controller (or the subject). Although the provision offers transparency in terms of information for the data subject, this may create headaches for researchers with regard to transfer of data that are lawfully collected and stored for the purpose of their research. There also exists no clarity in this provision as to the extent of data that a controller may be required to transfer.

A final issue raised by GDPR is the requirement for EU member states to introduce further limitations in the processing of individual genetic, genomic, proteomic, metabolomic, biometric and health data. Although on the one hand this may mean increased control over data sets used in genomic research, the good news for researchers is that an exemption is provided in the case of processing for archiving purposes in the public interest, for scientific or historical research purposes, or for statistical purposes involving organizational structures, such as ethics committees, that would assess the processing of data in accordance with GDPR (ref. 1, Article 89).

An important principle in GDPR is respect for data minimization (i.e., personal data should be processed only where relevant). Thus, for a research study, anonymized data are preferable but not always necessary. Pseudonymization can also be adopted to conform with the principle of data minimization. GDPR requires consent of the research subject to be limited to one or more specific purposes in an intelligible and easily accessible form, using clear and plain language. Thus, there is a requirement for explicit and informed consent for the processing of personal data, unless public interest or scientific, historical or statistical purposes are served by a broader consent. GDPR acknowledges that it is often not possible to fully identify the purpose of data processing for scientific research purposes at the time of data collection. Therefore, data subjects should be allowed to give their consent to certain areas of scientific research, while keeping within recognized ethical standards for scientific research. In such cases, data subjects should have the opportunity to give their consent only to certain areas of research or to parts of research projects based on their purpose (ref. 1, Recital 33). Thus, it may be essential for researchers to secure a re-consent if they plan to use a subject's data for new research directions if the aims of the new study differ from those stated at the time when the data were originally collected, and consent obtained.

The GDPR is a major step to meet the challenges for protection of personal data in the context of big data research and increased cross-border flow of data within shifting paradigms of research alliances. Although it does place additional burdens on researchers, its aim is to interpret the processing of personal data for scientific research in the broadest manner and with a view to facilitate technological development, fundamental research and applied research in both the public and the private domains. For instance, although GDPR requires that sensitive personal data be processed only for the specified purposes for which the data subject offered consent, in the research context GDPR considers that personal data can be processed for another purpose, provided appropriate standards and safeguards have been applied (ref. 1, Article 6(4)). Relevant considerations include weighing how close the new purpose is to the initial purpose of data collection, what is the nature of the data and what would be the possible consequences of processing such data for the new purpose.

A final take-away is that researchers intending to use personal data generated from EU citizens must acquaint themselves fully with their obligations under the new law. Although GDPR offers a great deal of leeway in the processing of data for research within biorepositories and is a binding legislative act, EU member states are still required to make provisions in their laws for making certain specific exemption for the purposes of research within biobanks in the interest of research for public benefits (e.g., for exemptions in relation to data portability or rights of access of data subjects, right of rectification and restrictions on processing). Thus, researchers will need to make themselves aware of national laws as they pertain to these issues and follow recognized ethical standards for scientific research in handling, recording, storing and transmitting data.

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Ethical lessons from a tale of two genetically modified insects

To the Editor:

Genetically modified (GM) insects have arrived. Engineered mosquitoes have already been deployed in countries that regularly face outbreaks of mosquito-borne diseases[1]. Many hope that genetically modified insects and pests will prove to be 'greener', more cost-effective solutions to public health and agricultural threats. But how can their safety and efficacy be tested? Several recent papers and reports offer ways of mitigating risks of field trials to animals, humans, and the environment[2–6]. Nearly all agree that public engagement is a necessary component of rolling out this new biological technology. A key outstanding ethical question remains: what level of control should community members and other stakeholders have over the decision to release GM insects as part of a field trial?

Answering this question takes on a new urgency in light of two proposed, but ultimately abandoned, field trials of GM insects in the United States. Furthermore, rapid advances in genome editing mean that larger numbers of proposals for field trials of GM insects in the United States, not to mention other GM animals, will be forthcoming. Insects with gene drives are an especially exciting, but also potentially irreversibly dangerous, manifestation of GM insects.

Insects pose an enormous public health threat and wreak havoc on our food supply. The *Aedes aegypti* mosquito transmits malaria, chikungunya, dengue fever, and the Zika virus. In 2016, the Zika virus spread throughout the Americas and to Southeast Asia. Of 76 countries with evidence of mosquito-borne Zika virus transmission since 2015, 59 reported their first autochthonous mosquito-borne Zika virus infections[7]. Countries that have never had to worry about *Aedes aegypti* are increasingly concerned

about the rise of a new, poorly understood, public health threat. The diamondback moth, *Plutella xylostella*, feasts off of cabbage, broccoli, kale, and other crops, costing farmers around the world $4–5 billion per year[8] and threatening fragile food supplies.

Pesticides are the best weapon against mosquitoes, moths, and many other insect pests. Often, however, insects adapt to chemical pesticides, making them ineffective. Moreover, public opposition to pesticide use presents legal and political challenges[9], pesticide runoff can contaminate water supplies[10], and pesticides are not cheap. Farmers in the United States spent ~$12 billion on pesticides in 2008 (ref. 11). The ethical mandate to protect public health, both through preventing disease and securing safe food supplies, supports, if not requires, research on alternative ways to reduce insect and pest populations.

The case studies we review here, involving Cornell University's (Ithaca, New York) request to the Animal and Plant Health Inspection Service (APHIS) to release GM moths and Oxitec's (Abingdon, UK) to the US Food and Drug Administration to release GM mosquitoes, provide an overview of the US federal regulations and guidance governing field trials of GM insects (**Figs. 1** and **2**). Ethical analysis of these cases shows that current regulations and guidance miss the mark when it comes to public engagement in the approval process for field trials of GM insects. Questions remain about how to improve the process and incorporate community members into oversight mechanisms. Three suggestions merit consideration. First, use ecological risk assessments to characterize and quantify the risks of field trials and alternative methods of pest control; second, involve community members in designing field trials well ahead of releasing GM insects; and third, seek community authorization for field trials. These three suggestions are rooted in the ethical necessity of securing trust in novel scientific research.

Ethical lessons

Ethical analysis of the two cases centers on opportunities for public engagement. The outreach and engagement efforts undertaken in these two cases, and codified in federal laws, arguably fall short in three ways.

First, the public comment period—the only legally mandated public engagement activity in these cases—is a one-size-fits-all approach to public engagement. It does not distinguish community engagement from outreach to the general public. The National Environmental Policy Act (NEPA) requires executive branch agencies to consider the environmental effects of their actions, including actions which would permit release of GM insects in a field trial. In both cases discussed (**Figs. 1** and **2**), the lead agencies reviewed an environmental assessment (EA) of the proposed release, and concluded that the action would have no significant impact (FONSI) on the environment or human health. In both cases, the agency made the EA and FONSI available for public comment before making a final determination whether to prepare an Environmental Impact Statement (EIS) before the action was executed. Review of public comments, received from interested parties all over the country, did not change the agencies' FONSI. In contrast to this one-size-fits-all approach to public engagement, a recent US National Academies of Sciences, Engineering, and Medicine (NASEM) report on gene drives distinguishes between communities, stakeholders, and the public. Communities are "groups of people who live near enough to a potential field trial or release site that they have a tangible and immediate interest in the project"[5]. Stakeholders "have professional or personal interests sufficient to justify engagement, but may not have geographic proximity to a potential release site for a gene drive technology"[5]. The public "represent groups who lack the direct connection to a project that stakeholders and communities have but nonetheless have interests, concerns, hopes, fears, and values that can contribute to democratic decision making"[5]. The NASEM report recommends tailoring engagement strategies to the target audience, with special emphasis on community engagement because they represent the group with the most tangible and immediate interest in the project.

Second, social science research points out that citizens must believe that their comments and opinions matter for them to genuinely engage in deliberations or conversations about state actions or policies[12]. Mechanisms that weakly engage citizens but do not give them formal power to sway state actions may actually erode trust, discourage participation, and encourage retreat into ideological siloes. The Florida Keys Mosquito Control District's (FKMCD) use of a non-binding referendum on Oxitec's application did not give voters formal deciding power. A non-binding referendum is merely advisory. Though members of the FKMCD listened to voters in this case, it should be noted that doing so was not—and is not—required.

Finally, neither Oxitec's nor Cornell University's public engagement strategy fully realized genuine deliberation over what communities, stakeholders, or the public think about GM insects. To be fair, Oxitec was eager to engage the public in the Florida Keys from the get-go. This may have been a response to previous allegations that Oxitec acted covertly when it released their GM mosquito in other countries[13,14]. Oxitec enlisted the help of the FKMCD to engage with the community and educate residents about the project. FKMCD delivered presentations to local clubs as well as city and county commissions as early as April 2012 (ref. 15).

But town hall meetings tend to be more about eliciting public opinions and answering questions than having a debate. And the federally mandated comment period is largely one-sided, too. Agencies need only respond

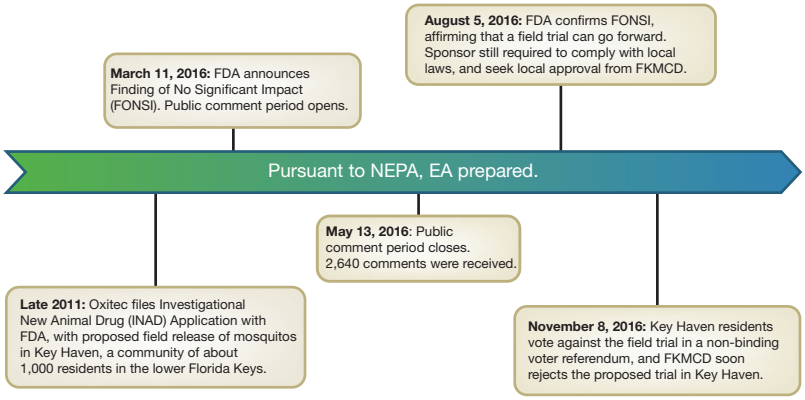

Figure 1 Annotated timeline of proposed *A. aegypti* field trial. At the time of submission, Oxitec's transgenic *A. aegypti* was classified as an animal drug and fell under the purview of the FDA's Center for Veterinary Medicine (CVM). It was regulated as such because the inserted genetic material constituted an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." FDA guidance released in January 2017 indicates that the following GM insect products are drugs for regulatory purposes: first, products intended to reduce the virus/pathogen load within an insect (e.g., mosquito); second, products intended to prevent insect-borne diseases in humans or animals.

to US Federal Register comments that raise substantive issues in the environmental assessment. They can ignore opposition that is summed up in comments like "Hell No, GMO!" or comments expressing suspicion of a sponsor's motives. Even when the agency does respond to comments, their response is often the last word. In both cases, the agency's response was accompanied by an action, rather than further dialog. Indeed, various groups, on behalf of organic farmers in upstate New York, registered complaints with the US Department of Agriculture (USDA), Cornell University, and the governor of New York for "quietly" approving the GM moth trial[16], even though APHIS responded to comments that raised substantive issues when it approved the permit for release in November 2014 (ref. 17). In contrast, the NASEM report calls for "robust forms of engagement"[5]. The goal of pubic engagement is not merely to poll the public or to elicit their opinions, but rather to foster mutual engagement.

Two insects, three suggestions

On the basis of the above lessons, we put forward three suggestions below that, when incorporated into decision-making procedures for field trials of GM insects, could prove beneficial. These suggestions relate to ecological risk assessments (ERAs), incorporating community feedback into field trial design and community authorization for field trials.

ERAs. It is ethically less problematic to put a GM insect field trial in a place that is already adversely affected by the insect under investigation[3,6]. The potential risks to the local community associated with field trials of GM insects are then seen as outweighed by the possibility of benefit to the same community, if the intervention is effective. But residents may disagree about the extent to which the insect under investigation poses genuine risks, and some people may be simply misinformed and either underestimate or overestimate the risk of a particular problem, leading to substantial differences in risk assessment. At the same time, uncertainty of the outcome of field trials and the risks of releasing GM insects may also lead to substantial disagreement within the community about whether the potential benefits of GM insects outweigh other risks. Weighing the risks and benefits of GM insects, as well as available alternatives to controlling insect and pest populations, involves subjective value judgments.

ERAs are a useful tool for developing comprehensive risk–benefit analyses amidst uncertainty by taking into account subjective values and local concerns. An ERA is the "study and use of probabilistic decision-making tools to evaluate the likely benefits and harms of a proposed activity on the wellbeing of humans and environment, often under conditions of uncertainty"[5]. It is "a more robust and appropriate framework for assessing the potential ecological harms and benefits of [genetically] modified organisms"[5] than National Environmental Protection Act (NEPA)-mandated environmental assessments or environmental impact statements (EIS), as neither an environmental assessment nor an EIS "requires a clear formulation of the problem that requires a quantitative cause–effect model"[5]. The US Environmental Protection Agency (EPA) already uses ERAs to guide decisions like building hazardous waste sites. But the application of ERAs could be broadened[18] to capture a comprehensive assessment of the causes and effects of a particular insect on human or plant health, and available ways to mitigate the threat of insects, including field trials of GM insects and the use of terminator genes. There is a growing literature on the nuances of ERAs, and ways of simplifying such analyses[5,19].

The moral argument for incorporating ERAs or any other tool to assess uncertain risks and benefits into the regulatory and decision-making process stems from the ethical requirement that field trials of GM insects are performed in places with a favorable risk–benefit calculus. The ERA is a necessary first step when deciding and defending a field trial's location. It also helps meet the need for clear communication to those affected by the research project. A recent study showed that fears of the possible harmful impacts of GM mosquitoes were among the most common reasons for local opposition to the Florida Keys trial (**Fig. 1**; ref. 20).

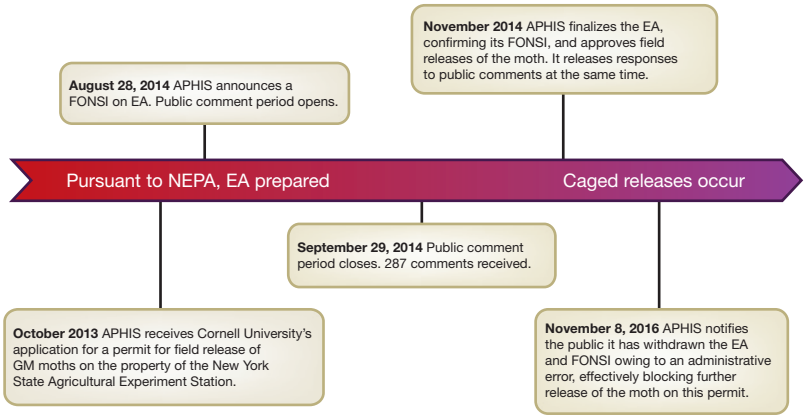

Figure 2 Annotated timeline of proposed field trial of the moth *Plutella xylostella*. The transgenic *P. xylostella*, initially developed by Oxitec and subsequently tested in field trials by researchers at Cornell University, was regulated as a plant pest for regulatory purposes under the Plant Pest Act. Plant pests fall under the purview of the USDA's APHIS.

Involve community members in field trial design. An exciting model for community engagement is being developed as part of a partnership between researchers at the Massachusetts Institute of Technology, who are developing gene drives to control Lyme disease spread by rodents, and residents of Martha's Vineyard and Nantucket. Residents of those Massachusetts islands are being called upon to weigh in on experimental design and safety measures well in advance of even creating GM animals, and researchers are committed to designing experiments responsive to the residents' concerns[21]. Community members' ideas about risk mitigation have been incorporated into the design of the GM mice and choice of field trial sites.

Even when the particular GM insect is already beyond the design stages, as the transgenic Oxitec mosquito or transgenic Cornell moth were, community involvement in field-trial design might aid decisions about the location of collection boxes, inform scientists about topographical quirks, and help shape the timing of the experiment and data collection methods. Community members might also aid in the development of ERAs. This kind of information improves the experiment as it simultaneously encourages mutual engagement and builds trust. When researchers adopt an approach to field trials that mirrors 'citizen science', community members are seen as allies and even as members of the scientific team, rather than just a roadblock.

One way to operationalize mutual engagement is to create community advisory boards (CABs) for experiments involving field trials. CABs are commonly used in international clinical research to overcome cultural barriers between research teams and study populations[22]. The purpose of a

CAB is to bridge gaps in knowledge and to direct research and research-related practices consistent with participants' expectations and values.

Seek community authorization for field trials. Even after involving stakeholders and community members in developing ERAs, and seeking input from a CAB on site selection and other elements of the design of field trials, field trial sponsors ought to obtain community authorization before the release of GM insects. One reason that community authorization is ethically desirable is that informed consent is neither ethically required nor practically feasible[6]. There 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. Thus, rather than go door-to-door to seek consent from every person who lives in a particular area, investigators and sponsors should seek community authorization for their field trials.

This suggestion is rooted in a commitment to democratic self-control. At the heart of democracy is the idea that citizens exercise control over policies or actions that could affect their activities or lifestyles—this includes actions that would release GM insects into their airspace. Deliberative democracy is distinct from other types of democratic decision-making procedures because the decision must issue from deliberating and reasoning with community members about how to move forward. Participants in deliberative democratic forums are exposed to the views of other people, encouraged to consider others' views, and invited to assess the collective best interest in addition to being afforded the opportunity to advance and explain their own subjective preferences[23].

There remain obstacles to operationalizing community authorization. Ways to delineate affected communities and to design and test methods of eliciting community authorization are still evolving. Still, requiring community authorization for field trials is a way of respecting persons and ceding some control to community members over what happens in their backyards, to their pets, and on their children's playgrounds.

Conclusions

None of the three suggestions in this paper is new or radical. Yet, all three are underused and have not been incorporated into decision-making procedures regarding field trials of GM insects. Taken together, they may seem like too much, like another case of ethics 'getting in the way'. But it is clear from the case studies that US Food and Drug Administration or EPA approval for a field trial of GM insects means nothing without community support. Field trials of GM insects ought not founder simply because communities have been left out of discussions. Trust and cooperation among community members, stakeholders, and the public more generally are essential to the success of field trials, and thus essential to science itself.

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Rules of the road for insect gene drive research and testing

To the Editor:

Approximately two years ago, two of us (E.B. and V.G.) demonstrated the first experimental application of CRISPR–Cas9 to 'drive' a desired trait throughout a population of fruit flies[1]. In November 2015, this same team at the University of California, San Diego, joined with A.A.J. and others at the University of California, Irvine, to develop a CRISPR-based gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*[2]. A month later, a group in the United Kingdom applied a CRISPR-based gene drive to another malaria vector, *Anopheles gambiae*[3].

Many researchers around the world, including several additional authors of this Correspondence, are working to apply gene editing technologies, with the hope of safely and effectively engineering populations of insects and other pest arthropods in the wild, either to reduce diseases, such as malaria or dengue fever, or to control agricultural pests, such as those that transmit the bacterium that causes citrus greening disease. Important benefits could be realized if these research efforts are successful, but realizing these benefits requires sustained, open, and inclusive attention to potential environmental and social impacts, and regulatory and implementation challenges. Many of these challenges were outlined in the recent report by a committee convened by the US National Academy of Sciences, Engineering, and Medicine (NASEM) to review the science of gene drives and examine considerations for their responsible use[4].

In January 2016, the J. Craig Venter Institute (JCVI; La Jolla, CA, USA) and University of California, San Diego convened