



OPEN LETTER

Informed consent in field trials of gene-drive mosquitoes

[version 1; peer review: 4 approved]

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Abstract
The US National Academies' (NAS) recent report 'Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values' examines the requirements of responsible conduct in research involving gene drives in non-human organisms. Many of the complex ethical issues raised by the introduction of gene drive technologies for mosquito population control have been anticipated during the development and field-testing of earlier-generation genetic engineering approaches with mosquitoes. One issue—the requirement for informed consent in field trials—is not addressed explicitly in the NAS' report. Some commentators have presumed that informed consent should play a role as a protection for research participants in studies of genetically modified mosquitoes. Others have argued that there are no human subjects of field trials, so the informed consent requirement does not apply. It is both ethically and practically important that these presumptions are adequately scrutinized to ensure that any applications of informed consent in these trials are properly justified. We argue that informed consent from individual research participants in gene drive trials may be required: (1) when blood and other forms of clinical data are collected from them, as will likely be the case in some studies involving epidemiological endpoints, such as the incidence of new infections with dengue and malaria; (2) when they participate in social science and/or behavioral research involving the completion of surveys and questionnaires; or (3) when their home or property is accessed and the location recorded as a spatial variable for the release or collection of mosquitoes because the precise location of the household is important for entomological reasons and these data constitute identifiable private information at the household level. Importantly, most regulations and guidelines allow these requirements to be waived or modified, to various degrees, according to the judgment of Institutional Review Boards.

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Approval Status

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- 1. Jason A. Delborne^{id}, North Carolina State University, Raleigh, USA
- 2. Carolyn P. Neuhaus^{id}, The Hastings Center, Garrison, USA
- 3. George J. Annas, Boston University School of Public Health, Boston, USA
- 4. Cynthia E. Schairer, University of California San Diego, La Jolla, USA
- Cinnamon S. Bloss, UC San Diego School of Medicine, La Jolla, USA

Any reports and responses or comments on the article can be found at the end of the article.

Keywords

informed consent, research ethics, gene-drive, genetically-modified mosquitoes, field trials, global health

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Introduction

The US National Academies' (NAS) recent report 'Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values'¹ examines the requirements of responsible conduct in research involving gene drives in non-human organisms. One of the most promising applications of gene drive technologies on the horizon is the modification of disease-transmitting mosquitoes in attempts to diminish their populations or compromise their capacities as vectors. Many of the complex ethical, social, and cultural issues raised by the introduction of gene drive technologies for mosquito population control have been anticipated during the development and field-testing of earlier-generation genetic engineering approaches with mosquitoes²⁻⁵. These studies are complex and require unique designs⁶ involving various combinations of outcome measures and a progression of activities—from purely entomological studies to characterize effects on mosquito populations⁷ to studies involving the measurement of epidemiological outcomes associated with modified mosquitoes in defined areas.

Extensive media coverage of these early approaches has thrust the many challenges associated with testing these new technologies squarely into the public spotlight. One issue—the requirement for informed consent in field trials—is not addressed explicitly in the NAS' report¹, but has gained international attention most recently around a planned field trial of genetically modified *Aedes aegypti* mosquitoes to prevent Zika virus transmission in Florida. The proposed field trial sparked considerable controversy. In the run-up to a Monroe County, Florida, ballot measure about the proposed trial in the US general election on November 8, 2016 'No Consent' signs dotted the landscape in Key Haven, Florida⁸, the proposed site of the planned trial. In addition, almost 170,000 people signed a petition that, among other things, claimed that the planned releases will be conducted "against the wishes of the locals and the scientific community"⁹. Conflicting votes on the ballot measure across Monroe County on November 8 stalled a decision by the Florida Keys Mosquito Control District Board of Commissioners about the fate of the proposed trial¹⁰, and a subsequent meeting of the Board saw community members claiming human rights violations if the proposed release trial were to be conducted without the informed consent of residents¹¹.

Conflicting presumptions about the role of informed consent

Even though the genetically modified mosquitoes in the proposed Florida trial did not involve gene drives, the response to their planned introduction in open field trials foreshadows some of the issues that are likely to be even more vigorously contested in future trials involving gene-drive mosquitoes and other insects. Some commentators have presumed that informed consent should play a role as a protection for research participants in studies of genetically modified mosquitoes⁴, under-pinned by competent regulatory oversight and robust community engagement⁵. This presumption has been reinforced in some early experiences with the testing of biologically-modified mosquitoes, in which regulators insisted on household level informed consent as a condition of approval for open-release trials¹². Other commentators have argued that "(t)here are, strictly speaking, no human subjects of field trials, so the

regulations governing human subjects research, which require informed consent from every participant, do not apply." (13, p. 716) It is both ethically and practically important that these presumptions are properly scrutinized to ensure that any appeals to apply informed consent in future trials of genetically modified mosquitoes constitute an appropriate response to the ethical stakes involved, and not simply a reflexive appeal to the most familiar tool in the research ethics toolbox.

Informed consent to participate in research is fundamentally a way for individuals to authorize researchers to perform various research-related actions that would otherwise constitute some form of violation of the individual's rights. For example, administering an experimental drug to someone in a research study without their consent would normally constitute battery. But because the central actions of researchers in research involving genetically-modified and gene-drive mosquitoes—the release, tracking, and collection of mosquitoes—are not targeted at individuals, a key question for all of these trials is who should be considered a research subject, and under what conditions informed consent should be applied as a protection.

Who is a human research subject?

These questions have caused confusion in several complex research designs—in particular, cluster-randomized trials—and in response McRae *et al.*¹⁴ have proposed a general definition of a human research subject based on their analysis of the common elements of informed consent represented in international research ethics guidelines and influential policies, including the US Common Rule regulations governing research with human subjects. Their analysis remains consistent with the recent 'Final Rule' revisions of the Common Rule (<https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html>). According to their definition, "a human research subject is an individual whose interests may be compromised as a result of interventions in a research study"¹⁴. By "interventions", McRae *et al.*¹⁴ refer both to the experimental procedure being investigated as well as to non-experimental data collection procedures. More specifically, a human research subject is an individual: 1) who is directly intervened upon by an investigator as either (a) a recipient of a study intervention or (b) as someone who undergoes non-experimental interventions to collect data; 2) who is deliberately intervened upon via manipulation of the individual's environment by the investigator in such a way as to have a direct effect on the individual; 3) who communicates or has interpersonal contact with an investigator for the purpose of collecting data through, for example, interviews, focus groups, or questionnaires; and 4) about whom an investigator obtains identifiable private information for the purpose of collecting data¹⁴.

Given the nature of the interventions, it does not seem plausible to claim that any individual at or near a release site will be "directly intervened upon" by an investigator as a recipient of a study intervention (criterion 1(a) above) or "deliberately intervened upon via manipulation of the individual's environment"¹⁴ (criterion 2 above). Most release trials will involve male mosquitoes, which do not bite humans, and the mosquitoes will bring about the hoped-for population suppression or replacement through competition

for reproductive opportunities with wild-type mosquitoes, rather than through deliberate interactions with humans.

Appropriate applications of informed consent

In line with the definition of McRae *et al.*¹⁴, we believe individuals satisfy the conventional requirements to be considered human subjects in research with genetically modified mosquitoes in the following circumstances: (1) when blood and other forms of clinical data are collected from them, as will likely be the case in some studies involving epidemiological endpoints, such as the incidence of new infections with dengue and malaria; (2) when they participate in social science and/or behavioral research involving the completion of surveys and questionnaires; or (3) when their home or property is accessed and the location recorded as a spatial variable for the release or collection of mosquitoes because the precise location of the household is important for entomological reasons and these data constitute identifiable private information at the household level.

Importantly, it also does not follow that the normal requirements may not be waived or modified according to the judgment of research ethics committees or institutional review boards, as most regulations and guidelines anticipate, and allow, to various degrees. Our circumstance (3) above, may be better understood as more general requests for permission and gestures of common respect and decency, governed by social convention and relevant laws related to privacy and trespass, rather than applications of informed consent to protect research subjects.

Living in the vicinity of a release trial does not automatically render someone a research subject and therefore it is inappropriate to require informed consent from every individual in the vicinity simply because the technologies being deployed are still in their testing and development stages. Arbitrarily requiring informed consent from every individual and household in geographic proximity to a release trial misrepresents and undermines the value of informed consent in research and establishes worrisome precedents about the appropriate application of research ethics policies and procedures. It also raises potentially insurmountable logistical challenges that will ultimately impede important science, with no clear ethical rationale.

Field trials of gene drive and other genetically modified mosquitoes do not fit neatly into our current regulatory definitions of clinical

trials—including the National Institutes of Health's recent revision to its definition of clinical trials, a definition that distinguishes between clinical trials and other types of clinical research and automatically triggers a set of regulatory procedures, including individual informed consent from human subjects (<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>). And concern about an overly expansive definition of “clinical trials” also figured prominently in the public comments on the recently adopted ‘Final Rule’ revisions (<https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf>). As a result, there is likely to be considerable debate about the appropriate regulatory standards for these trials, particularly as the trials begin to incorporate epidemiological endpoints. It is also likely that funders and regulatory agencies will seek refuge in familiar policy tools, whether or not they represent the most appropriate response to the specific challenges at hand.

Conclusion

What constitutes fair and legitimate authorization for field trials of gene drive and genetically modified mosquitoes is a critically important question¹⁵, and ensuring individual informed consent to specific research processes and procedures surely has a role to play in the overall balance. But it is a narrow role and should not deflect attention from the more complex governance challenges of developing the appropriate regulatory regimes and authentic stakeholder engagement.

Competing interests

No competing interests were disclosed.

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Disclaimer

The views expressed in this article are those of the author(s). Publication in Gates Open Research does not imply endorsement by the Gates Foundation.

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Kolopack and Lavery argue that informed consent in field trials of gene-drive mosquitoes should be applied only when individuals satisfy the conventional requirements to be considered human subjects in research, i.e., when there is effectively a reasonable expectation of individual risk. Defining the circumstances under which field trials require informed consent is useful; it carves out a practical space for informed consent to be used in field trials of different designs and, as the authors point out, avoids “misrepresent[ing] and undermin[ing] the value of informed consent.” In the final sentence of the piece, the authors acknowledge the limitations of informed consent as a tool for coping with community-level risks by calling for serious attention to regulatory regimes and stakeholder engagement, but this message is obscured by three aspects of the article that want clarification.

First, the abstract concludes with a somewhat different message than the body of the piece, pointing to the allowance of informed consent requirements to be waived or modified by Institutional Review Boards (IRB). The wording is ambiguous, but might be read as a complaint or warning that stronger informed consent requirements are not in place. Or perhaps it is meant to be a reminder that informed consent is not always sacrosanct, as the requirement may be waived by an IRB. But the argument made in the body of the article focuses on a cogent proposal for the proper limitations of informed consent in the context of field trials and ends with a late reminder of other, critically important “governance challenges”, that need to be met for “fair and legitimate” field trials to go forward.

Second, the final criteria for when consent may be required – when property is accessed and location recorded – requires further consideration, in our estimation. The authors argue that this information is both private and identifiable and that if collected, would therefore meet criteria for human subjects research and require individual informed consent. We question, however, the

extent to which there is a reasonable expectation of privacy when a property is accessed in the manner the authors describe. Specifically, property is accessed and recorded in this way when homes are bought and sold and in the name of other public utilities, goods, and services (e.g., provision of clean water, and even environmental mosquito control services). Therefore, merely recording entomological data based on observations made at a specific location or on a person's property, may not constitute a scenario in which there is a reasonable expectation of privacy. In fact, the authors also seem to acknowledge this in a later paragraph in their article when they state that this "may be better understood as more general...gestures of common respect and decency," but further discussion of this point is warranted.

Finally, as Kolopack and Lavery suggest at the end of their article, informed consent guidelines should not overshadow the challenges of developing "appropriate regulatory regimes and authentic stakeholder engagement." It is worth mentioning that in the case of the Florida Oxitec trial, a regulatory mechanism was in place – though arguably insufficient – but the process did little to quell anxiety about the unknown consequences of the intervention to be tested among the vocal minority of residents in Key Haven who were opposed to the trial. The appeal to informed consent, then, could be construed as an attempt to wield individual power over a collective mechanism (and an apparently successful attempt as the proposed Oxitec trial has been postponed until a different trial site is identified). Though the authors do not claim this, we believe it warrants mention that guidelines about when to require informed consent cannot address the underlying issue at stake in the protests against the Florida Oxitec trial. Ultimately, local protestors did not trust Oxitec, the Food and Drug Administration, or the local mosquito control board to adequately manage community-level risk associated with the trial. Thus, despite the provocative language of informed consent, Florida residents and activists were concerned about unintended consequences secondary to a release – risks that cannot be managed with informed consent.

The authors also have an opportunity to mention the existing structures in place to help us make collective choices about how to act in the face of such risks. Specifically, regulatory bodies are set up to have experts assess risks before approving field trials so that the lay public will not be asked to evaluate risk without the necessary expertise or accept unreasonable risks (see for example, epa.gov). For instance, like the risks of pesticides, the risks associated with field trials of genetically engineered insects cannot be managed by individuals in the ways that risks associated with blood draws or surveys may be. Nor is it appropriate to react to the protests of some with outright rejection of a technology with great potential to protect public health. There certainly needs to be greater clarity on and agreement in the field regarding the "rules" of informed consent for field trials, and we applaud Kolopack and Lavery for their proposal in this regard. We also note, however, that a focus on informed consent in the landscape of field trials of gene-drive mosquitoes and other insects runs the risk of allowing a vocal minority to set the terms of the debate, obscuring the need for transparent and independent regulatory structures and effective two-way communication between researchers and the communities they wish to help.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately

supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Partly

Competing Interests: Some of our work is funded through DARPA's Safe Genes program, with which James Lavery is also affiliated.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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George J. Annas

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Time to declare informed consent to field trials of gene-drive mosquitoes a dead issue.

George J. Annas

Kolopack and Lavery (1) are correct both to suggest that the NAS report on "Gene Drives on the Horizon" (2) is the most authoritative report on the subject to date, and that the report did not "explicitly" address informed consent of the people who live in the area in which genetically-modified mosquitoes are released for study. Nonetheless, I think it is time to call an end to what's left of the informed consent debate in this context. This is not only, as others have written, because "informed consent is neither ethically required nor practically feasible,"(3) but most centrally because what is at issue *is* ethically required and practically necessary: community engagement (sometimes referred to as community consultation). The NAS gene drives report, for example, quotes an earlier (1996) National Research Council report as saying, "The normative rationale [for broad participation in risk decisions] derives from the principle that government should obtain the consent of the governed. Related to this principle is the idea that citizens have rights to participate meaningfully in public decision making and to be informed about the bases for governmental decisions." (p. 133) Immediately after the quotation, the gene drives report goes on: "...engagement enhances transparency and ensures some level of meaningful participation and consent." It is fair to say that just what "meaningful participation" means can vary from

community to community, as well as from one “public” to another, and is the subject of on-going debates. It is also fair to say, I think, that the notion that “consent” means “informed consent” from individuals at potential risk from mosquito release experiments is not suggested in the gene drives report, and, I think, it is time to declare informed consent in this context dead.

Kolopack and Lavery may seem to disagree with this unequivocal conclusion, but I’m not convinced that they do. (The Vietnam example of regulators insisting on “household level informed consent as a condition of approval for open-release trials” is not a counter example, as there is no such thing as “household level informed consent,” just individual informed consent.[4]) Kolopack and Lavery suggest only 3 instances in which members of the population living in an area where modified mosquitoes will be released could qualify as “research subjects” and hence as people whose informed consent may have to be sought: (a) when blood or similar biologic samples are collected from individuals for the study; (2) when individuals are asked to respond to questionnaires or surveys; and (3) when the home or property of individuals is being assessed to obtain data relevant to the research. There are two points to be made about this list. The first is made by Kolopack and Lavery themselves, who observe that even if one accepts this list in its entirety, “it does not follow that the normal requirements may not be waived or modified according to the judgment of...institutional review boards [IRBs]...” Anticipating waiver of consent must mean, it seems to me, that the authors do not think formal informed consent is ethically-required in these circumstances. More centrally, however, is that the first two examples, blood draws and survey responses, are interventions routinely dealt with by IRBs, and the context of mosquito-release studies present no novel or unique ethical issues.(5) Finally, number 3, entry into one’s home or property, is something routinely done by friends, delivery persons, and even public officials, and requires only the oral agreement or authorization of the inhabitant, as Kolopack and Lavery themselves point out.

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Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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Kolopack & Lavery outline conditions under which persons involved in research on gene-drive mosquitoes may also be considered “human subjects of research.” They identify three conditions under which informed consent from individual research participants in gene-drive trials may be required: (1) when blood and other forms of clinical data are collected from them; (2) when they participate in social science and/or behavioral research involving the completion of surveys and questionnaires; or (3) when their home or property is accessed and the location recorded as a spatial variable for the release or collection of mosquitoes.

I don't think anyone would take issue with (1) or (2). I might suggest distinguishing, though, between research activities undertaken as part of a field trial of gene-drive mosquitoes, which might study primarily ecological effects, and activities undertaken as part of subsidiary epidemiological or behavioral research on the impact of field trials on human health or well-being. The former may proceed without the latter. Field trials with epidemiological endpoints may collapse the distinction between ecological research and epidemiological research; though study design and choice of endpoints in field trials also merit closer ethical analysis.

Kolopack & Lavery's condition (3) will require a bit more development I think. The stated rationale for (3) is, "the precise location of the household is important for entomological reasons and these data constitute identifiable private information at the household level."

While I can appreciate that it would be wise, if not also necessary, to ask for permission to access someone's property for the purpose of data collection, it is debatable whether that act renders the occupant a "human subject of research." It seems somewhat strange that knowledge of the location of a release/catch site or its specific address constitutes "identifiable private information." I know that there is a house at 10 Main Street, but that tells me nothing about its occupants. To find out that mosquitoes were released at 10 Main Street provides no further information about them -- except, perhaps, that the occupants of that address agreed to allow the release of gene-drive mosquitoes on their property. Does this constitute "identifiable private information"? Perhaps additional private information would be collected; it'd be worth specifying what in order to clarify which data constitute identifiable private information such that its collection would require informed consent.

The authors further state that it does not follow from their assertion that home dwellers may be human subjects of research that informed consent, in the legal sense, would be required of them prior to the release of insects on their property. They say that instead, "general requests for permission and gestures of common respect and decency" could substitute obtaining informed consent to research participation. But the rationale for this substitution is lacking. Perhaps this gets to the point that one should ask permission before entering someone's property, but this is not the same thing as obtaining informed consent to research participation.

Research ethics committees considering whether to waive or modify informed consent requirements for field trial research will likely need further guidance if they find themselves debating these matters. Kolopack & Lavery ask the right questions and make an excellent contribution to discussion about the rationale for informed consent in field trials of insects and animals with gene drives. I look forward to continued conversation.

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Yes

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Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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This open letter considers the manner in which informed consent might apply to trials of genetically modified (GM) or gene drive modified (GDM) mosquitoes during field trials. At issue are two important questions: 1) when should we consider humans who live near field trial sites as "human subjects," thus triggering requirements for informed consent, and 2) how well does "informed consent" capture ethical and normative requirements for the authorization of GM or GDM mosquito field trials?

The three criteria posed for when "individuals satisfy the conventional requirements to be considered human subjects in research with genetically modified mosquitoes" (p. 4) are reasonable and defensible, and they answer question #1 above. The first criteria - "when blood and other forms of clinical data are collected from them" (p. 4) - could be highly relevant during field trials of mosquitoes whose sponsors seek to make an epidemiological claim about the organism. In the U.S. regulatory context, such data will be required if the Food and Drug Administration is measuring, for example, whether dengue incidence decreases with the release of the mosquitoes. Claims solely about population suppression may not require such data. The second criteria - "when they participate in social science and/or behavioral research" (p. 4) - will likely be triggered with such high levels of interest by social scientists in GM and GDM field trials. Of note, however, such social science research may not always be well integrated into field trial research, suggesting only that the collection of typical social science data will require typical human subjects informed consent. The third criteria - related to the collection of precise household location data - is a thoughtful extension of criterion #2, as issues of identity and privacy are well-worn modes of concern in social science research.

The authors also provide some perspective on the question of whether "informed consent" is the right lens for discerning ethical and responsible research in GM and GDM field trials. Importantly, they gesture to their paper on community engagement (ref #15) and also state that "ensuring individual informed consent...is a narrow role and should not deflect attention from the more complex governance challenges of developing the appropriate regulatory regimes and authentic stakeholder engagement" (p. 4). In other words, while understanding how informed consent applies to GM and GDM field trials is important, it is not sufficient. From my perspective as a reviewer, this claim is at least as important as the identification of criteria 1-3 (described above)

and somewhat unfortunately buried in the conclusion. The authors discussion of the case study of the Florida Keys Mosquito Control District would be an excellent place to explicitly acknowledge how questions of informed consent are very unlikely to capture the complex normative and political dimensions that will accompany at least the early years of GM and GDM organism field trials. As the authors note, public debates often map onto existing regulatory structures - hence the claims in Florida of human rights violations associated with a lack of informed consent. Such mapping reflects issues of power and authority in specific contexts - for example, the ability of community members or stakeholders to have a voice in the authorization of a field trial. Clarifying the specific application criteria of informed consent - the focus of this paper - may do little to improve the quality of debate unless and until the development of "appropriate regulatory regimes and authentic stakeholder engagement" (p. 4), which remains a rich area for research and public discourse.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Partly

Competing Interests: I am a Co-PI on a funded project on gene drive research from DARPA's Safe Genes program, on which James Lavery serves on the Legal, Ethical, Environmental, Dual-Use, and Responsible research (LEEDR) team.

Reviewer Expertise: biotechnology and public engagement

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.