Chapter 7
Research Ethics in Geriatric Psychiatry

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Introduction

Research gaps outnumber what is known about the treatment of psychiatric disorders in late life. The increase in the population of older adults with psychiatric and neurocognitive disorders, and the relative lack of evidence-based treatments for their symptoms and syndromes, argue strongly for an ongoing research imperative—i.e., for basic, translational, and clinical investigations focused on psychiatric and neurocognitive disorders of late life. These studies will require human volunteers, including those with and without specific disorders, to participate in research. In some cases, the studies might benefit the volunteers directly; however, in many if not most cases, the only beneficiaries are science and—hopefully—future patients.

Moreover, as neuroscience research makes forays into increasingly innovative territory (e.g., responsive neuromodulation, brain-machine interfaces), and as research frameworks

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M. Balasubramaniam et al. (eds.), *Psychiatric Ethics in Late-Life Patients*, https://doi.org/10.1007/978-3-030-15172-0_7

evolve—leading to the possibility of earlier and earlier prediction of neurocognitive disorders (e.g., preclinical Alzheimer's disease [AD])—the array of ethical issues confronting researchers as well as clinicians will expand.

Ethical considerations in research with older populations arise at all stages of the research endeavor, from conceptualization of the research question, to study design, to recruitment and retention, to the actual study conduct itself, to analysis of results, and dissemination of findings. Research ethics encompasses a broad range of topics—e.g., informed consent, decision-making capacity and its assessment, surrogate consent, investigator conflicts of interest, and institutional review board (IRB)/research ethics committee review, approval, and oversight. For the purposes of this chapter, however, we will focus only on a few of these topics, i.e., informed consent, decision-making capacity, and surrogate consent to research, as these topics have been the subject of substantial empirical ethics study.

Informed Consent for Research

The pillars of ethical research conduct have been outlined in numerous important codes, declarations, and documents over the last 70-plus years—including the Nuremberg Code, the Declaration of Helsinki, and The Belmont Report (for a more detailed review of important documents in the history of research ethics, see [1]). In the United States, the Belmont Report (formally titled, "Ethical Principles and Guidelines for the Protection of Human Subjects of Research") laid out three broad principles for the ethical conduct of research [2]. The Report also very usefully discussed the operationalization of these principles (i.e., via informed consent, analysis of risks and benefits, and appropriate subject selection). Further, the Report illustrates how the three principles may exist in tension in the research context, acknowledging in plain language that there are not always simple solutions to complex issues that arise in research. In other words, the Report is not

a list of hard-and-fast rules, or a checklist to be followed, but rather is meant to serve as a guide to thoughtful deliberation and decision-making by researchers and reviewers. In this sense, the Belmont Report has been an extremely important document in the field of research ethics. The three principles, as defined in the Belmont Report, are as follows:

- *"Respect for persons: Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy."*
- *"Beneficence: Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being.… Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms."*
- *"Justice: Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of 'fairness in distribution' or 'what is deserved'. An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly"* [2].

Informed consent flows directly from the first principle, respect for persons, as it mandates respecting the autonomy of individuals, operationalized in their willing and informed decision-making. In circumstances where informed consent by the potential participant is not possible (e.g., advanced dementia), the protection of the individual with diminished autonomy takes precedence, as discussed in the section on Surrogate Consent.

As has been discussed in detail elsewhere [3], informed consent for research is generally viewed as consisting of three

required components: (1) disclosure of information relevant to the research decision, i.e., the purpose, nature, and procedures of the study; study risks, benefits, and alternatives; (2) decision-making capacity; and (3) voluntariness (a free and genuine choice made without of coercion) [4].

Decision-making capacity itself has been sub-divided into four requisite abilities, namely (1) understanding, i.e., adequate comprehension of relevant information; (2) appreciation, i.e., the ability to grasp how the research-related information applies to one's own circumstances; (3) reasoning, i.e., abilities to weigh information and reason through the consequences of one's decision; and (4) choice, i.e., the ability to communicate a clear and consistent choice—in the case of research, this amounts to a stable decision regarding participation [3]. It should be noted that this model of decision-making capacity is just that—a model meant to serve as a guide for covering key aspects of the decision at hand. Although there are several instruments available to aid in capacity assessment, there remains no true "gold standard" for assessing capacity [5]. Furthermore, reasonable physicians can come to different conclusions about whether a patient possesses or lacks capacity for a specific task. Importantly, most experts would argue that the standard for capacity should vary depending on the nature of the decision, i.e., a sliding scale should be used wherein higher-stakes decisions require a higher threshold of capacity. In general, because of the relative lack of consensus regarding tools and cut-points, we do not recommend a specific cut-point on a specific capacity assessment tool. However, investigators should consult with their local Institutional Review Board/Research Ethics Committee (IRB/REC) to ensure that appropriate capacity assessments are incorporated into their research protocols when needed. Of note, there is also no consistent regulatory guidance about this aspect of psychiatric research; in the United States, only a few states, for example, have specific laws related to assigning a surrogate for consent for research [6].

It should be noted, though, that numerous studies examining capacity to consent to research among people with a

variety of psychiatric disorders have demonstrated that, while the majority of adults with psychiatric disorders retain the requisite abilities to provide informed consent for research, there is substantial heterogeneity among this population. In other words, some individuals with mental illness are vulnerable to impaired decision-making capacity; these impairments tend to be associated with cognitive deficits rather than with psychiatric symptoms per se [7].

It follows, then, that when older adults who may have cognitive impairment (regardless of underlying etiology) are being considered as potential research participants, additional safeguards around informed consent are likely needed. Such safeguards may include capacity screening, use of enhanced consent procedures, or inclusion of a study "partner" (an individual, often a relative of the patient, who is involved in the consent process and study visits) or subject advocate [8, 9].

Surrogate Consent

In studying geriatric patients with a known diagnosis of a neurodegenerative disorder such as AD or other forms of dementia, investigators inevitably must grapple with the issue of determining how they will ethically enroll these participants. In most cases, ethical research conduct will require obtaining informed consent from someone other than the patient, as well as obtaining "assent" from the patient him/herself. The person providing informed consent on behalf of the patient is variously referred to as the patient's surrogate, proxy, alternate decision-maker, or legally authorized representative (with the caveat that the latter term can be confusing when the law is silent on who is legally authorized to make research decisions on behalf of the patient).

The reality is that in neurodegenerative disorders, patients inevitably lose decisional capacity during the course of the illness. One of the more challenging issues has been determining when this loss of capacity tends to occur. In studies

that used detailed capacity assessment tools (e.g., the MacArthur Competence Assessment Tool for Clinical Research), the consistent finding has been that most patients lose capacity at some point during the transition from mild to moderate AD [10–12]. However, given the move to a biologically defined research framework for AD [13], further research will be needed to determine how the new biologically defined categories of disease relate to levels of capacity, as well as whether certain disease characteristics correspond to specific decisional deficits.

Although surrogate consent is widely used in dementia research, relatively little is known about the nature of surrogates' decision-making processes, i.e., how they make a decision on behalf of their loved one. The ethics literature (as well as a few state laws) emphasize that surrogate decision-makers should make a decision using a "substituted judgment" standard (i.e., stepping into the decisionally incapable person's shoes to make a decision based on how that person would have decided). However, it is not apparent that this is actually how surrogates make these decisions. In a study of surrogate decision-makers for people with AD (who were given a hypothetical clinical trial protocol and asked to discuss whether and why they would enroll their relative), surrogates described using both substituted judgment as well as considering the patient's best interests [14]. Essentially, these surrogates were engaged in a balancing act—trying to honor (their perception of the) patient's wishes and abiding values while simultaneously striving to maintain the patient's quality of life. For example, one participant described trying to consider the type of person her mother was, as well as the potential risks of the study:

> Now with her, you have to take into consideration what kind of person she is to begin with. Then you have to think about, at this age, do you subject somebody to any unnecessary risk? And you have to evaluate…well, the trade-off. Is the likelihood of benefiting science large enough to offset the likelihood of her inconvenience and her discomfort? It's very different when you're thinking about it for somebody else than for yourself [14].

It is not even clear that cognitively impaired individuals and their surrogate decision-makers actually perceive the

decision process similarly. For example, Black and colleagues interviewed research pairs (cognitively impaired adults and their surrogates), asking them about the process they had used when deciding to enroll in a research study (in this case, a study they had actually participated in). Frequent disagreement was noted between the surrogate and the cognitively impaired individual regarding how the decision was made [15]. Several other studies found that surrogates' decisions about research appeared to more closely track their own preferences as opposed to those of the patient [16, 17].

When asked specifically about their motivations for enrolling their relative with dementia in research, surrogate decision-makers have cited the following reasons: potential for direct benefit to the patient; altruism or benefits in the future to others; medical evaluation/diagnostic procedures; compensation; attention from research staff/clinicians; access to more precise treatment; trust in researchers/research; and educational value [18].

The potential for overestimation of direct benefit remains a problem in clinical research, including research focusing on dementia. In some instances, this overestimation may stem from difficulty understanding that clinical research is not the same as standard-of-care treatment. While less studied so far in dementia research, concerns about the "therapeutic misconception" (a failure to appreciate key distinctions between research and treatment) have been raised in clinical research generally [19–21].

Clearly describing for potential subjects and their family members the purpose of the research, as well as (when applicable) the limits of what is currently known about the treatment being studied, may help mitigate this sort of misunderstanding. Nancy King, in an effort to reduce misplaced optimism about direct benefits of research for participants, argued for a more clear-cut delineation of types of potential benefit in trials, i.e. [22],

- *Direct benefit, …properly defined as benefit arising from receiving the intervention being studied*

- *Collateral benefit to subjects …benefit arising from being a subject, even if one does not receive the experimental intervention (e.g., a free physical examination and testing, free medical care and other extras, or personal gratification of altruism)*
- *Aspirational benefit, or benefit to society and to future patients, which arises from the results of the study* [22]

Whether such description of benefits in consent forms and discussions would help participants better appreciate the nature and likelihood of benefit in dementia research is, thus far, unclear.

Future Directions

Geriatric psychiatry deals with some of the most difficult-to-treat conditions in medicine. Ethical enrollment of older adults with a wide range of psychiatric and cognitive disorders will remain of paramount importance for the knowledge base to advance. Numerous issues related to the ethics of research involving older adults with psychiatric and cognitive disorders remain understudied and unaddressed. These include the following:

- Legal and policy issues—e.g., the legal status of research on individuals with diminished capacity due to neurocognitive disorders; legal and regulatory guidance regarding surrogate consent for research
- Empirical questions about decision-making capacity—e.g., when is it appropriate or necessary to conduct formal capacity assessment; what tools should be used to conduct such assessments; who should do these assessments; where should the line be drawn between adequate and impaired capacity; and how should this line vary depending on the nature of the research?
- Surrogate consent issues—e.g., how best to engage surrogates in the consent process; when and how to assess surrogates' own understanding of research; how to evaluate

whether surrogates are weighing the risks and benefits of research appropriately for the patient?
- Review and oversight issues—e.g., how should IRBs define and weigh risks and benefits in considering research involving individuals with diminished capacity.

Conclusions

Geriatric psychiatry research will become increasingly needed in an era of major demographic shifts to an aging population. While we have attempted to provide an overview of some of the ethical issues that arise in the conduct of research with older adults, undoubtedly there are additional issues that are likely to emerge. Investigators who are conducting—or hope to conduct—research involving older adults and their families need to be versed in the ethical foundations of human subjects research, including past history of abuses and exploitation particularly involving vulnerable populations such as people with mental illness. The "research imperative" can be met while also meeting our ethical obligations to participants, but this requires ongoing vigilance regarding the ethics of research, as well as the humility to acknowledge how much we do not know about the human brain, as well as human motivations. Research on the ethics of research is also needed to continue to flesh out these important issues, particularly as research on the brain moves into ever more technologically sophisticated realms.

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