

SELECTED SUMMARY

Beyond the age of consent: clinical research in the neurologically or cognitively impaired

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Kim SYH, Kim HM, Langa KM, Karlawish JHT, Knopman DS, Appelbaum PS. Surrogate consent for dementia research: a national survey of older Americans. *Neurology*. 2009 Jan; 72(2): 149-55.

The Nuremberg trials of Nazi war criminals were conducted over 60 years ago. The first of these 12 trials was the "Doctors Trial". Of the 23 defendants, 20 were German physicians arraigned for major roles in the human experiments carried out at Auschwitz and other concentration camps. As part of their defence some of the accused argued that there was no law that specifically banned human experimentation. The judges at the trial delivered their verdict in August 1947 and seven of the defendants including five doctors received the death sentence. As part of their judgment the judges included their opinion on human experimentation for medical research. This was largely based on the submissions of an American neurologist of Austrian-Jewish origin, Leo Alexander. The 10 points that emerged constitute the Nuremberg Code (1). The Declaration of Helsinki (2) follows from this code and although neither the Code nor the Declaration directly have any legal validity, they have been incorporated into the various national legislations that codify medical ethics principles governing human experimentation.

The first point of the Nuremberg Code begins thus: "The voluntary consent of the human subject is absolutely essential." Beyond exercising free choice, the subject "should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision." This obviously presupposes a conscious and neurologically (for example: not aphasic) and cognitively intact individual and, taken literally, would probably rule out trials in decisionally impaired individuals. This kind of absolutism has not been possible in practice. For instance in many neurology and psychiatric patients and also in critical care, consent has to be obtained from an acceptable proxy or surrogate. How does one decide if the surrogate consent is valid? Ideally this would have to be from a legally authorised representative of the patient. In the absence of such an individual, due legal processes can be used to appoint one, but often at the cost of time and substantial effort. The short cut that most of us use is to ask the spouse or other close relative for surrogate consent. Whoever the surrogate is, she/he is supposed to use "substituted judgment" to decide in place of the patient, to decide what might or might

not be in the patient's best interests. The ideal situation of course is the presence of advance directives from the patient and a legally acceptable proxy appointed by the patient. In the absence of directives there is no easy way of deciphering what might have been acceptable to the subject had he/she been able to decide. Perhaps the best way forward is a broad poll to assess attitudes in the community. And who better to ask than the individuals who might themselves be at risk?

One example of this is based on Alzheimer's disease (AD), the commonest form of dementia across the globe. Most AD patients rapidly lose decision making capacity once the disease progresses beyond the mild stage. This may be at a stage when they are still largely able to maintain themselves in the community with intact activities of daily living. To assess public views about this situation, Kim et al designed a survey amongst older Americans by including 1,500 randomly chosen participants from the ongoing Health and Retirement Study which tracks over 30,000 Americans above the age of 51. After a brief introduction to AD and the rationale for the survey, the subjects were randomly given one of four scenarios: a lumbar puncture based study, a randomised controlled trial of a new drug, a vaccine study and a human gene transfer requiring a neurosurgical procedure. There have been real studies close to these scenarios and this list generates a fairly wide range of risk and benefits. Each respondent then answered three questions. The first question tested societal attitudes: asking whether families should make decisions regarding participation in case the patient cannot do so. The second checked self-perspective: whether the respondent would personally want to be put into the study in case he/she was unable to decide. The third was the question of how much leeway the respondent would permit the surrogate to go against his/her wishes. They found broad support (68-83% depending on the scenario) for a general policy of accepting family surrogate consent for AD research. Personal willingness to participate was also high, ranging from 57 to 80%. The concept of leeway is relatively complex since it rests on an acceptance of an uncertain future together with trust in the surrogate. Here the figures were more evenly split with a substantial minority (33-45%) not willing to grant any leeway. The authors take these results as evidence that a substantial majority of American seniors would be willing to be co-opted into medical research as subjects even when they could no longer decide for themselves. Would these figures be any different in an Indian population? Without an actual survey this is difficult to say but given our family

networks, they might even be larger. My own experience with a planned AD trial certainly bears this out.

But the Nuremberg Code was not just about consent. It also introduced the standard of "necessity". As stated: "the experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study...." This would mean that including subjects with impaired decision making capacity in a trial is valid only if the research question cannot be answered otherwise. This is obviously not an unusual situation and has been discussed in the critical care literature. Most would feel that including individuals with varying levels of incapacity would be more likely to enhance the discriminatory power of the study. Whether this is a proposition that requires to be proven or is a self evident truth may well depend on prior ideological positions.

Fortunately this issue has been explored by Flaherty et al using data acquired in the pivotal NINDS trial for early thrombolysis of ischaemic stroke using r-TPA (3). This trial was completed in 1994 and forms the major basis for the widespread use of this "clot busting treatment" in the initial three hours of stroke. The authors accessed the original database to identify those patients who could give their own consent and those who required a surrogate. This paper is probably the only one so far to show that including decisionally impaired subjects actually provides information relevant to clinical decision making. In this study, surrogate consent was used to enrol the majority, 439 of 624 patients (70%). In fact Flaherty et al estimated that had surrogate consent not been acceptable for this study, it would have required about 12 years for completion. In addition subjects enrolled by surrogate consent were likely to be older, had more severe strokes and were less likely to make a good recovery. Excluding these patients would have significantly limited the trial's applicability in severe stroke and would in turn have delayed the usage of this extremely useful drug in many of those patients who required it most. In an accompanying editorial in the same issue, Chen however made it clear that involving decisionally impaired could be justified only by a very strict interpretation of the necessity doctrine (5). Under this standard, convenience (eg, making enrolment easier) or expedience (eg, exclusion prolongs the study) are not

ethically acceptable reasons.

Given these uncertainties, determining best practices to balance between scientific and ethical necessities is still a major challenge. One way forward in assessing an individual study or trial would be to apply graded levels of safeguards depending on the risk and/or the justification for any given study. A matrix can be generated with the level of risk (minimal versus more than minimal) and the prospect of benefit or none for the individual participant (5). As of now this is the responsibility of the individual researcher as well the ethics committee or institutional review board overseeing the process. Unfortunately too often it is an ostrich-like "don't ask, don't tell" policy that serves nobody's interests. It may also not be feasible as the broad trend in society is to require more, not less accountability in medical research ethics (6). Neurologic, psychiatric and cognitive diseases are amongst the last frontiers of current medical research and there is little doubt that the tension between scientific necessity and ethical limits will grow.

Statement of competing interests: *The author is the principal investigator at Hinduja Hospital, Mumbai for a randomised controlled trial on a drug for AD.*

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Workshops on biostatistics and research ethics

SGPGI will be organising workshops on biostatistics and research ethics between July and September 2009 at Lucknow. Travel support may be available.

Those interested in further details may please contact Dr Rakesh Aggarwal at the Department of Gastroenterology, SGPGI, Lucknow at sgpgi.course@gmail.com