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AHC Media

French study's death recalls 2006 UK clinical trial disaster

Were mistakes repeated?

By Melinda Young, Editor

It was an unsettling sense of deja vu for researchers and bioethicists when French authorities reported in January that one man died and five others were seriously injured after being administered an investigational drug in a Phase I clinical trial.

The clinical trial community had followed a seemingly similar Phase I disaster in London, England, a decade earlier when a study drug critically injured six men, resulting in swollen heads, unconsciousness, and extreme pain. In the 2016 incident, one study volunteer died and five others suffered from serious neurological problems, according to a report by ANSM, the French national drug safety agency.

"My initial thought was that history had repeated itself," says **Stephen Senn**, PhD, head of the Competence Center for Methodology and Statistics General Management at the Luxembourg Institute of Health.

"However, although the outcome — six affected and one severely so — was extremely similar, the background to what happened was very different," Senn says. "If anything, this trial is more worrying."

> "MY INITIAL THOUGHT WAS THAT HISTORY HAD REPEATED ITSELF ... IF ANYTHING, THIS TRIAL IS MORE WORRYING."

The 2006 trial was later seen to have been conducted rashly, giving too many volunteers the study drug at once when the trial began. The 2016 study had taken a more cautious approach.

"In the case of [the 2006 trial], it is easy to see how with more care the problems could have been avoided," Senn says.

In both cases, the volunteers' adverse reactions occurred quickly and

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virulently, and there were no early indications of how it could have happened. Both disasters also raise questions about informed consent in Phase I trials and whether volunteers can truly appreciate the risks of first-in-human investigational drug studies.

The most recent incident involves a study drug referred to as BIA 10-2474. The Phase I trial was conducted by Biotrial, a clinical research organization, on behalf of Bial, a Portuguese pharmaceutical company. The new molecule under development was an FAAH enzyme inhibitor for treating pain, and the trial had been approved by French regulatory authorities, according to a February 2016 news release by Bial.

The 2006 case involved a humanized agonistic anti-CD28 monoclonal antibody, called TGN1412, which was studied by TeGenero AG of Wurzburg, Germany. *(For more information, see the May 2006 issue of* IRB Advisor*.)*

"Clearly, there is a comparison to be made with TGN1412 in that both ended in disaster, but it's difficult to say more yet," says **Noel Snell**, an honorary senior lecturer at the National Heart & Lung Institute in Great Britain.

"TGN1412 was a biological, and, as I understand it, BIA 10-2474 is a low-molecular-weight compound, a standard enzyme inhibitor," Snell explains.

In the 2006 British trial, six young volunteers were injected with the first doses of TGN1412 about the same time. All six began to exhibit serious symptoms, eventually requiring organ support and weeks of hospitalization. Critics said the trial should have begun with just one person receiving the first dose of the study drug and then proceeded slowly after monitoring the first volunteer's reaction to the new agent, according to a December 2006 report by the *Pharmaceutical Journal*.

The report concluded that doses of study drugs should be calculated according to a minimal anticipated biological effect for new classes of medicines.

A recent ANSM report outlined the steps taken to study the BIA 10-2474 drug's effect on volunteers, beginning with the first cohort of subjects on July 7, 2015. In that cohort, two volunteers were given the treatment (one placebo and one study drug) and 24 hours later, five more volunteers were given the study drug and one the placebo. There were no adverse events. The study proceeded, solely escalating the dose with second, third, and fourth cohorts in August, and fifth, sixth, and seventh cohorts in September and an eighth cohort in October.

After the initial single administration phases, the trial began a study of the interaction with food, followed by a multiple-dose stage. There were multiple, ascending doses, from 2.5 mg to 50 mg, and each dose involved a cohort of eight volunteers, with six receiving the product and two a placebo. For cohorts one through four, there were no serious adverse events, the ANSM report says.

Then, what had been a fairly routine Phase I trial changed: On Jan. 6, 19 days after the fourth cohort, six volunteers received the study drug at a dose of 50 mg. Three days after receiving the first dose of the study drug, one of the volunteers had an adverse reaction and was hospitalized. Within a few days, the remaining five volunteers who received the study drug also were hospitalized, French officials say.

"The study's design was fine, and it was cautious," says **Arthur Caplan**, PhD, director of the division of medical ethics at New York University School of Medicine in New York City.

In using a careful initial approach, it appears that researchers of investigational drugs have learned at least one lesson from the 2006 disaster, Caplan adds.

The Royal Statistical Society in Great Britain urged French investigators to include independent statistician members in their research into what went wrong. The society also called for greater transparency in the study's regimen and information sharing.

The very fact that the French trial gave only one patient the study drug at initiation was an improvement over the TGN1412 trial, notes Senn, who commented about the tragedy in a Jan. 22, 2016, statement by the Royal Statistical Society.

"Here, it seems that a cautious dose-escalation was involved, with single doses first and then moving to multiple doses, a reduction in the unit dose," Senn adds. "Furthermore, the problem arose with the last multiple dose cohort and, that, after an intended 10 days. The volunteer who died had only received five doses at the time he was hospitalized."

IRBs and bioethicists might point to Bial and Biotrial's decision to dose all subjects simultaneously after the first cohort as one factor in the disaster. "Bial and Biotrial seem to have ignored the advice to not dose all subjects simultaneously — although, of course, this has always been standard practice until the TGN1412 problems," Snell says. "Although this may reduce risks — depending on how long it takes for adverse reactions to develop — it only reduces the number of subjects potentially at hazard because the first one still has a problem."

IRBs and clinical research sites could use the two Phase I trial disasters as a cautionary tale, suggesting that greater attention needs to be paid to informed consent, bioethicists suggest.

"Informed consent should give an idea of the overall risk to subjects in Phase I studies, which is incredibly low over the years, and also potential specific risks from the agent being studied," Snell says. "This will be highly dependent on the pre-clinical tox [finding], which we know is a poor predictor of human side effects, but I'd like to see the tox package for this drug."

> "SADLY, THE LESSON IS THERE IS DANGER IN EVERY PHASE I STUDY, BUT IT'S JUST NOT COMMON. TWO DISASTERS IN 10 YEARS IS LIKE THE AIRLINES — A GOOD SAFETY RECORD."

But anecdotal evidence suggests that Phase I study volunteers might ignore the risks and focus on other things, including the money they receive for participating: "It's debatable how 'informed' the consent process is," Snell says. "When the TGN1412 disaster was all over the media, applications to participate in Phase I studies actually increased."

As the British Phase I trial disaster showed, healthy volunteers for these first-in-human drugs often are seduced by the money and don't consider the risks, Caplan says.

"People who sign up for Phase I studies are younger and pretty much think of themselves as invulnerable," he said.

Senn would recommend that informed consent documents in Phase I studies include a separate document that explains the risk assessment that was made before the trial began.

There is one way that the research community could enhance participant safety in Phase I trials, and that would be to create a systematic registry that is used to prevent people from signing up for more than one Phase I trial at a time, Caplan says.

"People can shop around and lie about their participation," he adds.

"Sadly, the lesson is there is danger in every Phase I study, but it's just not common," Caplan says. "Two disasters in 10 years is like the airlines — a good safety record."

IRBs and clinical research sites simply need to make certain Phase I studies have a plan for dealing with any adverse event or catastrophe that might occur, including prompt reporting, transparency, shutting down the trial quickly in the event of a problem, and having a failure plan, he suggests.

From an IRB and investigators' perspective, the take-home message is to never get comfortable in any Phase I trial. "You still must proceed cautiously and wait and see what happens," Caplan explains. "That's the best chance of minimizing risk." ■

FIRST study proves a point, but which one?

'Flexible' hours, current duty limits both deemed safe

A controversial study that was branded as unethical by some critics because it altered surgical residents' training hours without informed consent from patients has found that "flexible, less restrictive" duty hours did not increase patient mortality or serious complications.

The recently published Flexibility in Duty Hour Requirements for Surgical Trainees (FIRST) trial[1] was determined to be non-human subject research by the IRB at Northwestern University in Chicago. In addition, the Accreditation Council for Graduate Medical Education (ACGME) waived some of its current requirements to allow the study to proceed.

"This national, prospective, randomized trial showed that flexible, less-restrictive duty-hour policies for surgical residents were noninferior to standard ACGME duty-hour policies with respect to our primary patient outcome of the 30-day rate of postoperative death or serious complications," the authors concluded. "There was also no significant difference between the standard-policy and flexible-policy groups with respect to residents' satisfaction regarding their well-being and education."

The ACGME waivers of its current requirements for the FIRST study and the ongoing Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE) trial were strongly criticized last November by the watchdog group Public Citizen and the American Medical Student Association (AMSA). They charged that the studies were unethical due to the waived requirements and the lack of informed consent to patients. *(For more information, see the January 2016 issue of* IRB Advisor*.)* Public Citizen stayed on the attack after publication of the FIRST trial, saying in a statement[2] that it produced "self-serving results … needed to roll back the ACGME's 2011 mandatory limits on physician resident work hours that were adopted to protect both the residents and their patients from serious harm."

The ACGME has completely refuted the charges and did not rescind waivers of its 2011 duty-hour requirements for physician training that allowed the FIRST trial and iCOMPARE study to proceed. While the current 16 consecutive duty-hour limits adopted in 2011 were designed to protect patients, studies comparing the 2011 to the 2003 ACGME (24 consecutive hours on-site; six additional for other activities) duty-hour requirements suggests that patient safety has not been improved, ACGME argued in granting the waivers.

The FIRST study compared standard ACGME duty-hour policies with flexible duty-hour policies in general surgery residency programs from July 1, 2014 to June 30, 2015. The investigators randomly assigned general surgery residency programs to use one of two types of duty hour policies. However, both groups adhered to three main ACGME policies: the workweek was limited to 80 hours, one day off in seven was required, and residents could not be on call more often than every third night.

A total of 117 programs at 151 hospitals completed the study. One group of 59 programs and their affiliated 71 hospitals participated in the "standard policy" arm of the study, complying with all current ACGME duty hour policies. The other group, consisting of 58 programs and 80 affiliated hospitals, received permission from the ACGME to waive rules on maximum shift lengths and time off between shifts. In this flexible duty-hour group, programs were allowed to implement one or more of the following policy changes:

- interns' work shifts could extend beyond the current maximum of 16 hours,
- more senior residents' duty-hour periods could exceed 24 hours,
- residents were not required to have at least eight hours off between shifts, and
- residents were not required to have at least 14 hours off after 24 hours of continuous duty.

Focus on 'handoffs'

"Our goal was to revise only the policies that would interfere with continuity of care or would result in increased 'handoffs,' [between surgeons] particularly at unsafe times," lead study investigator **Karl Bilimoria**, MD, MS, FACS, director of the Surgical Outcomes and Quality Improvement Center at Northwestern, said in a statement released with the study. "In surgery, this more frequent turnover may compromise continuity of patient care, potentially jeopardize patient safety, and decrease the quality of resident education by forcing residents to leave at critical times, such as in the middle of an operation or while stabilizing a critically ill patient."

The rate of death or serious complications did not differ significantly between study groups (9.1% in the flexible policy group and 9.0% in the standard policy group). In addition, the

risk of death or serious complications did not differ significantly between patients who underwent surgery in hospitals affiliated with programs assigned to flexible, less-restrictive duty-hour policies and those who underwent surgery in standard policy hospitals. Flexible policies were noninferior to standard policies with respect to serious complications, any complication, unplanned reoperation, sepsis, surgical-site infection, and urinary tract infection in unadjusted and adjusted models, the investigators reported.

In addition, survey data were obtained from 4,330 general surgery residents who were undergoing training in 117 FIRST trial programs (2,110 residents in the flexible policy group and 2,220 in the standard policy group). Residents in flexible policy programs were not significantly more likely than those in standard policy programs to be dissatisfied with overall education quality (11.0% in the flexible policy group and 10.7% in the standard policy group); or overall well-being (14.9% and 12.0%, respectively).

Flexible policy residents were significantly less likely than standard policy residents to be dissatisfied with continuity of care but were more likely to be dissatisfied with time for rest, the authors noted. There was no significant difference between study groups regarding resident satisfaction with the duty-hour regulations of their program. Flexible policy residents were significantly less likely than standard policy residents to perceive a negative effect of institutional duty-hour policies on patient safety, continuity of care, clinical skills acquisition, operative skills acquisition, autonomy, operative volume, availability for elective and urgent cases, conference attendance, time for teaching medical students, the relationship between interns and residents, and professionalism.

However, flexible policy residents were more likely to perceive negative effects of duty-hour policies on resident outcomes that depended on time away from the hospital, such as case preparation after work, research participation, time with family and friends, time for extracurricular activities, rest, and health. Nonetheless, there were no significant differences between study groups regarding the perceived effects of duty hours on job satisfaction, satisfaction with career choice, or morale, the authors concluded.

In an editorial[3] accompanying the study, a leading surgeon did not challenge the results but took a contrarian's view of the perceived benefits and risks experienced by patients and surgical residents. Yes, the study showed that flexible hours did not increase risk, but — since the findings for the two groups were essentially a wash — it also confirmed that the residents working under the existing policies were not putting patients at higher risk, either.

"It is not surprising that outcomes did not vary according to whether programs adhered to ACGME requirements on maximum shift length and time off between shifts," noted **John D. Birkmeyer**, MD, surgeon and executive vice president at Dartmouth Hitchcock Health System in Lebanon, NH. "The patients most likely to be affected by resident handoffs — those with acute or deteriorating clinical conditions — represent only a small percentage of surgical patients at teaching hospitals. More important, teaching hospitals have become far less reliant on surgical residents than they used to be. In earlier eras, surgical residents had considerable autonomy. During my own residency, surgical residents often operated independently, particularly at night and on weekends. Today, they operate almost exclusively in the presence of an attending surgeon."

Birkmeyer then raises the critical question: What do the results of the FIRST Trial mean for ACGME policy on resident duty hours?

"The authors conclude, as will many surgeons, that surgical training programs should be afforded more flexibility in applying work-hour rules," he stated in the editorial. "…I reach a different conclusion. The FIRST Trial effectively debunks concerns that patients will suffer as a result of increased handoffs and breaks in the continuity of care. Rather than backtrack on the ACGME duty-hour rules, surgical leaders should focus on developing safe, resilient health systems that do not depend on overworked resident physicians. They should also recognize the changing expectations of postmillennial learners. To many current residents and medical students, 80-hour (or even 72-hour) workweeks and 24-hour shifts probably seem long enough. Although few surgical residents would ever acknowledge this publicly, I'm sure that many love to hear, 'We can take care of this case without you. Go home, see your family, and come in fresh tomorrow.'"

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Staff training program marries efficiency with modular tools

Training can take years

IRB professionals often need specialized, intensive staff training, as well as the standard online educational sessions such as CITI. This is why one human research protection program developed a formal training program that empowers staff to become experts.

"We found that CITI does not address the operations of our office because of its broad, educational-awareness program that generally covers research ethics and regulatory issues," says **Martha F. Jones**, executive director of the human research protection office at Washington University in St. Louis.

"It's hard to have a single program that will provide appropriate training at the institutional level," Jones says. "So we developed our training tools in a way to make them portable to other institutions, as well."

Jones has discussed and shared information about the training program at a Public Responsibility in Medicine & Research (PRIM&R) conference and received overwhelming requests for more information, she notes.

"What we have are some tools we've developed that are modular in nature," Jones says. "Because they're specific to each position in our office, they start with basic template everyone goes through."

For example, new employees are expected to learn the university's telephone exchanges, website URLs, software and email programs, and Web browers. On their first day, employees also register for research news, sign the IRB assurance form, schedule a meeting with the operations manager, and get acquainted with the office's kitchen, suite access, equipment, and supplies.

Each new employee has a designated trainer who is responsible for overall training. Employees also train with content experts. A 43-page training tool provides a clear overview of staff training, including very brief descriptions of each step in a chart that includes columns for employees and trainers to initial and date.

"There's a spot in the tool where you can document each item, writing down who trained the person, and show the date it was complete," Jones says.

The idea is to make the training all-dimensional and not just reading material and passing tests. "They read first and then watch a trainer," Jones explains. "The trainer watches them doing it and reviews what they're doing."

As a progressive training process, it uses different methods that might engage adult learners, she adds.

"We use different tools, understanding that not everyone learns in the same way," she says. "Some people are very visual, and others are hands on; some learn by hearing, and we try to incorporate as many different methods as we can."

The tool provides a stated path to follow for the training, but it's also flexible to be adaptable with employees who have different backgrounds, Jones says.

"They can go through the training at different speeds," she adds. "Some people who come from a clinical training background can go through the training quickly."

The idea is to not require new employees to complete it within a set time frame. For many people, it will take months or even a couple of years to fully complete the training, Jones says.

"Some people will be up to speed within six months, and others will take longer, and that's fine," she adds. "They're not handed all their responsibilities at once."

Quizzes at each level identify the employees who have retained the knowledge and those who need more training. Its interactive features allow for trainers to give new staff responsibilities as they demonstrate competency in those particular tasks. The new hire's independence grows as he or she goes through the training course, Jones explains.

Besides being useful for training staff, the tool has been used for quality assurance efforts, she notes. *(See sample items from the training tool, page 43.)*

"If we have someone who is having an area of trouble and maybe needs more training or re-education, then once we identify that area, we can go back to our training tool and pull out that section to use as a guide for the quality assurance activity," Jones says. "We want the tool to be a living resource for them — that's where quality assurance comes in."

The training occurs both in electronic and hard copy formats. "The layout looks like a spreadsheet or database visually," Jones says.

All IRB staff are expected to obtain a CIP designation, so the tool also can be used as training for the CIP exam, she notes.

"It's been very effective in providing that training, as well," Jones says. "It's extremely comprehensive and has everything they need to learn for the CIP exam." ■

A sample of IRB's comprehensive training manual

References expand learning

The human research protection office at Washington University in St. Louis has a 43-page training tool that covers general and specific research protection information and tasks for new IRB staff.

The following are some sample items in the tool's section on criteria for review of risks, monitoring:

• Risks are minimized.

- Review the assessing risk guideline on the IRB website under biomedical guidelines, risk and data monitoring guidelines.

- See myIRB section VI (participants) section VII (project description) and section VIII (risks).

• Risks are reasonable.

- Read the Belmont Report found on the OHRP website at http://www.hhs.gov/ohrp/humansubjects/index.html.

- Read the IRB policies and procedures on unanticipated problems found under policies on the IRB website in the policies and procedures document.

- On the OHRP website, review "Reviewing and Reporting Unanticipated Problems Involving Risks to others and Adverse Events; Withdrawal of Subjects from Research" at http://www.hhs.gov/ohrp/policy/investigators/index.html.

- See myIRB section VIII (risks) and section IX (benefits).

• The research plan makes adequate provision for monitoring the data collected to ensure the safety of participants.

- On the OHRP website, http://www.hhs.gov/ohrp/policy/index.html, review the guidelines found under "For Investigators" documents that will be of particular interest to research investigators, such as how to handle subject withdrawal from a protocol, how to assess unanticipated problems and adverse events that may occur during the conduct of research, and the general responsibilities of research investigators.

- On the IRB website, under "Risk and Data Monitoring Guidance," review the data monitoring guideline.

- See myIRB section VIII (risks).

In another example, the sample items for criteria for review and participant selection, recruitment, and consent include the following:

• Participant selection is equitable.

- On the OHRP website, http://www.hhs.gov/ohrp/policy/index.html, review the guidelines found under the vulnerable populations, including guidance addressing vulnerable groups such as children, prisoners, and subjects for whom a certificate of confidentiality may offer appropriate additional protections

- Review 45 CFR 46, subparts B, C, and D: http://www.hhs.gov/ohrp/humansubjects/index.html.

- Review 21 CFR 50, subpart D: http://1.usa.gov/1pbjWBf.

- See myIRB section VI (participants) and section VII.D (recruitment and consent).

• Recruitment methods are fair, appropriate, and designed to allow to ensure equitable selection of subjects.

- Review the FDA recruiting study subjects — information sheet at http://1.usa.gov/1TZX7wB.

- Review OHRP guidance research participants — employees in the workplace.

• With your manager, discuss the following recruitment issues:

- What does the IRB need to see?

- What should be in an advertisement; what is an acceptable ad?

- Use of SS# to recruit or follow-up.

- Use of Facebook and such.

- Use of commercial groups to recruit.

- Recruitment vs. engagement in the study. ■

Using eFeedback helps promote subject safety

Goal is to use untapped resources

Seattle Children's Research Institute in Seattle has found that an eFeedback tool helps the organization improve and ensure the safety of pediatric patients who are enrolled in clinical trials.

"The IRB and research institute at Seattle embraces performance improvement, and we realized that we have an untapped resource in the patient safety office that we could leverage to improve research subject protections," says **Jessica Huening,** JD, human subjects protection analyst at Seattle Children's Research Institute.

After discussions on how to improve study participant safety

and better integrate processes, they decided on a systems approach that incorporates an electronic feedback model, using the patient safety office's eFeedback.

The eFeedback process was created for the health system's employees to report any safety or care issues pertaining to patients, families, visitors, and staff. Submissions to eFeedback contain summaries of potential safety concerns that are sent to specialists and experts to determine how they should be handled.[1]

Research staff or others who identify an adverse event or other safety issue can write about what happened in eFeedback, and the information is sent to the patient safety office. The office staff reviews it and triages it based on the incident's specific details, and they send the information to the hospital's experts on that particular subject, Huening explains.

The IRB's idea was to leverage the eFeedback process to identify the root causes of protocol deviations that are associated with adverse events or might cause harm to participants. The IRB reviews the eFeedback recommendations to determine whether additional actions are required.[1]

"It was one of those things where we said, 'Why didn't we think of this before?'" Huening says. "Everyone was excited to optimize more protection for our patients and our participants, so it was a very collaborative process."

Here's a theoretical example of how eFeedback works for the IRB: A human subjects research study has a problem where, possibly due to how supplies were organized in a department, the wrong supplies were used in a trial and this resulted in some type of harm, Huening says.

"That's a good example of the type of scenario that would benefit from our leveraging the eFeedback process," she says. "Generally, it could be used when there are institutional failures beyond the scope of the investigator or an institutional process that could benefit from changing."

So in the theoretical example, investigators might submit information to the patient safety office, via eFeedback, about the supplies mix-up. The eFeedback analysis might respond, saying, "Okay, it looks like the materials are organized in a way that is unclear and maybe we need to have better labeling," Huening suggests.

"Or maybe we need to institute an institutional change and manage our materials so this does not happen again," she says.

These suggestions can be included in the study team's corrective actions, as well.

The idea is that the entire institution will benefit from changes made as a result of eFeedback because the incident could have been the result of an institutional process failure, Huening notes.

Although eFeedback is Seattle Children's Research Institute's solution to improving safety, the idea of having an IRB leverage infrastructure from within a hospital is not unique, Huening says.

"Other institutions might have infrastructure they can leverage to optimize human research subjects protection and improve overall patient safety," she adds.

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Human germline gene editing holds great promise, dire possibilities

International summit says basic research should proceed

An international summit on human gene editing recently concluded with a consensus statement to continue basic research in the controversial area, but warned against any clinical trials or human experiments because "once introduced into the human population, genetic alterations would be difficult to remove and would not remain within any single community or country."[1]

So-called "germline editing" is now possible, meaning genetic alterations can be made in human gametes or embryos that can "be carried by all of the cells of a resulting child and will be passed on to subsequent generations as part of the in-human gene pool," according to a closing statement issued by

the organizing committee of the International Summit on Human Gene Editing in Washington, DC.

While there are certainly risks, the benefits could include prevention of severe inherited diseases. Therefore, the committee recommended that intensive basic and preclinical research is clearly needed and should proceed. This basic research should be subject to appropriate legal and ethical rules and oversight on the following:

- technologies for editing genetic sequences in human cells,
- the potential benefits and risks of proposed clinical uses, and
- understanding the biology of human embryos and germline cells.

"If, in the process of research, early human embryos or germline cells undergo gene editing, the modified cells should not be used to establish a pregnancy," the committee warned.

While IRBs may not be involved in oversight at present, the emerging science warrants careful scrutiny and ethics boards may ultimately have important roles to play. *(See guest column, page 46.)*

Many promising and valuable clinical applications of gene editing are directed at altering genetic sequences only in somatic cells, whose genomes are not transmitted to the next generation. Examples that have been proposed include editing genes for sickle-cell anemia in blood cells or for improving the ability of immune cells to target cancer. However, there is a need to understand the risks, such as inaccurate editing, and the potential benefits of each proposed genetic modification. Because proposed clinical uses involving somatic cells are intended to affect only the individual who receives them, they can be appropriately and rigorously evaluated within existing and evolving regulatory frameworks for gene therapy, and regulators can weigh risks and potential benefits in approving clinical trials and therapies, the summit committee noted.

"While each nation ultimately has the authority to regulate activities under its jurisdiction, the human genome is shared among all nations," the panel stated. "The international community should strive to establish norms concerning acceptable uses of human germline editing and to harmonize regulations, in order to discourage unacceptable activities while advancing human health and welfare."

THERE ARE PROFOUND MORAL AND ETHICAL CONSIDERATIONS IN THE RESEARCH, WHICH COULD PURPOSEFULLY OR ACCIDENTALLY ALTER HUMAN EVOLUTION.

Germline editing carries the risk of inaccurate editing — such as off-target mutations — as well as the possibility of incomplete editing of the cells of early-stage embryos (mosaicism). Moreover, it is difficult to predict harmful effects that genetic changes may have under the wide range of circumstances experienced by the human population, including interactions with other genetic variants and with the environment, the panel conceded.

Thus, there is an obligation to consider implications for both the individual and the future generations who will carry the genetic alterations. The committee cited "the possibility that permanent genetic 'enhancements' to subsets of the population could exacerbate social inequities or be used coercively." There are profound moral and ethical considerations in the research, which could purposefully or accidentally alter human evolution.

"It would be irresponsible to proceed with any clinical use of germline editing unless and until the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and there is broad societal consensus about the appropriateness of the proposed application," the organizing committee concluded. "Moreover, any clinical use should proceed only under appropriate regulatory oversight. At present, these criteria have not been met for any proposed clinical use: The safety issues have not yet been adequately explored; the cases of most compelling benefit are limited; and many nations have legislative or regulatory bans on germline modification. However, as scientific knowledge advances and societal views evolve, the clinical use of germline editing should be revisited on a regular basis."

REFERENCE

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IRBs and germline editing research: The outer limits of oversight

By J. Benjamin Hurlbut, PhD, assistant professor of Biology and Society in the School of Life Sciences at Arizona State University, Tempe.

Editor's note: Considering the far-ranging implications of gene editing of germline cells outlined at a recent international summit, IRBs may be at somewhat of a loss as to their current and future role in this emerging body of research. We sought out someone who ponders these imponderables for a living, and here follows his assessment of possible roles IRBs may play as this line of research unfolds.

It strikes me that IRBs can and should play a role in the emerging public discussion about germline applications of gene editing, even if only by making quite clear how they are limited in their jurisdiction and remit to evaluate research in this area. The range of research that is at issue is quite broad. There is certainly the potential for experiments that would fall within IRB jurisdiction by virtue of involving human subjects — that is, experiments that involve transferring "edited" embryos or embryos created with edited gametes. But to my knowledge no one is contemplating this or advocating it at this time.

A few ways that IRB jurisdiction may kick in could include the following:

- the use of human subjects in experiments as described above,
- the use of human gametes and embryos that would require (or not require) the consent of the donors in the same way as any research involving human biological materials, and
- research involving other sorts of biomaterials that come from a donating human subject, e.g., induced pluripotent stem cells.

Yet researchers' responsibilities to seek consent from donors are limited in all the standard ways (e.g., if consent has already been given at the time of donation, including if generically for "research" or if the tissues are anonymized). Thus, there is nothing special about the research per se that might place it within the jurisdiction of IRBs.

This is odd, given the fact that the most affected human subject from "clinical applications" of this technology is a person who does not yet exist, and thus isn't really given consideration as such. It is worth reflection upon the fact that no matter how thorough the risk assessments, there can be no circumstance under which this technology would be without risk for the child produced through it. A child who already exists and is being treated for a disease with a risky therapy is a radically different case than applying a technology to bring a child into existence who may be affected in unknown ways. This is, I think, something IRBs ought to be reflecting upon.

Indeed, there have been a number of developments in assisted reproductive technology, including in vitro fertilization (IVF) itself, where the babies produced were de facto subjects of experiments, but were not accorded the protections normally accorded to experimental subjects, since when the experiments were initiated they did not (yet) exist: consider intra-cytoplasmic sperm injection (ICSI), cryopreservation, pre-implantation genetic diagnosis (PGD), and in vitro fertilization itself. Indeed, the ways IRBs are tasked with thinking about and protecting human subjects does not fit well with the kinds of risks that these technologies may pose to human beings who do not yet exist — and who will not exist but for the very application of the questionable technology.

This points to something important: a lack of clarity over what institutional oversight body or mechanism has authority— or ought to have authority — over such research. Some institutions have Embryonic Stem Cell Research Oversight committees (ESCROs), which are mostly voluntary, though required by law in a few states. There is variation between them in terms of what kinds of research they have jurisdiction over. Would gene editing research on human embryos require ESCRO review at an institution that has an ESCRO? Perhaps, but not necessarily. What about institutions that don't have such bodies? A human embryo in vitro is not considered a human subject under federal regulations, and though there are many Americans who think embryos are persons and should be treated as such, there are many others who do not. It is not necessary, though, to answer that particular question to recognize that there are ethically difficult issues — or, if you prefer, issues about which there are deeply held beliefs and conflicting opinions. So, it does seems reasonable that a research institution ought to have well-established and transparent processes for reviewing and deliberating over the appropriateness of particular proposals for research in this domain.

I think these questions apply (or ought to apply) not just to research

on "human subjects" but to research that is not intended to be "clinical," but aspires to move technique in that direction. After all, this is a very sensitive domain, and if clinical applications are in principle unimaginable for the reasons outlined above, then drawing a bright line between such applications and mere research, and saying nothing goes for the former and anything goes for the latter seems problematic. It is problematic because it imposes a rather artificial distinction between a range of activities that are linked — and are intended to be linked.

In my view, the most important question to ask about institutional structures like IRBs is whether they are adequate to the task of engaging in the forms of thoughtful reflection and deliberation that techniques like application of gene editing to human gametes and embryos warrant. There has been a general affirmation that a public dialogue is needed. Yet the most sustained dialogues are likely to happen in institutional spaces whose charge it is to engage in them, not bodies that have secondarily elected to take up the issues. The remit of IRBs does include these sorts of issues.

IRBs might reflect, therefore, on their own jurisdictional remit, and the ways in which they are invited to contribute, or precluded from contributing, to the work of shaping applications of these techniques in research. IRBs are spaces where questions can be asked that might otherwise not be — for instance, questions on how to think about ethical obligations to the human subject who will also the experimental product of these techniques. Yet the range and focus of questions is potentially constrained, and may as a result leave aside questions that if asked earlier on, would orient trajectories of research — and of corollary ethical discussions — in better directions. It is particularly important for IRBs to think about how they stand in relation to other oversight bodies that would potentially deal with such research, and whether, taken together, those bodies are capable of addressing the issues that IRB members or others see as significant. By making explicit their sense of their own jurisdictional remit, and inviting other oversight bodies to do the same, they would make more visible the questions that may go unasked and the cracks through which key issues might fall.

For an area of research like this, my sense is that there are a lot of questions that go unasked, and that this is in no small part because of prior commitments to ideas of what matters to ethical oversight bodies, and what is beyond their focus or remit. One of the points I tried to make in a recent article[1] was that we confront these questions suddenly and urgently not because we couldn't have anticipated them, but because we have excluded the capacity to anticipate them from institutionalized mechanisms of oversight, reflection and deliberation, often because they have been deemed too hypothetical, to complex, or someone else's responsibility. Engendering the capacity to develop awareness of what questions go systematically unasked, and in what ways the workings of bodies like IRBs contribute to this, is an important thing for such bodies to do, not least because people tend to think that because structures like IRBs exist, problems are being taken care of. IRBs should be more reflexive and explicit about what they are not taking care of. They can do this more effectively if they imagine possible experiments and reflect on what dimensions of them are outside of their purview, but maybe ought not be.

It is indeed possible that even IRBs that do not do what I have suggested above may eventually have a protocol land on their agenda that involves human germ-line gene editing. The complex ethical questions associated with such research cannot be solved purely by technical assessment of risk and safety, although there will be pressure to limit deliberation to such issues. The problem is not merely a matter of having adequate knowledge, but of having developed the capacity to think well about these challenging possibilities. If that means recognizing the limits of IRBs' capacity and authority to review such research, then that should be recognized up front as a problem, and not taken as an indication that there is nothing here that warrants reflection and review. One of the central problems of governing research in this domain is determining how — and by whom — such problems will be recognized and acted upon.

REFERENCE

1. Hurlbut JB. Limits of Responsibility: Genome Editing, Asilomar, and the Politics of Deliberation. Hastings Center Report 2015;45(5) 11-14. bit.ly/1NT13XB ■

COMING IN FUTURE MONTHS

- Spruce up your pre-review process
- New model: in-person express reviews
- Handling single-patient exceptions
- Babies in some studies not given pain relief for routine procedures

IRB ADVISOR

CME/CE INSTRUCTIONS

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CME/CE QUESTIONS

1. Which of the following were similarities between the 2006 TGN1412 and 2016 BIA 10-2474 European Phase I clinical trials?

A. Both involved humanized agonistic anti-CD28 monoclonal antibodies.
B. Both resulted in at least one death among participants receiving the investigational drug.
C. Both resulted in serious injuries requiring hospitalization among volunteers who had taken the investigational drug.
D. Both trials were conducted in France.

2. In an editorial accompanying the recent FIRST Trial, John D. Birkmeyer, MD, said which of the following?

A. The authors conclude, as will many surgeons, that surgical training programs should be afforded more flexibility in applying work-hour rules.
B. The FIRST Trial effectively debunks concerns that patients will suffer as a result of increased handoffs.
C. Rather than backtrack on the ACGME duty-hour rules, surgical leaders should focus on developing safe, resilient health systems that do not depend on overworked resident physicians.
D. All of the above.

3. According to a staff training program used by the IRB at Washington University in St. Louis, which of the following is a good question for managers to discuss with new staff about recruitment issues?

A. What information should be private?
B. What should be in an advertisement?
C. What are acceptable forms of advertisement?
D. None of the above.

4. An international summit on human gene editing recently recommended in a closing statement that if any early human embryos or germline cells undergo gene editing, they can be used to establish a pregnancy with IRB approval.

A. True
B. False