# IBCs – A cornerstone of public trust in research

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*Kathryn L. Harris, Ryan Bayha, Jacqueline Corrigan-Curay and Carrie D. Wolinetz*

## Chapter Outline



## Introduction

Recombinant DNA has been a transformative technology, providing tools that not only have enabled tremendous understanding of life at the most fundamental levels, but that have also led to a myriad of medical and agricultural applications. Progress in recombinant DNA research continues to revolutionize approaches to life science research and biotechnology and has been possible because scientists taking the lead in developing this technology had the foresight to recognize that the promise of

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recombinant DNA could only be realized if they assumed responsibility for addressing the safety and ethical concerns that it raised.

The current system of oversight of recombinant DNA research was established almost 40 years ago when the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*) were first written [1]. At the federal level, the *NIH Guidelines* were initially administered by the Office of Recombinant DNA Activities (ORDA) that later became the Office of Biotechnology Activities (OBA) within the Office of Science Policy.

The *NIH Guidelines* outline the requirements for local oversight, including the establishment of an institutional oversight committee. The first *NIH Guidelines* articulated the requirements for "Institutional Biohazards Committees" that were later renamed "Institutional Biosafety Committees" (IBCs) to more clearly reflect their role. IBCs must review recombinant and synthetic nucleic acid molecule research for conformity with the *NIH Guidelines*. In addition, they assess the research for potential risks to health and the environment. This is accomplished by reviewing physical and biological containment for the research and ensuring that researchers are adequately trained to conduct the research they are proposing safely.

The hallmarks of this oversight system from its inception were public participation and transparency. Attention to the concerns of the community and local interests is a major theme that carries forward in the system of biosafety oversight today. This key element has served to preserve public trust in the safety of the life sciences research enterprise. In retrospect, the risks of recombinant DNA technology that were feared early in its evolution did not materialize. That fact notwithstanding, the development of a scientifically based oversight system with the IBCs as the centerpiece permitted the safe development of recombinant DNA as an essential technology in research. Over the years, oversight by IBCs has proven critically important to ensuring safety throughout various research fields – medical, occupational, environmental – as well as in promoting responsible scientific practice. Due to the dynamic nature of the life sciences there remains an ongoing need to assess biosafety dimensions of the research being conducted and to manage any risks associated with work. As life sciences research continues to advance, many lines of research, particularly involving highly pathogenic organisms, continue to generate public concern. Financial support for life sciences research comes primarily from publicly derived tax dollars, and so the life sciences community must demonstrate to the public that it is being a responsible steward of those funds. IBCs today remain critically important in preserving public trust and thus facilitating continued scientific progress. The National Institutes of Health (NIH) and the institutions it funds must continue to ensure that IBCs are equipped to fulfill their responsibilities so that biosafety risks are responsibly managed and public safety and trust are preserved.

## Evolution of an oversight framework – Asilomar and beyond

The landmark Asilomar Conference of 1975, involving leading scientists from a variety of disciplines, launched the development of what was to become an enduring

system of institutional and federal oversight for research utilizing recombinant DNA technology guided by the NIH [2]. With the advent of recombinant DNA techniques in the early 1970s, a debate arose in the scientific community regarding the potential health and environmental risks of genetically manipulated organisms. The public also became involved in this debate. The concern about the dangers of emerging recombinant DNA technologies led to the scientific community calling for an unprecedented voluntary moratorium on certain experiments with recombinant DNA until the risks could be further characterized and procedures developed to minimize those risks. Scientists called for the formation of a national oversight body to ensure public discussion and ongoing oversight of this emerging technology [3]. One of the outcomes of this process was the formation of the National Institutes of Health Recombinant DNA Molecule Program Advisory Committee, subsequently renamed the Recombinant DNA Advisory Committee (RAC), a Federal advisory committee that was tasked with developing the first recombinant DNA research guidelines, formalized in the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*).

In the mid-1970s, recombinant DNA was a nascent and poorly understood technology, but was emerging as an important tool for conducting biomedical research. The public was apprehensive about this novel technology, related to the potential impact on the environment and public health, as well as a host of ethical and social issues due to its capacity to modify the molecular centerpiece of life. The debate over safety captured congressional attention, resulting in over a dozen legislative proposals that would have statutorily imposed a number of restrictions on the development and use of this technology [4]. A number of local jurisdictions were also considering similar ordinances that would have precluded the use of recombinant DNA altogether. Most notable among these was the city of Cambridge, Massachusetts, that in 1977 became the first jurisdiction in the United States to directly regulate basic scientific research using recombinant DNA [5]. The Cambridge Recombinant DNA Technology Ordinance also established strict oversight of university and commercial laboratories that engaged in recombinant DNA research. The requirements set forth in that city ordinance were based on the *NIH Guidelines* and the Cambridge Biosafety Committee carried out enforcement. The Committee, staffed by the Cambridge Public Health Department, is comprised of Cambridge residents and still operates to this day.

## The *NIH Guidelines* as a dynamic oversight framework

The initial version of the *NIH Guidelines* [6] was drafted by the RAC a year after the Asilomar Conference. Unlike the statutes being contemplated, the *NIH Guidelines* were intended to be a "living" document detailing required biosafety practices for institutions and investigators to follow, consonant with current scientific understanding. By design the *NIH Guidelines* is a dynamic document that maintains its relevance by evolving along with science and technology and it has undergone multiple revisions since 1976. In 1978, almost immediately after the completion of the first iteration of the *NIH Guidelines*, the then-Department of Health, Education,

and Welfare (now the Department of Health and Human Services) held a national conference to take a fresh look at the state of our understanding of risks posed by recombinant DNA technology. Up to that time, the RAC had reviewed every single recombinant DNA protocol that was conducted. NIH decided that RAC review of all protocols, as well as other restrictions on the field of research outlined in the first iteration of the *NIH Guidelines*, were no longer necessary. Instead, the transparency provisions of the oversight system and public access to the institutional review processes were enhanced, substituting for the diminished role of the RAC in protocol reviews. Toward that end, several revisions were made to the *NIH Guidelines* including significantly increased public access to information about recombinant DNA research activities and public participation in the administration of the *NIH Guidelines* in local communities. The *NIH Guidelines* originally required that no less than 20% of the IBC would be comprised of members who had no affiliation with the institution and were in a position to represent community interests. The changes to the *NIH Guidelines* eliminated the "no less than 20%" clause and instead, required there be at least two IBC members who had no affiliation with the institution and were in a position to represent community interests. Furthermore, important records of the IBC, including minutes, memoranda of understanding and agreement, registration documents, and other materials submitted to the Federal government had to be made available to the public upon request.

In the early 1980s, many observers of the field of recombinant DNA research were prescient enough to foresee its eventual application to humans. Among these were a coalition of religious leaders who asked then President Reagan's Commission for the Study of Ethical Problems in Biomedical and Behavioral Research – a group set up to look at the ethics of human subjects research – to undertake the special topic of genetic engineering with humans [7]. The result of that analysis was the report "Splicing Life: The Social and Ethical Issues of Genetic Engineering with Human Beings (1982)." This report was conveyed to the RAC for its consideration, which led the RAC to recommend a number of changes to the *NIH Guidelines* that went into effect in April 1984. These included giving IBCs the formal mandate to review and approve human gene transfer (HGT) research. Subsequently in 1986, a document titled "Points to Consider in the Design and Submission of Gene Therapy Trials to the NIH" was developed by the RAC, and incorporated into the *NIH Guidelines* as Appendix M. It outlined for IBCs the kinds of matters they were expected to evaluate when reviewing proposals for the administration of recombinant DNA to human subjects in clinical trials at a time of substantial advances in HGT, coincident with the first gene transfer trial being approved by the NIH Director in 1989.

In the mid-1990s, the United States Department of Agriculture (USDA) had a RAC-like body known as the Agricultural Biotechnology Research Advisory Committee (ABRAC), which was in the process of developing containment guidelines for agricultural research taking place outside the context of the laboratory – such as in greenhouses and large animal facilities. The NIH, in consultation with the Federal *ex-officio* members of the RAC, determined that it would make more sense to consolidate all of the requirements concerning the containment of recombinant DNA

into the *NIH Guidelines*. Consequently, the USDA guidelines were incorporated into the *NIH Guidelines* as Appendices P (for plants) and Q (for animals). The addition of these appendices also included modifications to the IBC's membership requirements to ensure that appropriate expertise existed on the IBC when the institution was conducting this type of research.

The mid-1990s also proved to be a time of introspection for the NIH with regard to recombinant DNA oversight, especially in the realm of HGT research, which had become the leading matter brought before the RAC. The NIH director at the time called for a thorough analysis of the investment that NIH was making in the field of HGT research, and the optimal mechanisms for NIH oversight of the field. This was accomplished through the efforts of two committees: The Orkin-Motulsky Committee looked at the question of NIH's investment in the field and concluded that, while the field still had great promise, progress was hampered by gaps in scientific knowledge, and the Committee urged the NIH to fund proportionately more basic research to build a stronger scientific foundation that would inform clinical science [8]; the Verma Committee looked at optimizing the value of the RAC and concluded that it was not necessary for the RAC to publicly review every protocol submitted to the NIH, nor was it necessary for NIH to approve every protocol. IBCs and other bodies such as the Institutional Review Boards (IRBs) and the Food and Drug Administration (FDA) had approval authority, and the RAC process could be of optimal value as a means of informing the deliberations of these other groups. Consequently, they recommended that the RAC only review in public those protocols that raise special or novel scientific, safety, or ethical issues [9]. The recommendations of the Verma Committee were embodied in the October 1997 revisions to the *NIH Guidelines* and eliminated the need for the NIH to approve each HGT trial.

The *NIH Guidelines* have continued to be updated since 1997 to address various issues in both HGT and basic laboratory research. The last major change to the *NIH Guidelines* occurred in 2012 when they were amended to specifically cover certain basic and clinical research with nucleic acid molecules created solely by synthetic means. At the time, it was likely that most research with synthetic nucleic acids also involved the use of recombinant techniques and thus was already covered by the *NIH Guidelines*. However, this change was designed to be forward-looking, recognizing that new technologies can rapidly expand. The amendment to the *NIH Guidelines* also made it clear that the focus of biosafety review for new genetic constructs should focus on the product, not the technique used to produce it. Reflecting this change, the name of the *NIH Guidelines* was changed to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules.*

The *NIH Guidelines* will never be complete as it is impossible to foresee all future advances in science. It is therefore important that all who are involved in both the conduct and the oversight of research adhere not only to the specifics of the *NIH Guidelines*, but also to the intent and spirit of the document. The dynamic nature of the *NIH Guidelines* has served to promote comprehensive oversight of a field that is continually advancing in a much more flexible manner than a statutory framework could, while permitting the science to proceed in a safe and responsible manner.

## The NIH Guidelines today

Currently, the *NIH Guidelines* apply to research that is conducted at or sponsored by institutions receiving NIH funding for recombinant or synthetic nucleic acid molecule research. However, the *NIH Guidelines* have a "reach-through" provision. If an institution receives any NIH funding for projects involving recombinant or synthetic nucleic acid molecules, then all research involving recombinant or synthetic nucleic acid molecules conducted at or sponsored by the institution – even those that are not NIH-funded – become subject to the requirements of the *NIH Guidelines*. The logic for the broad applicability of the *NIH Guidelines* is that, to be effective, the same system of oversight has to be observed by all researchers at a given institution. Thus, the *NIH Guidelines* have become the universal standard for safe, scientific practice in recombinant and synthetic nucleic acid molecule research. As such, many private entities, federal agencies, and other institutions also follow the *NIH Guidelines* voluntarily even though they are not otherwise subject to its requirements.

The *NIH Guidelines* are termed "guidelines" because they establish principles and basic safety practices. The document articulates performance standards without being unduly prescriptive. The title of the document is not meant to convey, however, that the *NIH Guidelines* are optional. The requirement to abide by the *NIH Guidelines* is a term and condition of NIH funding for research that is subject to their scope. Noncompliance with the *NIH Guidelines* could result in suspension or termination of NIH funds for research with recombinant or synthetic nucleic acid molecules, or the requirement to have all the projects subject to the *NIH Guidelines* at the institution receive prior NIH approval. At the same time, the *NIH Guidelines* permit a great deal of flexibility, particularly in implementation of the administrative aspects of research oversight. This enables institutions to tailor their programs to meet specific needs. It is the responsibility of institutions to establish and implement policies for the safe conduct of research subject to the *NIH Guidelines*. A key part of this responsibility is the establishment of an IBC.

## IBCs as the linchpin in our framework of biosafety oversight

Receipt of NIH funding for recombinant or synthetic nucleic acid molecule research comes with a requirement that the institution establish an IBC. The IBC must be composed of at least five individuals who collectively have the appropriate expertise to be able to review the research conducted at the institution (including plant or animal biosafety experts if applicable). In addition to their scientific expertise, members of the IBC should have knowledge of biosafety and physical containment principles, and have an understanding of the institution's safety policies. The institution must appoint a Biological Safety Officer (BSO), who serves on the IBC if the institution is conducting any high containment recombinant or synthetic nucleic acid research (i.e. at Biosafety Level 3 or 4) or any large-scale research (i.e. the use of cultures of greater than ten

liters aggregate volume). At least two members of the IBC must not be affiliated with the institution and represent community interests. The requirement for two nonaffiliated members derives from the core principles of the NIH system of oversight – that IBC review and oversight be transparent and involve public participation.

## Current scope of responsibilities

Under the *NIH Guidelines*, IBCs are responsible for local oversight of recombinant and synthetic nucleic acid molecule research (although their responsibilities need not be restricted to such research), and review proposed experiments to ensure that they are conducted in a manner consistent with the biosafety practices outlined in the *NIH Guidelines*. With respect to HGT trials, the IBCs have additional responsibilities (under Appendix M of the *NIH Guidelines*) for reviewing these protocols to ensure the safe and proper design of this research, including the analysis of adverse event reports and findings from animal studies germane to the design and conduct of human studies. Accordingly, specific IBC responsibilities articulated in the *NIH Guidelines* include:

- Reviewing research conducted at or sponsored by the institution for compliance with the *NIH Guidelines*. Such review requires different levels of evaluation depending on the nature of the work.
- Helping investigators determine the appropriate containment conditions in which to conduct their research. IBC recommendations are guided by one of several appendices in the *NIH Guidelines* that specify safety and containment practices for the various forms of research subject to the document.
- Assessing the adequacy of facilities, institutional procedures and practices, and investigator training and expertise for the type(s) of research being conducted.
- Periodically reviewing research conducted at the institution to ensure ongoing compliance.
- Adopting emergency plans covering accidental spills and personnel contamination resulting from research activities.
- Reporting any significant problems with or violations of regulations and any significant research-related accidents or illnesses to the appropriate institutional official and relevant federal entities.
- Ensuring investigators and laboratory staff are adequately trained to conduct all proposed work safely.

## Importance of partnerships for promoting IBC excellence

It is incumbent upon both federal funders of research and the institutions that conduct the work to ensure that IBCs are well positioned to serve their pivotal role in upholding biosafety standards and practices, thereby sustaining public trust in the life sciences research enterprise. At the institutional level, this means having robust, well-run biological safety programs. The heart of these programs is the IBC. Supporting IBCs and promoting the importance of biosafety from the level of individual researchers

all the way to senior levels of institutional administration is a shared responsibility of the NIH and the research community who must work together toward ensuring the optimal functioning of IBCs.

## NIH's role in supporting IBCs

The NIH has made it a priority to develop a program of outreach and education that is multifaceted and uses multiple modalities to communicate with IBCs and other elements of the institutional infrastructure with key responsibilities in upholding the biosafety principles and practices of the *NIH Guidelines*. NIH's outreach program is extensive and includes giving presentations and briefings at major national and regional scientific conferences, and professional development meetings of key stakeholder groups on compliance with the *NIH Guidelines*. Outreach staff develop and conduct individualized workshops and training sessions to educate about the NIH system of oversight of recombinant and synthetic nucleic acid molecule research under the *NIH Guidelines*. Target audiences include investigators, IBC members and staff, BSOs, industry representatives, and institutional compliance officials. Of particular note are the NIH-developed and -supported national training courses: "IBC Basics" and "Effective IBCs" that provide in-depth information on establishing and running an effective and compliant IBC program. In addition, NIH also hosts the IBC professional development conference series, a biannual event that is the only national professional development forum for members and staff of IBCs. NIH has also developed an array of electronic and printed educational materials including training presentations which institutions can tailor to their own needs, sets of Frequently Asked Questions, biosafety guidance tools on many topics of interest to institutions subject to the *NIH Guidelines*, brochures on investigator responsibilities, and posters to promote awareness of biosafety and biosecurity policies.

## The NIH IBC site visit program

In November 2006, NIH launched the IBC site visit program [10]. The program is an essential element of NIH's outreach activities since it offers a tailored and interactive experience, providing a forum for institutions to ask questions about the *NIH Guidelines* and enabling them to make informed enhancements to their IBC programs to incorporate best practices and remedy any deficiencies. To date, NIH has visited a diverse set of over 100 institutions including universities, medical schools, research institutes, and commercial entities that conduct varied types of research programs, with a range of emphasis from basic biomedical or agricultural programs to clinical research. In addition to helping institutions improve their programs in the immediate term, this program aims to assist the IBC community in the longer term by:

- identifying common challenges facing institutions for the purpose of customizing NIH educational programs to assist institutions in overcoming them;

- developing a body of best practices that institutions may consider, as appropriate, to optimize the functioning of their own programs; and
- creating a self-evaluation tool that institutions can use to assess and improve their IBC programs.

## Lessons learned from the site visit program

One of the major goals of the site visit program was to develop a body of information that could be shared with the IBC community with an eye towards enhancing IBC function. A number of common features and practices have been observed at institutions that have particularly well-run and effective programs:

- **Charter and standard operating procedures (SOPs)**
  An IBC charter and well-written SOPs can foster the development of a consistently well-run and compliant biosafety program. These documents define the authority of the IBC, outline its operating and review practices, describe protocol registration requirements that investigators must follow, and keep IBC members and investigators alike informed of the biosafety standards and review requirements that must be observed at the institution.
- **Mechanisms for ongoing review and oversight of research**
  The IBC is not simply responsible for approving research, but also for ensuring the ongoing safe conduct of that research. Under the *NIH Guidelines*, the IBC must conduct "periodic" review of research involving recombinant DNA. The *NIH Guidelines* do not prescribe the frequency of review, because the nature and biosafety profile of research involving recombinant DNA is extremely diverse, and the IBC must make its own judgments about the appropriate frequency with which to revisit ongoing work.
- **Robust training programs for IBC members, investigators and laboratory staff**
  The *NIH Guidelines* place a great deal of emphasis on training and education. Institutions are responsible for ensuring the training of everyone involved in the conduct or oversight of recombinant DNA research and conducting training is also a responsibility of BSOs and PIs. A clear understanding of the biosafety practices and individual responsibilities articulated in the *NIH Guidelines* is pivotal to an effective biosafety program.
- **Records of IBC activities**
  Committee minutes are critically important for a number of reasons. First, they create institutional memory and create a record of Committee decision-making that, in turn, fosters consistency in research reviews. Second, they document the IBC's fulfillment of its responsibilities under the *NIH Guidelines*. Finally, as part of the transparency fostered by the *NIH Guidelines*, IBCs must make their meeting minutes available to the public upon request, providing an important view into institutional safety practices.

## Impact of the site visit program

Since its inception, there is strong evidence that the NIH site visit program has enhanced the effectiveness of institutional biosafety programs. Hackney et al. [11] presented the results of a 2010 survey conducted to examine trends in IBC practices. The authors compared their results to similar surveys that they conducted in 2002 and 2007. The

results of the 2010 survey showed that IBCs have made significant improvements since 2002 in levels of staffing support, conducing training, and increasing transparency to the public and overall compliance with the *NIH Guidelines*. A primary reason cited by the authors 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 the institutions' oversight of recombinant and synthetic nucleic acid molecule research. The results of the survey also showed that institutions that have undergone site visits were better poised to effectively carry out their responsibilities under the *NIH Guidelines* than institutions that have not had a site visit. This can be attributed to the awareness-raising nature of the NIH site visit program. For example, the survey found that 85% of institutions that had a site visit have reported an incident involving a significant problem, violation of the *NIH Guidelines*, or a significant research-related accident or illness to NIH, while only 25% of the non-site-visited institutions had reported such incidents as required by the *NIH Guidelines*. Similarly, 70% of respondents who had received a site visit have PI training in place, whereas only 44% of institutions that have not had a site visit have similar training. The NIH has noted that incident reporting compliance increases after a site visit because the importance of incident reporting is strongly emphasized during the site visits.

Enhanced institutional compliance with the requirements of the *NIH Guidelines* may also be attributed to institutions utilizing the *Institutional Biosafety Committee Self-Assessment Tool* [12]. NIH first issued the Self-Assessment Tool in 2009, and revised the tool in 2014. The aim of the tool was twofold. First, it was quickly realized that NIH would not be able to perform a site visit to all of the registered IBCs (~890 in 2014). The Self-Assessment Tool was created to encourage institutions to assess their own programs using the same performance indicators as NIH does during a visit. The tool consists of 83 core questions relating to specific requirements of the *NIH Guidelines*. The tool poses a question, 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 institution. The tool also contains NIH's recommendations on a number of best practices not specifically articulated as requirements in the *NIH Guidelines* but nonetheless could enhance the effectiveness of the IBC.

## Institutional roles in supporting IBCs

The *NIH Guidelines* articulate a number of responsibilities for institutions conducting research subject to the scope of the document, including the establishment and implementation of policies that provide for the safe conduct of the research. To effectively carry out their functions, it is essential that IBCs receive the full support and collaboration of senior institutional officials. IBCs must have the authority to fulfill their responsibilities properly. IBCs not only approve research, but also may reject proposed activities or shut down ongoing research if there are concerns about an activity meeting the biosafety standards articulated in the *NIH Guidelines*. IBCs must have the backing of senior institutional administration if they are to exert this authority meaningfully.

IBCs need to be sufficiently staffed and resourced to properly fulfill their responsibilities. One benchmark is to consider the number of protocols reviewed annually by the IRB, Institutional Animal Care and Use Committee (IACUC) and IBC, and consider whether the resources accorded each committee are in proportion to their respective workloads. In addition to the IBC's protocol review and approval responsibilities, IBCs and biosafety program staff should conduct training, laboratory inspections, and ongoing oversight of research. As research portfolios expand, institutions should also periodically conduct thorough assessments of the resources necessary for their programs to effectively fulfill the roles and responsibilities articulated in the *NIH Guidelines*, taking into account all of the responsibilities of the institution, the IBC and the biosafety staff. The NIH will continue to provide outreach and education resources to assist institutions, but encourages all institutions to take a rigorous and ongoing examination of their IBC programs.

## The future face of IBCs

### *The changing research landscape and emerging life science technologies*

Although many of the fears about the impact of recombinant DNA technology did not come to pass, many aspects of life sciences research continue to warrant review and oversight. The pace at which scientists can bring about changes in biological systems is ever-increasing. Experiments that took weeks or months to complete only a few years ago can now be performed in days or even hours. At the same time, there is increasingly more interdisciplinary research being conducted, with life science technologies being employed in areas such as material science and chemical engineering. Synthetic biology is a prime example combining methods, principles and knowledge from disciplines including biology, engineering, mathematics and computational science. Thus, IBCs will almost certainly be faced with reviewing increasingly more novel protocols in the interdisciplinary realm.

In addition to conducting risk assessments, an important responsibility of IBCs is to ensure that those conducting the research have the experience and training to conduct the research safely. It is likely that some scientists educated in fields other than traditional life sciences disciplines may not have had comprehensive biosafety training and may be unfamiliar with potential risks and how best to manage them. In such instances it will be particularly important that IBCs ensure that the risks of the research are evaluated as rigorously as possible and that all researchers involved have been appropriately trained.

### *Genome editing technologies*

Scientists have recently developed several new genetic engineering tools, including genome editing technologies such as CRISPR [13], TALENS and zinc finger nucleases. Such new tools and capabilities may transform biological research, further benefiting

human heath, agriculture, industry and the environment. While many of these new technologies may pose minimal biosafety risk, emerging technologies can raise uncertainties about their environmental safety and effects on human health and it is incumbent on those conducting and overseeing such research to ensure that potential risks are evaluated and managed as necessary. Data-driven risk assessments and commensurate oversight are key to demonstrating that the life science community continues to uphold a culture of responsibility in ensuring that science proceeds safely.

## *HGT research*

In 2012, the NIH was asked by the American Society for Gene and Cell Therapy, the professional organization of scientists who conduct HGT research, to review the role of the RAC to determine whether in-depth individual reviews of every HGT protocol were still warranted given the state of the science after many years of conducting such trials, and whether the scientific, safety, ethical, and other concerns continue to justify a special level of oversight for this area of research. A review was then carried out as part of NIH's ongoing evaluation of its oversight framework for gene transfer and recombinant DNA research. In 2013, the NIH Director commissioned the Institute of Medicine (IOM) to establish an independent committee to specifically look at the question of whether HGT research raises issues of concern that warrant extra oversight by the RAC in the form of the review of individual clinical protocols and, that if such oversight was warranted, to recommend criteria to guide when the RAC should review this research.

In the report "Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee" [14], the IOM committee concluded that although gene transfer research continues to raise important scientific, social and ethical questions, not all gene transfer research is novel enough or controversial enough to justify the current forms of additional oversight at the national level. The committee also recommended that all individual protocols should continue to be registered with the NIH, but these protocols should not be subject to public review by the RAC except in exceptional circumstances. More specifically, the IOM recommended that individual gene transfer protocol reviews by the RAC be restricted to situations where protocol review could not be adequately performed by other regulatory and oversight processes (for example, IBCs and IRBs). The IOM report stated that all protocols should continue to be registered with NIH and that review of adverse events on protocols should continue as the evaluation of trends may lead to greater awareness of safety concerns.

The NIH carefully considered and accepted the IOM recommendations on RAC review of HGT research [15]. If the IOM recommendations are implemented, protocols will continue to be registered with the NIH, but in-depth, public RAC review of individual gene transfer protocols will be limited to exceptional cases, such as when IBCs and other oversight bodies may need assistance in reviewing exceptionally novel protocols. The NIH will likely continue to provide key information on protocols, including the evolution of their design and details on the products used, to augment institutional review bodies' resources.

## Research on highly pathogenic agents

Infectious diseases are a significant cause of mortality and morbidity. Diarrheal diseases, malaria, tuberculosis and influenza exact a huge toll on human health [16]. In addition, exotic pathogens associated with high morbidity and mortality in humans frequently emerge – a recent example being the highly lethal Middle East respiratory syndrome coronavirus that emerged in 2012. At the NIH, the National Institute of Allergy and Infectious Diseases (NIAID) research portfolio has expanded considerably in recent years in response to new challenges such as biodefense and emerging and re-emerging infectious diseases. While research on pathogenic diseases is vitally important to the design of appropriate medical countermeasures against them in the form of diagnostics, therapies and vaccines, such research, particularly work conducted in high and maximum containment laboratories, has been frequently scrutinized in terms of the potential risks posed to the public from laboratory accidents or intentional misuse [17].

The *NIH Guidelines* require that IBCs are established specifically for the review of research involving recombinant and synthetic nucleic acid molecules, and IBCs have the responsibility to ensure that such research activities are performed with appropriate biosafety precautions. However, because of their expertise, many institutions have assigned these committees additional authority, which may include the oversight of research involving other biohazardous materials, such as non-recombinant infectious agents. Other guidance documents, such as the CDC/NIH publication *Biosafety in Microbiological and Biomedical Laboratories (BMBL)* [18], suggest that IBCs should have a broader purview to determine the appropriate biosafety levels for experiments with pathogenic agents. Surveys of IBCs [11] indicate that the vast majority of IBCs do in fact have a broader purview than that assigned to them specifically under the *NIH Guidelines*. Many academic institutions are investing in high-containment laboratory facilities and as research portfolios expand into the arena of highly pathogenic diseases it will become ever more important that IBCs are poised to ensure the research is conducted as safely as possible with well-trained research staff using robust standard operating procedures in well-maintained facilities.

## Oversight of dual use research of concern

Life sciences research is vital to improving public health, agriculture and the environment, and to strengthening our national security and economy. Yet the very research designed to find ways to better the health, welfare and safety of humankind can also yield information or technologies that could potentially be misused for harmful purposes. For instance, information from certain life sciences research could be misapplied to weaponize dangerous pathogens, to bypass or diminish the effectiveness of medical countermeasures, or to threaten in other ways the health and safety of humans, animals, plants and the environment.

Research yielding new technologies or information with the potential for both benevolent and malevolent applications is referred to as “dual use research.” The dual

use potential of certain life sciences research has been recognized as an important biosecurity issue for a number of years. Some degree of dual use potential may be inherent in a significant portion of life sciences research. However, the small subset of life sciences research with the highest potential for yielding knowledge, products or technology that could be misapplied to threaten public health or national security is referred to as "dual use research of concern." The US Government (USG) has defined "dual use research of concern" as:

> *Life Sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security.*

It is vitally important that researchers and their institutions are vigilant with respect to the dual use potential of life sciences research that they carry out.

In September 2014, the USG issued a *Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern* [19]. The policy requires research institutions to establish a process for identifying dual use research of concern and articulates and formalizes the roles and responsibilities of institutions and investigators when they are conducting research supported by the Federal government that falls under the scope of the policy, with the aim of preserving the benefits of life sciences research while minimizing the risk that the knowledge, information, products or technologies generated by such research could be used in a manner that results in harm. Institutions subject to the policy are required to establish and implement internal policies and practices that provide for the identification and effective oversight of dual use research of concern. A key responsibility is the establishment of an Institutional Review Entity (IRE) to execute the requirements of the policy. While the policy states that "a range of mechanisms for fulfilling the role of an IRE are acceptable as long as the review entity is appropriately constituted and authorized by the institution to conduct the dual use review," it is likely, that in many instances, institutions will choose to utilize their IBCs to perform the functions of the IRE. The NIH and the other Federal government agencies that conduct or support life sciences research, have developed a number of resources to assist IREs in their review of research that is potentially dual use research of concern.

## Conclusion

In 2015, 40 years after Asilomar, IBCs continue to play a relevant and vital role in the life sciences oversight system and have proven to be a key component in the biosafety management of research activities. Today, our understanding of recombinant DNA technology and its attendant risks is far greater, and although many of the initial fears about the technology have turned out to be unfounded, there remains the need to be vigilant over many aspects of the research enterprise. Capabilities in the life sciences

have advanced rapidly in the past four decades and our capacity to manipulate organisms is likely to continue to advance at a similar, if not accelerating, pace for the foreseeable future.

The scientific community has long demonstrated a culture of responsibility in ensuring the safety of researchers, the public and the environment, but must also remain cognizant of the potential risks of emerging technologies and manage them accordingly. The public continues to be pointedly concerned about many aspects of life sciences research, especially in the context of human studies and research involving infectious agents. While the public continues to support biomedical research, its trust in the endeavor may be fragile. The IBCs have been central to a transparent demonstration of the ability of the scientific community to serve as responsible stewards of publicly funded research, and in helping to earn and preserve the trust placed in it.

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## References

[1] NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. 2013.
[2] Berg P, Baltimore D, Brenner S, Roblin R, Singer MF. Asilomar conference on recombinant DNA molecules. Science 1975;188(4192):991–4.
[3] Berg P, Baltimore D, Boyer HW, Cohen SN, Davis RW, Hogness DS, et al. Potential hazards of recombinant DNA molecules. Science 1974;185(4148):303.
[4] Talbot B. Development of the National Institutes of Health Guidelines for recombinant DNA research. Public Health Rep 1983;98(4):361–8.
[5] Lipson S. The cambridge model. Gene Watch 2003;15(5):7–10.
[6] Recombinant DNA Research-Guidelines. Fed Reg 1976;41 (131, pt. II): 27902–27943.
[7] President's commission for the study of ethical problems in medicine and biomedical and behavioral research. Splicing Life: a report on the social and ethical issues in genetic engineering with human beings. 1982.
[8] Orkin SH, Motulsky AG. Report and recommendations of the panel to assess the NIH Investment in research on gene therapy. 1995.
[9] Ad Hoc Review Committee-Recombinant DNA Advisory Committee. Verma Report: Executive summary of findings and recommendations. National Institutes of Health; 1995. Available from: <http://osp.od.nih.gov/office-biotechnology-activities/verma-report>.
[10] Bayha R, Harris KL, Shipp AC, Corrigan-Curay J, Wolinetz CD. The NIH office of biotechnology activities site visit program: Observations about institutional oversight of recombinant and synthetic nucleic acid molecule research. Application of Biosafety 2015;20(2):75–80.
[11] Hackney RW, Myatt TA, Gilbert KM, Caruso RR, Simon SL. Current trends in Institutional biosafety committee practices. Application of Biosafety 2011;17(1):11–14.
[12] Institutional Biosafety Committee Self-Assessment Tool. National Institutes of Health; 2014. Available from: <http://osp.od.nih.gov/office-biotechnology-activities/biosafety-guidance-institutional-biosafety-committees/ibc-self-assessment-2014>.

[13] Pennisi E. The CRISPR craze. Science 2013;341(6148):833–6. Available from: http://www.sciencemag.org/content/341/6148/833.summary%3Fintcmp%3Dcollection-crispr.
[14] Lenzi RN, Altevogt BM, Gostin LO, editors. Oversight and review of clinical gene transfer protocols: assessing the role of the recombinant DNA advisory committee. Washington, DC: National Academies Press; 2014;374–8.
[15] Collins FS. Statement by the NIH Director on the IOM report addressing the role of the Recombinant DNA Advisory Committee in oversight of clinical gene transfer protocols. National Institutes of Health; 2014. Available from: http://www.nih.gov/about/director/05222014_statement_iom_rac.htm.
[16] Fauci AS. New and reemerging diseases: the importance of biomedical research. Emerging Infectious Diseases 1998;4(3):374–8. Available from: http://wwwnc.cdc.gov/eid/article/4/3/98-0308.
[17] Gottron F, Shea DA. Oversight of high-containment biological laboratories: Issues for Congress. Washington, DC, USA: Congressional Research Service; 2009.
[18] Wilson DE, Chosewood LC, editors. Biosafety in Microbiological and Biomedical Laboratories (BMBL) (5th ed.). U.S. Department of Health and Human Services; 2009. HHS Publication No. (CDC) 21-1112. Available from: http://www.cdc.gov/biosafety/publications/bmbl5/.
[19] United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern. U.S. Government Science, Safety, Security (S3); 2014. Available at: <http://www.phe.gov/s3/dualuse/Pages/default.aspx>.