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INSIDE

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Ethical Controversy Erupts Over Alzheimer's Drug Approval

By Stacey Kusterbeck

The first new Alzheimer's drug to be approved in almost 20 years has sparked a major ethical controversy.[1-3] Of the 11-member advisory committee convened by the FDA to review the application for aducanumab, no one voted yes (10 voted no, one voted uncertain).

Nonetheless, the FDA granted accelerated approval of the drug. "As an advisory committee member, I am extraordinarily disappointed that our unbiased advisory committee review was not valued," says **Joel S. Perlmutter**, MD, a neurologist at Washington University in St. Louis. "Approval of a drug that is not effective has serious potential to impair future research into new treatments that may be effective for treating Alzheimer's disease."

For example, new studies may be required to compare investigational drugs to aducanumab instead of a placebo. "Enthusiasm, from either potential volunteer participants or funders, for new treatments may wane due to thinking that we already have an effective treatment when, in fact, we do not," Perlmutter says.

"FDA will continue to monitor aducanumab as it reaches the market and ultimately the patient's bedside," **Patrizia Cavazzoni**, MD, director of the FDA Center for Drug Evaluation and Research, said in a statement.[4] "Additionally, FDA is requiring Biogen [the drug's manufacturer] to conduct a post-approval clinical trial to verify the drug's clinical benefit. If the drug does not work as intended, we can take steps to remove it from the market. But, hopefully, we will see further evidence of benefit in the clinical trial and as greater numbers of people receive Aduhelm."

On July 9, FDA Acting Commissioner Janet Woodcock, MD, sent a letter to Acting Inspector Christi Grimm to request an Office of Inspector General investigation into the Aduhelm approval process.

"To the extent these concerns could undermine the public's confidence in FDA's decision, I believe it is critical that the events at issue be reviewed by an independent body such as the Office of Inspector General in order to determine

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whether any interactions that occurred between Biogen and FDA review staff were inconsistent with FDA policies and procedures," Woodcock wrote.[5]

Meanwhile, some advisory committee members have resigned.[6-8] "Many in the field disagree with the decision [to approve the drug], and the efficacy is very much in question," says **Joshua D. Grill**, PhD, director of the UC Irvine Institute for Memory Impairments and Neurological Disorders.

It is possible patients who take aducanumab are risking adverse events without potential clinical benefit, according to Grill. The available prescribing information does not recommend confirming the presence of brain amyloid, despite the drug being approved for lowering it, Grill says.

Initially, the available prescribing information suggested the drug was broadly approved for "Alzheimer's disease," and did not restrict the drug to patients with disease severity similar to those in the clinical trials (i.e., patients with mild cognitive impairment and mild dementia). "To treat moderately severe patients for whom there are neither safety nor efficacy data would be inappropriate," Grill says.

On July 8, Biogen, the company that produces Aduhelm, announced the FDA had approved a language update for the drug's prescribing label. The added language reads: "Treatment with Aduhelm should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied."[9]

On top of all this is price. Grill notes "the drug price tag of $56,000 is very high, and that is just the price from the sponsor. The patient costs are unknown at this time." If any portion of this cost is passed to the patient (either in the form of a monthly copay or due to partial coverage), it will be more than many can afford. "This disease itself is already tremendously burdensome and costly," Grill observes. "The amyloid scans that should be ordered to know if the drug is appropriate are not currently covered and cost several thousands of dollars."

The cost of the drug "could be unprecedented," says **Tia Powell**, MD, director of Montefiore Einstein Center for Bioethics at Albert Einstein College of Medicine in New York City. Depending on whether Medicare and other insurance companies cover the drug, and how widely prescribed it is, Powell believes this could double Medicare's budget.

"Since it is highly unlikely that Medicare will receive twice as much money from the government, that could mean substantial cuts in other medical care for older people, including for cancer, heart disease, and all else," Powell says.

The drug's costs also might preclude other proven beneficial interventions (like support for caregivers and better end-of-life care) for the large number of people with moderate to severe Alzheimer's who likely will not benefit from aducanumab, Powell adds.

Because the drug is so expensive, it is likely to include high out-of-pocket costs. "This will further exacerbate disparities in access for low-income and minority populations," Powell laments.

"The most obvious ethical concern is that aducanumab treatment will either be limited to those in upper income brackets, or the medication will serve to drain the savings of individuals whose resources are more

limited," says **David S. Knopman**, MD, a consultant and professor of neurology at the Mayo Clinic in Rochester, MN. Dementia care already is unevenly available in the United States because this type of specialty care is geographically limited.[10] "Furthermore, because the clinical resources necessary to administer aducanumab safely are considerable, the geographic disparities between well-resourced health systems and safety net healthcare systems will also disproportionately reduce access to aducanumab," Knopman offers.

Further studies might show evidence for or against benefit. "But it is unclear when those studies will happen," says **Dena S. Davis**, JD, PhD, professor of bioethics at Lehigh University in Bethlehem, PA.

Most people for whom aducanumab is considered have limited decisional capacity. That means other people need to make decisions about whether the patient should take the drug. "Risks I might ethically take on myself, as a cognitively competent person, are probably much higher than the risks I would or should take on for a cognitively impaired adult," Davis observes.

Additionally, pretesting to be eligible for the drug involves at least one PET scan and one MRI. Taking the drug involves regular MRIs and monthly infusions. "Taking this drug presents serious risks of discomfort and disruption to the lives of people whose days are already challenged by confusion and disorientation," Davis argues. The drug's approval spotlights ethical challenges with clinical trials of Alzheimer's drugs in general. Davis puts these into two categories. The first is clinical trials with participants who already are experiencing disease symptoms. "These raise the same issues of any trials that involve patients who are no longer competent," Davis says.

For these participants, someone competent usually must give consent. That person often is a family member. "They may be motivated by a need to do something and overestimate the likelihood that the clinical trial will lead to benefit," Davis says.

The second category is clinical trials that include participants who show markers for elevated risk for the disease but are not currently experiencing symptoms (and, in fact, they may never show symptoms).

"There is a strong belief that if a drug is to work well, it must be started long before the person shows symptoms," Davis notes.

These trials raise complex ethical questions because they rely on some sort of marker of higher risk (a genetic marker or elevated amyloid). Ethical questions involving biomarkers are "extremely complex," Davis says.

Biomarkers are crucial to effective research, and can help people make long-term plans. On the other hand, insurers and continuing care communities have an interest in gathering that same information to deny coverage or to raise premiums.

"There are real risks to research subjects if information gets into the wrong hands," Davis cautions. "But there is also value to subjects who want information for planning purposes." ■

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Underrepresented Groups in Alzheimer's Trials Remain Persistent Ethical Concern

By Stacey Kusterbeck

Despite ongoing efforts to address disparities in Alzheimer's disease and dementia care, "there is still a lot of work to be done," says **Carl V. Hill**, PhD, MPH, chief diversity, equity, and inclusion officer at The Alzheimer's Association.

A recent report identifies some of the barriers diverse populations are facing in accessing and receiving dementia care.[1] Some key findings:

• 36% of Black Americans, 18% of Hispanic Americans, and 19% of Asian Americans believe discrimination would be a barrier to receiving Alzheimer's care.

• Among Alzheimer's caregivers, half or more of non-white caregivers say they have faced discrimination when navigating healthcare for their care recipient. The top concern is that providers do not listen to what caregivers are saying because of the caregivers' race, color, or ethnicity.

"The combination of having populations at higher risk for dementia while receiving less care means poorer outcomes," Hill notes. "It's a big concern and something all healthcare stakeholders need to work to improve."

Most current participants in Alzheimer's research and clinical trials are white. Blacks are disproportionately more likely to have Alzheimer's but are more reluctant to participate in clinical trial research.[1] Researchers found 67% of Blacks are interested in trial participation vs. 82% of whites.

The Alzheimer's Association is working with the American College of Radiology to recruit participants for the New IDEAS study.[2] Investigators are examining if using a brain amyloid PET scan can help inform an individual's memory care plan and improve their health outcomes. There will be 7,000 participants, including 2,000 Hispanics/Latinos and 2,000 Blacks, according to Hill.

Without appropriate participation from Asian, Native American, Black, and Hispanic communities, it is difficult to understand how ethnic and racial differences may affect the safety and efficacy of potential new treatments. "If we don't investigate the effects of Alzheimer's drugs in all groups, we will only learn whether they benefit those who enroll in the trials — namely, white people," says **John C. Morris**, MD, professor of neurology at Washington University in St. Louis.

To understand how a drug may produce benefits (or cause side effects) in all patients, researchers must study all groups. "The clinical trial cohorts have not been very diverse — nor, frankly, have the cohorts in the vast majority of observational research in Alzheimer's disease," Morris argues.

Researchers have relied on the willingness of people to volunteer for these studies. The most likely to volunteer are white people. "As an entire field, we want to learn about Alzheimer's disease in all people. We have to be more welcoming to all people," Morris says.

That means researchers cannot just wait for volunteers to call. "Instead, we must engage with people who are underrepresented in research and find a way to increase their participation rates," Morris offers.

In 2000, shortly after Morris became the director of Washington University's Knight Alzheimer Disease Research Center (ADRC), he noted research volunteers were about 90% white. Morris turned to community leaders to learn more about how to increase participation in the African American community of St. Louis. One leader agreed to volunteer as a research participant, but privately told Morris that it bothered him there was not one person of color on the entire research team.

Morris and the Knight ADRC took this to heart and actively worked to become more diverse. About 18% are now African American.

"We found that the advice and counsel of the Knight ADRC's African American Advisory Board were instrumental in helping us become more welcoming," Morris says.

Another obstacle to research participation is the fact many African Americans distrust academic medical centers, knowing there is a history of discrimination. Many are reluctant to agree to take an experimental drug or undergo invasive diagnostic tests. "A great advantage would be if we had more diverse research teams," Morris says. "If it takes extra work, or takes more resources or time, we are obligated to do that so we understand this illness in all groups." ■

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Ethical Challenges of AI Coming Soon

By Stacey Kusterbeck

Medical schools should be teaching students about artificial intelligence (AI) ethics, the authors of a recently published paper argued.[1]

"The motivation for the paper came from thinking about how AI was pervading medical care, and worrying that medical students were not equipped to think through the ethical implications of emerging AI applications," says **Sara Gerke**, co-author and research fellow at Harvard's Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics.

Numerous real-life examples of AI in healthcare already pose difficult ethical questions: Informed consent, patient privacy, transparency, allocation, and safety are a few. "We hope that all medical schools will dedicate time within their curricula to discuss AI through an ethical lens by discussing these issues," Gerke says.

In medical schools, AI ethics should be "embedded into broader ethics training. Currently, I don't think AI ethics is covered in medical school at all," says **Satish Gattadahalli**, director of digital health and health informatics, public sector, at Grant Thornton.

Gattadahalli says a good place to start is areas where AI is becoming prevalent — radiology, care planning recommendations for chronic diseases, and predictions of ICU mortality. Some ethical concerns surrounding health AI center around data — who owns it, how it is used, and how it is kept private. Quality of data also is a concern, since decisions could be based on questionable information.

"We want to make sure that the inherent data biases are not going to exacerbate health inequities," Gattadahalli says.

There is a need to ensure data that are captured are heterogenous. This information should represent various demographics and disease cohorts. "Whatever we do, we need to make sure our underlying principle is 'Do No Harm,' with patient safety issues always front and center," Gattadahalli stresses.

Medical professionals — not just clinicians, but also support staff and nursing — "need to become AI-literate over the coming years," says **Jason Corso**, PhD, director of the Stevens Institute for Artificial Intelligence in Hoboken, NJ.

This includes both ethical and technical aspects of AI. "AI will not replace clinicians. But they will need to understand AI technology more deeply than they perhaps believe will be necessary in order to properly integrate and benefit from the information provided by AI technologies," Corso offers.

Some hospitals have not designated a specific person to be responsible for implementing data management principles throughout the organization. Typically, hospital chief information officers are focused mainly on computer networks and bringing systems back online after outages. "There needs to be some leadership around AI. Someone needs to own this problem," Gattadahalli says.

AI systems should promote equity and fairness, be safe, preserve patient autonomy, and be "traceable, explainable, with transparent data and models," Gattadahalli says.

How to explain it all to patients is yet another ethical challenge. "Patients are not AI experts. Neither are doctors," Gattadahalli notes. Physicians must explain in simple terms that AI is a factor in clinical decision-making, but it is not the only factor. Otherwise, patients could misperceive that doctors are relying solely on AI to make a diagnosis. On the positive side, patients would benefit if AI took away physicians' documentation burdens, allowing doctors to spend more time listening to patients. "The key thing is to make sure it does not get in the way of the patient/provider relationship," Gattadahalli cautions.

Long-standing bioethics principles (including autonomy, beneficence, and justice) can be applied to AI in the field of pathology and laboratory medicine, the authors of another paper argued.[2] **Brian R. Jackson**, MD, MS, lead author, says bioethicists in clinical settings can give input on specific issues — for example, transparency of data-sharing agreements between the hospital and outside entities.

"Just because a data-sharing agreement may be legal doesn't automatically mean that it's ethical," says Jackson, vice president and chief medical informatics officer at University of Utah School of Medicine.

Another example is the patient consent process — specifically, whether patients are asked to separately consent to use their health information for industry research, development, and other nonclinical purposes (regardless of whether the data are de-identified).

Also, bioethicists can weigh in on how clinicians can validate AI systems before use in patient care, with ongoing monitoring for bias and other problems.

Protecting patient information is a key ethical concern, says **Michael McCarthy**, PhD, an associate professor in the Neiswanger Institute for Bioethics at Loyola University Chicago.

Beyond that, as AI becomes a tool used in providing accurate, rapid diagnoses (e.g., radiology or dermatology), it will be important that physicians can explain how the diagnosis was obtained.

"In addition to protecting the privacy of the patient information being used in developing AI technology, one has to consider the health inequities that already exist and the ways in which existing injustice can introduce further bias," McCarthy says.

Another question to consider is one of justice. Who will benefit as advances in AI are made? "Will those who already have access to care and treatment receive better care?" McCarthy asks. "Or is there a way to use the information to enhance the care of those who bear disproportionately the burden of disease?" ■

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Survey: Ethics Consultations Gap Widening Between Small and Large Hospitals

By Stacey Kusterbeck

Small and large hospitals vary widely in terms of ethics consultation volume, and the gap is widening, according to the authors of a recent study.[1] "When ethics consultation practitioners compare their own practices to other hospitals, it's important to compare apples to apples," says **Ellen Fox**, MD, HEC-C, the study's lead author and president of Fox Ethics Consulting.

In a study conducted in 2000, a group of researchers led by Fox surveyed 600 hospitals about ethics consultation practices.[2] "That study was described as a 'wake-up call' by leading bioethicists who were alarmed by its results," Fox recalls.

Back then, Fox and colleagues learned the median number of consults performed annually was only three. Just 5% of ethics consult practitioners had completed a graduate degree program or fellowship in bioethics. Only 28% of ethics consult services included a formal evaluation process that involved the collection and analysis of data. That 2000 study has been widely read and cited in the ethics field. "But a lot has changed in the last two decades. There was a need for up-to-date information," Fox notes.

Recently, Fox led a follow-up survey, also of 600 hospitals. The new study mirrored the methods of the 2000 survey, but was much broader in scope. Researchers wanted to learn more about the determinants of ethics consult volume and to what extent consultation practices adhere to established standards. The investigators also wanted to hear ethics practitioners share opinions related to training and how consultations might have improved since 2000.

Fox and colleagues are publishing the findings from this study in a series of seven articles, one devoted to each of seven research questions. The first is about how ethics consult practices have changed over time. "We included some of the questions from the previous survey, which allowed us to draw direct comparisons between the two data sets," Fox says. Some key findings:

• **There was a dramatic increase in the number of consults, but only in large hospitals.** "The number of case consultations increased dramatically in hospitals with 400 or more beds, but did not change in small hospitals, which make up the majority of hospitals in this country," Fox reports.

Compared to 2000, the estimated number of consults performed in U.S. hospitals annually increased by 94%, from 35,000 to 68,000. However, the median number of consults per hospital remained unchanged, at only three.

• **Most hospitals said they needed more financial support for ethics.** In the 2000 study, 83% of hospitals found financial support sufficient. In the new study, only 56.5% of hospitals did. Again, this varied depending on the hospital's size. Financial support was perceived to be sufficient in most small hospitals and non-teaching hospitals. In most large hospitals and major teaching hospitals, it was thought to be insufficient.

"In a lot of small hospitals, ethics consultation services receive no funding, but this is not seen as a problem. The level of activity is low, so the idea of a specific budget line for ethics doesn't make sense to people," Fox says.

In contrast, in large hospitals, "it may be that workload is increasing faster than financial support," Fox adds.

• There was no change in the average percentage of ethics consultation practitioners (8%) who completed an advanced degree or fellowship program in bioethics. "People might find this surprising, given that there has been a strong movement toward professionalizing ethics consultation," Fox says.

However, those efforts have been driven largely by academic bioethicists. That possibly resulted in a major impact on large hospitals and major teaching hospitals, but a limited impact on hospitals with few ties to academic medicine.

"Changes that occur in academic medical centers may not have much of an effect on averages, since these hospitals make up only about 5% of all U.S. hospitals," Fox says.[3] When considering all hospitals, says Fox, "the changes that occur in the academic medical centers are not going to have a huge impact on the overall numbers."

Apples-to-apples comparisons are useful for benchmarking or determining if a hospital is out of step with comparable hospitals. For example, the data show a major teaching hospital that performs only 10 ethics consults a year, or that uses the full committee model for most of its consults, is an outlier among its peers. That way, hospital's ethics consult service can use the data to determine what, if anything, it should be doing differently.

"These data might also be useful to hospital leadership when they are deciding what sort of resources to devote to ethics consultation," Fox says. ■

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Ethical Concerns with Variation in Hospitals' Code Status Options

By Stacey Kusterbeck

Code status options, how they are named and defined, vary depending on the hospital, according to the results of a recent study.[1] "Hospitals are doing this differently from one another. And we have no idea what the consequence is," says lead study author **Jason Neil Batten**, MD, a researcher at the Stanford Center for Biomedical Ethics.

As just one example, each of the seven hospitals in the study named and defined DNR orders somewhat differently. "We have decades of research showing that people do not always understand the very same DNR order in the same way. Now, we find that a DNR at one hospital is very different from another hospital," Batten explains.

Stanford Hospital had changed the code status system and policies about a decade ago at the adult hospital, and made a similar change at the children's hospital several years later.

"But we had no data about whether the changes were good, or even what other hospitals were doing, other than a few anecdotes," says **David Magnus**, PhD, the study's senior author and director of the Stanford Center for Biomedical Ethics.

For example, a "Do Not Escalate" (DNE) order was added. The change was popular with some clinicians but opposed by others.

"We decided that a qualitative study with purposive sampling would be a good way to proceed," Magnus says. There was much greater variation than expected across the different institutions. Code status ordering systems were asked to perform different functions. Some specified what interventions will be limited. Some specified whether a patient will be sent to the ICU or a higher level of care. Others specified an overall philosophy of care.

"The results suggested that the code status ordering systems can sometimes contribute to goal-discordant care and miscommunication about patient wishes," Magnus reports.

One or more clinicians speaks to the patient or surrogate, then translates the goals of care into a set of orders. Later, other clinicians interpret those orders to make

concrete decisions. "That process is fraught with potential for misalignment," Magnus says. "Our findings suggest that there are better and worse systems for avoiding these problems."

The researchers followed up by testing Stanford's own code status system to see whether physicians would put in the same orders for the same scenarios or take the same actions for the same scenario and code status. "We found significant rates of discordance," Magnus observes.

Whether a patient was intubated or sent to the ICU varied depending on the physician. Based on these data, Stanford designed and tested a new code status system. It has dramatically reduced the degree of discordance. "We hope that other hospitals will consider our findings and do more actual testing of how well their systems really work at achieving their goals," Magnus offers.

Currently, there really is no hard evidence indicating which code status options are best. "I have my opinions as a clinician, but I can't tell you as a researcher which way is better, or even the effects of it," Batten admits. "None of this has been adequately researched. We just don't know."

Traditionally, a DNR order is supposed to be narrowly focused on what to do if the patient is in cardiac arrest. "It's not supposed to have any impact on any other areas of their care," Batten says.

But at Stanford, the "DNR/DNE" option carries broader implications. It means the overall philosophy of care is comfort care.

"At a place like Stanford, the code status options have a very different role. They are not just telling you what to do for cardiac arrest. In some cases, they are guiding the entire trajectory of a patient's care," Batten says.

Some ethics consults revealed unintended consequences of the new code status options. For instance, nurses questioned if they should give pain medications to a patient who is DNR/DNE, who is not at the point of comfort care, but with symptoms not as well-controlled as they should be. Clinicians also wondered if treating pneumonia is compatible with comfort care, or if changing antibiotics counted as "escalation."

"There are also some pretty straightforward patient safety issues in accurately capturing the code status orders and how those were interpreted in an emergency scenario," Batten adds. This can happen if a patient wants to be intubated for respiratory distress, but is not intubated because different people understood a Do Not Intubate (DNI) order in different ways. "If you as a patient thought that DNI meant something, and the clinician thinks it means something different, that means we thought we knew your code status but you still didn't get what you wanted," Batten explains.

When patients move between hospitals, variations present other challenges. Patients might come from one hospital with a narrowly defined DNR order, then they come to Stanford where there are several different DNR orders. Clinicians have to "translate" which one is appropriate for that person. A well-documented discussion on goals of care can help in that regard. Ideally, the patient is not just handed a list of code status options to pick and choose from. "In some places, this is just becoming like a menu that's guiding the conversation," Batten says.

Patients really do not need to know all the different terminology of code status options. A clinician might put it this way: "If your heart were to stop, we will just let you pass peacefully and we're not going to add any more intensive therapies to your care."

"That's a patient-friendly way to say 'You are a DNR/Do Not Escalate,'" Batten notes. There can be confusion even among clinicians. Some medical trainees learn the code status options at Stanford, then go practice at a different hospital. Others practice at multiple institutions. "A lot of them are not that aware that code status functions differently at different hospitals," Batten says.

The same is true of clinical ethicists. Some ethicists are unaware of how code status options are named and defined at their institutions. Notably, the researchers found that at some hospitals, code status options in the electronic medical record did not even match what was in the hospital policy. "Ethics should be one of the experts on this — maybe not the only expert, but you should be able to ask the ethics committee for the policy, and what are the options in the electronic medical record, and are they the same?" Batten argues.

Ethicists also can consider the scope of DNR orders, whether they are narrowly focused on cardiac arrest, or if they broadly address all aspects of care — and if it is clear to everybody. "You really need to do QI work at your institution, to get out there and understand how these things are functioning," Batten says. "That can improve the quality of care on a systems-level basis." ■

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Video Results in Slightly Better Informed Consent, More Satisfaction

By Stacey Kusterbeck

When obtaining informed consent from research participants, there is much information to convey and it is not always well understood. "Boilerplate information is sometimes more complex than it needs to be. But you have an important obligation to be sure people can make a thoughtful decision," says **Holly Taylor**, PhD, MPH, a research bioethicist in the NIH Clinical Center's Department of Bioethics.

To date, many interventions to improve research participant understanding of informed consent information have been conducted in simulated research settings. The authors of a recent study tested two approaches used to present information to 273 participants enrolling in six actual studies from 2017-2019.[1]

"The literature about the ability of any type of informed consent intervention to improve understanding is either slim or inconclusive," says Taylor, the study's lead author.

The two interventions tested were a fact sheet and a video showing a conversation between the actual principal investigator and an actor playing the role of the subject. The participants who received the fact sheet did not express better understanding or satisfaction compared to the standard consent form process. Participants recorded slightly better understanding scores if they watched the video vs. the standard consent form process, and also were more satisfied.

"The video was relatively inexpensive to produce. My feeling is that it would be a very worthwhile investment for large clinical trials," suggests Taylor, who adds that hospital IT departments could help create a video for researchers.

The challenge is to cover all the important information but without needless confusion. An open-ended question can reveal what the person actually understood. Investigators might ask, "When you go home tonight, how are you going to describe the study to your family?" or "When you see a friend tomorrow, how will you explain this trial to them?"

Sometimes, participants talk about how they will personally benefit from the trial. "This gives researchers a chance to correct this misconception," Taylor notes.

It is an opportunity to explain the individual is unlikely to benefit, but the study might benefit others with the same disease or condition. Taylor says it also is important to keep in mind the person who will be reading a consent form. This is a way to avoid using complex terminology.

"It's not like writing for the *New England Journal of Medicine*. It's like writing for your grandmother," Taylor says. ■

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Community Input Ensures Ethical Informed Consent

By Stacey Kusterbeck

A one-size-fits-all model for informed consent fails to meet the needs of patients and clinicians, according to the authors a new report.[1]

"Indeed, we believe that the current approach is primarily concerned with legal coverage," says **Philip G. Day**, PhD, the paper's lead author and an assistant professor in the department of family and community medicine at UT Southwestern Medical Center in Dallas.

Day and colleagues presented a novel idea — involving community members in the process of drafting consent forms.

"We argue that the idea of a 'community standard' that holds in consenting for clinical care could be extended to research contexts," Day reports. The result would be consent forms, and a consenting process, that is primarily suited to meeting the needs of potential participants. "It was surprising to find a lack of research in this area or much data on a community-oriented consent process," Day says.

Informed consent "has lost a lot of its meaning," says **Robert P. Lennon**, MD, JD, FAAFP, another paper co-author. Clinicians have gotten used to simply asking patients to sign consent waivers, and forms have evolved into complex legal documents.

"As our culture become less homogenous, we're finding that our traditional concept of informed consent does not always match a given patient's concept of consent," says Lennon, director of resident scholarly activity in the department of family and community medicine at Penn State Milton S. Hershey Medical Center. The goal is to have a consent process that is less cumbersome and more culturally competent. "We need to get back to the intent of informed consent, an effort to achieve mutual understanding for risks, benefits, and alternatives to any given intervention," Lennon says. ■

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Day-Long Ethics Training for Graduate Students Is Effective

By Stacey Kusterbeck

It is challenging to fit ethics training into graduate programs, and smaller organizations sometimes lack the resources. At Angelo State University in Texas, faculty shortened an existing, successful two-day professional and research ethics training program for graduate students to a single day. Researchers evaluated the effectiveness of the new one-day program. *(Read more at: https://bit.ly/3keacWo.)*

"A shorter program could potentially be more useful for smaller universities that may not have the resources available to implement a two-day program," explains **Cheryl Stenmark**, PhD, lead author and professor in Angelo State's department of psychology and sociology. To cut the time allotted for ethics training to just one day, faculty eliminated a lengthy assessment conducted before and after the program in favor of shorter ones. "We retained all of the informational content of the original training," Stenmark notes.

The modified training program still includes lecture, discussion, and case activities. However, the original training included multiple case study activities for students that covered the same ground. "We selected one of those activities and eliminated the others," Stenmark reports.

Researchers wanted to know if the shorter program still would be effective in terms of improving ethical decision-making. "We measured several indices of ethical decision-making and compared those measurements from before the training to after the training," Stenmark explains.

Stenmark and a colleague measured perceptions of ethical issues, markers of cognition involved in ethical decision-making, and reactions to the training. "There were significant findings in all three categories of measurement, indicating that the one-day program was, indeed, effective," Stenmark says.

Notably, the shorter program resulted in significantly improved ethical decision-making. Participants reacted positively to the training. "The modified program was effective," Stenmark concludes. A program that is similar to this also could work in clinical practice settings. "In fact, it could be particularly useful in applied settings, where organizations may have limited time and resources to devote to training programs," she offers. ■

Ethics of Fertility Preservation for Transgender and Nonbinary Youth

By Stacey Kusterbeck

Ethical considerations of providing fertility services to transgender patients are examined in an updated policy statement from the American Society for Reproductive Medicine.[1] The statement authors concluded transgender status should not prevent a patient from accessing fertility preservation. Reproductive services should be offered to all interested transgender or nonbinary individuals, barring other disqualifying factors

(based on empirical evidence as opposed to bias or stereotypes).

The authors of another recent paper support the right of transgender and nonbinary youth to reproductive technologies and providing gender-affirming care to transgender patients.[2]

"We realized that there was a growing population of prepubescent children seeking care for gender-affirming care," says **Kavita Shah Arora**, MD, MBE, MS, an associate professor of reproductive biology and bioethics at Case Western Reserve University.

Gender-affirming therapy may impair future fertility. Arora and colleagues advocated for wider access to fertility preservation counseling and options before providing gender-affirming care in this population.

"This is aligned with a reproductive justice framework that centers each person's family-building goals rather than making assumptions based on sex, gender identity, gender expression, and sexual orientation," Arora says.

She adds: "Greater training in how to operationalize shared decision-making in this complex situation, bridging pediatrics and reproductive medicine, is needed." ■

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Prepare for an Unexpected PI Transition

By Sue Coons, MA

No one wants to prepare for the worst, but an offhand comment during a team meeting led a principal investigator (PI) to create a transition plan in case he suddenly died or became incapacitated. He suggests others take the time in the initial stages of a study to make such preparations, rather than making these decisions during the emotional aftermath of an event. The management transition path began for study PI **Brandon Brown**, MPH, PhD, when he expressed gratitude for a team member's work. Brown said the member's "big shoes" would be hard to fill if he were hit by a bus. Already touched by a colleague's recent sudden death, Brown then started to think: What happens if I get hit by a bus?

After the meeting, Brown, a health services researcher and an associate professor at the University of California, Riverside School of Medicine, began working with another investigator, **Annie Lu Nguyen**, PhD, MPH, an assistant professor at the University of Southern California Keck School of Medicine, to create a "just in case" transition plan. Nguyen started with a literature search for such transition plans and came up empty. *(Read more at: https://bit.ly/2U4RJAQ.)* Like writing a will, clinical researchers can preplan for potential transitions. "There are too many cases of unexpected death that occur, leaving more questions than answers," Brown says.

Sometimes, the funds for a research project are returned to the sponsor when the PI dies. Other times, the institution designates a new PI. "But if the institution is not heavily involved in the research, they may not know who might fit, and many (perhaps most) institutions do not have a plan of how to handle studies in case of the death of a PI. I applaud those who have a plan," Brown says.

When developing their plan, Brown ensured all study documents were backed up and accessible in case of his absence. He approached the financial administrators at his university and his grantor about what would happen to the funding if he died. The answers were unclear.

Brown then requested Nguyen lead the study if he no longer could. Assigning a proxy PI is a step away from the direction of complete confusion that has happened in many cases when a PI died, Brown says. Once the study PI selects a proxy PI, he or she should be informed of the selection and agree to it. "Then, the study team should be informed that this person is the proxy PI, and the proxy PI name should be included in the IRB application documents listed as proxy PI." These documents include contracts, manuscripts, funding agreements, and research ethics applications.

Selecting a proxy PI would add little work to the IRB, Brown says. IRBs can add a single cell to applications to request the PI (at the time he or she submits the IRB application) list someone as the proxy PI in the application.

"This way, in case the PI leaves the institution or has an unplanned illness or death, or for whatever other reason, another PI can be contacted as the 'next of kin' in the research," Brown says. "If the proxy PI must also sign the application, it means that they are more likely to read through and digest all of the written materials, providing them more training to take over the

project when necessary." For many studies, the PI is the only person listed on the informed consent document. "This is administratively problematic since if the PI does not or cannot check their email or phone messages, any communication from participants will be lost, or at least unanswered," Brown says. "If there is a 'study email' that is accessible by both the PI and proxy PI, then this should be less of an issue. All study data and documents should be accessible by both the PI and proxy PI. Data can be stored in a repository that is secured by the institution, but only accessible by the PI and proxy."

Brown says he does not believe there should be any necessary documentation above and beyond listing the proxy PI in the IRB application. "The proxy PI should adhere to the same legal requirements as the PI," he notes.

Naming a proxy PI can be a tricky and sensitive discussion with the study team, the sponsor, the IRB, the community advisory board, and other partners. To help with this, a space should be designated for a proxy PI in all new IRB applications to make it an automated process. "In this sense, there wouldn't be a discussion, but the IRB is informed about the proxy at the earliest stage," Brown says. "Since sponsors do not select PIs (the PI is self-selected as the lead for applications), they should not select proxy PIs. The PI of any study will likely have a much better gauge of who can lead in their absence than a study sponsor, IRB, or any administrator at their institution."

Brown also assigned a percent effort of the research to each team member and how the funds would be distributed in his absence. "Payment to the proxy PI (in place of the PI) should be handled in the exact same way as it was proposed and handled for the PI," he explains. Sometimes, this depends on the progress of the study; other times, this is paid as a lump sum. "Most important is to remember the proxy PI is PI [when needed], so there may be some up-front training to ensure the proxy is prepared to take on the role and understand all aspects of the study similar to the current PI," Brown says.

One major complication of distributing payment to the proxy PI is if he or she works at another institution. "It is often the case when a PI is the only investigator at their institution, and their collaborators are at external institutions," Brown says. "This is a complication that I leave to those who have to think about the financial implications of losing funding to their institution."

Researchers also should create a process for notifying a regulatory agency in case the PI dies or becomes incapacitated. "In some cases, IRBs or grants management offices at different institutions have no experience with a PI dying, so they have to figure it out themselves," Brown explains. "The idea of a proxy PI is broader than an IRB issue. It must be something implemented/understood at various levels (IRB, sponsor, study team, grants management, administration, department) for it to work and be useful when the unexpected happens. Each of those levels may decide on the best way forward to record and be prepared for a change from PI to proxy PI, but there should be some harmony." Other questions to consider in the transition plan are instructions on whether the PI would like to be included as an author on publications, or at least acknowledged on them. Also, where should any royalties be directed?

The impetus for thinking about this topic was cemented by various deaths in academia due to the COVID-19 pandemic. "Death is a part of life, and we need to be prepared. Discussing death seems to be taboo in general, and perhaps spoken less about in research than our personal lives," Brown says. "Unfortunately, many of us are spending more time or just as much time in our academic work as we spend on self-care and with our loved ones. This is yet another reason to plan ahead for the unexpected in the research that is so important to us and may define our lives."

"Contemplating and talking about our own deaths can be uncomfortable," Brown and Nguyen wrote in their article. "But by planning ahead, we find peace in knowing that we are doing our best to help our life's work continue beyond our physical presence." ■

Clinical Research as an Equalizer

By Sue Coons, MA

Differences in outcomes and responses to treatment in diverse populations often have been attributed to biological factors. However, standardized treatment can tell a divergent story, one in which parameters, such as geographic location and financial status, play a significant role in how a person responds. This underscores the importance of a diverse study population in clinical trials, researchers say. An example of the difference in outcomes has played out in the area of prostate cancer. One long-standing observation is Black men

appear to present earlier and younger with this disease and experience a higher mortality rate, says **Charles Ryan**, MD, an oncologist with the University of Minnesota Medical School. "A number of biological differences have been identified between African Americans and Caucasian men with regards to a prostate cancer, but I don't think we've effectively made the case to say why, biologically, African Americans had a perceived worse outcome," he says.

Over the last several years, researchers have studied differences in outcomes of Black men based on where and how they are treated. "The question is always, is it a biological difference, which people have been trying to figure out and never anything definitive has emerged, or whether it is a societal or treatment difference, or bias in healthcare practitioners," Ryan says.

In one study of men in the Medicare database, researchers suggested African Americans received a worse prognosis and a worse outcome when diagnosed with prostate cancer,[1] Ryan says. A separate study of men in the Veterans Affairs (VA) database revealed improved outcomes. Unlike Medicare patients, the VA treats veterans according to its protocols. Their access to care is based on veteran status, not income or other factors. "The VA system analysis appeared to not erase, but lessen, the differences between African Americans and Caucasians with regards to outcome and prostate cancer,"[2] he explained.

Susan Halabi, PhD, professor of biostatistics and bioinformatics at Duke University, analyzed data from nine randomized Phase III trials to compare survival rates of Black and white men. The 8,820 participants received an advanced prostate cancer diagnosis, and all were treated with chemotherapy. In comments at the meeting of the American Society of Clinical Oncology (ASCO) in 2018, Halabi said they were testing the hypothesis that Black men experience higher rates of death and incidence of prostate cancer than Caucasian men.[3] "When we did the analysis, to our surprise, we found that it was contrary to what we assumed," Halabi said.

The findings showed the median survival rate was the same in Black men and white men overall (21 months). However, Black men showed a 19% lower risk for death than white men when research adjusted for prognostic factors, such as patient age, performance status, site of metastasis, prostate-specific antigen level, and alkaline phosphatase and hemoglobin levels.[4]

The lower risk of death in Black men might be a reflection of "differences in the biology of the disease," or Black men might experience higher tolerance to docetaxel-prednisone combination, Halabi said. Perhaps the selection of the men was a factor as well. "This is an open question that needs further research."

A clinical trial is another situation in which all patients are treated the same, Ryan says. "That's the point of the clinical trial — to treat them according to a very strict protocol," he notes.

When studying Black men vs. Caucasian men in an arm of a prostate cancer clinical trial, the outcome of the Black men was not only "not worse" but might, in fact, have been slightly better with certain drug categories. "The aggregate effect of those analyses has been to say, 'When we make these claims, we need to be correcting for therapy administered,'" Ryan explains. "When you correct for therapy administered and the protocol with which the therapy is delivered, these differences may go away."

This essentially upended the long-held assumption that Black men experience categorically worse outcomes. "I think we need to say that in situations where access or other factors are integrated, there still may be significant disparities. But if we can correct access, if we can correct therapy, we may be able to correct some of these underlying challenges," Ryan says.

This is an important lesson because it speaks to the importance of treating people according to a standard protocol. "It speaks to the importance of integrating African Americans into clinical trials, for sure," Ryan adds.

Elisabeth Heath, MD, FACP, a medical oncologist at Barbara Ann Karmanos Cancer Institute in Detroit, recently spoke about these additional factors when talking about differences in prostate cancer patterns and response to treatment. In addition to racial disparities in prostate cancer outcomes and treatment, disparities in ethnicity, geographic location, financial status, and socioeconomic status influence treatment decision-making. Heath presented her session, "Evolution of Disparities in Prostate Cancer Treatment: Is This a New Normal?" at the 2021 ASCO Annual Meeting in June.[5]

Heath presented data from the National Cancer Database among 214,972 men with high-risk prostate cancer diagnosed between 2004 and 2016. "Utilization of prostatectomy, compared to radiotherapy, was associated with higher income, private insurance, and treatment at an academic center. Black men were less likely to undergo radical prostatectomy, though, over time, this difference is diminishing," she said.

Among men who underwent radical prostatectomy, Black men experienced a 20% higher mortality

rate than white men. The mortality rate for Asian men is 35% lower than for white men. "These disparities are actually greatest among those without comorbidities and those with less aggressive disease (early-stage and low-grade disease). For example, among men with Gleason 6 prostate cancer, Black men are twice as likely to die of prostate cancer compared with non-Black men. However, these data are limited by a lack of data on recurrence, cause of death, and short follow-up time," Heath said.

Radiotherapy is used more commonly among Black men than Hispanic or white men, Heath noted. However, rates of radiotherapy noncompletion were higher among Black men. Stereotactic body radiotherapy might diminish these disparities, she said.

There exist many different types of research studies with varying conclusions. "The examples I cited in the ASCO 2021 presentation were retrospective. Meta-analysis publications that concluded that there are no differences in outcomes with patients on clinical trials based on race," Heath tells *Medical Ethics Advisor*. "However, these are data from patients enrolled in clinical trials. As seen in the ASCO 2021 claims data in men with castrate-sensitive prostate cancer, only one-third to one-half receive the intended treatment intensification as part of standard of care treatment. In the case of Black men, this number is again lower. The take-home message is that enrolling prostate cancer patients in clinical trials will reduce health disparity."

In her ASCO presentation, Heath spoke about considering the effect of ethnicity. Lumping Hispanic populations together does not account for the meaningful differences in cancer rates among Hispanic populations. For example, "it is important to distinguish Hispanic populations (who descend from Spanish-speaking countries, such as Mexico) and Latino groups (who descend from Latin American countries, such as Brazil)."

"Ethnicity remains a difficult topic to address," Heath says. "Clinical trials are primarily focused on addressing race."

Ryan and Heath discussed Heath's presentation in a video. Ryan said he thought Heath was constructing "multivariate determinants of potential outcome" she wanted to study.[6]

Heath agreed. "[B]ecause we know no matter how you tease it out, each one man always has all those factors going on," she said. What makes it important is recognizing the parameters. "Every time we think disparity, we think Black, white. I look at the sort of Latino, Hispanic … just the ethnicity question is so underexplored. The heterogeneity there is tremendous, and we just kind of clump everybody."[6]

The factors driving the disparity gap are complex and multifaceted. "It is difficult to isolate one specific biological difference when the everyday challenges of access to care or ZIP code also dictate the care that a prostate cancer patient receives," Heath tells *Medical Ethics Advisor*. "Our approach to reduce the disparity gap has to be equally aggressive and multifaceted. Otherwise, the gap will continue to grow."

To help close the gap, Heath recommends IRBs ask if eligibility criteria should be broadened to include specific groups as well as asking how investigators plan to recruit special populations.

However, showing consistent results through standardization of treatment can be undermined by disparities in clinical trial enrollment. Heath also addressed this in her presentation. Nationwide, 6.2% of clinical trial participants are African American, she said. This is substantially lower than the general population, or among cancer patients.

"In addition, in prostate cancer, Latino and Asian men are also underrepresented," Health explained. "Further, only 12% of the sample in the TCGA [The Cancer Genome Atlas] are from African Americans, thus limiting the ability to provide generalizable genomic data."

Globally, the data are no better, she continued. "Among 72 global Phase III and III prevention, screening, and treatment trials in prostate cancer from 1987 to 2016, 96% of enrolled men were white. Further, African countries and Caribbean countries were underrepresented."

A growing number of programs are addressing this underrepresentation. Partnering Around Cancer Clinical Trials is a multilevel, multisite intervention addressing patients and physicians.[7] Genentech's Advancing Inclusive Research Site Alliance is a partnership with several community-based research hospitals that is set up to increase representation and to test enrollment approaches.[8]

Advancing People of Color in Clinical Trials Now! (ACT Now!) studied a "culturally tailored website designed to influence clinical trial decision-making among people of color." ACT Now! used a community steering committee (CSC) to apply a community-based participatory research approach. The CSC gave input through the study conception, development, implementation, and enrollment.[9]

The study included two randomized groups. The intervention group accessed the ACT Now! website, while the control group was exposed to a standard clinical recruitment website. Researchers measured the groups' clinical trial literacy and

willingness to enroll in a clinical trial before and after exposure to the website. Surveys were given at baseline, at one month post-intervention, and a three-month follow-up. As of December 2019, 100 participants had been enrolled.

It is too early to say if these efforts are working, Ryan says, although the topic is front and center at academic sites, including his own. "There's a lot of research money going into looking at disparities and outcomes. It's a topic that is top of mind for a lot of people right now."

Overall, the conversation is not just about race, and not just about one group of people. "Disparity is not only in race, but ethnicity, geography, socioeconomic, and so on," Heath says. "When we discuss and focus on one particular group, it may appear as if the other groups are not getting equal attention. The goal is to engage more researchers and stakeholders in the community to be involved in the conversation so that all groups can be represented."

The discussion does not discount biological differences either, Ryan says, because they do exist in prostate cancer among people of different racial backgrounds. Researchers recently reviewed tumor genomic data and found "clinically significant alterations may occur at different frequencies across races." Black men with metastatic prostate cancer were more likely than either white or Asian men to experience tumor mutations in AR, along with mutations in DNA-repair genes, and actionable genetic mutations.[10]

"Still, we cannot say that all the differences in outcomes are due to biological differences," Ryan says. "In fact, we might be getting to the point of saying most of the differences in outcome are not related to biology but are related to access or patterns of care … and the conversation continues." ■

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CME/CE QUESTIONS

1. **How have ethics consults changed over time, according to a recent survey?**
   a. Most ethics consult services now include a formal evaluation process that involves the collection and analysis of data.
   b. There is significant variation in the median number of ethics consultations conducted annually based on the hospital's size.
   c. There was a dramatic increase in the number of annual consults, but only in small community hospitals.
   d. Most small hospitals found financial support to be insufficient, but most major teaching hospitals reported adequate ethics resources.

2. **Which did a study reveal regarding training of ethics consultation practitioners?**
   a. Most have completed a fellowship program in bioethics, regardless of hospital size.
   b. Smaller hospitals reported dramatic gains in percentages of ethics consultation practitioners who completed a fellowship program in bioethics.
   c. There has been no change in the average percentage of ethics consultation practitioners who completed a fellowship program in bioethics.
   d. Smaller hospitals have caught up to teaching hospitals regarding professionalized consultation.

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3. **Which did a study reveal regarding variation in code status options?**
   a. All hospitals named and defined DNR orders similarly.
   b. Code status ordering systems differed somewhat, but all specified an overall philosophy of care.
   c. Code status ordering systems can contribute to goal-discordant care.
   d. All code status options in hospital systems matched what was in the hospital policy.

4. **Which did a study reveal regarding the research informed consent process?**
   a. Participants' scores of understanding were slightly better if they watched a video compared to the standard consent form process.
   b. People were less likely to participate after watching the video.
   c. Participation rates declined if researchers asked open-ended questions to gauge comprehension.
   d. Researchers need to do a better job of conveying how participants will personally benefit from the trial.

5. **Which did a study reveal regarding graduate students' ethics training?**
   a. A shortened program was effective in improving ethical decision-making.
   b. Students were dissatisfied with a shortened program because they believed it left them unprepared for ethical challenges.
   c. A one-day program was effective only in larger universities offering more overall ethics training.
   d. Trainees reported significant difficulty with basic ethical principles encountered in clinical practice.

6. **When could naming a proxy principal investigator (PI) become more complicated?**
   a. If several researchers want the title
   b. If the sponsor wants to name the proxy PI
   c. If the institution wants to name the proxy PI
   d. If the proxy PI resides at another institution

7. **Clinical trials already offer which advantage in the treatment of diverse populations?**
   a. Standardized treatment for all trial subjects
   b. Wider access to care for minority populations
   c. A way to evaluate ethnic groups generally
   d. Categories to highlight geographic location and financial status

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Discuss new developments in clinical ethics and research regulation and their implications in healthcare systems for patient care, healthcare delivery, and research;
- Discuss the implications of developments in clinical ethics for patients, families, physicians, other healthcare professionals, and society;
- Review and apply principles of human subject protection in clinical trial programs, including compliance with mandated regulatory safeguards and educational requirements for human subject research.