evidence that a concern is valid. For risk assessment and management, the development of risk frameworks are necessary whereby qualitative, and where possible, quantitative pieces of evidence are used to assess the

probability that an adverse event will occur and the consequences associated with the occurrence of that event. A risk analysis procedure accounts for the possibility of an event happening but which may or may not be harmful in particular circumstances. Ultimately, effective risk management can render many risks acceptable and manageable (WHO GMM, p. 33).

Per the WHO framework, biosafety risk assessment aims to determine,

(i) the potential hazards and the mechanisms of impact for GMM on wild populations of target and non-target organisms; (ii) the likelihood and magnitude of impact of the GMM on the receiving environment; (iii) the levels and consequences of uncertainty associated with the effects; and, (iv) appropriate risk management measures needed to mitigate any harm or uncertainty associated with changes to target organism populations or the wider receiving environments. Risk communication ensures that there is a well-documented explanation of what risks have been identified, how they have been assessed, what the acceptable level of risk is, and how risk management may be able to achieve acceptable levels of risk with implementation (WHO GMM, p. 33).

Just like the ethics and community engagement approach, biosafety measures are phased in with the different stages of the trial protocol during which specific possible hazards are addressed at their respective appropriate stages – from laboratory and cage environments to open field releases. In this way further testing stages that follow are made more workable and the protocol becomes better defined as appropriate decisions are reached. With respect to the GMM project, possible relevant hazards that might occur are covered in the following questions, “Will release of the GMM increase transmission of the target or other diseases? Will release of the GMM cause a significant biting nuisance? And, will release of the GMM result in disruption to valued ecosystem components?” (WHO GMM, p. 33).

It is apparent that estimating the degree of ecological risk from the introduction of a new technology such as GMM, involves an admixture of ethics, culture, science, economics and health. As noted already, the complexity can be illustrated by the experience of genetically engineered crops. An instance that helps to underline this abstruseness in the GMM project is the locomotive capabilities of mosquitoes. The framework confirms what we have long known about mosquitoes that they make unpredictable movements between locations, in which case, it will be impossible, in advance, to say for sure all persons (or non-human animals) with whom they make contact. Moreover, knowledge from vector biology research had previously proposed that biosafety oversight may be a more appropriate model than individual human subject protection.

Equally useful would be to apply lessons from other environmental health programs, which typically involve unavoidable risks and as such not amenable to ethical procedures that presume an opportunity to exit or opt out of the risk bearing situation. “What is more, environmental risks raise ethical questions about the way that risks are distributed across economically, politically or ethnically vulnerable populations—problems of environmental justice. There are no ready analogs to environmental justice in standard human subject research ethics. Thus, research intended to better understand environmental health or that involves exposure to potential environmental hazards may need to be evaluated from an ethical perspective that incorporates considerations rarely contemplated within standard human subject deliberations” (WHO GMM, p. 69).

In releasing transgenic mosquitoes into a designated site, it was hypothesized that some of the key consequences will likely be the alteration of ecosystem functions (such as role of mosquito larvae in the food chain for predators) and other impacts on target organisms through destabilization of local mosquito populations. The possibility of these unintended reality may pose a risk, according to the guideline, particularly to human health if the GMM vector control system fails after a release program is well advanced. “This might include assessing local mosquito populations for the evolution of resistance to the transgene function, the evolution of the disease pathogen to resist transgene function or changes in host range of targeted mosquito species” (pp. 49 and 50).

To itemize specifics, the ecological consequences that might occur, as identified by the GMM report, include, effects on biological diversity; persistence of the transgene in the ecosystem; evolutionary responses (especially in target mosquito vectors or pathogens); and, unintentional trans-boundary movement (including international borders) (p. 49).

The GMM literature therefore suggests that evolution and adaptive processes be considered and appropriate regulatory structures, mechanisms and methods need to be in place as integral parts of the risk assessment to ensure that clear lines of responsibility are delineated on post-implementation surveillance. In effect, post implementation monitoring should draw on evidence from earlier Phases to determine the need for and design of monitoring to observe the key impacts identified.

The guidelines conclude that biosafety measures ought to be buoyed further by independent constituencies or review boards. This appears to fit with its promise of maintaining transparency and permitting of objectivity and candor. “The establishment of independent safety review groups or the formulation of GMM biosafety regulations for consideration by existing review groups (local bodies such as Institutional Biosafety Committees, national advisory bodies such as Advisory Committee on Release to the Environment, and regional or supranational agencies such as European Food Safety Authority,) is recommended. Such groups can provide oversight of the risk assessment and risk management within each phase of testing and provide independent scientific advice on the risks of GMM to human health and the environment” (p. 51).

All in all, the foregoing mark a shift from considering ethics of research within the bare bones of principlism, to considering the ethics of research in a much broader sense. For instance, the GMM model for biosafety and ethics of engagement, reveal the need to improve the links between research and health care delivery and to promote the environmental, cultural, socio-political and economic processes that are involved so we can begin to widen our understanding of the vicissitudes of the impacts of public health research – or any other research for that matter.

As observed, the successful implementation of GMM interventions requires transparent, focused, proportionate and credible biosafety assessments. The significance of the role of stakeholder groups and individual communities is evident as they provide the key to appropriately deal with the ethical and cultural dimensions. They should likewise provide consistent and strong voice within both biosafety and benefit-cost analyses associated with the testing and implementation of GMMs.

Some observers might think that the GMM model and traditional clinical trial model are like apples and oranges. But, in actuality, there are more similarities than dissimilarities. It is true the GMM model contains no typical human subjects; that is about the only major difference. When we think comprehensively, the tunnel vision we’ve had will give way to a quick realization why the GMM recommendation extends to just about all clinical trials.

Couched within the philosophical commitment to evaluate clinical trials in terms of ecological and human health, the GMM project seem to have rejiggered a healthy debate. It does so while resolutely pursuing efficacy, transparency, responsible sense of purpose, quality and consistency in the process of testing and regulating new genetic technologies. After several decades of treating bioethics and environmental ethics as distinct disciplines, it appears that our collective capacity to understand and discuss them jointly need revamping. Biomedical researchers, bioethicists and environmental philosophers should hence forth take up the gauntlet to refocus on that discussion.

5.0 Environmental ethics and bioethics

Not many people are aware that environmental ethics used to be part of bioethics. The question now is, can they reconcile as they were originally conceived, so as to address practical concerns that are common to them? The opening salvo in *Pierce and Jameton’s (2004)* book laments that apparent separation even as both fields remain hinged on a common philosophical substratum. For sure, the inspiration that GMM

framework presents already has given us a solid heads-up in that direction. Properly considered, environmental and human matters should not be separated from each other; that in practical terms includes, ecological and human health issues.

When in 1970 Van Porter used the term *bioethics*,⁷ his concern went beyond the confines of medical ethics. He was troubled by the emerging global environmental crisis and the challenges of the earth's survival. That explains why, two decades later, he reframed it as *global bioethics*, to accurately reflect his thinking and foster a re-conceptualization of an ethics of health care as it relates to Earth care and global survival. Porter, an oncologist, saw a constant thread of unity whether it was in his cancer research or any other aspect of life and concluded that much of mankind's problems were our inability to forge a synergy between the two broad cultures of science and the humanities. "Ethical values cannot be separated from biological facts. We are in great need of a Land Ethic, a Wildlife Ethic, a Population Ethic, a Consumption Ethic, an Urban Ethic, an International Ethic, a Geriatric Ethic, and so on" (Potter, 1970).⁸

To the extent that we have endured this disconnect for too long presses the need for the immediate bridging of medical and ecological ethics recognizing (them as one) its critical role in the future of health and environmental planning for all species, human and non-human. Peter Whitehouse draws directly from Van Potter's original intuition to characterize the syndrome and to recommend a treatment plan. The bridging effort should be seen as the most expansive aspiration that contributes to the "development of viable programs of sustainable medicines in a sustainable environment" (Whitehouse, 1999, p. 41).

Similarly, the work of Pierce and Jameton (2004, p. vi)⁹ is primed exactly to achieve that aim. It maintains that high quality, ethically sound health care is guaranteed to be available, if and only if the larger environment is robustly viable enough to sustain good health.

⁷ There seems to be more than one account of how the term "bioethics" originated. Robert Martensen credits statesman Sargent Shriver, for coining the word "bioethics" in his own Bethesda, Maryland living room one night in 1970. It was at the instance of meeting with physician Andre'e Hellegers, a Jesuit philosopher and then president of Georgetown University and others to discuss (President) Kennedy family sponsorship of an institute for the application of moral philosophy to concrete medical dilemmas. Martensen however cedes that Van Rensselaer Potter, "conceptualized bioethics expansively." Read more from Martensen's 2001, "The History of Bioethics: An Essay Review." *Journal of the History of Medicine and Allied Sciences*, 56, 2: 168-175. Dianne Irving on her part, locates the formal embryonic formation of "bioethics" in the 1960s following Congressional and Senate hearings which were called to "address an increasing number of knotty and bewildering problems especially being generated by medical research and the abuse of human subjects." See details in Irving's 2000 unpublished essay, "What is 'bioethics'? (*Quid est "bioethics"?*). Now rewind and listen, the Internet Encyclopedia of Philosophy labels these oft-cited stories as incorrect. Crediting H. M. Sass' 2007 work, it states that indeed it was the German Theologian Fritz Jahr whose three published articles in 1927, 1928, and 1934, that first used the German term "Bio-Ethik" (which translates as "Bio-Ethics"). From then on, a new academic discipline was established, and gradually the commencement of "the practice of a new, more civilized, ethical approach to issues concerning human beings and the environment. Jahr famously proclaimed his bioethical imperative: 'Respect every living being, in principle, as an end in itself and treat it accordingly wherever it is possible.'"

⁸ Potter, Van. 1971. *Bioethics: Bridge to the Future*. Englewood Cliffs, New Jersey: Prentice-Hall, Inc. There is little wonder why he dedicated this work to the memory of Aldo Leopold who he says anticipated the extension of ethics to bioethics. More of the author's exegesis on this subject matter are available in the following publications: *Global Bioethics: Building on the Leopold Legacy*. East Lansing Michigan: Michigan State University Press, 1988; "Getting to the Year 3000: Can global bioethics overcome evolution's fatal flaw?" *Perspectives in Biology and Medicine*, 34, 1:89-98, 1990; Potter, Van and Potter, Lisa. 1995. "Forum: Global Bioethics: Converting Sustainable Development to Global Survival." *Medicine and Global Survival*, 2, 3:185-91; Porter, Van and Whitehouse, Peter. 1998. "Deep and Global Bioethics for a Livable world." *The Scientist*, 12: 9; and, "Fragmented Ethics and 'Bridges Bioethics.'" *Hastings Center Report* 29, 1:38-40, 1999.

⁹ While I certainly agree with these authors on most of their arguments, some of the explicit ideals they identify as underlying the moral principles of both fields fail by way of not accurately accounting for their supposed defining differences. For instance, they state that health-care ethics (read, bioethics) focus on "individual patients and their care givers" while "environmental ethics deals in large populations; and that clinical ethics episodes are usually resolved in days and months, while ecological issues play out over decades and even millennia. Many concrete bioethical instances don't bear these claims out. Yes, some bioethical issues might be short-term, but most outlast generations. And yes, some also deal with individual patients but most deal with very large populations too. In essence, the authors' argument for a more integration of the two fields would be made stronger if they recognize that defining similarities are far greater, and that differences (between bioethics and environmental ethics) are far fewer than they have articulated.

It all seems so intuitive yet we are reminded that we cannot, in our constant quest for specialization, continue to compartmentalize our daily lives, our health and wellbeing, from reality – essentially, the myriad elements in the ecosystem (human and non-human) that are interdependent on each other in the web of life. From microorganisms and tiny entomological species to large mammals, and the role each plays; to thinking about the safety of the water we drink to thinking about the quality of air we breathe. That we have continued to simply insist that there is a distinction between environmental implications of our decisions and ethical judgments in health care policies and paying little attention to axiomatic philosophical action theory, seems a serious lapse in scholarly rigor. Genetic epidemiology has long proven that human diseases result from a combination of genetic inheritance and the environment and no other affirmation highlights the premise of that argument better (Khoury, M. 1997).

It is easy to discern why there is constant connection in everything. As an illustration, consider the long process in a drug or medical device production whereby biomedical scientists produce a medical device or cancer drug; IRB committees determine which of them meet clinical trial protocols – federal and state laws; and FDA decides when to approve for market-wide use. What is less known is how often, if at all, any of the actors involved pauses to ponder the ecological root cause or causes of the cancer disease that is being targeted. But a 2013 WHO study may have put paid to that disconnection just as Porter envisioned. Data for the WHO finding claim that 223,000 deaths from lung cancer around the world were caused by air pollution in 2013.

The International Agency for Research on Cancer, a branch of the WHO that did the study, now classifies air pollution in the same category as tobacco smoke, UV radiation and plutonium. And although air pollution had been known to cause heart and lung diseases, latest evidence provides additional reliable data supporting the fact it also was causing cancer.

Questions that Pierce and Jameton (2004) pose, and the compelling answers they proffer to prove their point are instructive. Their core questions include, “What concepts from environmental ethics can be applied to health care and how can they be combined with more traditional health-care ethics concepts? What kinds of case studies in health care highlight both clinical and environmental principles?” Ultimately, they are of the view that environmental principles are the pivot of a responsible inclusive understanding of bioethics and conduct of health care (and probably, vice-versa).

Prescriptions in the GMM guideline regarding ecological and human health could have been informed by sentiments akin to the ones echoed in the complex theory of environmental responsibility that Kiadó (2011) has developed. In its broadest form, Kiadó’s theory covers such areas as political, bioethical, scientific, and economic systems. Its emphasis on environmental protection is palpable in the way it simultaneously applies numerous systems of responsibility. “The whole theory of environmental responsibility is impregnated by the ubiquitous natural and civilizational responsibilities (borne by humans), whose presence and proportions determine both the quality and quantity of responsibility for the environment. In brief, the theory of complex environmental responsibility not only extends theoretical science, but also promotes orientation in the practice of environmental protection. It may be regarded as a new means of interpretation, though its main goal is to promote the practice of environmental protection” (p. 303).

6.0 GMM, holism and African philosophy

There is a moral burden to maintaining this order or else, the positive relation between individuals, and between humans and the natural ecosystem will be negatively impacted. In African philosophy, nature (reality) is an organic whole, and the creation and sustenance of ecological balance or interdependence between human and non-humans, the visible and the invisible is most desired. It points to the holistic perspective, as opposed to Western anthropocentrism (a social paradigm that values nature instrumentally and in so doing maintains the isolation of humans from nature and only sees its usefulness to humans).

One influential view that seemed to differ from this was that of John Muir, a Scottish-American naturalist and early advocate of preservation of wilderness in the U.S. While he believed in the intrinsic value and rights of all creatures and that a divine spirit flows in nature; he also equally valued nature for the sake of scientific research, for recreation, aesthetic enjoyment and spiritual inspiration. It was an attribute that didn't quite distinguish him just like most of his 19th century contemporary preservationists in America. However, one distinctive 19th century perspective – that of Aldo Leopold's – seems to hit the point well out of the ball park. In advocating a “land ethic” – the view that our moral concern should cover the natural environment and its nonhuman contents – he inspired several thinkers to advance the idea for “moral obligations toward ecological wholes, such as species, communities, and ecosystems, not just their individual constituents” (Stanford Encyclopedia of Philosophy). At Leopold's urging the argument goes that individual interests and well-being should be subsumed under the holistic good of the earth's biotic community. Hence his famous line:

That land is a community is the basic concept of ecology, but that land is to be loved and respected is an extension of ethics... A thing is right when it tends to preserve the integrity, stability, and beauty of the biotic community. It is wrong when it tends otherwise (Leopold, 1949, pp. 224.225).

I segue to the more expansive African philosophical point of view about which Kelbessa (2011) illuminates with the Oromo ecotheology which teaches a positive relationship between the environment, humanity and their deity.¹⁰

There is a positive relationship between God and the Earth, humans and the natural environment. All creatures are essentially effected and affected by the harmonious relationship between Waaqa and the Earth. Waaqa is the creator of various creatures and is responsible for their existence. He requires humans to responsibly cohabit the Earth with other creatures... (p. 55).

For the Oromo, the land is not simply property to be exploited by humans without due respect and care. It is intrinsically valuable and requires respect and protection on the part of its inhabitants. If humans continuously despoil the land by breaking traditional rules and the cosmic purpose, it may not support all creatures indefinitely. The Oromo believe that the present generation has responsibility to pass on natural resources in good order to a future generation. That is why the Oromo are concerned with the health and peace of the environment and its inhabitants. They depend on environmental resources to heal themselves (Kelbessa, 2011).

The point seems to be that the continued neglect of this philosophical perspective in favor exclusively of anthropocentrism, is the bane of much of human crisis. A review paper (Ingwe, R.; Ebegbulem, J.; & Ikeji, C., 2010) has tried to effectively link anthropocentric policies and crises in climate/environment, finance and economy (especially by advanced economies) to the complete neglect of ecocentric world view as it pertains to contemporary African situation. “Specifically, pursuing the objectives, goals and interests of human beings without considering ecological principles or the inter-relatedness of human and non-human natural systems is responsible for the climate-environmental crisis (p. 03).

They recommend a back-to-the-roots solution refocus and reinstitute various disciplines in the nexus of the development of both human and non-human natural environmental systems.

In smithing the word ‘eco-bio-communitarianism’ Tangwa (2004), a pioneer and influential theorist who has blazed a trail in philosophical discussions on environmental ethics from an African point of view, attempts to strike some balance. Though preferring eco-bio-communal (or ecocentrism) outlook over anthropocentric ethic, Tangwa however concedes it doesn't necessarily mean it is an end-all panacea to all health and environmental problems. However, he thinks it is certainly a better option that is guaranteed to abate the urgent global hazards which have arguably been traced to anthropocentrism:

¹⁰ All African communities, with a varying wealth of symbolism, have akin interpretations. I could have used any ethnic group anywhere on the African continent to make this point, but Kelbessa's research of the world view of the Oromo ethnic group, the largest in Ethiopia, is indeed representative of a typical perspective that can easily be replicated across Africa. Kelbessa used a combination of desk research, descriptive methods, and field research to analyze primary and secondary data.

“myriad problems of global pollution (of air, water, and soil); global climate change; of massive risks to plants, animals, and humans from toxic industrial wastes and from sophisticated weapons (conventional, nuclear, chemical, and biological); risks of upsetting nature’s ecological balance; risk of accidentally triggering the collapse of the very foundations of life via gene technology, etc.” (p. 393).

In case the reader has not yet noticed my discussion of holism and eco-centrism as if they were synonymous; it is intentional particularly as they ease into my preferred nomenclature, bio-eco-communitarianism, BEC. There is the claim that in the last few decades, environmental ethics has become an inherently holistic pursuit in large part due to Leopold’s earlier mentioned outstanding influence. Also, the rapid calls for its adoption in environmental ethics have assumed Doppler proportions each time the matter comes up for discussion (Iyioke, 2016).

Nelson (2010) delineates environmental ethical holism as “the position that moral significance attaches to wholes over and above the individuals they include, or the idea that environmental wholes can and do matter morally and directly, or that they possess intrinsic value ... what we are pointing to or looking for... we are exploring or desiring a system that allows us to directly morally include species, ecosystems, watersheds, biotic communities, or entities we typically consider collectives.”

Charles Verharen’s (2006) three-pronged view of holism is as well illuminating. First, it is a claim that all reality constitutes a single being; then that it is a commitment to join together what has been split apart; and lastly, that it is a claim that a single principle binds all existence together.¹¹ While Aldo Leopold is probably modern time’s most authoritative influence on those who propose holistic ethics, very little (if any) credit has been attributed to the ancient African root of that philosophical orientation. Citing Cheikh Anta Diop, Verharen explains that most ancient Egyptian cosmologies attribute the origins of the universe to a single principle such as *Nun*, through a process of becoming out of an original chaotic matter (water). “Through that same creative process, *Khepera*, the basic physical elements come into being, and from those elements evolve the gods, humans, and the world as we know it.” The ancient Egyptians joined spirit together with matter, in which case humans were not separate from animals and even gods. Hence, the ancient African progenitor inspired holistic philosophies that have exerted a powerful hold on human imagination (p. 960).

By some unintended way, I have come to think that globalization might shed off its negative image with the saving grace embedded in the ontological concept of African holism. For one, the immensely complex global economy (and everything else), have within the last 20-odd years, surged to integrate at a vortex, thanks to globalization (even with some unalterable consequences). By the same token, the ultimate reduction of complexity to simplicity which is found in the philosophy of holism might just be the solution we need. Verharen seems to share the same vision, “Unlike the history of the universe [the Big Bang Theory], the history of thought has moved in the direction of simplicity, defined as the smallest number of symbols capable of describing the greatest range of experience.” Consequently, he urges for a return to our roots. “The roots of all humans, as the whole world is finally beginning to discover, are in Africa” (p. 961). I agree.

To wrap up, I reference a clarion call from Australia – one of the few efforts resembling the African perspective – that aims at “reinterpreting the definition of sustainable development for a more ecocentric reorientation.” If this typifies similar calls from a Western bloc from ‘Down Under,’ it could be a sign that signals the shifting posture which adds impetus to the fact that ecocentrism could be catching on. It examines the limitations in the contemporary anthropocentric conceptualization of sustainable development with a utilitarian ethic and argues for a more ecocentric reinterpretation of its definition that is more inclusive and incorporates recognition of the socio-ecological values. That in practical terms, is a recourse to finding lasting global resolution and a framework for sustainable development based on a reinterpretation that recognizes the interdependence of humans with the rest of the ecosphere, nay ecocentrism (Imran; Khorshed; & Beaumont, 2014).

¹¹ This view point is however original to Don Marietta and espoused in his 1995 work, *For People and the Planet: Holism and Humanism in Environmental ethics*, Philadelphia: Temple University Press.

7.0 Conclusion

This chapter is a rich constellation of ideas that analyzes the blaze-trailing clinical trial GMM protocol that threads together eco-centric environmental philosophy which origin could be traced to the ancient African thought. As summarized in Figure 1, the GMM framework has rendered a catalogue of services that fit perfectly with my thesis. 1) The in-built ingenuity as a model and of pragmatic importance to the latest outbreak of Zika virus disease. 2) My over-arching aim to reconceive responsibility in clinical trials with comprehensive considerations that include research subjects and family, community engagement, respect for culture, and biosafety. 3) By calling to mind the intimate connection, namely the inseparability between environmental and human health, the GMM report hits at the heart of a long-nursed intuition that brings together bioethics (here via clinical trials) with environmental ethics. 4) The GMM's methodology buoys my inclination for eco-centrism – a widely shared philosophical perspective in African thought and holism or interconnectedness; and the intrinsic value of the biosphere in ranked order of being. 5) The GMM protocol doesn't directly deal with human study subjects, nonetheless its approach is yet another indictment of sorts on the four principles of research ethics. It marks a shift from considering ethics of research solely within the bare bones of principlism to considering the ethics of research in a much broader sense. It engages the transgenic project in the fight against malaria and dengue fever as an all-encompassing endeavor (now including Zika virus); revealing the need to improve the links between environmental health research and health care delivery, and to promote the cultural, socio-political and economic processes that are embedded.

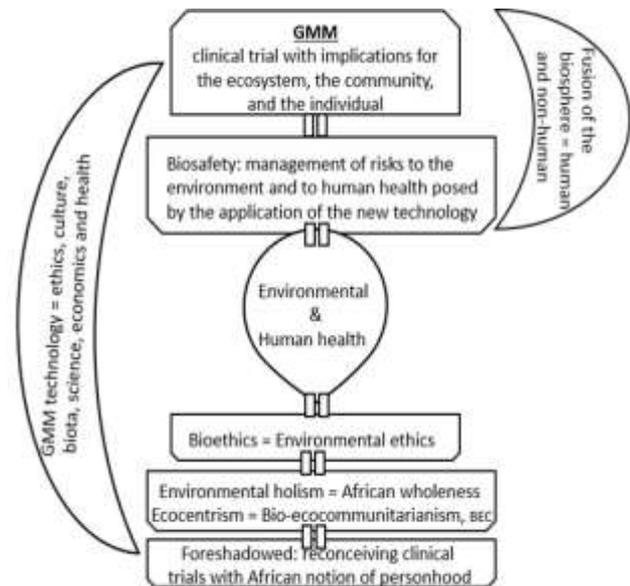


Figure 1: Meeting of GMM framework, environmental/human health, and African holism.

Put together, this essay benefits from relevant parts of the WHO compendium to build a persuasive argument. From the outset, I tried to string together pertinent aspects of the GMM framework which have collectively been the recurrent index for reflection. As a clinical trial protocol with an exceptional merit, I have argued that the steps it recommends should be standard practice for *all* clinical trial protocols including those that use human subjects. For instance, this public health intervention tool lays out a well-developed ethical and engagement strategies by reducing the chance of misunderstanding the science needed to meet the goals, and improving the performance of the research project in both technical and social contexts, while retaining respect for individuals within communities the arrow head of its overarching ethical goal.

Then, for unusually melding human and environmental health – a move that bolsters the views of a section of the philosophy community (me included) that have pined for the urgent reconciliation of bioethics and environmental ethics – two areas (that should remain as one specialized field) with a fundamental basis for the pursuit of a common purpose. So fundamentally similar that they both share significant overlap on many issues – ethical approaches, concepts, and moral considerations. That, in and of itself, extends to the eco-centric philosophical view point of holism and the intrinsic value of the biospherical elements in ranked order of being. It comes as no surprise that these two broad issues can be merged into what I have referred to as BEC.

It is thus unprecedented that a clinical trial protocol with a Western origin has gone beyond the four pillars of principlism to recognize the possibility of a new technology (e.g., GMM), having the potential to simultaneously impact human individuals, the community and the ecosystem in tandem. This fusion of elements (human and non-human) by implication makes a strong statement about the interrelatedness/

interconnectedness of such factors as ethics, culture, the biota, science, economics and health (environmental and human). In so doing it has adequately positioned biosafety, namely the management of risks, as an integral point of consideration on issues relating to the environment and to human health as brought about by the application of the new technology. All this might not have happened without the thoughtful precautionary deliberations that fashioned the GMM project. It has thus engendered the potentials of its application to a wide range of possibilities.

The wider policy implications resulting from the inter-disciplinary approach in formulating the clinical trials process are many. They include that (the autonomy-based) research ethics principles can no longer be assumed to be universal everlasting ideas or transcendental truths (Rendtorff, 2002). More objections to Beauchamp and Childress' version of common morality have continued to find it dubious that "we could convincingly show that there are general rules of principles that 'everyone' accepts" (Kukla, 2014, p. 79). It behooves us therefore to harness the newfound energy and stand clear of the tall shadow of universalism in principlism. Furthermore, the desire to consolidate the comprehensive fields of bioethics and environmental ethics as one unified field of philosophical inquiry seems closer to fulfilment. The GMM project encourages the development of a reliable and appropriate framework of analysis for the field made whole. With the right awareness, bioethicists, biomedical researchers, technocrats, scholars, policy makers, and students stand to benefit immensely from this reformulated approach. Lastly, it is hoped that Africanists, particularly native African thinkers would find reason to be more engaged in shaping the discussion and promoting traditional philosophical and multicultural values from this perspective.

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