Ethical Issues in Geriatric Research

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Case Presentation
Imagine yourself as a new research investigator conducting your first pilot study. Your ultimate goal is to develop an intervention that will alleviate detrimental health outcomes in the older adult population. In your first interaction with a potential study participant, Mrs. S., you suspect she may have dementia because she has asked the same question about the study at least five times. How should you proceed with the informed consent process? Should you enroll Mrs. S, despite your suspicion that she may not understand your study? Both new research investigators and experienced investigators will face ethical dilemmas like this one with Mrs. S. on a regular basis.

Introduction

Adults 65 years of age and older are the fastest-growing segment of the US population and, due to longer life spans and the aging of the baby boomers, are expected to double to 72 million by 2030 [1]. With greater longevity, older adults incur multiple chronic conditions which contribute to the leading causes of death and 66 % of the healthcare budget [1]. Despite these impressive statistics, older adults are frequently underrepresented or completely excluded from clinical trials without adequate justification [2]. This lack of inclusion is alarming given the fact that many prescription drugs and medical procedures have not been properly evaluated in the population in whom they are most likely to be used.

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In the early 1990s, the International Conference on Harmonisation (ICH) attempted to address this issue by issuing guidance regarding inclusion of older adults in clinical trials of study drugs likely to be used in this population [3]. It was recommended that this guideline, which stated the following, be adopted by regulatory agencies in the United States, Japan, and the European Union:

> The geriatric population is arbitrarily defined, for the purpose of this guideline, as comprising patients aged 65 years or older. It is important, however, to seek patients in the older age range, 75 and above, to the extent possible. Protocols should not ordinarily include arbitrary cutoffs. It is also import not to exclude unnecessarily patients with concomitant illnesses; it is only by observing such patients that drug-disease interactions can be detected. The older the population likely to use the drug, the more important it is to include the very old (pg. 2) [3].

Despite this and other efforts from regulatory agencies, the widespread exclusion of the geriatric population is still evident among clinical intervention trials [2, 4]. For example, studies on hypertension and heart failure tend to include older adults who are younger, healthier, and cognitively intact, thus making it difficult to generalize the results to more complex individuals. The more complex cases, including those normally cared for in geriatric medicine clinics, typically include individuals over 80 years of age with multiple comorbidities, polypharmacy, functional decline, cognitive impairment, and inadequate social support networks [2]. The exclusion of this more complex, real-life population from research is widespread. For example, only a small percentage of older adults discharged from an acute hospitalization with the primary diagnosis of heart failure meet eligibility criteria for heart failure trials [5]. Similarly, in a systematic review of clinical trials for cancer treatment, less than a third of possibly eligible older adults were recruited [6]. In a review of 440 clinical trials regarding type 2 diabetes mellitus, Cruz-Jentoft and colleagues found that only 1.4 % are designed for older adults [7]. In this review, the majority of the trials excluded older adults for the following reasons: 65.7 % based on an arbitrary upper age limit, 76.8 % on comorbidity, 29.5 % for polypharmacy, 18.4 % for

Table 14.1 Educational pearls regarding research in older adults: connecting ethical issues to daily dilemmas

Use good clinical acumen when evaluating new drug therapy for older adults when this population is not representative of the study sample
If engaging in clinical research, adequately justify exclusion of subjects 75 years of age and older with comorbid conditions
Be aware of the challenges, and possible solutions, in research involving older adults
For potential research participants, assess decision-making capacity prior to obtaining informed consent, particularly in vulnerable populations
As there is currently no general consensus, be aware of laws regarding surrogate consent for research in the state in which you practice
Regarding surrogate consent, be aware of the ethical principles of substituted judgment, pure autonomy, and best interest for the older adult who lacks decision-making capacity
Encourage older adult to complete research advance directives to resolve potential ethical dilemmas

cognitive impairment, 8.9 % for short life expectancy, and other poorly justified reasons.

To increase representation of the geriatric population in clinical trials, researchers must understand and be comfortable with the ethical challenges which may arise in this population. Familiarity with basic educational pearls regarding research in geriatric subjects can help researchers safely and ethically include older adults in their studies (Table 14.1). In addition, to minimize the exclusion of older patients from appropriate clinical trials, researchers should be well versed in appropriate informed consent procedures, strategies to prevent under-recruitment, and information security risks.

Informed Consent Issues in Geriatric Research

Informed consent is a process that is intended to ensure human research subjects are provided with the necessary information to make an informed decision to voluntarily participate in research. Agencies and regulations including the Food and Drug Administration (FDA), the Federal Policy for the Protection of Human Subjects (commonly called the Common Rule), the Office for Human Research Protections (OHRP), and the Institutional Review Boards (IRB) require informed consent for human research subjects in research studies. Based on ethical principles delineated in the *Belmont Report*, the informed consent process is intended to ensure that the autonomy of potential research subjects is protected by ensuring that they have decisional capacity and are free from coercion to participate [8].

Decisional Capacity

Decisional capacity is the ability to understand and process information and make judgments based on rational understanding of choosing one alternative instead of another [9, 10]. Hence, decisional capacity is the first requirement of informed consent. A consistent set of criteria for assessing decisional capacity has not been published; however, standards of incapacity include the inability to: express or communicate a preference or choice; understand one's situation and its consequences; understand relevant information; give a rational reason, give risk- or benefit-related reasons, and/or to reach a reasonable decision [11]. Individuals who are capable of demonstrating understanding of the presented information, ability to reason, and consent or refusal to participate may be able to consent and participate in research.

Cognitively and mentally impaired persons are the most challenging to assess in terms of decisional capacity [12]. In some situations, individuals who are cognitively or mentally impaired have substantial impairment to decisional capacity, whereas in other situations individuals may be able to provide consent [13]. For example, older adults who are diagnosed with mental disorders, neurological disorders such as stroke and dementia, and metabolic disorders may retain decisional capacity, but these conditions can cause transient or persistent impairment in individual's capacity to consent [13]. Not only can medical conditions affect decisional

capacity, but the complexity of a research study may hinder the older person's ability to fully comprehend the study and consent to participate [14]. For example, a potential subject may not be able to understand the implications of a randomized control drug trial, whereas they are able to understand and consent to a simple observational study [14]. Determining an individual's capacity for consent and conveying information in an organized, understandable manner that allows for questioning and full consideration of all possible options are important ethical principles of the informed consent process [8].

Procedures for assessing decision-making capacity are defined by the research protocol and may include standardized and validated instruments with cutoff scores for participation, post-consent quizzes documenting the critical elements of the research, or alternative procedures [15]. Although decisional capacity is assessed during the recruitment and the enrollment phase of research, researchers must continue to assess for decisional capacity throughout the duration of the study. If participants lose the ability to consent after enrolling, the participation should be placed on hold for IRB review [16].

In the United States, additional protections of vulnerable research subjects are regulated by federal regulations and state statute. Federal regulations include cognitively impaired persons as "vulnerable" research populations that require additional consideration or protection. This may include individuals with Alzheimer's disease, dementia, mental illness, and developmental disabilities [17]. Consequently, detailed procedures to determine decisional capacity and the ability to consent must be reviewed by the IRB when recruiting subjects with cognitive impairment [17].

Consensus is lacking on the degree of protection that should be afforded to individuals enrolled in surrogate-based research [18, 19]. In certain situations, federal regulations and state statute allow surrogate consent from a legally authorized representative. However, states define legally authorized representatives differently, and many states have no laws regarding surrogate consent for research [20]. Not surprisingly, the role of surrogate consent is contentious, and judgment on the part of all involved in conducting the research is required [21].

Competency

Although the terms are often used interchangeably, the legal concept of competency is not synonymous with decisional capacity. Competency refers to a court decision, usually by state probate court, which determines if an individual has the ability to make competent decisions [22]. In the case of an older person who is determined to be incompetent, a guardian (or conservator) may be appointed as the legally responsible decision-maker through the process of guardianship. The guardian is usually a family member, but can also be a court-appointed friend or impartial person [23]. Legal guardians have the authority to make decisions on behalf of the individual who was deemed incompetent, including participation in research as a legally authorized representative via surrogate consent. In situations where a guardianship is in place, obtaining proof of guardianship status and following strict research protocols to comply with guardianship requirements are important to conducting ethical research and protecting human subjects [23].

Surrogate Consent

Surrogate consent is based upon the ethical principles of *substituted judgment*, *pure autonomy*, and *best interest* standards of the research subject [24, 25]. According to the *substituted judgment* standard of surrogate consent, the exact preferences of the incapacitated person are unknown, and a surrogate determines these preferences based upon preexisting knowledge through understanding of the participant's life history, values, and beliefs [25, 26]. The *pure autonomy* standard requires prior and formal prospective authorization of the incapacitated person to participate in research [25]. Lack of prior communication between an incapacitated person and a surrogate regarding the incapacitated person's desire to participate in research is based upon the *best interest* principle whereby the surrogate makes decisions based upon what he/she judges to be the best for the incapacitated person [25, 27]. The *best interest* standard has been criticized in part because prior studies have demonstrated discordant judgments made by surrogates pertaining to an individual's desire to participate in future research [18]. Without the *pure autonomy* standard of surrogate consent being met, the *substituted judgment* standard has been considered to be the only ethically permissible method of surrogate consent that demonstrates true respect [27].

The NIH and the National Bioethics Advisory Commission have proposed safeguards which are concomitant with the risk-benefit ratio. The required evidence from surrogate decision-makers increases as the risk-benefit ratio for the participant becomes less favorable. For example, in cases where research has the potential to directly benefit the subject, no positive evidence from the past is required as long as the research does not conflict with the person's remaining preferences and interests. However, in cases of research studies that do not have a potential for direct benefit, it is suggested that participation be supported by positive evidence from the past [16]. When working with research participants who have diminished decisional capacity and require surrogate consent, researchers should respect the ethical framework laid out in the Belmont Report based on the tenets of respect, beneficence, and justice. Equal moral force of each principle is required to conduct ethical research, meaning that in certain situations, ethical principles will conflict and one principle should not outweigh another. In addition, from a practical perspective, researchers should clarify the current regulations and seek guidance from their IRB for each proposed research study to prevent adverse consequences for incapacitated adults [28].

Research Advance Directives

Bioethics researchers have maintained the best way to ensure respect for incapacitated participants (i.e., research participants with dementia) when subjects grant advance permission in a research advance directive [27]. However, few competent adults complete research advance directives, while the majority of those who do not complete research advance directives are willing to participate in research that may provide them with benefit [29]. As such, some researchers believe that requirement of formal research advance directives may hinder important research in dementia [29]. Suggestions have been made to develop advanced directives to encompass both medical and research directives and to require research advance

directives for subjects who are competent, but at high risk for losing decisional capacity, such as individuals with mild Alzheimer's disease who are enrolled in longitudinal studies [29].

Overcoming Challenges of Under-Recruitment of Older Adults in Research

Investigators are faced with many challenges in engaging older adults in clinical trials. One of the challenges is recruiting a homogenous sample to reduce confounding variables. However, older adults are a very heterogeneous sample, depending on the number and type of comorbid conditions, their cognitive and functional status, and whether they reside in the community or long-term care settings. Therefore, investigators need to simplify inclusion and exclusion criteria, but also include older adults from different ethnicities and lower socioeconomic classes to ensure the results are generalizable [30, 31]. High attrition rates, whether due to an acute hospitalization, loss to follow-up (i.e., relocated to long-term care), or death, present an additional challenge to the participation of older adults in research. Attrition rates have an effect on statistical power as well as generalization of study results. A suggested solution is to shorten the length of the study (i.e., 3–6 months versus 1–2 years), if possible, for interventional trials using study treatments [30]. A third challenge in enrolling large numbers of older adults in research studies is the consent process. Often, this process is too complex and time intensive secondary to the language level used and highly detailed explanation of the study protocol and risk-benefit ratio. One way to overcome this challenge is to use terminology at the fifth-grade education level which will benefit many older adults without a high school education. In addition, consent forms should detail only the essential components of the study, thereby reducing the amount of paperwork involved with the usual consent forms. If the older adult has impaired cognition, a legally authorized representative needs to be present during the consent process unless information is included in the older adult's advanced directives stating a desire to participate in research. Investigators should detail this process for consenting subjects with cognitive impairment in the study design section of the proposal [32]. More detailed information on impaired cognition in research can be found elsewhere in this chapter.

Privacy and Information Security Risks

Ensuring privacy and information security is a priority for anyone working in healthcare, including researchers. Specific requirements for security of personal information in healthcare are outlined by federal legislation in the United States and are included in the Health Insurance Portability and Accountability Act of 1996 [33]. According to the federal guidelines, all health-related information concerning any identifiable person is considered sensitive. In addition, only those healthcare professionals who have a professional relationship with the identified person should

have access to that person's health information, unless the person has given consent for others to access the information [33].

The International Organization for Standardization (ISO) is an independent, non-government international organization with over 162 national standards bodies. Through the members, ISO brings experts together to share knowledge and develop voluntary, consensus-based international standards that support quality, safety, and efficiency. According to ISO, essential elements of information security include confidentiality, integrity, and availability [34]. These are defined as follows:

- *Confidentiality* refers to the idea that information is not made available for or disclosed to unauthorized persons, entities, or processes.
- *Integrity* refers to the trustworthiness of the information. Specifically, that data have not been deliberately tampered with or accidentally changed.
- *Availability* refers to the idea that information is accessible and usable when needed by authorized personnel or entity.

Due to the sensitivity of personal health information, all three of these essential elements are important in any aspect of healthcare, including research. Researchers must take steps to ensure all subject names, birthdates, addresses, phone numbers, and any other identifying personal information are secure at all times. Whether the personal health information is maintained in paper documents or electronic records, researchers should store personal health information in a locked and secured location. This includes not leaving personal health information at the data collection site, including the hospital, clinic, or car. Additionally, storage of personal health information in an office or computer should occur in a locked area or room with restricted access. The storage method of protected health information should be approved by the appropriate institutional IRB.

Cyber-Crime

Not surprisingly, one of the biggest threats to security of personal information in recent years is cyber-crime. Cyber-crime is a crime that involves a computer and a network. It is defined as "Offenses that are committed against individuals or groups of individuals with a criminal motive to intentionally harm the reputation of the victim or cause physical or mental harm, or loss, to the victim directly or indirectly, using modern telecommunication networks such as Internet and mobile phones" [35].

Cyber-crime is a real and significant threat to governments in every country, their citizens, businesses, and overall economy [36]. The impact of cyber-crime is staggering and includes billions of dollars lost and the risk of disrupting or disabling entire businesses, hospital systems, and banks [37]. Motivations to launch a cyber-attack vary and can include stealing personal information to sell on the black market; spies and terrorists look for vital information related to national security; and even kids that are known as hackers [37]. Unfortunately, security of personal health

information stored electronically for the purpose of research is not immune to this threat. Methods of cyber-attack have evolved and become more sophisticated. Some of the most common types of threats are:

- *Hacking*: Breaking into a computer or network to gain some form of control
- *Malware*: Software designed to infiltrate or damage a computer system without the owner's knowledge or consent
- *Misuse*: Abuse of computer systems, abuse of personal privileges for malicious intent, and abuse of system privileges
- *Deception*: Manipulating an individual to gain unauthorized access to a computer system or network
- *Physical*: Trespass or threat to gain unauthorized access to a computer system or network

The methods can also be combined resulting in a multifaceted and intricate attack.

How to Protect Your Computer-Stored Data and Personal Health Information

The same advice parents might deliver to young drivers on their first solo journey was mirrored by suggestions from a special agent in the Federal Bureau of Investigation's Cyber Division regarding navigating safely online [37].

- "Don't drive in bad neighborhoods."
- "If you don't lock your car, it's vulnerable; if you don't secure your computer, it's vulnerable."
- "Reduce your vulnerability, and you reduce the threat."

Additional steps to protect your computer from intrusion include [37]:

- *Keep your fire wall turned on:* A firewall helps protect your computer from hackers who might try to gain access to crash it, delete information, or even steal passwords or other sensitive information. Software firewalls are widely recommended for single computers. The software is prepackaged on some operating systems or can be purchased for individual computers. For multiple networked computers, hardware routers typically provide firewall protection.
- *Install or update your antivirus software:* Antivirus software is designed to prevent malicious software programs from embedding on your computer. If it detects malicious code, like a virus or a worm, it works to disarm or remove it. Viruses can infect computers without users' knowledge. Most types of antivirus software can be set up to update automatically.
- *Install or update your antispyware technology:* Spyware is just what it sounds like – software that is surreptitiously installed on your computer to let others peer

into your activities on the computer. Some spyware collects information about you without your consent or produces unwanted pop-up ads on your web browser. Some operating systems offer free spyware protection, and inexpensive software is readily available for download on the Internet or at your local computer store. Be wary of ads on the Internet offering downloadable antispyware – in some cases these products may be fake and may actually contain spyware or other malicious code. It's like buying groceries – shop where you trust.

- *Keep your operating system up to date:* Computer operating systems are periodically updated to stay in tune with technology requirements and to fix security holes. Be sure to install the updates to ensure your computer has the latest protection.
- *Be careful what you download:* Carelessly downloading e-mail attachments can circumvent even the most vigilant antivirus software. Never open an e-mail attachment from someone you don't know, and be wary of forwarded attachments from people you do know. They may have unwittingly advanced malicious code.
- *Turn off your computer:* With the growth of high-speed Internet connections, many opt to leave their computers on and ready for action. The downside is that being "always on" renders computers more susceptible. Beyond fire wall protection, which is designed to fend off unwanted attacks, turning the computer off effectively severs an attacker's connection – be it spyware or a botnet that employs your computer's resources to reach out to other unwitting users.

Conclusions

Ethics is the study of conduct and character and is an integral component when interacting with clients in any capacity, including research. In this chapter we described basic ethical issues in geriatric research including ageism, informed consent concerns, challenges of under-recruitment, and information security risks that concern geriatric researchers. Whether you are a new research investigator or a senior scientist, the goal is for all geriatric researchers to understand and consider the complexities of the aging population in order to make the best decisions when ethical dilemmas present themselves.

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