Umesh Chandra Gupta, Saifuddin Kharawala[1]

Sr. Research Scientist, Medical Affairs and Clinical Research, Fresenius Kabi India Pvt. Ltd. Gurgaon, [1]Clinical Research Consultant, Consultant Psychiatrist, Mumbai, India

Address for correspondence:
Mr. Umesh Chandra Gupta, Sr. Research Scientist, Medical Affairs and Clinical Research, Fresenius Kabi India Pvt. Ltd., Echelon Institutional Area, Plot no. 11, Sector - 32, Gurgaon – 122 001, India.
E-mail: gupta.umesh15@gmail.com

Informed consent in psychiatry clinical research: A conceptual review of issues, challenges, and recommendations

Abstract

Obtaining informed consent in psychiatry clinical research involving subjects with diminished mental abilities and impaired consent capacity has been a challenge for researchers, posing many ethical concerns and procedural hurdles due to participants' cognitive deficits and impaired ability to judge reality. Regulations seem inadequate and provide limited guidance, not sufficient to address all the ethical issues inherent in different situations related to obtaining consent from decisionally impaired persons. Researchers are struggling to find a balance between risk-benefit ratio, research advancement, and autonomy of study subjects. Inspired to improve the consent process in psychiatry clinical research, many studies have been conducted focusing on various informed consent–related ethical concerns, with the aim of developing appropriate strategies and optimizing the informed consent procedure in psychiatry clinical research, overcoming the ethical concerns. This article critically reviews the various ethical issues and consent challenges, their underlying reasons, and investigates the appropriate strategies and practices needed to be adopted while obtaining informed consent from subjects with impaired consent capacity, participating in psychiatry clinical research.

Key words: Clinical research, clinical trials, ethics, informed consent, psychiatry

INTRODUCTION

Psychiatry clinical research involving decisionally impaired subjects, depending on its design, nature, and purpose, has been associated with various ethical concerns including issues related to drug-withdrawal, use of placebo, and validity of informed consent.[1-4] The decision-making capability of a person may be affected by a neuropsychiatric disorder due to significant deficits in their mental abilities, therefore, hindering their capacity to provide a logical consent. This may in turn lead participants to enter in the study without fully understanding the inherent risks, and this poses ethical concerns over the validity of informed consent in psychiatry clinical research involving subjects with mental illness, because a valid informed consent may require a competent person to take informed and voluntary decision. A research should not involve decisionally incapable subjects, if it can be performed with capable subjects;[5-7] but unfortunately there are health-conditions causing decisional impairment and research on these conditions can only be conducted involving these subjects. Diminished mental ability and the consent capacity of subjects with psychiatric illnesses, due to cognitive deficits and altered mental function such as impairments in

Access this article online

Quick Response Code:

Website: www.picronline.org

DOI: 10.4103/2229-3485.92301

attention, mood, information assimilation, understanding, and reasoning make them vulnerable. Therefore, the informed consent procedure (ICP), by raising questions for preserving autonomy of an individual subject and validity of consent, remains as the most controversial ethical aspect in psychiatry clinical research[8] and this area of ethical sensitivity has long been a source of much debate and controversy.[5,9-11]

INADEQUACY OF REGULATIONS

Necessity of informed consent is an essential element of biomedical research involving human subjects.[12-15] Major dilemma and debate, in obtaining informed consent from subjects with cognitive impairment, exist with regard to validity of the subject's consent, implications and validity of third party consent, and protection of human subjects. Regulations and guidelines merely endorse the idea of requiring consent from the legally acceptable representative (LAR) in conducting research involving incapable subjects.[12,16,17] Regulations do not provide much guidance regarding the ethical issues of psychiatry research and specify inadequately the procedures and standards for ICP, suitability of LAR, consent capacity assessment, third party consent, protection and safeguard criteria, and responsibilities of investigators and Institutional Review Boards (IRBs) involved in psychiatry research involving subjects with impaired consent capacity.

ELEMENTS OF INFORMED CONSENT

Elements, onto which the informed consent is built, include voluntarism, information disclosure, and decisional capacity.[18] For an ethically valid consent, these critical elements are needed to be adequately present and essentially employed. Capacity for making rational decisions comprises of the ability to understand, logical reasoning, communicating a well-reasoned choice, and appreciating the significance of the decision made.[19,20] Issues and related aspects of consent capacity are expressed elsewhere in the article.

Information disclosure to the potential participants should disclose relevant information important for decision-making on study participation, including the nature and purpose of the study; treatment and experimental procedures; risks and benefits of study participation; nature of illness; availability, risks and benefits of alternatives; and right to withdraw.[18,21-23] Information disclosure to the subject, however, may be shortened appropriately in certain practical situations of emergency, therapeutic privilege, and incompetence. In aiming to enhance clinical collaboration with the subjects to achieve more knowledgeable participation and treatment adherence, the investigator may encourage them to ask for additional information. Interestingly, '*talking with a researcher*' has been identified as one of the most favorable parameters for a subject's willingness to participate in the study.[24] Repeat contacts between investigator and subject may help to develop a relationship and to provide the information before the formal consent is obtained.[25]

Despite being elaborated in ethical codes and regulations, the concept of voluntarism has not been realized and practiced much in the clinical research scenario. Roberts[18] defined voluntarism as *the ability of an individual to judge, freely, independently, and in the absence of coercion, what is good, right, and best subjected to his / her own situation, values, and prior history.* Roberts also provided a voluntarism framework, pertaining to consent decisions in clinical research, comprising of four domains of influence that could potentially influence the participants' capacity of voluntarism. These domains included: (1) Developmental factors, such as progressive, intellectual, and emotional maturity of young people to make complex decisions; (2) illness-related considerations, such as ambivalence and pessimism of depression, compulsive use, and impulsive behavior in substance use disorders; (3) psychological issues and cultural and religious values, such as family autonomy in some Hispanic, Native American, and Asian cultures or catholic beliefs regarding moral action at the beginning and end of life; and (4) external features and pressures, such as relationship with caregiver and economic burdens of extended care.[18,26]

CONSENT CAPACITY ASSESSMENT

Assessment of a participant's capacity to make rational decisions is a core component playing a vital role in the context of obtaining consent in the psychiatry clinical research settings as, (a) capacity assessment has many interrelated implications over third party consent, as discussed later in the text, (b) a meaningful consent is only possible when participants possess or attain the capacity to comprehend the disclosed information and use it to come up with a reasoned decision, and (c) it is important to distinguish between capable and incapable subjects prior to participation, which would probably help in supporting and informing them continuously as the study progresses.

Many authorities have recommended the evaluation of the consent capacity of mentally challenged subjects participating in the clinical studies, particularly those involving higher risk.[7,23,27] Few journals also require the capacity assessment for manuscript publication.[28-30] As the risk-benefit ratio increases, the rigor and thoroughness of standards for the participants' capacity evaluation

are required to be enhanced by IRBs.[27] The threshold for capacity should be adjusted as guided by the risks-benefits context and the desirability of having a qualified independent assessor (independent of the study team) increases, as the risk increases and the benefit decreases.[7,31]

Cognitive and non-cognitive evaluations are two hallmarks of decisional capacity assessment. A cornerstone of capacity assessment has been the evaluation of cognitive functioning, which has largely improved the capacity assessment in psychiatry research. Previous studies have derived the cognitive indices to assess the decisional capacity including, (a) understanding (of disclosed information including the purpose of research, research procedures, and human subject protection); (b) appreciation (of disorder or health condition, its treatment, and consequences / effects of participation in research); (c) reasoning (to participate, not to participate, and choice); and (d) communicating a choice (stating the reasoned choice).[32,20] Few authors critically reviewed the existing instruments and tools for consent capacity assessment and found some tools having more empirical support; however, there is no clear consensus for the most effective one.[33,34] The MacArthur competence assessment tool (MacCAT) is best tested for the assessment of competence in both treatment and research conditions, and its clinical research version (MacCAT-CR) possesses good content validity with adequate assessment of all the cognitive abilities or the indices of consent capacity, that is, understanding, appreciation, reasoning, and communication.[35-39]

Results of a standardized assessment tool can be connected with clinical decision-making in three ways: (a) by setting *a priori* performance threshold on the instrument,[40] which relies heavily on investigator's values and theoretical assumptions; (b) by determining a statistically defined cutoff, such as deviations from the standard distribution of normative values of healthy comparison subjects, distinguishing between competent versus incompetent or impaired versus unimpaired;[36,41] and (c) by employing the capacity evaluation judgment of the experts as a gold standard.[42-45] Researchers have also attempted categorical judgment regarding competence, that is, capable or incapable, by comparing two methods.[46]

There is no doubt that cognitive evaluation will continue to stand as a primary mode for decisional capacity. However, despite being practiced less often, non-cognitive elements such as voluntarism may also potentially influence the decisional capacity of individuals particularly when no serious cognitive dysfunctions are detected. Voluntarism capacity assessment may help serve different useful purposes, including assessment of the extent of vulnerability of participants or the extent of voluntarism exercised in decision-making. In case of lesser voluntarism careful precautions need to be taken, particularly when the risk-benefit ratio is less favorable for study intervention. Based on the previously reported voluntarism framework, some authors have suggested a questionnaire matrix for voluntarism assessment. This matrix, despite being purely qualitative, could serve as a basis for the development of a quantitative tool.[26]

Apart from personal abilities, the consent capacity depends in part on the complexity of the faced decision. A more complex study is harder to understand and vice versa, that is, understanding and consent capacity bear an inverse relationship to the complexity of the study.[47] Complexity of the study depends on various aspects including direct or indirect risks and benefits, study design, and the safeguards used to minimize the risks.[48] Therefore, while determining the individual's capability to provide the consent, complexity of study factors should also be considered.[23]

PROXY AND SURROGATE CONSENT

Validity of third-party decision-making, such as proxy and surrogate consent, on behalf of the study subjects in psychiatry clinical studies has been a debatable topic, especially for clinical studies involving irreversible or greater than minimal risk and lesser direct benefits. The ethical tension is further expected to increase due to unknown, but significant risks, with emerging innovative treatment approaches based on vaccines, gene transfer, and stem cells.[49-51]

In general, consent is obtained from LAR in case the subject is incompetent and a legal guardian represents the most-accepted LAR. When an LAR does not exist for an incompetent subject, the American Psychiatric Association recommends pursuing other options including: involving an IRB or a patient advocate authorizing the subject's participation; obtaining and document a second physician's opinion regarding the subject's participation.[22] Third-party decision makers may include legal guardians, surrogates such as caregivers and family members, and proxies as appointed by the participants in advance. There is no clear regulatory guidance that in the absence of legal authorization, the proxy or surrogate consenters or even guardians are permitted or ethically suitable to give consent to a research that poses risks to the participants or deprives them of benefits.[31] Approaches to be selected by IRB for the safeguard of participants need to be guided by analysis of risks and benefits.[7,31] The evaluation of risks should include the nature, magnitude, and probability of any discomfort or harm to the participants; whereas, evaluation of benefits should differentiate direct benefits from other types of benefits for the participants.[7]

A person possessing the consent capacity may not be enrolled in a research without his / her consent and he / she may accept or refuse to participate without involvement or irrespective of a third-party consenter. When the study subject is assessed as incompetent to give consent, an LAR should be involved in providing the consent and the subject must be notified of the assessment before obtaining the LAR's consent. Furthermore, if consent is given by the LAR, the potential subject must be notified of the consent and subject's objection, if any, should be heeded.[7] Whenever any doubt persists / exists regarding the subject's capacity, benefit of doubt should always be shifted toward the subject, and the subject's consent should be obtained may be in addition to the LAR's consent. For a study involving a higher risk, relying on surrogate consent alone may not be acceptable and would also require the subject's consent, tailored to the subject's capacity. In conditions involving the LAR's consent, the investigators should seek the subject's assent with due respect to the individual's autonomy, and their objection to initial or continued research participation should be honored and heeded.[7,23]

The LAR may not always be able to predict what the subject would otherwise have wanted,[6] and some authors comment that proxy consent should replace the subject's consent only when there is strong reason / evidence to justify / believe that the proxy consent is similar to the subject's treatment preferences.[52] As the study risks increase and direct benefits decrease, acceptability of the LAR's consent decreases and desirability of positive evidence regarding the subject's treatment preferences increases and vice versa. For studies with lesser risks and greater direct benefits, the LAR's consent may be acceptable, unless there is strong evidence showing opposed preferences of the subject.[23]

NEED FOR TAILORED INFORMED CONSENT PROCESS

All subjects suffering from psychiatric disorders may not be fully incompetent, and few could have limited or comparably lesser impairment. Some study subjects can appreciate the involved risks in the study and make a reasoned decision,[53-55] and an inverse relationship between participants' willingness to participate and perceived study harm has been affirmed by the data.[24] Studies have shown that subjects with mental disorders and impaired capacity are usually impaired, not over all indices of consent capacity, but over one or two indices, primarily understanding and reasoning,[32,46] and they may attain a capacity comparable to those without mental illness and can understand and give reasoned consent if consent process and information disclosure are tailored to their cognitive deficits (such as memory, language, attention, and comprehension) by using appropriate approaches such as detailed discussion and presentation of study, simplified easy-to-understand language, information disclosure in small consecutive pieces, single-unit disclosure format, repeated information, and enough opportunity to ask questions.[24,32] Therefore, while assessing the consent capacity, there is a need to identify the impaired capacity indices of the subjects and ICP is required to be customized for the subjects with impaired consent capacity, focusing more on their impaired indices, and the measures taken for ICP customization should to be documented. Further research, however, is required to help understand, which component of ICP (such as investigator's personal talk and meeting with subject, two-way discussion, information disclosure pattern, assessment of understanding, or obtaining consent) is required to be customized, how, and to what extent.

THERAPEUTIC MISCONCEPTION

Failing to understand the difference between research and the usual / routine clinical care is referred to as therapeutic misconception.[56,57] It is a critical element for ICP in psychiatry research involving subjects with impaired consent capacity, and literature quotes several evidences of therapeutic misconception.[58-65] Associated factors with therapeutic misconception may include lower education, age, and worse self-described health.[66] Of late, Dunn and colleagues[67] investigated the correlation between therapeutic misconception and related factors such as demographic differences, decisional capacity, psychopathology, and cognitive functioning. Misconceptions were mainly recorded for disbeliefs and misperceptions regarding individual clinical care, receiving most beneficial treatment, and randomization, which were found to be strongly correlated with lower education, poor insight, cognitive deficits, and impaired decisional capacity (primarily for understanding, appreciation, and reasoning), but not with psychopathology. The scale used in this study could be adapted for typical clinical research based on the study considerations for the assessment of therapeutic misconception.

The National Institute of Health (NIH) recommended that (a) documents should clearly differentiate between research and clinical care; (b) special attention should be given to the wording of study purpose, and precision about experimental procedures is required, avoiding even a minimal source of confusion; and (c) effects of the study participation on access to clinical care should be addressed clearly.[23] Although there is no clear consensus, regarding whether and when to question the consent

validity due to therapeutic misconception,[58] it is among the key ethical challenges. Identifying and mitigating therapeutic misconception must be an overriding goal of the investigators, which requires making a clear distinction between clinical care and research. Concerted efforts are required to ask the participants regarding any possible misunderstanding, overestimation of benefits, and underestimation of risks, to ensure that the prospective subjects have clearly understood that the investigator's focus is on producing generalizable scientific knowledge rather than on providing clinical care.[23]

PARTICIPANTS' UNDERSTANDING

Understanding of the prospective participants regarding the key study aspects, relevant to consent-related decision-making, is another important issue in research involving decisionally impaired subjects, because poor or limited understanding may lead to study participation without appreciation of study risks and diminished consent capacity. It can also lead to therapeutic misconception.[67] Data have shown that a fair proportion of subjects have difficulty in understanding the information, presented to them.[68,69] Therefore, investigators should ensure an adequate understanding of the participants prior to obtaining the consent. This can be done by asking a series of questions to assess their understanding of key issues most relevant to decision making, such as the purpose of the research, foreseeable risks, anticipated benefits, treatment alternatives, constraints imposed by study participation, randomization probability, use of placebo, therapeutic misconception if any, voluntary nature of research, right to withdraw, and right to be informed. Stress should be given on documenting the subjects' understanding of the key study aspects, especially of those generally perceived as harmful.

The subjects' understanding has been shown to be enhanced, making them able to comprehend consent from the information, with enhanced ICPs employing various educational or informational techniques, such as re-educating the subjects regarding the study protocol,[40,70] using structured video-assisted or computerized presentation and explanatory tools with sequential bullet points and summaries of key information,[71-73] obtaining oral consent in addition to written consent,[74] repetition of misunderstood information,[75] and interactive questioning in between the consent process.[76] Interactive questioning may have many other benefits, such as, (a) important elements, needed to focus on, can be highlighted; (b) ensuring understanding of previous information may allow improved understanding of the subsequent one; and (c) allowing assessment of understanding in between the process. An imperative conclusion that can be drawn is that if ICP is enhanced and implemented adequately, with concerted efforts, subjects with neuropsychiatric disorders may become more able to understand and retain the critical information crucial for providing the consent, with enhanced decisional abilities. Enhancement of understanding should be encouraged by IRBs.[31]

CONTINUED CONSENT

Continued consent refers to obtaining consent repeatedly from the subjects or LAR, whenever required or indicated during the course of study, even if the initial consent was obtained at the study entry. Generally, if any new information arises during the study, which can affect the rights, safety, and well-being of the study subjects, informed consent is to be obtained again.[12,22]

Continued consent is another ethical issue[77] and has special relevance to the research involving subjects with mental illness because: (a) subject's consent capacity can be expected to deteriorate or fluctuate or improve, either due to research treatment or progressive or fluctuating disorder, during the study, especially in long-term research; and (b) subjects hold the right to refuse study interventions or to revoke their or their LAR's previous consent at any time if they regain or lose the decision capacity.[78] There are possibilities that (a) a subject who originally possessed the consent capacity may lose the competency, or (b) an originally incompetent subject regains the consent capacity. In the first condition timely transition to LAR's consent and decision-making would be appropriate; whereas, the second situation would require consent and the decision-making duties to be transferred to the subject.[23] Therefore, the consent capacity needs to be monitored on an ongoing basis and consent- and withdrawal-related responsibilities should be transitioned timely between subject and LAR for obtaining repeat consent, when the consent capacity changes considerably. In all cases the subject, throughout the study, should be reminded of their right to withdraw,[32] which should not be limited by their diminished capacity[23]

CONSIDERATIONS FOR RESEARCHERS AND IRBS

The NIH has provided guidance on developing recruitment plans for studies involving subjects with questionable capacity. This guidance helps addressing key questions, such as for which subjects, how, and when consent capacity should be assessed [Figure 1].[23] Screening may be useful if the inclusion criteria require subjects with illness usually affecting the decisional capacity. Initial screening may include an informal screening prior to the consent discussion (based on the investigator's expertise

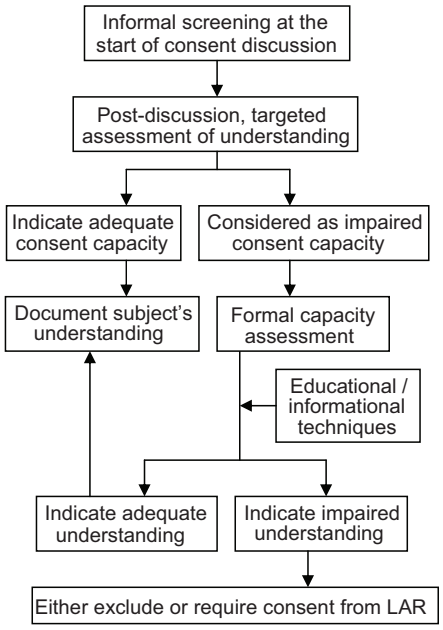

Figure 1: Recruitment plan considerations

and experience and simple questions, to judge which subject may have impaired understanding of consent-related issues), and post-discussion a more targeted assessment of the subject's understanding by asking him/her either to describe the key aspects or to answer the questions related to these aspects. If initial screening indicates adequate understanding and consent capacity, consent may be obtained with documentation of the subject's understanding of the key issues. For subjects indicated with impaired understanding, a formal capacity assessment may be required and various informational / educational techniques may be considered to enhance their understanding. Investigators bear the primary responsibility of ensuring that no consent would be sought unless the subject demonstrates an adequate understanding. Depending on the recruitment plan, prospective subjects judged to have impaired consent capacity may either be excluded or may be enrolled with the consent of the LAR.

Investigators should be aware of suitable screening methods, IRB policies, and useful approaches for enhancing the subjects' comprehension. IRBs that frequently receive and review research protocols involving subjects with impaired consent capacity should involve individual(s) with adequate knowledge and experience of working with research involving subjects with impaired consent capacity,[79] and also to become more equipped they should seek appointing or requiring outside consultation, from representatives of patient advocacy groups, experts in consent capacity assessment, representatives from the subject population, and scientific, medical, legal, and ethical experts.[23] While reviewing such type of studies IRBs should consider whether to include additional safeguards.[80] When evaluating study proposals and deciding about what additional safeguards may be required, researchers and IRBs should consider study complexity, risks, anticipated benefits, availability of LAR, type of disorder, expected severity of capacity impairment of the population under the study, and the human subjects' protection. Additional safeguards may include one or more of the following: appointing consent monitors, consent capacity assessment, use of approaches to enhance comprehension, waiting periods involving a two-step consent process, inclusion of LAR, and other suitable safeguards.[23]

REFERENCES

1. Du Val G. Ethics in psychiatric research: Study design issues. Can J Psychiatry 2004;49:55-9.
2. Pinals DA, Appelbaum PS. Ethical aspects of neuropsychiatric research with human subjects. Available from: http://www.acnp.org/asset.axd?id=56a79957-3cc2-43c0-a18e-62b745ade0c3. [Last accessed on 2011 Mar 20].
3. Tharyan P. Placebo-controlled trials in psychiatry on trial. Indian J Med Ethics 2006;3:13-6.
4. Patel V. Ethics of placebo controlled trial in severe mania. Indian J Med Ethics 2006;3:11-2.
5. Bonnie R. Research with cognitively impaired subjects: Unfinished business in the regulation of human research. Arch Gen Psychiatry 1997;54:105-11.
6. Wendler D, Prasad K. Core safeguards for clinical research with adults who are unable to consent. Ann Intern Med 2001;135:514-23.
7. Research involving persons with mental disorders that may affect decision making capacity: Report and recommendations of the National Bioethics Advisory Commission, Volume 1, December 1998. Available from: http://bioethics.georgetown.edu/nbac/capacity/TOC.htm. [Last accessed on 2011 Feb 25].
8. Helmchen H. Problems of informed consent for clinical trials in psychiatry. Control Clin Trials 1981;1:435-40.
9. Berg JW. Legal and ethical complexities of consent with cognitively impaired research subjects: Proposed guidelines. J Law Med Ethics 1996;24:18-35.
10. Fleischman AR. Developing regulations for research involving adults who lack decision-making capacity: Transactions of the American Clinical and Climatological Association, vol. 110, 1999. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2194305/pdf/tacca00006-0186.pdf. [Last accessed on 2011 Mar 04].
11. Appelbaum PS. Involving decisionally impaired subjects in research: The need for legislation. Am J Geriatr Psychiatry 2002;10:120-4.
12. ICH harmonised tripartite guideline-Guideline for good clinical practice: E6(R1). Available from: http://www.ich.org/LOB/media/MEDIA482.pdf. [Last accessed on 2010 Nov 10].
13. WMA Declaration of Helsinki - Ethical principles for medical research involving human subjects. Available from: http://www.wma.net/en/30publications/10policies/b3/index.html. [Last accessed 2010 Nov 10].
14. The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research. Available from: http://ohsr.od.nih.gov/guidelines/belmont.html. [Last accessed on 2010 Nov 10].
15. Nuremberg Code: Directives for Human Experimentation. Available from: http://ohsr.od.nih.gov/guidelines/nuremberg.html. [Last accessed on 2011 Mar 04].
16. Code of Federal Regulations, Title 45, Section 46.102c
17. Code of Federal Regulations, Title 21, Sections 50.20, 50.3(l)
18. Roberts LW. Informed consent and the capacity for voluntarism. Am J Psychiatry 2002;159:705-12.

19. Roberts L. The ethical basis of psychiatric research: Conceptual issues and empirical findings. Compr Psychiatry 1998;39:99-110.
20. Appelbaum PS, Grisso T. Assessing patients' capacities to consent to treatment. N Engl J Med 1988;319:1635-8.
21. Lidz CW, Meisel A, Osterweis M, Holden JL, Marx JH, Munetz MR. Barriers to informed consent. Ann Intern Med 1983;99:539-43.
22. The American Psychiatric Association: Principles of informed consent in psychiatry- Resource document. Available from: http://archive.psych.org/edu/other_res/lib_archives/archives/199601.pdf. [Last accessed on 2010 Oct 21].
23. Office of Extramural Research-National Institute of Health: Research involving individuals with questionable capacity to consent: Points to consider (November 2009). Available from: http://grants.nih.gov/grants/policy/questionablecapacity.htm. [Last accessed on 2011 Feb 25].
24. Roberts LW, Hammond KG, Hoop J. An inverse relationship between perceived harm and participation willingness in schizophrenia research protocols. Am J Psychiatry 2006;163:2002-4.
25. Appelbaum PS, Roth LH. The structure of informed consent in psychiatric research. Behav Sci Law 1983;1:9-19.
26. Geppert CM, Abbott C. Voluntarism in consultation psychiatry: The forgotten capacity. Am J Psychiatry 2007;164:409-13.
27. American Psychiatric Association: Guidelines for assessing the decision-making capacities of potential research subjects with cognitive impairment. Am J Psychiatry 1998;155:1649-50.
28. Charney DS, Innis B, Nestler EJ. New requirements for manuscripts submitted to Biological Psychiatry: Informed consent and protection of subjects. Biol Psychiatry 1999;46:1007-8.
29. Doyal L. Journals should not publish research to which patients have not given fully informed consent - with three exceptions. Br Med J 1997;314:1107-11.
30. Goodare H. Studies that do not have informed consent from participants should not be published. Br Med J 1998;316:1000-5.
31. Kim SY, Appelbaum PS, Jeste DV, Olin JT. Proxy and surrogate consent in geriatric neuropsychiatric research: Update and recommendations. Am J Psychiatry 2004;161:797-806.
32. Fisher CB, Cea CD, Davidson PW, Fried AL. Capacity of persons with mental retardation to consent to participate in randomized clinical trials. Am J Psychiatry 2006;163:1813-20.
33. Dunn LB, Nowrangi MA, Palmer BW, Jeste DV, Saks ER. Assessing decisional capacity for clinical research or treatment: A review of instruments. Am J Psychiatry 2006;163:1323-34.
34. Sturman ED. The capacity to consent to treatment and research: A review of standardized assessment tools. Clin Psychol Rev 2005;25:954-74.
35. Appelbaum PS, Grisso T. The MacArthur treatment competence study, I: Mental illness and competence to consent to treatment. Law Hum Behav 1995;19:105-26.
36. Grisso T, Appelbaum PS, Mulvey EP, Fletcher K. The MacArthur treatment competence study, II: Measures of abilities related to competence to consent to treatment. Law Hum Behav 1995;19: 127-48.
37. Grisso T, Appelbaum PS, Hill-Fotouhi C. The MacCAT-T: A clinical tool to assess patients' capacities to make treatment decisions. Psychiatr Serv 1997;48:1415-9.
38. Appelbaum PS, Grisso T, Frank E, O'Donnell S, Kupfer DJ. Competence of depressed patients for consent to research. Am J Psychiatry 1999;156:1380-4.
39. Carpenter WT, Gold JM, Lahti AC, Queern CA, Conley RR, Bartko JJ, *et al*. Decisional capacity for informed consent in schizophrenia research. Arch Gen Psychiatry 2000;57:533-8.
40. Wirshing DA, Wirshing WC, Marder SR, Liberman RP, Mintz J. Informed consent: Assessment of comprehension. Am J Psychiatry 1998;155:1508-11.
41. Marson DC, Ingram KK, Cody HA, Harrell LE. Assessing the competency of patients with Alzheimer's disease under different legal standards: A prototype instrument. Arch Neurol 1995;52: 949-54.
42. Schmand B, Gouwenberg B, Smit JH, Jonker C. Assessment of mental competency in community-dwelling elderly. Alzheimer Dis Assoc Disord 1999;13:80-7.
43. Fazel S, Hope T, Jacoby R. Assessment of competence to complete advance directives: Validation of a patient centered approach. Br Med J 1999;318:493-7.
44. Janofsky JS, McCarthy RJ, Folstein MF. The Hopkins Competency Assessment Test: A brief method for evaluating patients' capacity to give informed consent. Hosp Commun Psychiatry 1992;43:132-6.
45. Etchells E, Darzins P, Silberfeld M, Singer PA, McKenny J, Naglie G, *et al*. Assessment of patient capacity to consent to treatment. J Gen Intern Med 1999;14:27-34.
46. Kim SY, Caine ED, Currier GW, Leibovici A, Ryan JM. Assessing the competence of persons with Alzheimer's disease in providing informed consent for participation in research. Am J Psychiatry 2001;158:712-7.
47. Rosenstein DL. Decision-making capacity and disaster research. J Trauma Stress 2004;17:373-81.
48. Drane JF. Competency to give an informed consent: A model for making clinical assessments. JAMA 1984;252:925-7.
49. Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, *et al*. Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization. Neurology 2003;61:46-54.
50. Bjorklund A, Lindvall O. Cell replacement therapies for central nervous system disorders. Nat Neurosci 2000;3:537-44.
51. Silverberg GD, Levinthal E, Sullivan EV, Bloch DA, Chang SD, Leverenz J, *et al*. Assessment of low-flow CSF drainage as a treatment for AD: Results of a randomized pilot study. Neurology 2002;59:1139-45.
52. Eth S, Leong GB. Toward revising the ethical boundaries of research with noncompetent subjects. Am J Psychiatry 2009;166:131-4.
53. Roberts LW, Warner TD, Nguyen KP, Geppert CM, Rogers MK, Roberts BB. Schizophrenia patients' and psychiatrists' perspectives on ethical aspects of symptom re-emergence during psychopharmacological research participation. Psychopharmacology (Berl) 2003;171:58-67.
54. Stanley B, Stanley M, Lautin A, Kane J, Schwartz N. Preliminary findings on psychiatric patients as research participants: A population at risk? Am J Psychiatry 1981;138:669-71.
55. Roberts LW, Warner TD, Brody JL, Roberts B, Lauriello J, Lyketsos C. Patient and psychiatrist ratings of hypothetical schizophrenia research protocols: Assessment of harm potential and factors influencing participation decisions. Am J Psychiatry 2002;159:573-84.
56. Appelbaum PS, Roth LH, Lidz C. The therapeutic misconception: Informed consent in psychiatric research. Int J Law Psychiatry 1982;5:319-29.
57. Henderson GE, Churchill LR, Davis AM, Easter MM, Grady C, Joffe S, *et al*. Clinical trials and medical care: Defining the therapeutic misconception. PLoS Med 2007;4:e324.
58. Lidz CW, Appelbaum PS. The therapeutic misconception: Problems and solutions. Med Care 2002;40:V55-63.
59. Lidz CW, Appelbaum PS, Grisso T, Renaud M. Therapeutic misconception and the appreciation of risks in clinical trials. Soc Sci Med 2004;58:1689-97.
60. Penman DT, Holland JC, Bahna GF, Morrow G, Schmale AH, Derogatis LR, *et al*. Informed consent for investigational chemotherapy: Patients' and physicians' perceptions. J Clin Oncol 1984;2:849-55.
61. Daugherty C, Ratain MJ, Grochowski E, Stocking C, Kodish E, Mick R, *et al*. Perceptions of cancer patients and their physicians involved in phase 1 trials. J Clin Oncol 1995;13:1062-72.
62. Schaeffer MH, Krantz DS, Wichman A, Masur H, Reed E, Vinicky JK. The impact of disease severity on the informed consent process in clinical research. Am J Med 1996;100:261-8.
63. Featherstone K, Donovan JL. Random allocation or allocation at random? patients' perspectives of participation in a randomized controlled trial. Br Med J 1998;317:1177-80.
64. Joffe S, Cook EF, Clearly PD, Clark JW, Weeks JC. Quality of informed consent: A new measure of understanding among research subjects. J Natl Cancer Inst 2001;93:139-47.
65. Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent in cancer clinical trials: A cross-sectional survey. Lancet 2001;358:1772-7.

66. Appelbaum PS, Lidz CW, Grisso T. Therapeutic misconception in clinical research: Frequency and risk factors. IRB 2004;26:1-8.
67. Dunn LB, Palmer BW, Keehan M, Jeste DV, Appelbaum PS. Assessment of therapeutic misconception in older schizophrenia patients with a brief instrument. Am J Psychiatry 2006;163:500-6.
68. Grossman L, Summers F. A study of the capacity of schizophrenic patients to give informed consent. Hosp Commun Psychiatry 1980;31:205-6.
69. Roth L, Lidz CW, Meisel A, Soloff PH, Kaufman K, Spiker DG, *et al*. Competency to decide about treatment or research: An overview of some empirical data. Int J Law Psychiatry 1982;5:29-50.
70. Lapid MI, Rummans TA, Poole KL, Pankratz VS, Maurer MS, Rasmussen KG, *et al*. Decisional capacity of severely depressed patients requiring electroconvulsive therapy J ECT 2003;19:67-72.
71. Wirshing DA, Sergi MJ, Mintz J. A videotape intervention to enhance the informed consent process for medical and psychiatric treatment research. Am J Psychiatry 2005;162:186-8.
72. Dunn LB, Lindamer LA, Palmer BW, Schneiderman LJ, Jeste DV. Enhancing comprehension of consent for research in older patients with psychosis: A randomized study of a novel consent procedure. Am J Psychiatry 2001;158:1911-3.
73. Dunn L, Lindamer L, Palmer BW, Golshan S, Schneiderman L, Jeste DV. Improving understanding of research consent in middle-aged and elderly patients with psychotic disorders. Am J Geriatr Psychiatry 2002;10:142-50.
74. Eyler LT, Jeste DV. Enhancing the informed consent process: A conceptual overview. Behav Sci Law 2006;24:553-68.
75. Palmer BW, Jeste DV. Relationship of individual cognitive abilities to specific components of decisional capacity among middle-aged and older patients with schizophrenia. Schizophr Bull 2006;32:98-106.
76. Eyler LT, Mirzakhanian H, Jeste DV. A preliminary study of interactive questioning methods to assess and improve understanding of informed consent among patients with schizophrenia. Schizophr Res 2005;75:193-8.
77. Mueller MR, Instone S. Beyond the informed consent procedure: Continuing consent in human research. Cien Saude Colet 2008;13:381-9.
78. Jacob R, Chowdhury AN. Assessment of mental capacity in patients recruited in clinical trials in psychiatry and its relationship to informed consent. Indian J Med Ethics 2009;6:43-4.
79. Code of Federal Regulations, Title 45, Section 46.107 and Title 21, Section 56.107.
80. Code of Federal Regulations, Title 45, Section 46.111(b) and Title 21, Section 56.111(b).

How to cite this article: Gupta UC, Kharawala S. Informed consent in psychiatry clinical research: A conceptual review of issues, challenges, and recommendations. Perspect Clin Res 2012;3:8-15.

Source of Support: Nil. **Conflict of Interest:** None declared.