

Empirical Research on Informed Consent with the Cognitively Impaired

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Many groups have addressed the issue of the appropriateness of research with participants with impaired decisional capacity, but according to one recent interpretation, they base their recommendations “primarily on the authors’ intuitions.”¹ Empirical research on approaches to protecting research participants with varying levels and types of cognitive impairments can help determine whether experiences match expectations, and can suggest additional approaches to protecting potentially vulnerable persons while important and necessary research is conducted. However, even expert policy recommendations about the conduct of research with cognitively impaired persons made by the National Bioethics Advisory Commission (NBAC) are not heavily based on empirical research,² and NBAC itself has called for detailed empirical study of its own and related recommendations.³

One of the greatest challenges to getting things ethically “right” for the conduct of research, although not the only requirement,⁴ is the design of informed consent processes that balance the needs for research with an emerging social

concern that greater protections for research participants are necessary.⁵ Here, we summarize selected but as yet unpublished observations from several empirical research studies on informed consent with adult participants with impaired cognitive capacities. Our studies included persons with mild cognitive impairment or dementia, persons with a psychiatric disorder (e.g., schizophrenia, bipolar disorders), and family members of these participants. We abstracted and discussed our observations during one or more of the annual funded meetings of the grantees of the Informed Consent Projects (ICPs), or during a smaller group meeting (October 2001) of a subset of these grantees, and conference calls of those studying persons with cognitive impairments.

One of the observations emerging from our work is a growing sense that researchers must distinguish between mere membership in the class of persons with these types of disorders, and actual impairment of decisional capacities that might make autonomous, voluntary research participation problematic. Hence, we agree with Grisso and Appelbaum,⁶ as well as others who argue that there is only an incomplete overlap of decisional incapacity with psychiatric illness. For example, Grimes et al.⁷ reviewed the neuroanatomic bases of disordered executive function and the subsequent impact on decisionmaking


capacity. They found that some psychiatric illnesses leave these functions relatively unscathed, and these are functions intimately tied to voluntariness and intentionality of action.

We also note from our clinical and research experience with impaired individuals that, just as in pediatrics research,⁸ research decisions are usually made among three or more parties: the potential research participant, a legally authorized or de facto representative (usually a family member or members), and an investigator/clinician (or his or her designee, e.g., a research recruiter). Thus, empirical research into the informed consent process for this class of adults must account for the increasingly triadic nature of the clinical or research encounter as these disease processes typically render individuals less, or intermittently, capable of autonomous decisionmaking. Nevertheless, we conclude the paper with a caveat to acknowledge and incorporate the wishes of all potential research participants, regardless of the level of impairment, or the type or stage of underlying disease or syndrome.

Methodological Approaches

We used a variety of quantitative and qualitative methods, and observational, experimental, quasi-experimental, and interventional designs to study these issues. We

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generally used face-to-face interviews with a structured interview schedule. Some studies added neuropsychological and psychiatric testing. We sometimes video- or audio-taped actual or hypothetical informed consent discussions and then analyzed transcriptions or videotapes directly, often frame by frame. Finally, most of our studies have used both quantitative and qualitative approaches. Below are overviews of four ICP teams whose work focused on individuals with cognitive impairments.

■ *University of Chicago/Case Western Reserve University/University of Kentucky (Chicago/Case/Kentucky)*. This project studied the feasibility and effectiveness of different methods for facilitating research with subjects with dementia. In videotaped face-to-face interviews, the study used vignettes of five types of research of varying levels of risk and benefit to motivate hypothetical enrollment decisions from persons with dementia and their caregivers. The investigators sought to (1) determine the ability of dementia patients to participate in research decision making despite their impairments; (2) advance new methods of determining cognitive capacity to consent to research using linguistics-based and nonverbal communication analyses of informed consent conversations; (3) test the utility of multidisciplinary approaches to yielding a deeper understanding of subject and proxy consent for dementia research; and (4) test the effectiveness of an advance consent process involving both the dementia subject and proxy together. The study collected data longitudinally over 2 years, involving 150 subject/proxy dyads across three sites with different subject demographic profiles. Subjects were community-dwelling individuals with dementia who volunteered with family caregivers to participate in the study.

■ *Case Western Reserve*

University (CWRU). This research describes the disclosure and decisionmaking process with three patient populations of potential subjects of phase III clinical trials (adult cancer patients, critically ill children, and Alzheimer disease patients). Participants were observed and audiotaped during the consent process. Subjects were asked what they believed was important in making research participation decisions. Behavioral decision analysis theory was used to examine clinician-participant interactions to identify factors associated with better outcomes (e.g., participant understanding of trial details).

■ *University of New Mexico (UNM)*. This study sought to clarify the subjective responses of patients to informed consent processes in clinical research, and to determine whether an educational intervention for clinical researchers enhanced their awareness of the consent process. The first component of the study examined attitudes, motivations, and perceptions of different patient populations toward research through interviews with patients with psychiatric disorders (schizophrenia, major depression, post-traumatic stress disorder), lung cancer, AIDS, and healthy controls. The hypothesis guiding this research was that patients with different clinical syndromes would exhibit diagnostic-specific differences with respect to subjective aspects of informed consent. The second study component consisted of an educational intervention targeted to researchers that was designed to examine the effectiveness of the intervention in enhancing researchers' sensitivity to the subjective experiences of clinical populations.

■ *University of California at Los Angeles (UCLA)*. This study combined naturalistic and experimental methods to examine and enhance the informed consent process in psychiatric and medical treatment research. Participants

were diagnosed with either schizophrenia or bipolar disorder. Coronary transplant patients without mental illness served as a comparison group. All subjects were in the process of being recruited for one of several clinical trials of treatments for their serious, chronic illnesses. Prior to participation in the informed consent process for treatment research, those assigned to the informed consent experimental group viewed a CD-ROM that explained and described human subjects research, outlined the elements of "good" decisionmaking, and taught and encouraged an active participation style. Subjects were assessed for basic cognitive capacities, disturbances of thinking and mood, and social influence factors. Major dependent variables included recruitment rates, objective, and open-ended measures of acquisition and comprehension of mandated informed consent information, measures describing the coherence of the decisionmaking process, and assessment of the research staff's and participants' views of and satisfaction with the process.

What Are We Learning?

Here we summarize selected observations emerging from our separate empirical studies. Because we cannot present here all of the evidence necessary to support assertions to the extent usually found in empirical research reports, these observations should be read as preliminary. We are sufficiently motivated, however, by what is emerging from our work in aggregate to believe that these observations will stimulate discussion and additional research on open empirical questions about informed consent. We parenthetically cite the research group(s) from which these abstracts were drawn, but some meta-findings (numbers 1-3 below) emerged in discussions at one or more of our group meetings. Other observations are reported in no par-

tical order.

1) *The informed consent process starts far earlier than the official encounter, when research participants sign consent forms.* The consent process tends to be step-wise as information about the research is framed, shared, and processed by all involved parties. Starting with initial, tentative and often informal inquiries about the willingness to proceed to subsequent steps, much of the enrollment decisionmaking has already been made by the subject and/or others by the time of an official consent encounter in the clinical research setting. Regulatory reliance on the partial fiction of *an* informed consent encounter will continue to miss these temporal and sequential dimensions of real-life decisionmaking.

2) *Historical assumption of autonomous decisionmakers is too simplistic.* Dyads (participant/proxy, participant/investigator, investigator/proxy), triads (participants/proxies/investigators), and larger social groups (e.g., families, research teams) are involved in virtually every step of research enrollment decisionmaking. Simple participant/investigator models of informed consent may have heuristic value, but our experiences suggest that the number of simplifying assumptions necessary to sustain this model in real decisionmaking contexts, especially with the cognitively impaired, lead us far from real practice.

3) *The degree of trust within the physician/patient relationship and in medical institutions matters with respect to the reasons given for research participation.* We observed that trust is an important and often-reported reason for research participation by both participants and proxies. Some authorities cite trust as the foundational necessary condition to any successful medical encounter,⁹ and it appears to be even more important in some


research contexts (such as research with no direct medical benefits) where the very reason, sometimes the *only* reason, for participation was some version of: “I trust my doctor to do what is right.” Our repeated observations of such comments tend to support the notion that trust (as a public good) is so critical to the whole medical enterprise, and to the research enterprise in particular, that regulatory schemes that might erode trust (e.g., in some health insurance models) should be very carefully weighed for their impact on the public good aspects of trust.¹⁰ Another example might be certain practices supported by the pharmaceutical industry, where real or perceived conflicts of interest can also undermine trust. Even well-intentioned attempts to regulate greater protections for impaired research participants may have the unintended consequence of furthering an aura of distrust in medicine.

4) *The assessment of capacity to consent to research is still very much an open question.* No compelling “gold standard” of decisional capacity exists,¹¹ although the Appelbaum and Grisso (A&G) model¹² is probably the most widely adopted.¹³ According to these authors, “[S]tatutes and court decisions have done little to move beyond the vaguest descriptions of what constitutes general competence.”¹⁴ Early findings from one analysis of nonverbal communication during videotaped enrollment discussions suggest nonverbal behavioral clues to cognitive performance that may be typical in noncognitively impaired adults are possibly misleading when seen in those with cognitive impairment (*Kentucky*). Using a modified Facial Action Coding System,¹⁵ the Kentucky researchers found that nonverbal behaviors in cognitively intact persons that generally indicate attending to and understanding of the discussion, may suggest just the

opposite in those with cognitive deficits: a *lack* of understanding, with behavioral overcompensation with reflexive gestural behaviors. Observing and decoding these gestures in the context of real informed consent conversations will require special training. This suggests that nonexpert assessment of decisional capacity may be problematic.

5) *Even within a standard (A&G) capacity-assessment framework, experts from three different disciplines attended to different evidence of decisional capacity (Chicago/Case/Kentucky).* This analysis suggests that even expert rating of capacity may not alone be sufficient to insure consistent assessment of capacity. We found that different standards were used by different experts (a geriatrician, a neuropsychologist, a neurologist), and that they appeared to consistently attend to different aspects of the informed consent conversations with potential research participants.

6) *From another line of work on communication and the assessment of decisional capacity, preliminary findings from linguistic analyses suggest that those patients with dementia who demonstrated broad vocabulary usage, or whose utterances were judged most often to be intelligible, were also the ones judged most competent to make research enrollment decisions (Case).* Patients lacking *expressive* abilities may be at greater risk of being judged incapacitated than those with more developed (or more intact) expressive abilities, and are at greater risk of their voices being lost in research enrollment decisionmaking. Capacity assessment appears to be highly dependent on verbal expression, so measures of capacity that weigh heavily on expressive abilities may be oversensitive to deficits that may not necessarily render potential research participants incapable of decisionmaking. In addition, these researchers found that commonly used measures of



cognitive capacity, such as the Mini-Mental Status Examination (MMSE), track imperfectly with A&G-based measures of decisional capacity. Thus, simply using the MMSE as a proxy for decisional capacity should be approached with great caution.

7) *Judgments of decisional capacity in one of our studies correlated with performance on select standard neuropsychological tasks (e.g., verbal fluency, word list recognition, prose recall, auditory comprehension, verbal memory, attention)(Case)*. In particular, patients with better language comprehension skills were independently judged as more competent to decide about research participation than those with degraded test performance. While these more focused tests may be accurately reflective correlates of decisional capacity, an alternative explanation is that research recruiters (or capacity assessors) are highly influenced by the verbal communication domains of cognitive ability, discounting the capacity and, hence, autonomous enrollment wishes of those with less language skill. Further work on the neuropsychology of decisionmaking and the possible overdependence of our current measures of decisional capacity on language skills is warranted.

8) *The role of emotions and the “authenticity” of responses from impaired persons may provide important clues to levels of understanding, appreciation, and willingness to participate in research (Kentucky)*. Cognitive impairments may leave potential participants decisionally impaired by some standards of impairment, yet emotions (e.g., happiness, sadness, surprise, fear, anger, disgust) appear to be closely linked to individual appreciation of situations and may offer substantial clues to individuals’ understanding the research under discussion and their willingness to participate. Emotions may also be relevant markers of desperation (or vulnera-

bility) in the face of serious illness, another common reason for participation in research.

9) *The conversational skill and training of interviewers and recruiters making research enrollment capacity judgments of persons with dementia varies widely (Chicago)*. One of our linguistics-based analyses suggests that, at least for those with diminished but not exhausted cognitive abilities, capacity is not so much assessed by an outside party, as created or constructed by the joint actions (verbal and nonverbal behavior) and understandings (e.g., based on shared educational or socio-cultural backgrounds) of those in the consent conversation. Additional insights, some from discourse analysis of informed consent encounters, suggest a hierarchy of understanding that again belies the reality of so-called threshold capacity measures in favor of measures that account for the degree or task-specific nature of decisional capacity.

10) *Persons with mild cognitive impairments, dementia, and schizophrenia can and did make research enrollment decisions that suggest some understanding of the risks and benefits of participation in different types of trials (Chicago, UCLA)*. Patterns of their enrollment decisions are not unlike those that might be predicted for cognitively intact populations. In one of our studies (Chicago), as the riskiness and complexity of five hypothetical trials increased, the willingness to enroll decreased. In addition, preliminary analysis suggests that the order of presentation of decision tasks seemed to matter little to persons with dementia. To the extent that they were able to make decisions, they seemed to be able to make them on the merits of the specifics involved in the proposed research. That they may not remember, or be able to rearticulate their reasons later, is a possible conflation of standards of decisional capacity

with markers of cognitive impairment. For the most highly invasive trial offered in this study, an intracranial surgical stem cell implant, the remote possibility of therapeutic benefit was highly discounted relative to the inherent and perceived riskiness of this type of trial. Another of our analyses (Chicago) found that many proxies believed that nominally impaired patients do retain residual decisional capacities. This echoes our impressions favoring nonthreshold assessments of capacity, or at the least, recognition that enrollment decisions are based on complex weighing of the benefits and burdens of participation, and the simultaneous balancing of the current best interests of potential subjects with previously known or imagined wishes. An example of this may be seen in one proxy’s comment, “Well, Mom won’t get all of this, but she knows what she likes and what she doesn’t like—I’ll ask her.”

11) *Participants with severe psychiatric disorders were “teachable” with respect to understanding the elements of informed consent (UCLA)*. One of the studies used an 80-item “competence quiz” prior to allowing psychiatry or medicine service patients to enroll in actual research. These researchers found that patients can be taught using an educational videotape, and that comprehension scores could be improved by multiple screenings of the tape. More importantly, psychiatric symptom expression was not necessarily correlated with test scores, suggesting that psychiatric diagnoses may not by themselves be good indicators of decisional incapacity.

12) *The behavior of clinician investigators and the state of the science of the disabling conditions affects patient decisions to enter trials*. One of our studies (CWRU) observed that cancer patients, their proxies, and investigators, discuss this trial option within the context

of many treatment and trial options, while Alzheimer disease patients have fewer treatment options to discuss simply because the state of the science of the disease has fewer options to offer. As a result, Alzheimer disease patients and patients with other disorders or diseases with few treatment options may also come to informed consent discussions with higher levels of desperation. Informed consent discussions about research participation should consider placing the research option under consideration in the context of all other options available. Researchers generally found high levels of desperation among family members of potential research enrollees with chronic or serious disabling conditions, and a willingness to “gamble” with risks if the potential benefits were powerful enough. However, another study (Chicago) observed almost visceral emotional aversion to participating in extraordinarily novel and invasive (e.g., intracranial stem cell implantation) research options.

13) Proxy enrollment decisions were not highly concordant with those made by their pair-matched subjects with mild cognitive impairments or dementia, and agreement seemed to be mostly a function of the perceived risks and benefits of each trial (Chicago). These researchers observed that proxies tended to overenroll patients in low-risk trials, relative to subjects’ own decisions, while underenrolling patients in higher risk trials. On the other hand, some proxies would enroll patients with dementia in high-risk, no direct medical benefit trials, even when the patient would have chosen not to enter such trials. From another analysis of the same data, proxies often saw themselves as making shared decisions, regardless of how much the impaired person participated. Their motives, depending on the type of trial (e.g., drug versus other) ranged from altruism, potential for treatment benefit, hope

in vanishingly small probabilities of benefit, and, again, trust in the provider. Caregiver burden may also be important in this context. The riskiness of the proposed research, and the severity of potential subjects’ dementia, were both positively associated with levels of burden reported by proxies. This may have implications to future study design if we believe that burdens on proxies need to be added to any net calculation of the benefits and burdens of research.

14) In one of our studies, we observed a greater propensity for white men to enroll in research than other sociodemographic groups, adjusting for cognitive status (Chicago). In roughly decreasing order of willingness to enroll across five hypothetical trials, the other groups are: white women, black men, and then black women. Recruitment of nonwhite and female subjects with dementia into clinical trials may be difficult due to historical and social factors (not measured in this study) covarying with race and sex of potential trial enrollees. This propensity speaks to ongoing concerns with justice in research participation, and harkens again to the critical role of trust as a public good in medical research. It also raises important concerns about potential sociodemographic differences in beliefs in self-efficacy and power (e.g., to avoid bad research outcomes, or to control unfamiliar situations).

15) In another analysis of the same data, the probability of trial enrollment was positively associated with better cognitive performance for low-risk, low-benefit trials, but negatively associated for higher risk, higher benefit trials (Chicago). This suggests a weighing of the potential risks and burdens of enrolling in each type of trial against the marginal direct medical benefit that may accrue at varying levels of cognitive decline. Those with minimal cognitive deficits may have more to lose

or risk by enrolling in a high-risk trial than those with more advanced deficits. Recruitment of subjects with only mild cognitive deficits into risky trials that may offer great potential for direct medical benefits may be difficult due to this risk/marginal benefit ratio. Conversely, the greater willingness of cognitively impaired subjects to enroll in higher risk trials of no direct medical benefit (e.g., a lumbar puncture study to develop disease markers), suggests that NBAC’s call to build additional research oversight infrastructure may have some benefit in monitoring the interests of cognitively impaired persons.

16) Research advance directives to prospectively communicate the research participation wishes of persons with dementia or other impairment may have some utility, but the chief utility of research advance directives may be to help proxy decision makers confirm decisions they and other family decision makers make through other, less formal methods (Chicago/Case/Kentucky). These observations are especially provisional due to the long time spans (many years) that may ensue between advance directive execution and subsequent utilization, and the researchers conducting this study have not yet completely followed all members of their experimental cohort. Nevertheless, comments by participants suggested that some families found a quasi-formal (i.e., it did not carry the weight of statutory law) research advance directive helpful in subsequent research enrollment decisions (e.g., “It helped us know what Mom would want to do”), but in no cases followed to date have families used such directives as binding testamentary-like documents.

17) Even with mild to moderately impaired subjects, investigators tended to focus their informed consent discussions with surrogates to the exclusion of subjects (CWU, UNM). Because some investigators

directed their communication to family members and other surrogates, potential research subjects appeared even less capable of understanding and participating in the decision-making process than they may, in fact, have been. Few investigators in this study appeared to have spent the time necessary to help impaired subjects through the decisionmaking process, so in some ways, the presence of a surrogate at the informed consent discussion made it worse for the subjects in terms of their being really included in the informed consent process. This observation, along with some of our others, suggests that additional empirical research on the dynamics of small group decisionmaking and communication processes around the informed consent discussion should be pursued.

Conclusions and Policy Implications

Our investigations suggest, first, that persons with potentially cognitively disabling conditions are sometimes capable of making their own research participation decisions, and quite often capable of contributing to informed consent discussions directly. Thus, informed consent processes used with adults without impairment might sometimes apply, or could be applied, with some modifications. If a valued goal with this population is maintaining autonomous, voluntary decision making, we might consider doing more to facilitate impaired subjects' decisional capacity, such as constructing new measures of decisional capacity that are less reliant on the simple verbal facility of potential participants, or by training capacity assessors to be sensitive to nonverbal behaviors.

Research with participants with impaired cognitive capacity is necessary when the disabling condition itself is under study, but there are other studies where the participation of those with impairments would be

desirable but not strictly necessary, and informed consent procedures could be crafted to include these potential participants as well.¹⁶

Recalling our findings about how the assessment of cognitive capacity appears to be dependent on the verbal skills and ability to engage in nuanced conversation with capacity assessors, the problems of adequate and appropriate trial recruitment using such persons are likely to be exacerbated as the demographics of the U.S. change to include more non-native English speakers. Such persons may also share fewer of the sociocultural and historical understandings that have heretofore formed the foundation upon which the (we suggest partly fictional) individual, autonomous decisionmaker model was built. We do not know how these exogenous factors might impact the dynamics of the informed consent process, but they are certainly candidate topics for continued empirical research.

We observed in many of our studies that trust was an important reason or warrant for research participation. The role of trust in institutionalized medicine in an era of multiple challenges to it is another important area for continued research. The implementation of new demands on researchers (e.g., the creation or enhanced legitimacy of new professional gatekeepers such as capacity assessors or research monitors) may generate unintended consequences such as turf battles with nurses or other professionals, confusion, or further degradation of trust in physicians ("Who are you? Why isn't my doctor telling me all this?"), or additional costly burdens on all participants (investigators, subjects, families, funders, regulators) in the research enterprise. Empirical research could help address these issues as well.

Modifications to consent policies and procedures modeled on better understandings of how decision-making takes place in the real world

might help fine-tune the balance between the risks and benefits of research participation, and might also help demonstrate how policy formulation can be responsive to empirical research findings. Empirical research can test theory using well-known deductive approaches, or develop new ideas and theory using inductive approaches.¹⁷ Empirical findings and arguments also invite new participants, views, and audiences to the policy table, and can make different claims from arguments based on other paradigms. Just as concepts and argument from philosophy are central to clinical ethics,¹⁸ the concepts and techniques of empirical research¹⁹ must also become a central part of the clinical ethics/policy enterprise if we value not only arguments about what "ought" to be, but arguments grounded in "what is."

Further institutionalizing empirical research into ongoing dialogues about research ethics and policy development is critical, yet even evidence-based medicine²⁰ has experienced implementation challenges. "Clear research findings," notes Davis and Howden-Chapman, "are not always a passport to policy."²¹

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