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Case No. 11, Day 1
Date Due: Jan. 20, 2011

Learning Objective: How are mental health study participants identified and recruited? How can study findings be generalized to general population? What are the ethical implications of conducting mental health studies?

Studies Involving Subjects with Mental Illness Require Rigorous Safeguards to Ensure Patient Consent and Designs to Allow for Generalizability to Larger Populations

Abstract: *The historic abuse of persons with mental illnesses has led to stricter standards to protect the rights of patients who participate in clinical research. Federal and institutional measures designed to minimize patient risk and guarantee informed consent are also weighed by researchers, who seek to advance pharmacological and therapeutic interventions to help persons suffering from mental illnesses. Methods to recruit patient participants may not create a representative sample of the reference population for researchers to draw conclusions for those outside of the study group. The use of controlled trials on affected participants, particularly with drugs to treat specific mental health disorders, has been criticized. Trials using drug interventions often have failed to demonstrate efficacy because of criteria that limits who can and cannot participate, reducing the size of the study group and thus the generalizability of the research findings for the larger affected patient population.*

Introduction: The parent advocates seeking to persuade the Governor that academic success is closely tied to children's mental and emotional health will eventually need evidence to document their case. Their evidence ultimately will have been gathered in research almost certainly from studies on patients like their children, or adults, suffering from a form of mental illness such as depression, ADHD, and other disorders. To understand if such studies have applicability to the larger population of persons suffering from mental illness, the past pitfalls by societies and by those treating mental illness and the current methods for selecting such patients for studies need to be explored. The issue of using patients who may not be fully capable of understanding the implications of their decisions to be studied remains controversial today.

Historic Abuses of the Mentally Ill and Reforms: The formal treatment of mentally ill persons internationally has been marked by abuse, starting with their incarceration in so-called "insane asylums" in Western nations in the 1700s and 1800s. By the mid-20th century at government-run mental health facilities in industrial nations, lobotomies, insulin shock therapy, electro convulsive therapy, and the drug chlorpromazine were used on patients without their consent. In the United States, forced sterilization of patients was legal in 19 states and upheld by the U.S. Supreme court; Oregon did not ban the practice until 1983.[1] The most flagrant abuses occurred in Nazi Germany, where institutionalized mentally ill and handicapped persons were targeted with: first, mass sterilizations (up to 400,000 cases), and then extermination by mental

health professionals in collaboration with the Nazi state, in the name of racial eugenics through a program dubbed "Operation T-4." Up to 250,000 mentally ill and handicapped persons were mass murdered in mental health facilities from 1939 to 1945, mostly by carbon monoxide gas devices later used in Nazi death camps, with psychiatrists carrying out the crimes.[2] Given the tragic legacy of mental health treatment globally, ethical concerns surrounding the coercion of patients in mental health research remains controversial to this day.[3]

In the United States, ethical and legal guidelines concerning human-subjects research have evolved with the creation of safeguards for those patients. In response to Nazi war crimes, the Nuremberg Code of 1948 created the first international standard to require voluntary consent of patients participating in such studies. The Declaration of Helsinki in 1964 reaffirmed the principal of informed consent and called for independent committees to review research before it begins and the use of a standard that risks should not outweigh benefits. The U.S. federally run Tuskegee Syphilis Study (1932-77) on African American males prompted the development of the 1974 National Research Act, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. That body later released the Belmont Report in 1979, which laid the foundation for ethical guidelines for government-backed research on humans.

Following the report, in 1981, the U.S Government issued regulations to protect human subjects, including protecting human subjects in research with drugs. By 1991, 15 federal departments adopted the same guidelines involving human subject research called the Federal Policy for the Protection of Human Subjects, or "Common Rule." That rule calls for institutional research board (IRB) involvement in human-subject research, requirements for informed consent by patients, and additional safeguards for vulnerable patients, such as children and the mentally ill.[4,5] However, the National Institute of Mental Health (NIMH) notes that even today, "there is no clear consensus on which instruments are most effective in assessing consent capacity."[4] Numerous studies consistently have found mental illnesses impair the cognitive aspect of demonstrating informed consent.[5]

How Are Patients Recruited: Patient recruitment, participation, and retention in any mental health study are invaluable for developing successful interventions.[6] But methods to find willing participants for mental health research are distinctly non-random. The most common recruiting method for intervention studies is patients responding to paid announcements and to mass

mailings from databases.[6] For instance, a 2010 study on recruiting elderly minorities for mental health services research identifies two methods to find subjects. The gatekeeper referral, or "consumer-centered" method, involves the subjects' primary care provider referring them to a study. The "self-referral method" involves researchers advertising for subjects in print and electronic and broadcast media.[7] "Consumers" who volunteer for research may enter projects for many reasons: their therapies have failed, altruism, financial necessity, a misperception a study could help them more than other treatment. One psychiatrist notes that despite IRBs and institutional safeguards, "in academic centers there is often pressure on providers to provide enough subjects for studies."[8]

Individuals with mental health issues also can track down mental health research projects on the U.S. Government-run web site www.clinicaltrials.gov. Projects listed show the laboratory conducting the study, the corporate sponsor (such as Eli Lilly Co.), the trial number, the pharmacological drug under investigation (if there is one), and the principal investigator's name, among other data. A keyword search for "depression Seattle" yielded 181 studies, many that are actively recruiting subjects, including teens 13-17 in one study.[9]

Guidelines to protect the rights of mental health patients are enforced within the psychiatric and mental health community, at universities by IRBs, and through required protocols if the research receives NIMH funding. However, critics have faulted researchers and IRBs for failing to prevent unethical research.[5] The NIMH notes it is committed to promoting clinical research with patients with mental illnesses "in an ethical manner" that protects "the rights and welfare of research subjects while advancing scientific knowledge and treatment opportunities."[10] The NIMH publishes a detailed guide on participants' rights, including informed consent. Questions for subjects to ask researcher, particularly if a study involves medications or placebos in a control study, are provided.[4] Researchers conducting studies on subjects with mental health issues must generally satisfy these objectives[11]:

- Will knowledge gained from the study outweigh risks posed to a patient. If no new information can be gained, the study would be unethical.
- All efforts must be made to minimize risks to patients.[12]
- Principles of informed consent need to be followed strictly. Patients or their legal representatives should only participate if risks and benefits are fully explained.
- Research cannot be communicated as a treatment, in order to avoid "therapeutic fallacy," in which a patient may believe there is a health benefit.[5] The NIMH considers it critical that researchers during the informed consent process clearly communicate these differences.[10]

- Information from a study, positive or negative, should be published to the medical community in a timely manner.

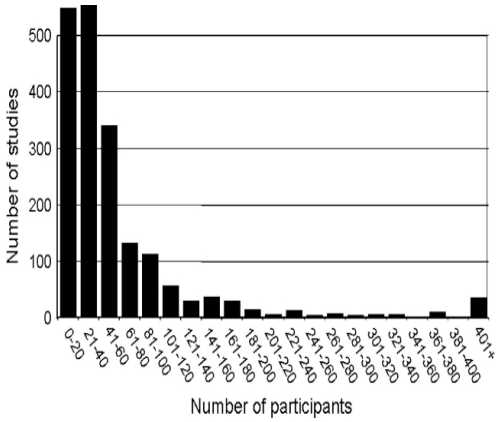
Controversy Concerning "Consent Capacity": The most controversial feature of research involving mentally ill patients is the subject's consent capacity. Researchers receiving federal funding must ensure that adult subjects understand information before making informed, voluntary decisions to participate in research. However, consent capacity can be impaired by mental illnesses, including neurological disorders like stroke and dementia, psychoactive medications, substance abuse, and head trauma.[10] However, excluding such persons from research can prevent the research community from developing better treatments or prevention strategies. What's more, research that does not directly help the patient may be beneficial to the subject's family and to society at large because new knowledge of a condition or disease can provide overall societal benefits.[10] Among the most controversial types of psychiatric studies are placebo-controlled trials and testing with pharmacological products that can induce symptoms. Because the mental health community believes important health benefits can be derived from such studies, these are sanctioned provided they can produce clearly defined scientific results and that the safety of patients is ensured.[11]

Yet, even with such supposedly rigorous standards, researchers have published suspect methods to boost patient involvement, even among children. One study to recruit kids for an in-patient trial of a new drug therapy suggests using patient "incentives." The authors suggest child patients can be enticed with $25-$50 gift certificates before and during the study.[13]

Generalizability of Studies on Mental Health: The goal of mental health research is to help to develop interventions to treat and cure patients suffering from mental illness. Ultimately these studies' effectiveness can be measured by their generalizability to the larger population impacted by a condition. In short, can we apply what we learn from the patients studied to all patients with a disease in question.[14]

A major problem in selecting specific mentally ill persons for drug trials is knowing whether the results can be generalized to the care of others with the illness in question.[15] Numerous studies on the generalizability of medication to treat mental illnesses have found fault with pharmacological trials.[16-19] Many randomized double-blind studies exclude patients with substance abuse or suicidality, though these conditions are often found in daily practice.[15] Two investigations on the efficacy of psychiatric study designs found the sample sizes of patients

participating in mental health sizes were too small to draw conclusions about a treatment's efficacy.[15,20] Precision requires sample sizes in the thousands, while very few clinical trials or observational studies have such sample sizes. Smaller-sample studies have led to publications that exaggerate true effects.[20] In fact, the bulk of randomized antipsychotic drug trials have 60 participants or less, making their generalizability questionable.[15]



Sample size of 2,000 controlled trials in schizophrenia; taken from Leucht et. al, 2008. [15]

In a 2008 study on the success of using antidepressant medications with children and adolescents, a team of researchers concluded that only 12 placebo-controlled trial studies were published by 2005, and most did not have high rates of efficacy because patients with psychiatric comorbidities were excluded from most randomized, controlled trials. A 2005 study also concluded antidepressants' efficacy trials exclude 79% of otherwise qualifying patients, favoring those with the greatest chance of demonstrating drug-placebo differences in a trial study. The researchers found that even with such small samples, antidepressant medications are approved and marketed without their generalizability for the impacted population demonstrated, except for a narrow range of patients.[16] In yet another study (Leucht et. al, 2008), researchers found high wash-out rates, with participants prematurely leaving short- and long-term trials—in up to half of all randomized antipsychotic drug trials. [15]

Back to the Case/Questions: Research involving therapeutic and pharmacological treatments on patients can provide numerous benefits to patients suffering from mental illness. Mental health research on patients may even provide evidence our parent group is seeking to demonstrate causality, that mental illnesses may adversely impact children's' academic performance. But not all of that research may be valid. Researchers frequently employ randomized trials on mental health patients, but their efficacy has been questioned because the results cannot be generalized to the affected population, often because of small sample sizes or protocols limiting patient selection. In addition, subjects who voluntarily participate in such studies, even with current safeguards to protect vulnerable populations, may not understand randomization, placeboes, double-blind procedures, and treatment limitations because they have "therapeutic misconceptions."[5]

Questions: 1) If too few subjects with mental health illnesses end up participating in the vast majority of pharmacological trials, how can the effectiveness of a particular drug be determined for the impacted population? 2) Who serves as the ombudsman for adult mentally ill subjects who voluntarily agree to participate in any study, given some may not be able to grasp informed consent, and is the profit motive by drug companies overriding patient protections?

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