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The NIH Office of Biotechnology Activities Site Visit Program: Observations About Institutional Oversight of Recombinant and Synthetic Nucleic Acid Molecule Research

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Abstract

Institutions that receive National Institutes of Health (NIH) funding for research involving recombinant or synthetic nucleic acid molecules are required, as a term and condition of their funding, to comply with the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) (*NIH, 2013*). Under the NIH Guidelines, institutions must establish and register an Institutional Biosafety Committee (IBC) with the NIH. The IBC is then responsible for reviewing and approving research projects subject to the NIH Guidelines. The IBC review of projects involving recombinant or synthetic nucleic acid molecules is critical to ensuring that such research is conducted in a safe and responsible manner.

In 2006, staff from NIH began conducting educational site visits to institutions that had an IBC registered with NIH. The purpose of these site visits is to assist IBCs with their institutional programs of oversight for recombinant or synthetic nucleic molecules. Based on our findings, the site visit program has been beneficial to institutional biosafety programs. The information gathered during the site visits has allowed NIH to tailor its educational materials to help institutions address their oversight challenges. Additionally, since NIH's visits are primarily educational in nature, we have been able to foster a positive environment in which IBC members and staff feel comfortable reaching out to NIH for advice and assistance.

Keywords

IBCs; NIH Guidelines; Recombinant DNA; Biosafety; Site Visit

Introduction

Since being introduced in 1976, the *NIH Guidelines* (and its subsequent revisions) have served as the national standard for the safe handling of recombinant and synthetic nucleic acid molecules used in research. The *NIH Guidelines* apply to research that is either sponsored by or conducted at an institution that receives NIH funding for recombinant or

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synthetic nucleic acid molecule research (NIH, 2013). As a term and condition of NIH funding, an institution receiving funding for recombinant or synthetic nucleic acid molecule research must establish and register an IBC with NIH. As of March 2015, approximately 900 IBCs were registered with NIH. NIH serves as a focal point for disseminating information on the safe conduct of research with recombinant or synthetic nucleic acid molecules and provides advice to institutions registered with our office about biosafety and how to effectively carry out their responsibilities under the *NIH Guidelines*.

Starting in 2006, NIH initiated a program of not-for-cause visits to institutions with an IBC registered with the NIH Office of Science Policy. The goal of this program is to proactively engage with IBCs and to make global observations about the performance of IBCs. The site visit program was also developed as a means to share information with the IBC community regarding best practices related to the oversight of research subject to the *NIH Guidelines*, as well identify the challenges that institutions are facing and discuss constructive solutions. As of March 2015, NIH staff has visited 107 IBCs. In selecting IBCs to visit, NIH has strived to achieve a geographical balance of institutions (Figure 1). NIH has also attempted to visit a cross-section representing the diverse types of registered institutions.

Methodology

The NIH site visit program consists of three components: the pre-visit review of program documentation, the onsite visit, and the post-visit report. Once NIH selects an institution to visit, the institution is given approximately 6 to 8 weeks advanced notice to prepare for the visit.

Pre-visit Documentation Review

Selected institutions receive a letter stating they have been chosen to participate in the NIH site visit program. The letter also asks the institution to provide some basic demographic information such as the scope of the research conducted at the institution (e.g., high-containment, human gene transfer, large-scale, etc.).

Also requested in the letter is a list of documentation that NIH asks to be provided in advance of the visit to familiarize the site visit team with the program and optimize the time onsite. Typically, NIH requests copies of:

- IBC meeting minutes from the last 2 years (in the same format that would be provided to a member of the public)
- IBC-approved emergency response plan
- Training materials to educate IBC members and investigators on their responsibilities under the *NIH Guidelines*
- Other documentation relevant to the program

The information provided by the institution is then reviewed by the site visit team before arriving onsite. The final element of the pre-visit review is organizing the onsite visit. A member of the NIH staff coordinates with the designated contact at the institution who then arranges the schedule for the day. Typically, the schedule consists of a day-long series of

interviews with the key program personnel and investigators conducting research subject to the *NIH Guidelines*.

Onsite Visit

The site visit begins with a short briefing with key institutional participants. During the in-briefing, NIH staff discusses the purpose of the site visit program and describes how the visit will proceed. The in-briefing is also used to answer any questions that the institutional participants have before the day begins. Throughout the day, NIH then conducts a series of interviews with key personnel involved in the institutional program for oversight of research subject to the *NIH Guidelines*. These include the biological safety officer (BSO) (or someone working in a similar capacity), the IBC chair, a senior research administration official, and the attending veterinarian (or a designee). The NIH team also requests to interview two to three principal investigators (PIs) who have active registrations with the IBC. These interviews, in conjunction with the material sent to NIH before the visit, help the site visit team understand how the program at the institution is functioning. Laboratory inspections are not a routine part of the visit since the primary focus of the visit is the institution's program of oversight for reviewing research involving recombinant or synthetic nucleic acid molecules.

Once the interviews are completed, an end-of-the-day debrief occurs. At that debriefing, the site visit team from NIH reviews some of its preliminary observations regarding the institution's program of recombinant and synthetic nucleic acid oversight. The observations are divided into three categories: positive practices, recommendations for enhancing the performance of the IBC, and identification of practices not in keeping with the *NIH Guidelines*.

Post-visit Report

Approximately 6 to 8 weeks after the site visit, the institution receives a written report detailing the observations of the site visit team. The report outlines the positive aspects of the institutional oversight system as well as suggestions for enhancing aspects of the oversight program. The report also describes any practices in the institutional oversight system that the site visit team has determined are not in keeping with the requirements of the *NIH Guidelines*. If such issues are identified, NIH provides the institution with a detailed description of what the *NIH Guidelines* specifically require, and how the issue should be addressed. NIH then works with the institution to ensure the issue is resolved in a timely manner.

Results

After performing over 100 site visits, NIH has been able to make a number of general observations about the performance of IBCs on a national level. NIH has noted several positive practices as well as some challenges and issues faced by the majority of institutions we visit. Below, we present some of the findings we have compiled throughout NIH's 8-year program of site visits.

Positive Practices

Standard operating procedures—In NIH's experience, institutions that have developed an IBC charter and standard operating procedures (SOPs) tend to be more effective in carrying out their responsibilities under the *NIH Guidelines* than institutions without these types of documents. Having a comprehensive charter and set of SOPs helps ensure that IBCs and others at the institution with biosafety responsibilities understand and correctly fulfill their duties. Additionally, well written SOPs are valuable training tools since they articulate clear performance expectations.

PI attendance at IBC meetings—Encouraging PIs to attend an IBC meeting to discuss their research is an effective way of enabling the IBC to gain a fuller understanding of the research being proposed. This is especially true if the research being proposed is novel or poses a unique biosafety concern. Encouraging PIs to attend an IBC meeting to discuss their research also helps elevate the visibility of the IBC and helps increase PI understanding of their responsibilities under the *NIH Guidelines*.

Rewarding IBC service—Acknowledging the value of the service of IBC members by members of the institution's higher administration is an effective way of signaling to the research community that the IBC is an important component of the institutional research oversight program. Institutions that we visited have employed a variety of mechanisms to acknowledge the service of IBC members. Most institutions consider service on the IBC as a component of institutional service when evaluating faculty for promotion and tenure. Other mechanisms include issuing annual certificates of appreciation or providing lunch for the members of the committee. In a small number of instances, institutions provide the IBC chair with fractional salary support in recognition of the investment of time required in this role.

Holding open IBC meetings—Section IV-B-2-a-(6) of the *NIH Guidelines* states: "When possible and consistent with the protection of privacy and proprietary interests, the institution is encouraged to open its IBC meetings to the public." (NIH, 2013). The *NIH Guidelines* were predicated on the notion that the system of oversight would be transparent. Institutions that openly advertise the time and place of their IBC meetings as well as allow the public to attend are fulfilling the spirit of the *NIH Guidelines* with respect to transparency. Transparency helps to promote public trust and support of the research enterprise by demonstrating that the institution is appropriately assessing and managing any risks posed by the research it is conducting.

Coordinating institutional oversight activities—Institutions that have a strong relationship among their IBC, Institutional Animal Care and Use Committee (IACUC), and Institutional Review Board (IRB) are far more likely to capture research subject to the *NIH Guidelines* than institutions that do not have a means of coordinating research oversight among these committees. Making the release of research funding by the institution's grants and contracts officer conditional on IBC approval is an additional checkpoint to ensure that all research subject to the *NIH Guidelines* is appropriately registered with the IBC for review and approval.

Suggestions for Improvement

NIH has observed a number of best practices that promote more effective and efficient programs of oversight. Many of the recommendations below describe the value of policies and procedures as a means of fostering compliance with various biosafety requirements of the *NIH Guidelines*. Many of the recommendations below highlight common areas where visited institutions needed improvement, and illustrate the value of policies and procedures.

Incident reporting—At many institutions, PI awareness of the incident reporting requirements of the *NIH Guidelines* is low. Incidents and accidents occurring during the conduct of research with recombinant or synthetic nucleic acid molecules as well as violations of the *NIH Guidelines*, such as failure to obtain IBC approval or failure to follow IBC approval conditions, must be reported to NIH within 30 calendar days. Incidents occurring under Biosafety Level 2 (BSL-2) conditions that result in an overt exposure to organisms containing recombinant or synthetic nucleic acid molecules must be reported to NIH immediately. Incidents occurring under BSL-3 or BSL-4 conditions that result in an overt or *potential* exposure to organisms containing recombinant or synthetic nucleic acid molecules also must be reported to NIH immediately. This information must be incorporated in the training provided to each PI and his or her laboratory staff so that each member of the research enterprise is aware of the unique reporting requirements.

Biohazardous waste policies—Although most of the institutions we visited have developed a policy for handling biohazardous waste, those policies often do not specifically define recombinant or synthetic nucleic acid molecules as a biohazard and therefore do not reinforce the applicability of the institution's biohazard waste disposal policies to this kind of research. We recommend that institutional biohazardous waste disposal SOPs clearly articulate procedures for the treatment and disposal of recombinant or synthetic nucleic acid containing waste (including transgenic animal and plant waste) that are in keeping with Appendix G, Appendix P, and Appendix Q of the *NIH Guidelines*.

Expiration of IBC-approved protocols—Some institutions do not have an expiration date attached to IBC-approved protocols. The *NIH Guidelines* task the IBC with periodically reviewing recombinant or synthetic nucleic acid molecule research. This can be accomplished by having each protocol approved for a specific timeframe with an expiration date; after that date has passed, a *de novo* review of the protocol is required. Many of the institutions approve protocols for a set length of time, and also require an annual update of the protocol whereby the PI must report yearly whether any changes to the active protocols have been made. Although the *NIH Guidelines* do not specify a specific approval timeframe, the typical length of protocol approval at the institutions that we visited ranged from 3 to 5 years. Human gene transfer protocol registrations are the exception; institutions sometimes review those *de novo* on a yearly basis.

Terms of IBC service—Some of the institutions that we visited do not have a fixed term of service for members on the IBC. We recommend that institutions include a term of IBC membership in their IBC Charter or SOPs in order to obtain fresh and diverse perspectives from other members of the institution's research community. Institutions that do have a

fixed term of membership usually allow members to serve anywhere from 1 to 3 years with an option to renew. In addition to having a fixed term of service, NIH recommends that IBC members are formally appointed by a senior research official at the institution.

Policies on handling public comments—Section IV-B-2-a-(7) of the *NIH Guidelines* states that if public comments are made on IBC actions, the institution shall forward both the public comments and the IBC's response to NIH. Although institutions are usually conscientious in responding to comments made by the public, many of the institutions we visited did not have a SOP for providing public comments and the institutional response to NIH. We recommend that institutions include this matter in their SOPs to ensure that comments from the public regarding the IBC's activities are handled appropriately and consistently.

Resources—In an era where many institutions are facing fiscal challenges, some institutions may be operating with a sub-optimal level of resources. While NIH does not specifically analyze which institutional activities could benefit from more resources, we do recommend that institutions conduct a thorough assessment of the resources necessary for it to fulfill all of the oversight responsibilities articulated in Section IV-B of the *NIH Guidelines*, taking into account not only the protocol review and approval process, but also all of the responsibilities of the institution, the IBC, and the BSO, including training, laboratory inspections, and other periodic research oversight, found under Sections IV-B-1 through IV-B-3.

Practices not in keeping with the *NIH Guidelines*

The site visit team has observed a number of issues at institutions that are not in keeping with the *NIH Guidelines* and, as such, require corrective action. NIH outreach staff work closely with the institutions so that the institutions fully understand what the *NIH Guidelines* specifically require. When an institution needs to address an issue, NIH works with the institution to ensure the issue is resolved in a timely manner. Many of the institutions we visited have been required to address at least one of the deficiencies presented below.

Content of IBC meeting minutes—NIH expects that IBCs adequately document fulfillment of their review and oversight responsibilities as articulated in Section IV-B-2-b of the *NIH Guidelines*. Many times, the IBC minutes provided to the site visit team do not contain sufficient information about the protocol. Additionally, the minutes have not included information such as the section of the *NIH Guidelines* that applies to the research being approved, details about the relevant biosafety discussions that IBC members had while reviewing the protocol, the PI's name, and the biosafety level under which the research is approved. Further information about the appropriate content of IBC meeting minutes and the level of detail they should contain may be found in the FAQs on IBC Meetings and Minutes that appears on the NIH website (NIH, 2014a).

Redaction of IBC meeting minutes—While most IBCs are diligent about fulfilling requests from the public for copies of IBC meeting minutes, we noted instances where the minutes provided are heavily redacted. In keeping with the *NIH Guidelines*, institutions may

redact certain information from their IBC minutes if there are privacy or proprietary concerns. However, NIH generally does not consider the identity of IBC members or investigators, or the names of the agents they are working with, to be private or proprietary considering the wide availability of this type of information from other sources, such as the investigator's website, the NIH RePORTER website (NIH, 2014c), and articles published by individual investigators in the scientific literature. Further guidance on the type of information we would expect to see in publicly available minutes are detailed in our FAQs on IBC Meetings and Minutes (NIH, 2014a).

Emergency response plans—Although many of the institutions that NIH visited have developed general laboratory emergency response procedures, these plans often do not specifically mention recombinant or synthetic nucleic acid molecules. Section IV-B-2-b-(6) of the *NIH Guidelines* (NIH, 2013) requires the development of IBC-approved emergency plans covering accidental spills and personnel contamination resulting from research subject to the *NIH Guidelines*. Although such plans are often specific to individual protocols, institutions should develop over-arching emergency plans related to the research subject to the *NIH Guidelines*. Individual laboratories may then tailor or further modify these plans to fit their specific circumstances. Furthermore, the emergency response plan should include details on what types of incidents are reportable to NIH and the specific timeframes in which these incidents need to be reported.

Review of protocols—Some institutions we visited are conducting so-called “expedited” or “delegated” reviews of research subject to the *NIH Guidelines*. This is a process by which one individual, or a group of individuals, is approving research on behalf of the IBC. All research subject to the *NIH Guidelines* must be reviewed at a convened meeting of the IBC with a quorum present. No one individual or group of individuals can be authorized to approve a protocol subject to the *NIH Guidelines* on behalf of the IBC. Similarly, we have also seen some institutions relying on email to conduct official IBC business. IBCs may not conduct formal business via email because email is not a real-time interaction and minutes cannot be kept of an email exchange. Furthermore, email exchanges are not publicly accessible. IBCs may meet either in person, over the telephone, through videoconference, or in any other real-time setting (e.g., Skype).

Training—At a number of the institutions that NIH visited, there has been a lack of training for investigators and laboratory staff specific to the requirements of the *NIH Guidelines*. Although the *NIH Guidelines* assign investigators the responsibility to train laboratory staff (Section IV-B-7-d-[2]), the institution must also “ensure appropriate training for...Principal Investigators (and laboratory staff) regarding laboratory safety and implementation of the *NIH Guidelines*” (Section IV-B-1-h) (NIH, 2013). To fulfill their responsibilities as articulated in the *NIH Guidelines*, institutions should develop mandatory training requirements to cover all investigators and laboratory research staff conducting research subject to the *NIH Guidelines* at the institution. Most of the institutions we visited have a general biosafety and bloodborne pathogen training program in place. In general, we strongly recommend that existing biosafety training materials give proportionately more attention to the content and requirements of the *NIH Guidelines*. Specific attention in

biosafety training materials to the roles and responsibilities of investigators and laboratory staff under the *NIH Guidelines* is fundamental to fostering a climate of awareness of, and compliance with, biosafety practices, including requirements that pertain specifically to research subject to the *NIH Guidelines*.

Discussion

The institutional oversight of recombinant and synthetic nucleic acid molecules has significantly improved over the last decade. Clearly, the NIH site visit program has played a large role in enhancing the performance of IBCs. In a 2010 survey of IBCs (Hackney et al., 2012), information on current trends in practices was solicited. The authors compared the 2010 data to similar surveys that they conducted in 2002 and 2007. The results of the 2010 survey showed that IBCs, as an aggregate group, have made significant strides since 2002 in staffing, training, transparency to the public, and overall compliance with the *NIH Guidelines* (Hackney et al., 2012). One of the major reasons cited for the improvement in IBC performance is the NIH site visit program. Of the institutions that responded to the survey, 80% stated that they believed the NIH site visit enhanced their programs of oversight for recombinant and synthetic nucleic acid molecule research. The results of the survey clearly show that institutions that have received site visits have a clearer understanding about the requirements of the *NIH Guidelines* than institutions that have not had a site visit and this has improved the functioning of their programs in keeping with the requirements of the *NIH Guidelines*. This can be attributed to the awareness-raising nature of the NIH site visit program. For example, 70% of respondents who had received a site visit have *NIH Guidelines*-specific PI training in place, whereas only 44% of institutions that have not had a site visit have similar training. Similarly, the survey found that 85% of institutions, with or without an affiliated hospital that had a site visit, have reported an incident to NIH, while only 25% of the non-site visited institutions reported an incident subject to the *NIH Guidelines*. NIH has interpreted these results to mean that although institutions that have and have not been site visited experience reportable incidents, institutions that have received a site visit are more aware of the reporting requirements than institutions that have not received a site visit and, hence, more likely to report the incident.

Another potential reason for the enhanced IBC compliance could be attributed to institutions utilizing the Institutional Biosafety Committee Self-Assessment Tool (Self-Assessment Tool) (NIH, 2014b). NIH developed the Self-Assessment Tool in 2009 and revised it in 2014. The aim of the tool was two-fold. First, NIH staff realized early on that they would not be able to conduct a site visit to all of the institutions with an IBC registered with our office (~900). The Self-Assessment Tool was created to allow institutions that have not had a site visit to assess their own programs in the same manner NIH would when onsite. The tool consists of 83 core questions relating to the requirements of the *NIH Guidelines* as well as best practices. The tool poses a question about the IBC program, lists the citation of the *NIH Guidelines* that is pertinent, and then provides NIH's guidance on how the requirement should be addressed by the IBC. It also contains NIH's recommendation on best practices for items not listed in the *NIH Guidelines* but nonetheless could be used to maximize the IBC's performance.

The second purpose of the Self-Assessment Tool was to allow IBCs to prepare for a site visit. Qualitatively speaking, institutions that have prepared for the visit in advance by studying the Self-Assessment Tool tend to have better outcomes than institutions that have not.

The Self-Assessment Tool will continue to evolve as changes to the *NIH Guidelines* are made. A copy of the tool can be found on the NIH website (NIH, 2014b).

Conclusions

Since the introduction of the site visit program in 2006, NIH has witnessed dramatic improvement in the performance of institutional biosafety programs subject to the *NIH Guidelines*. This improvement can be attributed, among other things, to the NIH site visit program and the NIH Self-Assessment Tool. Other contributing factors to the improved compliance could also be attributed to the outreach efforts of the NIH staff. The increased presence of NIH at national and local conferences and regional training events, combined with NIH's dedication to assisting IBCs by issuing guidance materials and other training materials, has made NIH readily accessible to its stakeholders. NIH will continue with its site visit program for the foreseeable future and will continue to update the Self-Assessment Tool when needed in order to clearly communicate the most up-to-date and timely information.

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Figure 1.
Number of NIH Site Visits Conducted by State