

TEENS AND CHILDREN IN CLINICAL RESEARCH: AN ETHICAL DISCUSSION

OVERVIEW

This module provides insight into the ethical challenges surrounding the involvement of children and teens in clinical research. It encourages students to think about what types of ethical challenges adolescents face in the medical community and the involvement of doctors, researchers, and parents/guardians in medical ethics. Students will be exposed to information concerning IRB regulations, FDA regulations, and the various pillars of medical ethics that researchers and doctors must adhere to whenever adolescents are involved in clinical research. This module relies on statistics and hypothetical situations, both of which are explained and analyzed so that the students may follow and comprehend accordingly.

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LEARNING OUTCOMES

1. Understand principles of informed consent and how they present unique challenges for children/adolescents in research.
2. Evaluate the potential risks and benefits that can result from children and adolescents participating in research.
3. Understand therapeutic misconception and the tension it causes between the goals of the researcher and the participant, particularly if the participant is a child or adolescent with a life-threatening illness.
4. Understand the specific ethical challenges associated with pediatric cancer and epilepsy research.

PROCEDURES AND ACTIVITIES

This unit uses a student-centered and interactive approach to teaching. Activities are designed to allow for student participation and are marked as an individual, partner or group activity.



Teacher-Directed Class Discussion



Individual Activity



Partner Activity



Group Activity

1. WHAT ARE RESEARCH ETHICS?

Research that involves the participation of humans, especially those under the age of 18, raises unique and complex ethical, legal, social, and political issues. Research ethics is concerned with the welfare and rights of participants in research studies, particularly those that test new drugs. The main three objectives of research ethics are: 1) to protect human participants, 2) to ensure that the research is conducted in a way that serves the interests of the individuals who participate, and 3) to examine specific research activities and projects for their ethical soundness, looking at issues such as the management of risk, protection of confidentiality, and the process of informed consent.

2. INTRODUCTION

Thousands of children and adolescents in the United States, from ages 0-18, are afflicted with diseases that have no known cure or treatment. Common examples of these conditions include epileptic disorders and fatal cancers. While medical journals boast the discovery of new treatments spawned from innovative clinical trials, many fail to recognize that a majority of these clinical trials only focus on the adult demographic and fail to properly cater to adolescents who are afflicted with the same or a similar disorder. This is due to a major misconception in the medical community that has prevailed for decades: that adolescents are “small adults.” The thought process behind this misconception stems from the scientific hypothesis that adult dosages of clinically tested medications can simply be modified for children depending on factors like height, weight, age, etc. Upon first consideration, this method seems logical, and thus is why researchers did not feel an urgency to enroll adolescents into clinical trials for several decades prior to the early 2000s. Unfortunately, the truth is that children are *not* small adults and cannot rely on dosages established by adult clinical trials. There remains an urgent need to include adolescents from ages 0-18 in clinical trials that study deadly diseases and disorders, for if this does not occur, the field of medical research will have failed the adolescent population in its promise of fair participant selection.

There is a lack of adolescents in clinical trials for myriad reasons, including the many protective regulations set upon children, the lack of adequate numbers of members suffering from rare disease that are willing to participate in research, and the financial implications concerning the lack of funding for research into a rare disease as opposed to a well-known one such as breast cancer or HIV. The developmental aspects of adolescent bodies also play a major role; there are “dynamics of growth and maturation of organs, changes in metabolism throughout infancy and childhood, changes in body proportion, and other developmental changes that affect how drugs are metabolized in children” (Center for Drug Evaluation and Research). These reasons are coupled with the three major ethical issues concerning the involvement of adolescents in clinical research: consent, confidentiality, and the protection of adolescents from harm. These reasons have served as legal and biological barriers for medical researchers that have made active efforts to discover cures for fatal diseases or disorders. It is important to note, however, that instead of avoiding pediatric research because of its challenges, it is much more crucial to build up support for such research in order for future pediatric research to advance. Without such support, adolescents are at great risk.

The challenge that looms in front of medical researchers that employ adolescents in their studies is the challenge of obtaining consent, for there is very little consensus in literature concerning the way researchers should go about doing so. Consent, confidentiality, and protection from harm are three major pillars to which all medical practitioners must adhere, and the most vital of these three is consent. Commonly cited issues with consent involve articulating clear criteria for obtaining truly informed consent, establishing an age at which a person is able to consent to research participation, and knowing to what extent parents and guardians should be involved. United States law does not consider most children to have the competency necessary to consent to medical treatment. Because the risks of involving children in research studies - in which the risks of benefits of an experimental intervention are not yet known - may be high, children are also not considered competent

enough to consent to participation in medical research under the law. Consent thus becomes an issue of convincing parents of the safety and efficacy of a particular medical treatment or trial. However, because it's not clear at what age children are able to fully consider the consequences of their ages, it is possible that some children are able to consent to participating in research without a parent intervening. Indeed, voluntary consent is a hallmark of ethical research conduct. This begs the question: How can a medical practitioner determine the level at which an adolescent can comprehend the information required to provide consent? Moreover, what should the adolescent patient be aware of in relation to that which his or her parent or guardian must be aware of? These are questions that medical practitioners must answer so that adolescents can be fairly included in medical research.

The ethics of involving adolescents in medical research lies in consent, confidentiality, and protection from harm. Should the medical practitioner rely on consent from the patient or the guardian? How much information should they provide to the adolescent or guardian? Can the safety and efficacy of the trial be guaranteed so as to protect the adolescent from harm? These questions often intimidate parents and adolescents. This is evident when one sees that, despite 22.8% of the US population being under the age of 18 (73,673,073 people), there are only 1,175 ongoing clinical trials involving adolescents being conducted in the United States. During the year 2014, an estimated 15,780 of these children and adolescents ages 0-19 were diagnosed with fatal cancers, and an estimated 1,960 died of the disease. Thus, the research ethics community must determine how to safely include adolescents in research, balancing their safety and their need for new treatments.

3. DEFINITIONS

VULNERABLE SUBJECTS

Vulnerable subjects are subjects whose ability to autonomously decide to participate in research may be compromised. Vulnerable subjects require special protections when giving consent to research participation, and precautions are taken to preserve the voluntary nature of their consent. Federal regulations specify additional protections for four classes of vulnerable subjects: pregnant women, fetuses and neonates, prisoners, and children.

INSTITUTIONAL REVIEW BOARD (IRB)

The institutional review board (IRB), also known as the ethical review board, is a committee that is formally designated to approve, monitor, and review biomedical and behavioral research. Each institution in the United States that conducts research with human participants has an IRB. The IRB reviews and approves all research involving human subjects in order to ensure that it is conducted in accordance with all federal, institutional, and ethical guidelines.

INFORMED CONSENT

The process by which a patient learns about and understands the purpose, benefits, and potential risks of a medical or surgical intervention. Many medical procedures, like receiving an MRI or having surgery, require that patients sign an informed consent document. To participate in medical research, a potential participant must agree to receive the experimental treatment or otherwise participate in the study. Informed consent generally requires the patient or responsible party to sign a statement confirming that they understand the risks and benefits of the procedure or treatment.

For children to participate in research, researchers must consider both the legal and developmental aspects of competence and capacity to give informed consent. By law, most children (individuals under the age of majority in the state where the research is being conducted) are not considered competent to give consent to medical treatment, let alone to consent to participation in medical research. Thus, researchers must provide information to both parent and child. The parent or guardian provides the *consent* while the adolescent provides the *assent*, or agreement to participate.

Adolescents generally fall under the category of “vulnerable subjects.” Because of this, federal regulations establish specific, special protections for children in order to follow the proper guidelines of consent and the preservation of voluntariness and autonomy. The details concerning the basic requirements for informed consent for research are displayed below.

<p>Table 1. Requirements for informed consent (Title 45 Code of Federal Regulations Part §46.116)</p> <p>Basic elements</p> <ol style="list-style-type: none"> 1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures which are experimental 2. A description of any reasonably foreseeable risks or discomforts to the subject 3. A description of any benefits to the subject or to others which may reasonably be expected from the research 4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject 5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained 6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained 7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject 8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled <p>Additional elements to be provided when appropriate</p> <ol style="list-style-type: none"> 1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable 2. Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent 3. Any additional costs to the subject that may result from participation in the research 4. The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject 5. A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject 6. The approximate number of subjects involved in the study

CONSENT & ASSENT

Legally, adolescents are not permitted to provide informed consent (defined above). However, researchers often request that they provide *assent*, which is an adolescent’s verbal agreement to take part in clinical research. Thought assent is not always required for research to begin, IRBs may require it depending on the type of research and how much harm it poses to the adolescent.

In order to provide assent, children must be mature enough to understand the trial and what they are expected to do in said trial. Children younger than seven are usually not considered eligible for clinical trials, but the age varies depending on the maturity of a specific child and policies of the institution running the trial. This may mean that an adolescent under the age of seven can give assent to participate in research.

The assent process goes as such:

1. Parents or a guardian provide the informed consent required for the adolescent to join a clinical trial.
2. The research team explains the trial to the child in simple, comprehensible language that he or she can understand, including the potential risks and benefits of trial participation and expectations placed on the child.
3. The child is encouraged to ask questions and is given the decision to provide assent or dissent (basically, a “yes” or “no” response).

RISKS RELATED TO PEDIATRIC RESEARCH: FEDERAL REGULATIONS

Federal regulations have different designations for pediatric research depending on the level of risk inherent for participants, especially those that are aimed at developing new cancer treatments. These four categories are displayed below:

Table 2. Research risk categories (Title 45 Code of Federal Regulations, Part 46 Subpart D)

§46.404. Research not involving greater than minimal risk
§46.405. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
§46.406. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition
§46.407. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

STANDARD OF CARE

The legal term “standard of care” mainly falls under the definition of “the degree of care and skill of the average health care provider who practices the provider’s specialty, taking into account the medical knowledge that is available to the physician” (Goguen, J.D.). Put another way, the standard of care describes treatments that an average physician would customarily or typically offer to a patient with a particular disease. In many studies, participants receive the standard of care so that researchers can compare the safety and efficacy of an experimental treatment against treatment that most patients with that particular medical condition are usually offered.



1. Are the IRB restrictions placed on adolescents reasonable? Do they accomplish their job in properly protecting adolescents from the dangers of clinical research?
2. Is it morally correct to have the parent/guardian provide the consent while the adolescent patient only provides the assent? Should the patient provide consent? If so, at what age is it safe to begin providing consent?

4. ADOLESCENTS IN ONCOLOGY RESEARCH

A particular field of research where ethical concerns are raised concerning the treatment of adolescents is the field of oncology, or cancer research. This is due to the fact that cancer therapy itself is usually characterized by its toxicity and its many harmful adverse effects (Berg, Stacey L.). Since such toxic therapy is currently the standard of care, oncology researchers testing new therapies hope that the safety and efficacy of these new treatments could potentially reduce the harmful effects of a variety of medicines that are currently in use. According to Dr. Archie Bleyer, Clinical Research Professor at Oregon Health and Science University and the Knight Cancer Institute, “Cancer in children, adolescents, and young adults are so different that each age group needs its own research effort.” He says that “adolescents and young adults have had low clinical trial participation levels in the past, but that’s changing.”

This claim has proven to be true. In recent years, there has been a doubling, even tripling, in the number of adolescents participating in clinical trials for cancer, which provides a beacon of hope for the thousands of patients suffering from different cancers. In 2017 alone, it is estimated that 10,270 children younger than 15 and about 5,000 adolescents between the ages 15 and 19 will be diagnosed with cancer in the United States. An estimated 1,190 deaths will occur for children under 15 and an additional 600 for those between the ages of 15 and 19. As of 2017, there are 4,574 clinical trials being conducted in the U.S. for children with cancer of ages 0-17. 511 of these trials are active, meaning that they are no longer recruiting and have begun to collect data.

It is important to remember that adult cancer treatments given to children at lower doses are not optimal therapeutic options, chiefly because there are so many types and subtypes of pediatric cancers and because the immune system of a child is not strong enough to withstand the intense adverse effects of adult cancer treatment. Many available therapeutic options, particularly radiation, actually do more harm than good. Children will experience severe adverse effects, such as hair loss, nausea, weight loss, weakened immune system, etc., and there is still no guarantee that the cancer will completely disappear despite the immense stress that treatments such as radiation put on the cancer.

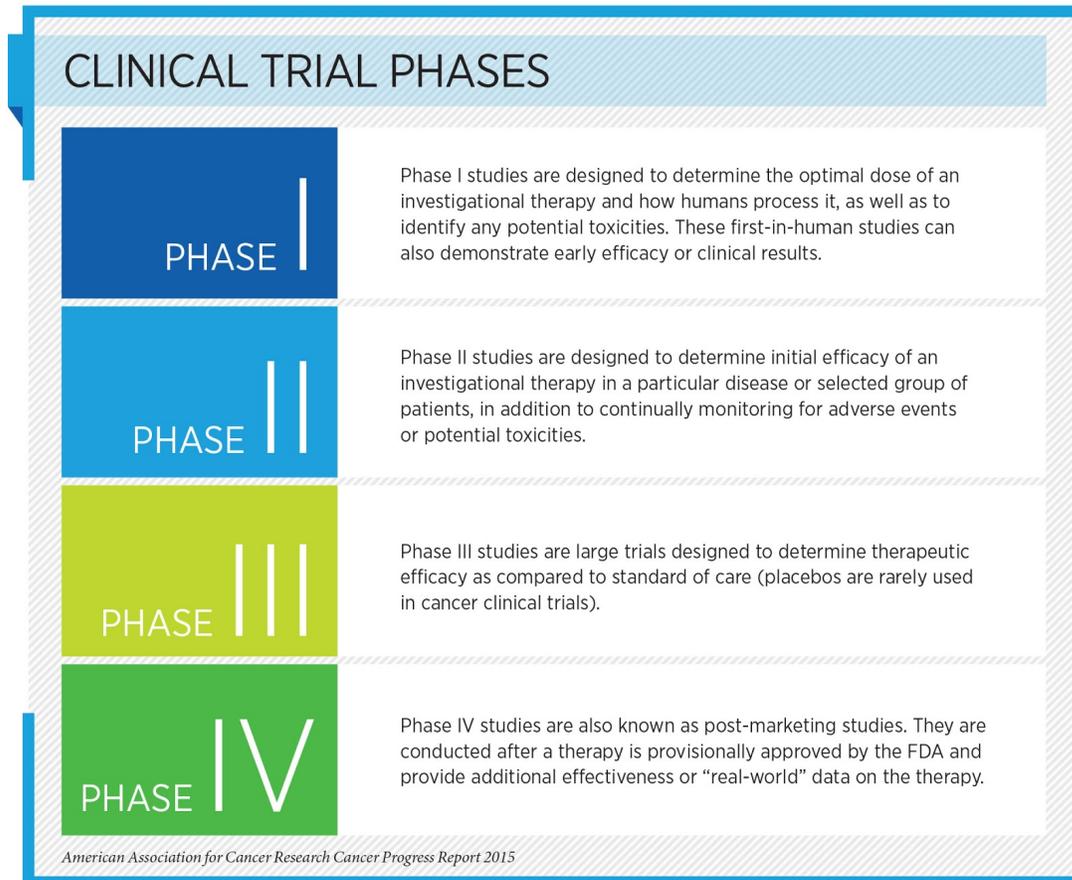
The ethics of oncology research has three specific challenges: the challenge of obtaining informed consent and assent from children/parents, the therapeutic misconception, and challenges related unknown safety and efficacy of these new, experimental treatments.

Obtaining Consent and Assent:

Clinical trial researchers often question the quality of consent they are provided because adolescent patients may not fully comprehend the risks, benefits, and potential outcomes of the study in which they are being asked to participate. Because adolescents are usually deemed to be lacking in “competence” and “mental awareness” as they have not reached full cognitive development, two forms of consent have been established: consent and assent. Consent comes from the parent, who signs off on any legal requirements so that neither the medical researcher nor the facility conducting the research faces legal consequences. This consent is in turn dependent on the assent provided by the adolescent, which is the agreement to participate in the trial after the details of the trial have been delivered and clarified to the adolescent. The ethical issues of using parental consent and patient assent, however, is the question of whether or not there should be “limits to parents’ ability to give permission for a child to participate” in clinical, nontherapeutic research. Adolescents have a right to their bodies and minds as all other human beings do; medical research is, however, one of the many places where the validity of such a statement is questioned. It is difficult to determine whether or not a parent of an adolescent knows what is truly best for the adolescent. And if the adolescent does provide assent, it is unclear as to “how this affirmative agreement can be measured, how seriously dissent should be taken, and at what developmental stage the child’s wishes should take precedence over all else” (Berg, Stacey L.). This means that each case is unique, for the medical researcher would have to determine, based on his/her perception of the adolescent, whether or not the patient can handle and process the information necessary to provide assent. There is no standard method

of obtaining consent, which makes it particularly difficult when one asks whose opinion takes precedence over the other: the adolescent or the parent?

After consent/assent is provided, there comes the issue of dealing with the risks that accompany each study phase: I, II, III and IV (though most oncology trials focus on discussing phase I, II, and III). Each phase focuses on a different scientific question, with the ultimate goal of having the medication or treatment being tested to be approved and adopted for use amongst the general population. Below is a graphic of what each phase entails:



Ethical concerns about study phases often revolve around “which components of the treatment actually represent research and how much potential risk and benefit those individual components represent” (Berg, Stacey L.). This claim compares risk and potential benefit. If one doctor, for instance, claims that a certain procedure presents more harm than benefit but another doctor disagrees, this conflict can sway the IRB against approving that particular study. It is basically a question of how much risk the doctor is willing to place the patient in for the sake of research. Since few are willing to put their daughter or son’s life on the line for the sake of research, this concept raises concern.

Therapeutic Misconception:

An additional struggle concerning study phases is a phenomenon known as “therapeutic misconception.” When many people consent to research participation, they do so because they believe that they will personally receive a benefit, most often in the form of improved health from receiving an experimental treatment. But individual benefit for individual participants is not the goal of clinical research. The goal of clinical research is to gather knowledge from a representative participant population that can be applied to all people who might benefit from the experimental treatment in development. The therapeutic misconception illustrates a tension between the stated goal of the researchers and the motive of the patient for participating in research, particularly a study that has the potential to offer a benefit. Because the patient seeks immediate relief or aid from the agent as opposed

to participating for the purpose of gathering generalizable knowledge, the therapeutic misconception can often interfere with the consent process, especially for adolescents. Parents do not wish to cede their children for the purpose of “experimentation.” Thus, parents and adolescents alike are often more likely to retract consent if the immediate purpose of the agent is not to “cure” the patient.

Safety and Efficacy of New Treatment:

The last ethical challenge relates to establishing safety and efficacy of the new treatment. Next to consent, this is likely the most prominent ethical concern that pediatric oncology researchers face. Let’s consider the example of a more recent technological breakthrough: molecularly targeted therapy.

Molecularly targeted therapy is designed to “specifically target a critical pathway within cancer cells” in order for doctors to tailor treatment to a particular type of tumor (Berg, Stacey L.). This removes the issue of excessive tests and screenings to determine the most effective form of treatment, whether it be chemotherapy or clinically tested pharmaceutical drugs. However, it does present an ethical concern for adolescents. At some point, this technology could be developed to target pediatric tumors without an analogous target in adult tumors, meaning that anticancer drugs and treatments could be developed to first be used in children instead of adults. While it is true that one cannot use treatment meant for adults on children, the fact that the safety and efficacy of a certain treatment was first tested on adults and thus found to be effective has provided some reassurance to doctors and parents for many years. Removing the safety barrier of first conducting research on adults to confirm safety and efficacy makes doctors, parents, and patients extremely hesitant to approach such new technologies like molecularly targeted therapy.

The development of molecularly targeted agents also includes assessments of the drugs on the target. “This brings into sharp focus the problem of more than minimal risk, non-therapeutic components included in therapeutic trials, such as tumor biopsies” (Berg, Stacey L.). This again raises the question of consent versus assent. An adult, of course, can consent to trials that pose more than minimal risk, but is it acceptable for a parent to provide consent for an adolescent to take part in such a trial?

The case of *Grimes v. Kennedy-Krieger* in the state of Maryland provides insight into this question. In the end of this 2001 case the court held that, “a parent...cannot consent to the participation of a child or other person under legal disability (this includes vulnerable subjects) in nontherapeutic research or studies in which there is any risk of injury or damage to the health of the subject.” Any risk was later defined as “greater than minimal risk.”

There is a questionable balance between the positive and negative aspects of adolescent involvement in oncology research. Though their participation is necessary, it can also be life threatening, and the implications surrounding the ethical challenges of oncology research should be first on the agenda of doctors and researchers to deal with before any further advancements are to be made.



Partner Activity

Discussion questions:

1. If the adolescent is willing, should an adolescent be able to risk his/her life in order to participate in clinical research? Why or why not?
2. Should research be approved that first tests on adolescents instead of adults? Why or why not?
3. Is the *Grimes v Kennedy-Krieger* decision a reasonable one? Why or why not?

5. ADOLESCENTS IN EPILEPSY RESEARCH

Another prominent field of research where ethical challenges are a major concern is epilepsy research. While cancers are widespread throughout the body, epilepsy deals with, arguably, the most crucial organ of the body: the brain. The brain is the basis for the development of a human being as a person; something like epilepsy, where excessive electrical activity can harm crucial areas of the brain, impairs this development in varying degrees. Extremely severe forms, such as Lennox-Gastaut Syndrome or Dravet Syndrome, can slow neurodevelopment by years, preventing children from reading, writing, speaking, and carrying out basic functions without the assistance of a caretaker until well past adulthood. Childhood epilepsies are most common among epilepsy diagnoses, thus placing childhood-onset epilepsy in the spotlight of clinical research for this condition.

Unfortunately, many childhood-onset epilepsies are refractory epilepsies, meaning that they do not respond to conventional antiepileptic drugs. This means that extremely severe epilepsies can wreak a path of destruction in an adolescent's brain because doctors do not have an effective way to drastically reduce or eradicate the seizures. There is thus an urgent need to find alternative methods to essentially "cure" refractory epilepsy, as the rate of sudden unexpected death is "6 per 1,000 patients with epilepsy per year, and the lifetime incidence is 7% to 35% with the greater end of this range applying to childhood-onset refractory epilepsy" (Laxer, Kenneth D.).

The ethical challenges surrounding epilepsy research have much more to do with the physical developments of the adolescent rather than federal regulations. The brain is a delicate organ, so childhood epilepsies present a broad range of treatment challenges that are particular to adolescents. This is due to the wide range of causes of epileptic syndromes, many of which doctors have yet to pin down. Because of these wide range of causes, the possible negative psychological and cognitive consequences of seizures, and the impact on quality of life, the management of children with epilepsy raises four key ethical issues: communication of diagnosis, the decision of starting a treatment after the first seizure, and the use of new drugs in children and diagnostic challenges.

Diagnostic challenges arise from a myriad of reasons. When an adolescent has a seizure, it must be recorded using an electroencephalogram, or an EEG, which detects electrical activity in the brain through the use of small, flat metal discs (electrodes) that attach to the patient's scalp. The results appear as spiked lines either on paper or on a computer, and any abnormally large spikes will indicate the appearance of a seizure. Seizures and epilepsy are not synonymous; one does not have to have epilepsy in order to have seizures. This is why "diagnostic challenges" is one of the ethical issues in the childhood epilepsy community, because treatment is dependent on the correct diagnoses and the child suffers for it if the doctor fails to properly diagnose. The doctor must be able to determine if the patient suffers from something like tonic-clonic seizures, whereby the entire body convulses and the patient may lose consciousness, or something less severe, like absence seizures, whereby the patient simply stares off into space without any physical indication of a seizure. These often require additional diagnostic tests, the dangers of which both the patient and guardian must be aware of. Both patient and guardian must also provide the informed consent and assent to undergo these additional diagnostic tests. Explaining its implications is crucial not only for the guardian, but also for the patient; an adolescent, whether five years old or fifteen years old, must still have a certain level of awareness of what treatments they must undergo.

Once the type of epilepsy is determined, treatment options are the next biggest hurdle. Does the patient wish to use antiepileptic drugs? If very severe, does the patient wish to opt for surgery, or even the ketogenic diet, which is heavy in fats and meant to slow electrical activity in the brain? These are the types of questions that must be addressed once diagnosis is determined. The problem is: who answers them?

The answer may seem very obvious, but if one has a five-year-old patient with extremely severe seizures and a parent who is seemingly oblivious about the disorder, the situation becomes very complicated. The doctor must

address the patient's guardian, who must make the decision about whether or not he/she should implement changes into the patient's life, sometimes ones that are very drastic, such as invasive neurosurgery. While necessary, these changes are not ones that can always be assented to by the oblivious five-year-old child with refractory epilepsy, who must undergo treatment with very little understanding of what that treatment actually entails. If the child feels uncomfortable and does not want the treatment, is it ethical, humane even, to ignore that protest and tell the child that this treatment is for his/her own good? Or should both doctor and guardian comply with the patient, who is not even old enough to be considered legally competent? This type of situation is what puts doctors in a bind when it comes to staying within ethical limits of a medical practitioner's job while also ensuring the patient receives the best standard of care possible.

There are, of course, individual risks that come with taking standard anti-epileptic drugs, of which both guardian and patient must be aware of and consent to. There must also be discussion of "potential risks of recurrent seizures, on and off medication," and other details about changes that treatments either entail or cannot control. As stated before, seizures are not synonymous with epilepsy, so "whether to treat a single unprovoked epileptic seizure becomes an individual decision for each patient, dependent from the possible detrimental effect of AEDs (antiepileptic drugs) on one hand and the risks and consequences of a second seizure on the other" (Barba, Carmen). If the seizures are not detrimental enough to cause significant change in the patient's life, or extremely sporadic and very unlikely to occur again, the question of taking AEDs and risking its side-effects as opposed to depending on the chance of a second seizure *not* occurring is something the patient must determine. These implications are also something that the doctor must discuss, even if the patient cannot fully comprehend it.

The use of new drugs is a common ethical challenge in any field of medicine, especially in those where it is common for adolescents to be unresponsive to standard treatment options. For adolescents who do not respond well or at all to standard AEDs, the "clinical goal is to find an optimal balance between the benefits and side effects of any medical treatment" (Barba, Carmen). There are two questions that accompany the topic of new drugs: are they safe enough to be tested and when should they be administered? Utilizing adolescents in clinical trials to test the safety and tolerability of a new drug is already accompanied by layers of regulations and safety concerns. Should a medication be approved even after a trial has been completed, the question of when it should be publicly administered hangs in the balance. Doctors and researchers must still keep track of the participants of the trial that allowed the new drug to be approved, for if any long term collateral effects occur, the safety and efficacy of the drug would automatically be negated. However, financially, the faster the new drug arrives on the market, the faster revenue will flow in. There is thus an ethical dilemma here concerning whether financial concerns should trump patient safety.

These are the most prevalent dangers in epilepsy research, but they should not stand in the way of adolescents participating in clinical trials. The most recent breakthrough in support of this claim is the near-approval of Epidiolex, a pure cannabidiol (CBD) plant extract developed by the British company GW Pharmaceuticals. In layman's terms, this is liquid medical marijuana. Under the supervision of GW Pharma, and in conjunction with Dr. Orrin Devinsky, director of the Comprehensive Epilepsy Center at NYU Langone Health in New York City, Epidiolex has advanced to Phase III trials in order to treat the severe, early-onset, treatment-resistant epilepsies of Dravet syndrome, Lennox-Gastaut Syndrome (LGS), Tuberous Sclerosis Complex (TSC), and Infantile Spasms (IS). For both Phase 3 trials in LGS and Dravet Syndrome, the researchers at GW Pharma noted a "significantly greater reductions in specific seizure types for patients taking Epidiolex compared to those taking placebo." This trial included patients under the age of 18 and has provided a beacon of hope for the thousands afflicted the treatment-resistant epilepsy. The positive results from these types of trials should prompt the continuous participation of adolescents in clinical trials, as this kind of participation is what advances the field of science and allows for new, alternative treatment options to become a reality.

 **Partner Activity*****Discussion questions:***

1. Should financial implications take precedence over the safety of patients when it comes to the introduction of new antiepileptic drugs, especially in such a highly competitive market? Why or why not?
2. If a child under the age of seven suffers from very severe epilepsy, should the parent be able to consent to treatment on behalf of that child, even if the child does not fully comprehend the treatment he/she is undergoing? Why or why not? (Remember: Seven-years-old and under is generally the age where doctors consider children unable to provide consent)
3. Hypothetical Situation: If a patient is diagnosed with epilepsy but is assured that it is not severe and its second-time occurrence is very unlikely, should that patient still take antiepileptic drugs? Why or why not?

6. CONCLUSION **Individual Activity**

1. List the benefits of parental consent and adolescent assent.
2. List the drawbacks of parental consent and adolescent assent.
3. Should adolescents be permitted to provide consent without a guardian? Why or why not?
4. What should be the minimum age of participation for adolescents to be involved in clinical trials?

 **Group Activity**

1. In what ways can the consent/assent system be improved?
2. Determine what the outcome of this situation should be: A child of age ten years old is diagnosed with pancreatic cancer. The doctor prescribes heavy doses of chemotherapy and radiation, but the child does not wish to undergo treatment. The doctor is convinced radiation will help the patient. The doctor turns to the parent/guardian for consent. Is it right of the doctor to only address the parent/guardian? Should the parent/guardian provide the consent, given that the child does not wish to undergo treatment?

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