RESEARCH ETHICS

The need for additional safeguards in the informed consent process in schizophrenia research

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The process of obtaining informed consent to participate in a clinical study presents many challenges for research conducted in a population of patients with schizophrenia. Morally valid, informed consent must include information sharing, decisional capacity, and capacity for voluntarism. This paper examines the unique features of schizophrenia that may threaten each of these elements of informed consent, and it proposes additional safeguards in the process of gaining informed consent from individuals with schizophrenia in order to maximise the decision-making potential of this patient population.

All research with human participants requires thorough consideration of ethical issues; however, research involving individuals with a mental illness poses unique ethical challenges due to the cognitive impairment, debilitation and stigma associated with many psychiatric diagnoses. These ethical challenges can arise at many points throughout the research process, including the trial design phase, the recruitment and inclusion stages, the process of gaining informed consent and the treatment washout period. Previous attempts to propose additional safeguards in research involving individuals with a mental illness have been met with accusations that such measures are stifling progress in psychiatric research. Opposition to the participation of individuals with mental illness usually arises from psychiatrists rather than from patients or their family members,[1] and there are differing opinions surrounding the extent to which this patient population actually desires special ethical consideration.[2] There is also concern that enacting special protections will further disenfranchise this socially stigmatised population.[3]

Although there is some opposition to the implementation of additional safeguards for participants in psychiatric research, many are advocating protections for this vulnerable group to prevent potential exploitation and abuse during the research process. One component of research that requires additional safeguards for individuals with a mental illness is the process of obtaining informed consent to participate in a clinical study. Informed consent involves a voluntary choice by an informed and capable individual to participate in research and should be thought of as an ongoing process between the investigator and participant throughout the duration of the study, rather than as a solitary, discrete event.[4 i]

Obtaining informed consent poses significant challenges when one is dealing with individuals who have schizophrenia. This chronic mental illness is characterised by delusions, hallucinations, disorganised speech and behavioural patterns, and flattened affect.[5] These symptoms may fluctuate over time, with individuals alternating between periods of lucidity and capacity and periods of psychosis and incapacity. Consequently, a unique feature of schizophrenia is that capacity is often fluctuating,[6] in comparison with other medical conditions or mental illnesses that render individuals permanently incapacitated. The vulnerable nature of this population does not preclude individuals with schizophrenia from giving informed and voluntary consent. Current thinking in research ethics has tended to move away from exclusions based on diagnostic status, such as schizophrenia, because of compromises to patient autonomy.[3]

Informed consent can be conceptualised as consisting of three primary elements: information sharing, decisional capacity and capacity for voluntarism.[6] Jeopardising any one of these elements can threaten the moral validity of the informed consent process. Each of these elements will be discussed in relation to the informed consent process in schizophrenia research.

INFORMATION SHARING

There is a lack of consensus with respect to the type and extent of information that should be disclosed to potential research participants during the process of gaining informed consent,[3 7 8] and there is no standard as to what amount of information is sufficient for making an informed choice.[4] The types of information that should be disclosed include the aims of the study, potential risks and benefits of participation, alternatives to participation, and relevant study design features such as the use of a placebo group or washout period.[8]

Some investigators conducting psychiatric research have paternalistically withheld information from patients, fearing that such information would be unnecessarily distressing for potential research participants. This failure to disclose sufficient information may arise from a confusion of the roles of clinician and investigator. Within the context of clinical practice, the ''therapeutic privilege'' allows physicians to withhold

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[i] For more information on informed consent, see Faden RB, Beauchamp TL, King NMP, *A history and theory of informed consent*, Oxford University Press: New York, 1986.

information from a patient when it is felt that disclosure of the information could have an adverse impact on the patient's well-being.[4] This exception allows clinicians to withhold specific details that may be distressing to patients, although the physician still has an obligation to provide as much information as possible.[9] Clinical investigators may inappropriately carry this practice over to the informed consent process in research, where the goals of research and therapy are fundamentally different and potentially conflicting. For example, the therapeutic privilege may permit a clinician to temporarily withhold details regarding the potential side effects of an antipsychotic medication when a patient is in the midst of a psychiatric crisis, with the expectation that this information will be disclosed once the crisis has subsided.[9] However, it would be entirely inappropriate to withhold information regarding the potential side effects of an investigational therapy when attempting to recruit a prospective participant for a clinical trial. Thus, the standards that are used in clinical practice may not be in the best interests of a patient within the research context.

Even when individuals with schizophrenia do receive adequate information, research has shown that the symptoms associated with many mental illnesses may compromise the information-sharing component of the informed consent process.[6] Learning and memory deficits frequently accompany a diagnosis of schizophrenia, and many patients exhibit difficulties with basic thought processes and verbal communication.[10] Studies examining participants' understanding of informed consent information have found that individuals with schizophrenia demonstrate lower levels of comprehension than various comparator groups, many of whom also have a psychiatric diagnosis.[11–13] These deficits in comprehension appear to be associated with the symptom of conceptual disorganisation that is often evident in individuals with schizophrenia, and not with the symptoms of hallucinations, unusual thought content or suspiciousness per se.[14] Safeguards are required in schizophrenia research to address these cognitive impairments.

The presentation of enhanced informed consent information has been found to be effective at improving information sharing. This strategy may include elements such as computerised presentations with structured text, oral reading of the information by research staff and providing an opportunity to ask questions throughout the presentation.[11] When using this technique, individuals with schizophrenia demonstrated a level of comprehension of the informed consent information equivalent to that of healthy control subjects undergoing a conventional consent procedure.[11] A similar study also found that information presented to patients with schizophrenia via the enhanced consent procedures is retained a week after the consent process.[14] A more structured and organised presentation of information may help individuals with schizophrenia who have learning and memory deficits to better comprehend and retain the relevant information about research participation and provide more meaningful consent.

Difficulties with comprehension of informed consent information are not unique to psychiatric research.[15] In fact, enhanced consent procedures have also been shown to improve comprehension for healthy research participants,[11] indicating that this safeguard may not only be necessary for psychiatric patient populations. Although the strategies outlined for improving the information-sharing element of informed consent may be relevant across all research populations, it is particularly important that they be adapted and implemented into informed consent in schizophrenia research, because of the increased comprehension difficulties among these patients.

DECISIONAL CAPACITY

Decisional capacity requires a comprehension of the information relevant to the study, the ability to think rationally about the decision at hand, an appreciation of the decision and possible consequences, and the ability to communicate a preference.[6] Symptoms of schizophrenia may threaten the decisional capacity element of the informed consent process. Avolition is a common feature of the diagnosis and is characterised by an inability to make decisions.[5] There is also evidence that the decreased neuropsychological functioning and negative symptoms (such as apathy, anhedonia, flattened affect) experienced by many patients with schizophrenia are associated with impairments in decisional capacity.[13 16] These symptoms can have a progressive course in individuals with schizophrenia, which poses a significant concern when informed consent is conceptualised as an ongoing process. For example, within the context of many pharmaceutical trials, the patient may demonstrate a marked progression of negative symptoms as a consequence of the investigational therapy. This patient will begin to appear immobile and emotionless, to decrease communication with others and to lack interest and motivation. These symptoms affect both the capacity for decision-making and interactions with others, thereby threatening the validity of ongoing informed consent.

Research has shown that in comparison with healthy control subjects, individuals with schizophrenia show marked impairments in decisional capacities that have implications for the informed consent process.[16] The cognitive impairments associated with schizophrenia may hinder an individual's ability to make a decision that is in his or her best interests. Conversely, individuals with schizophrenia may not be decisionally incapacitated on a regular basis, and many are able to function quite capably in daily affairs.[16] Many mental illnesses, including schizophrenia, are characterised by fluctuating periods of lucidity and cognitive functioning.[17] This fluctuation may also be accompanied by corresponding fluctuations in decisional capacity, and individuals with schizophrenia may be incapacitated in one realm of decisional functioning while being quite capable of making other decisions,[18] so that the assessment of decision-making capabilities for the purposes of obtaining ongoing informed consent poses significant challenges. For example, a lack of insight into the illness and a denial regarding the need for treatment are common characteristics of schizophrenia.[10] Consequently, the capacity to choose to participate in an experimental drug trial would be impaired by this belief that treatment is not needed, while the capacity to consent to participate in a genetic study involving patients with schizophrenia might be maintained. Decisional capacity should be assessed based on an individual's capacity in each specific context. Safeguards are required that will allow schizophrenia patients to exercise autonomous choice, while also providing protection for patients during periods or circumstances of decisional incapacity.

Many have advocated proxy consent as a solution for fluctuating decisional capacity in research participants with schizophrenia. Proxy consent is given by a surrogate decision-maker on behalf of an incapacitated individual who is unable to give informed consent.[7] A survey involving individuals with schizophrenia found that this patient population strongly endorses the importance of autonomous decision-making.[19] Referral to a surrogate decision-maker as a catch-all solution for problems with decisional capacity is not an adequate or ethically sound choice for research participants with schizophrenia. Consent by the participant is always preferred, and a surrogate decision-maker should be used only as a last resort. Many individuals with schizophrenia who have mild or moderate cognitive impairments may also have levels of

understanding and comprehension that are only slightly below those of individuals who are competent to consent.[20] Hence, this strategy may be counterproductive by infringing on the dignity and autonomy of these individuals while attempting to protect their dignity and personal interests through the use of a surrogate decision-maker.

Advance research directives are an alternative strategy proposed for dealing with individuals who may become cognitively impaired during research participation. A research directive involves a written document that provides explicit consent for ongoing participation in research, within certain parameters, in the event that an individual becomes incapacitated.[6 17] Such a document outlines various situations that may arise throughout the course of the research, and the participant specifies clear preferences for participation based on each scenario. A surrogate decision-maker may also be specified, if desired, in addition to acceptable thresholds for mental and emotional discomfort.[17] This strategy accommodates the potential for fluctuating periods of lucidity while capitalising on the time when participants are competent to exercise their right to autonomous decision-making. It also requires participants to explicitly state a preference that is consistent with personal value and belief systems, rather than relying on assumed preferences made by surrogate decision-makers. In addition, composing advance research directives forces individuals to fully consider all of the potential difficulties and consequences that may arise as a result of participation in a trial, thereby improving the information-sharing element of the informed consent process.

The proposed safeguards for promoting decisional capacity throughout the informed consent process have several limitations. The most significant quandary arises from the potential for a patient's wishes to change after the advance research directive has been signed. It is quite conceivable that an individual may express wishes that are contrary to the research directive while in a state of decisional incapacity. This raises the question of whether incompetent dissent should trump competent consent, or vice versa. Alternatively, given that individuals may be unable to adequately predict the extent of mental and emotional discomfort that may arise, one might also argue that this negates the research directive because consent was not fully informed. The strategies discussed here represent only preliminary proposals for the protection of decisional capacity while attempting to respect individual autonomy. Further research and discussion in this area will be crucial for the development of adaptable and specific safeguards addressing decisional capacity in populations of patients with schizophrenia.

VOLUNTARISM CAPACITY

The capacity for voluntarism refers to an individual's ability to act freely and without coercion and is crucial for obtaining meaningful informed consent. Four factors can potentially influence an individual's capacity for voluntarism: developmental factors, factors related to diagnosis, psychological, cultural and religious factors and external pressures.[6] These factors do not necessarily need to be overt or conscious to make consent involuntary.[7] Of the three elements of informed consent, the capacity for voluntarism is the element that is the least understood, and no guidelines have been developed to date for its assessment.[21]

The symptoms, severity and variable nature of schizophrenia may have a significant impact on an individual's capacity for voluntarism.[21] The decision to participate in psychiatric research is not truly voluntary if it is dictated by the symptoms of a mental illness,[18] and common symptoms of schizophrenia, such as apathy, anhedonia, bizarre thoughts and impaired insight, can influence participation decisions.[21] Many individuals with schizophrenia are non-compliant with their medication regimens because of side effects, and the desire to participate in a clinical trial may be motivated more by desperation and a lack of viable alternatives than by a truly voluntary desire to participate. These symptom-driven motivations for research participation significantly hinder an individual's capacity for voluntary consent.

Another potential threat to the voluntarism element of informed consent occurs in the context of the physician–patient relationship when the attending psychiatrist is involved in the research study. Many argue that informed consent is invalid when it is given by an individual who is dependent on an investigator–clinician for his or her continued well-being, as this consent may have been given out of a desire to please the psychiatrist.[4] Indeed, patients with schizophrenia do acknowledge that recommendations by psychiatrists play a role in their decision of whether or not to participate in a clinical trial.[22] Although this problem is prevalent in the physician–patient relationships of other medical disciplines, it is heightened among patients with schizophrenia, where deep levels of trust and dependency are inherent in the psychotherapeutic relationship.

One strategy that might reduce the effect of psychiatrist influence on the informed consent process is to have researchers who are not involved in patient care solicit participation in research studies and have participant advocates available to assist individuals who may have questions or concerns.[23] An additional strategy that might prove useful for increasing the capacity for voluntarism of patients with schizophrenia is to encourage the participation of the schizophrenia community in the research process. This could include involvement in areas such as setting the research agenda, designing projects and making ethical decisions.[3] Individuals with schizophrenia could also assist research ethics boards in the evaluation of psychiatric research protocols. Similar approaches incorporating participant involvement have been shown to be an effective strategy for other vulnerable populations[24] and may improve the voluntariness of participation in schizophrenia research by giving the population of patients with schizophrenia a voice in the research process.

Although some may argue that the capacity for voluntarism is the most important element of the informed consent process, it is unfortunately the least well understood, and very few studies have addressed this issue. This is in part because of the difficulties involved in measuring voluntarism, as the factors that erode voluntary choice may not be overt and participants may not be conscious of them.[7] Research into the variables that impede the ability to act voluntarily is desperately needed to advance the understanding of this element of informed consent and develop effective safeguards to protect the capacity for voluntarism.

CONCLUSIONS

The established effectiveness of the proposed safeguards for research in populations of people with schizophrenia demonstrates that patients with severe mental illnesses are capable of providing meaningful informed consent. It is important to note that the three elements of informed consent outlined above, namely, information sharing, decisional capacity and capacity for voluntarism, cannot be taken in isolation. If the informed consent of individuals with schizophrenia is to be truly meaningful, it must be built upon all three elements. The proposed safeguards for obtaining consent from this population must be used in combination to preserve all three of the elements of informed consent. The incorporation of safeguards should become a standard procedure for obtaining consent

from individuals with schizophrenia and should not be viewed as additional to the consent process. An in-depth consideration of the three elements of informed consent and the use of safeguards tailored to individuals with schizophrenia will maximise the decision-making potential of this population, thereby respecting their right to act as autonomous individuals.

What is critically needed in the field of psychiatric research is not stigmatisation or neglect, but rather an increase and expansion of psychiatric research while incorporating safeguards to protect the rights and autonomy of this vulnerable population. However, safeguards based on patient diagnoses need to be applied with caution, as the implementation may become over-inclusive. Although it is important to implement safeguards in the informed consent process for this population, it is also crucial to ensure that an adequate balance between population safeguards and personal autonomy is achieved. All individuals with schizophrenia should have their potential for giving informed consent recognised, and safeguards such as those proposed here are crucial for facilitating the informed consent process in individuals with schizophrenia.

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