Clinical research on conditions affecting cognitive capacity

HURST, Samia
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Samia Hurst MD

1. Institute for Biomedical Ethics, Geneva University Medical School

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1. Introduction

Research is crucial to improve medicine’s ability to care for the sick, and this includes research on conditions affecting cognition. At the same time, however, participation in clinical research places human subjects at risk of harm for the benefit of others, and this concern is particularly great in the case of vulnerable persons. Studies designed to address health problems specific to a vulnerable population, however, are needed to improve care for this very population and often cannot be conducted on others.

This tension - to protect participants in research while also taking into account the interests of future patients by allowing research to be conducted- is intrinsic to all clinical research, and underlies the need for protection of human subjects (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979; ICH Steering Committee 1996; CIOMS 2002; World Medical Association 2008; Department of Health and Human Services revised as of March 1983). The number and length of the relevant texts can be overwhelming to individual investigators, yet they all refer to similar basic principles, which have been synthesized thus: social value, scientific validity, fair subject selection, favourable risk/benefit ratio, independent review, informed consent and respect for enrolled participants (Emanuel, Wendler et al. 2000). Finding the right balance in the inherent ethical tension of research, and respecting specific criteria for its ethical conduct, are both particularly important and difficult in situations where vulnerable persons are potential research participants. In the case of persons with cognitive impairment, it is broadly recognized that special safeguards are needed (NBAC 1998; European Parliament and the Council of the European Union 2001; CIOMS 2002; Karlawish 2003). This chapter will focus first, on whether persons suffering from diseases affecting cognition can be enrolled in
research when the purpose is to investigate the condition leading to this impairment and second, on when they may be enrolled and on the precautions which are necessary if they are. Finally, it will examine, and reject, the idea that there could be circumstances in which persons suffering from diseases affecting cognition could have an obligation to participate in research addressing these disorders.

2. Can persons with cognitive impairment be enrolled in research?

That vulnerable persons require special protection in the conduct of research is recognized in a number of international (ICH Steering Committee 1996; CIOMS 2002; World Medical Association 2008) and national regulations, including the US federal regulations on research with human subjects (US Department of Health and Human Services 1991). When designing and conducting a research study, it is important to know which potential participants are vulnerable, which sorts of studies do or do not justify their inclusion, and what protections are necessary when they do participate in research.

‘Vulnerability’ in research on human subjects is usually linked either to consent (ICH Steering Committee 1996; CIOMS 2002), or to the risk of harm (Kottow 2004), or exploitation (Lott 2005): conditions which persons with cognitive impairment clearly sometimes meet. One way to synthesize these different definitions, and to make headway towards defining what protections are needed, is to consider that vulnerability as a claim to special protection is any identifiably increased likelihood of being wronged (Hurst 2008). Adequate protections require that we identify the sorts of wrongs likely to occur in the conduct of research and those more likely to suffer these wrongs. Protections then need to be tailored to specific wrongs, and specific sources of vulnerability, and outlined in the research project.

Concerns for coercion and exploitation

Concerns regarding the inclusion of vulnerable persons –including persons unable to give informed consent- in research often point to risks of coercion or exploitation. What is meant by that and does it apply here (Emanuel, Currie et al. 2005)? The clearest explanation defines coercion as a credible and strong threat exerted by a person that limits the options in a negative way available to another person (Hawkins and Emanuel 2005). Therefore having limited options through no fault of anyone’s does not constitute coercion. Rather than removing options, the possibility of enrolling in a clinical trial actually gives patients with
chronic conditions an additional option. Although coercion can exist in research, and although of course care should be taken to avoid it, the mere offer to participate in an otherwise ethically justifiable study does not constitute coercion.

Exploitation is the unfair distribution of the benefits and burdens of a transaction (Hawkins and Emanuel 2005). Are patients suffering from diseases affecting cognition at greater risk, or are they less likely to benefit from research participation, than they should? This is not an easy question to answer: effects deemed sufficient by researchers –and which underlie the choice of research questions and methodology- may or may not reflect what patients would consider a clinically interesting effect (Horrobin 2003). Our evaluation of both risks and benefits can shift during chronic disease and changes in cognitive ability, and we should expect this shift to vary between individuals. At minimum, the risks incurred by patients suffering from diseases affecting cognition should never be discounted. More specifically, the risk/benefit assessment must take into account their circumstances. This does, however, means that exploitation can be avoided in studies enrolling vulnerable persons, including persons with diseases affecting cognition.

Concerns for coercion or exploitation, then, cannot be sufficient to warrant a general exclusion of patients with diseases affecting cognition from research. Moreover, it would be ethically problematic for the need for special protection to mean that vulnerable persons should never be enrolled in research. Historically, scandals have involved abusive studies where vulnerable persons were included because they were less able to resist. This has led to concerns about involving them in research at all, and investigators are currently still often uncertain as to when they may or may not include vulnerable persons in a protocol, and under which conditions. Excluding vulnerable persons from research entirely, however, can lead to their exclusion from 1) research with potential benefit and 2) the more general benefits of the research endeavour: knowledge about conditions relevant to them, their sometimes specific needs and risks, and the possibility to generalize available data to the situations they present with. Exclusion thus carries a moral cost, which would be born by the very people such protections would attempt to protect. Inclusion with adequate protections will often be the morally preferable alternative.
3. Special precautions for research on conditions affecting cognition

Protections for vulnerable persons in research have two components: fair subject selection (when to enrol), and the specific care required to minimize wrongs to vulnerable persons once they are enrolled in research (how to enrol) (Hurst and Elger In Press). Recruitment of research subjects should respect fairness in the distribution of research-related risks and benefits. It is not justifiable to conduct research on an ‘easily available’ population –for example the rural poor in developing countries (Tangwa 2009)- simply because the study will be easier to conduct with them than with persons living in better circumstances. Neither is it defensible to reserve access to potentially beneficial research to the socially privileged. The rationale for the planned recruitment strategy must be based on the balance of potential harms and benefits and the need to obtain generalizable results, and discussed in the protocol.

The conduct of research with vulnerable persons once enrolled should start with a good grasp of criteria for ethical research in general (Emanuel, Wendler et al. 2000), and define protections based on which criteria are at risk of remaining unfulfilled without special protection. Under the definition provided above, persons suffering from disease affecting cognition are vulnerable in several ways. Although issues related to informed consent in the presence of cognitive impairment are the most obvious, they are not the only ones. Other aspects include difficulties related fair subject selection, scientific methodology, a favourable risk-benefit ratio, as well as respect and confidentiality.

In the context of diseases affecting cognition, it is also especially important to remember exactly whom we are trying to protect, and why. While such conditions can lead to impaired decision-making capacity, they do not by themselves signify such impairment. The relevant difference here is not the diagnosis, but whether or not a specific source of vulnerability is present. This is especially important as patients suffering from mental disorders have been – and often still are– subject to stigma (Michels 1999). There is a real risk of underestimating the cognitive ability of individuals who bear this label. Some special precautions will only apply when decision-making capacity is impaired. Attempts to substitute informed consent through proxy decision-making, assent, or advance research directives are of this kind, as are the more restrictive limits on the risk-benefit ratio, which the lack of patient consent imposes. Others, such as difficulties with scientific validity or misleading expectations, will apply to all patients with diseases affecting cognition. Some, such as concerns for respect and confidentiality, will apply especially to those whose decision-making capacity is not impaired, but whose diagnosis places them at special risk of seeing their abilities underestimated.
Fair subject selection: when to enrol

In some cases, excluding vulnerable persons from participation in a research project will be an appropriate way to minimize the risk of harm or other wrongs. Sometimes, however, it won’t be. A study could be designed to address health problems specific to a vulnerable population, and research on conditions affecting cognition often falls within this category. In such cases, preventing the enrolment of vulnerable persons in research would be harmful to the very individuals which regulations intended to protect (Michels 1999). It would also be harmful to them as a group: studies benefiting the same population of vulnerable persons from which subjects are recruited often cannot be conducted on non vulnerable subjects: a condition known as the subsidiarity principle. This characteristic of research projects helps to outline which can include vulnerable persons, and which should not.

Fair subject selection should also take into account the timing of a protocol within the course of a research program. Limiting risks acceptable in the case of cognitively impaired individuals who are unable to consent to research can imply that interventions relevant both to persons who are, or are not, capable of decision-making should first undergo testing on those able to understand the implications of research participation. The goal is to minimize unknown risks at the time when those with greater cognitive impairment will be recruited to assess questions more specific to them.

Timing within the course of the disease is also relevant. In research on degenerative disease, such as various forms of dementia, the disease stage at which potential subjects are recruited will affect research related risks and benefits. For example, the effect size of benefits will sometimes be predictably lower in the initial stages, where patients have fewer symptoms (Vellas, Coley et al. 2008). In some cases it will also be the case in late-stage disease, when impairments are too great for subjects to benefit significantly even from an intervention otherwise deemed successful. Late-stage patients are also more likely to be lost to follow-up (Vellas, Coley et al. 2008). Timing within the disease course can also affect how we value risks and benefits (Kahneman, Krueger et al. 2006; Gilbert and Wilson 2009), and this in turn can affect informed consent. In the period immediately following the diagnosis of a chronic disorder, patients’ priorities can be in a state of rapid flux. Recruiting patients at this time can lead to informed consent based on priorities which are more unstable than is usually the case, and could be problematic for this reason.


**Scientific validity**

Although individual patients may benefit indirectly from research participation, the main intention of research is to generate valid data to inform the care of future patients. The investigator is responsible for avoiding unnecessary harm to research subjects, and therefore accountable for the clinical relevance of the research question and scientific validity of the study design. Failure to give them proper attention to methodological issues can make the results of a trial difficult to interpret and prevent comparisons. This limits usefulness in clinical practice, causing research to come short of its purported goal and fail to fulfil its commitments towards patients and society. Inasmuch as risks to human subjects are justified, in part, by the social benefit of research, any risk, however small, run within a study that cannot answer its research question is an excessive risk.

Outcome measurements in diseases affecting cognition are subject to discussion. While several large primary prevention trials in Alzheimer type dementia (AD) have used incidence as a primary endpoint (Vellas, Andrieu et al. 2008), the transition between normal ageing, very early AD, and AD, makes a threshold difficult to identify (Petersen 2006). Proposed alternatives include delegating the identification of new cases to an independent attribution committee, or replacing the threshold altogether and using changes in cognitive performance instead (Vellas, Andrieu et al. 2008). This may have the added benefit of reducing the required sample size, thus making a greater number of studies feasible and perhaps reflecting the priorities of patients somewhat better (Horrobin 2003).

As clinical trials can continue for several years, selected outcome measures should be valid at different stages of the disease under study. At the same time, in degenerative dementias, distinct assessment tools can be needed depending on the disease stage, for both cognitive and functional domains of impairment. In the case of AD, the cognitive subscale of the AD assessment scale (ADAS-cog) has been considered the standard primary cognitive outcome for symptomatic trials. As a greater number of studies include patients with early disease, it has however been pointed out that this measurement may not be appropriate for trials in very early dementia, where it may need to be complemented with other tests. In complex diseases affecting different aspects of mental and social functioning, a single type of measurement is unlikely to be the best one in every stage of progression. A task force of the European Alzheimer Disease Consortium proposed to combine changes in the slope of cognitive decline with quality of life and activities and instrumental activities of daily living assessments, to
establish the clinical relevance of measured differences between treatment groups in clinical trials (Vellas, Andrieu et al. 2008). Behavioral and psychological symptoms should also be taken into account, but their diversity makes this difficult to do: changes in individual items, for example on the neuropsychiatric inventory (Cummings, Mega et al. 1994), may be masked if the overall result is used as the outcome. In studies of secondary prevention, the use of compound scores measuring performance on different validated tests is recommended (Vellas, Andrieu et al. 2008).

Biomarkers –for example cerebro-spinal fluid analysis or magnetic resonance imaging- are increasingly used in dementia research. Currently, none predicts clinical decline sufficiently to serve as surrogate endpoint (Coley, Andrieu et al. 2009). Although many correlate with diagnosis, and some do correlate with decline, their use still warrants caution: in one study (Fox, Black et al. 2005), greater cerebral atrophy was recorded in the active arm of the study, but without an increase in cognitive decline.

The large inherent variability of diseases affecting cognition means that the potential of multi-centre trials to introduce added site-related effects can be problematic. Specific training and assessment of investigators has been proposed (Morris JC Neurology 1997), as have higher thresholds for the minimum number of research subjects recruited in each included centre (Vellas, Andrieu et al. 2008).

For results to be readily understandable, data must be measured and reported in a way which relates to clinical practice. Currently, no true consensus exists on the definition of the minimally clinically important difference in dementia trials (Molnar, Man-Son-Hing et al. 2009). The important variability of disease and treatment effect will sometimes mean that giving mean values does not reflect clinical reality. Graphical representation of the data showing the full range of response has been proposed in other areas of research, and may be useful here as well (Farrar, Dworkin et al. 2006).

**A favourable risk-benefit ratio**

When cognitively impaired patients are recruited in research, protections are required to circumscribe acceptable risks, and to compensate the lack of valid consent. The CIOMS guidelines specify that: “When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no
more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them.” {CIOMS, 2002 #2050}(p49) In the somewhat similar case of research with children, US regulations stipulate that ethics review committees (ERCs) may approve research involving children under three sets of circumstances: “prospect of direct benefit”, “minimal risk”, and “minor increase over minimal risk”. A prospect of direct benefit is defined as a research situation where risks are “justified by the anticipated benefit to the subjects” and where “the relation of the anticipated benefit to the risk is at least as favourable” as that of alternatives available to potential subjects (US Department of Health and Human Services 1991).

Linking the acceptable risk threshold to the prospect of direct benefit has come under criticism in the case of children for conflating risks acceptable in therapy and in research (Wendler 2008). Wendler proposes an alternative based on the “net risks test” (Wendler 2006). As any assessment of risk in research, this one should focus on the research-related risk: risks which potential research subjects would not run outside the protocol. Patients enrolled in research will often undergo standard therapy as well as experimental interventions, and risks inherent to the standard therapy are not research-related. The assessment should further focus on the net risk: risks that are not balanced by the prospect of direct benefit to the research subject. Pharmacokinetic studies, for example, hold no prospect of direct benefit: their entire risk is a net risk. A phase III study of a novel therapy with promising results in phase II, however, does hold a prospect of direct benefit for subjects. Such a study can still have a net risk, however, especially if the expected benefit is modest. Finally, ERCs’ should assess this net research-related risk and accept it if it is no greater than “those associated with routine medical and psychological examination” (CIOMS 2002), or “those ordinarily encountered in daily life” (US Department of Health and Human Services 1991). US regulations combine these two thresholds.

What are risks “ordinarily encountered in daily life”? CIOMS proposes that research interventions considered to carry low or minimal risk be similar to clinical interventions that subjects may have experienced. This requirement, which would allow greater research-related risk in situations of greater therapy-related risk, is justified by CIOMS based on the likelihood that consent will then be better informed. But this may still be excessive. In the case of children, to avoid placing an excessive burden on patients suffering from diseases requiring
invasive treatment or living in circumstances such as war-torn countries, whose risks in daily life far exceed what is acceptable in research (Freedman 1993), stricter definitions of low or minimal risk has been proposed. Comparison of the net research-related risks posed by a study should be with “the level of risk average children face in daily life (or during routine examinations)” (Wendler 2006), or the level “normally encountered in the daily lives of people in a stable society” (South African Research Council 2006). Although the exact degree of net risk which is acceptable in a trial including adults incapable of giving consent is a point on which there is currently no consensus, these considerations do provide some guidance.

**Consent and decision-making capacity**

Informed consent is particularly important in research, because it allow subjects to make an informed and voluntary choice to participate— or refuse to participate—in a project where they will take risks for the benefit of others. Adequate informed consent requires that potential subjects understand the relevant aspects of their choice, are capable of decision-making and are free to accept or refuse participation (Faden and Beauchamp 1986). Importantly, the mere presence of a disease affecting cognition does not mean that a specific person is not capable of giving valid consent. The relevant difference here is not the diagnosis, but whether or not decision-making is impaired (Michels 1999). The disease may be in an early stage, or mild, and its effects on cognition limited. Moreover, the presence of cognitive impairment is itself imperfectly correlated with capacity to give consent (Warner, McCarney et al. 2008). This is not entirely surprising: valid consent requires not just understanding, but a degree of appreciation of the situation as well. It has affective and evaluative components (Elliott 1997), all of which can be affected by disease in a manner different from cognition. Studies planning the inclusion of patients suffering from a disease affecting cognition should provide for formal assessment of decision-making capacity. They should plan to evaluate the patient’s understanding of the relevant information, the patient’s appreciation of the significance of this information for the circumstances, the patient’s ability to reason with the relevant information and weigh options logically, and the patient’s ability to express a choice (American Psychiatric Association 1998; Grisso and Appelbaum 1998). This assessment must be described in the protocol, and the evaluation targeted specifically for the purposes of research participation. Even in persons who are capable of decision-making for clinical care, consent for research requires something more: research-related risks are born for the benefits of others, a fact potential subjects are at risk of misunderstanding even in the best of cases.
Decision-making capacity for research participation is thus distinct from the abilities required for capacity to consent to medical treatment or for decisions in everyday life (Karlawish 2008). For subject to understand, specifically, that they are involved in research can be demanding (Wendler and Grady 2008). Barring such an assessment, decision-making capacity in persons with conditions affecting cognition can be underestimated as well as overestimated (Stocking, Hougham et al. 2008). When decision-making capacity is present, consent for research on conditions affecting cognitive capacity shares the same process -and the same difficulties- as any other consent for research with human subjects (Flory and Emanuel 2004).

**The problem of misleading expectations**

Another difficulty is that patients suffering from chronic conditions, and their proxies, have often experienced various treatments which showed less than satisfactory efficacy, and are likely to welcome the opportunity to gain access to a novel treatment. This makes the likelihood of the ‘therapeutic misconception’ particularly high. Their hope for direct benefit to themselves or a sick loved one can also expose them to minimizing or overlooking inconveniences and risks. Furthermore, many persons suffering from diseases affecting cognition experience impaired physical, emotional and social functioning, all of which have been associated with the therapeutic misconception (Appelbaum, Lidz et al. 2004). Failure to address the therapeutic misconception in potential participants undermines the validity of consent, and constitutes a breach of obligations.

The therapeutic misconception is also ethically problematic because it is a case of misplaced trust, which can endanger the physician-patient relation (de Melo-Martin and Ho 2008). Participants, of their family members, may come to question the researcher’s competence and blame him if their expectations are not fulfilled. Patients’ distrust towards physician investigators can extend and impact on their relationship with their own physician. It will then affect and possibly jeopardize routine clinical care (Escher and Hurst In Press).

**Assent and dissent**

When persons who are not capable of decision-making are recruited for research, the investigator should seek the person’s agreement –officialised in some jurisdictions as ‘assent’- to the extent of the potential subject’s capabilities, and respect his or her dissent (CIOMS
Concern underlying the requirement for assent are based on the need to continue respecting the priorities of potential subjects of research, and their right to self-determination to the degree they are capable of it (Jaworska 1999). Rejecting potential subjects stated choices outright, when they are capable of voicing them even in part, can also be humiliating to them (Winick and Goodman 2006).

While the requirement to respect assent and dissent in cognitively impaired subjects is accepted, there are no widely accepted standards either for judging the extent to which persons can assent to participation, or for obtaining such assent. When agreement—or assent—is sought, a formal process should nevertheless be planned. Relying on simple indications of willingness to participate is insufficient. Difficulties in verbal and non-verbal communication are frequent in dementia, making the risk of misunderstanding high (Warner and Nomani 2008). Investigators should indicate what abilities will determine whether a potential subject can assent, and ERCs should examine these procedures (Karlawish 2003).

Dissent - disagreement or resistance- to participation in a research project should be respected regardless of ability to assent. Respect for dissent is not only required because we should respect the expression of the patient’s priorities (as in assent), but also to avoid exerting abusive power, and to avoid causing harm through constraints in the conduct of research.

**Advance research directives**

In some cases, subjects can be recruited before a predictable loss of capacity occurs and advance informed consent then becomes an option. When this is done, research subjects should also be asked to name a person to serve as their proxy for decisions to be reached at a future date during the conduct of the study. Advance informed consent only applies to specific projects enrolling persons known to be eligible, who are capable of decision-making at the outset, and who may loose this capacity during the course of the same study. Informed consent is thus close enough to present potential subjects with information likely to be relevant in their current situation. In cases where loss of decision-making capacity is predictable, but the question of research participation relates to research in general rather than to a specific protocol because it addresses participation in future research, it has been proposed that a ‘advance research directive’ could stipulate potential subjects’ preferences independently of an actual study. This would allow competent individuals who know in advance that they wish to participate in research, to prospectively state this rather than depend
exclusively on surrogate decision-makers in the future (Pierce 2009). The legal status of advance research directives is, however, unclear (Lotjonen 2006; Pierce 2009). A number of difficulties with their use have also been put forward. Concerns focus on the difficulty of anticipating a future experience of research participation as an incompetent subject, and lack of ability to withdraw consent after capacity is lost. There are also questions regarding abilities required to write such directives, the degree of risk which can be consented to in advance, and the legitimacy of binding an incompetent future self (Pierce 2009). Despite this, advance research directives have been endorsed by advocacy groups, as a means of fostering research designed to help persons with diseases affecting cognition. Advances in early diagnosis also make advance research directives before any loss of capacity appears a more realistic option. One study of such directives found that a significant minority of adult inpatients (9%) indicated willingness to participate in research that would not help them and posed greater than minimal risk (Muthappan, Forster et al. 2005). Although further research is required to define appropriate conditions for advance research directives, their implementation may thus provide such patients with a way of accepting research which may otherwise not be considered ethically acceptable.

**Proxies and surrogates**

In some countries including the US, patients who are incapable of giving consent can be enrolled in research following proxy consent (US Department of Health and Human Services 1991; CIOMS 2002). The possibility for proxy, or surrogate, consent is designed to delegate the decision to someone who is likely to know what the potential subject would have wanted (Buchanan and Brock 1990), and who takes their best interest to heart (Karlawish 2003). It also reflects a prevalent – though not general- attitude of willingness on the part of potential subjects to give leeway to their family members for such decisions (Chenaud, Merlani et al. 2009; Karlawish, Rubright et al. 2009; Kim, Kim et al. 2009).

Identifying the most appropriate proxy is not easy, and legally provided hierarchies among family members may be misaligned with affective proximity and knowledge of a potential subject’s preferences. This has led to a proposal that investigators should identify the ethically most appropriate surrogate, and obtain consent from both proxies when the law requires them to obtain is from a legal representative as well (Karlawish 2003). Even when an appropriate surrogate is identified, there is no clear guidance on how ERCs should oversee their involvement (Kim, Appelbaum et al. 2004). Moreover substituted judgment, attempting to
decide as the patient would have done, is a difficult exercise. A fact reflected in the finding that next-of-kin as well as patient designated proxies incorrectly predict patient preferences in approximately a third of cases (Shalowitz, Garrett-Mayer et al. 2006). Among patients, reluctance to give leeway to a surrogate was found to increase with the risk of the research scenarios (Stocking, Hougham et al. 2006). Despite these difficulties, it is important to note that patients may remain capable of appointing a proxy even when they are no longer capable of writing an advance research directive (Kim and Kieburz 2006).

**Respect and confidentiality**

Respect for research subjects as persons also includes respect of patients’ more general clinical needs, concerns for their safety including at times when it becomes necessary to withdraw them from a research protocol, and protection of their private sphere. Like clinical care, research often involves the collection of intimate information, which persons would not otherwise divulge. In clinical care, respect for patient confidentiality is based on the requirement to respect a patient’s private sphere and her control over personal information. It is also based on the need to provide patients with a private space where they can divulge to clinicians the information needed in order to treat them, without fear that others will hear it. These considerations also apply in research but, in both research and clinical care, confidentiality is more difficult to implement in the case of conditions affecting cognition. When decision-making capacity is impaired, reliance on proxies and surrogates will mean that the relevant information must be made available to them. This is not the case for patients whose decision-making capacity is intact. As outlined above, however, decision-making capacity in persons with conditions affecting cognition can be underestimated (Stocking, Hougham et al. 2008). Confidentiality is thus an additional reason to assess decision-making capacity specifically. Furthermore, diseases affecting cognition are often chronic disorders, during which health care providers will often rely to varying degrees on support from family members in the care of the patient. This can lead them to value disclosure to family caregivers as being in the patient’s best interest. Patients, however, still value a high degree of control over disclosure of personal information to family members (Tracy, Drummond et al. 2004), and researchers should be aware that confidentiality is not less important in their case than in others.
4. Research to prevent the loss of self: a special case?

Much focus rests on whether, and how, we may enrol persons with diseases affecting cognition in research. Part of the reason why special protections are needed, however, is that impaired cognition can lead to loss of autonomy. The value we attach to self-determination thus underlies much of the special attention prescribed when such persons are enrolled in research. This can seem to lead to something of a paradox. The entire field of research on conditions affecting cognition, or most of it, can be fairly described as attempting to find interventions likely to protect, or hopefully correct the loss of, self-determination in affected patients. Yet we assume as a default position that patients with diseases affecting cognition should not be enrolled in research unless there is a good reason to do so. Would we have reason, based on the importance of protecting autonomy in such patients, to assume enrolment unless there are good reasons against it? Perhaps even to place limits on the sorts of research project patients, or their surrogates, can refuse to participation for? A similar, stronger point is sometimes made as regards end-of-life choices: that making a choice which could lead to the loss of autonomy may be considered contradictory, and thus not part of the scope of choices we should allow persons to make even for themselves (ten Have and Clark 2002). Although I will argue that this argument fails, it is worth presenting here as it focuses on a rather specific characteristic of research on conditions affecting cognition: a concern to prevent the loss of self (Dekkers and Rikkert 2007). If the worth of persons -their Kantian dignity- is based on their rational nature, why does it not follow that persons affected with a disease affecting cognition have an obligation to take all available chances of maintaining autonomy, including research participation?

There are three arguments against this conclusion. First, accepting it would require that we buy into the therapeutic misconception (Appelbaum, Lidz et al. 2004), and presume that research interventions are effective whereas this is by definition uncertain. Nevertheless, uncertainty cannot truly counter this argument, as the mere chance of maintaining the capacity for self-determination may still be sufficient. Second, as Dekkers points out, the currently available drugs are not effective enough to truly prevent the loss of self brought about by diseases affecting cognition. Although this reason is contingent on the current state of medical progress, it does seem valid for now. Third, as McMahan argues in the context of end-of-life choices, for a person to have worth, or dignity, is for this person to matter in some way. True, one possibility is to consider that a person’s ‘rational nature’ provides us with a reason why this person should matter to us. But even under such a view, the end of a person’s ‘rational
nature’ does not cause this person to cease to matter (McMahan 2002). Even if we accept that self-determination is central to that which we should protect in persons, this does not mean we should protect self-determination exclusively, or that persons have a duty to protect their own self-determination above all other considerations. Velleman put it as follows: “Respecting …people is not necessarily a matter of keeping them in existence; it is a matter of treating them in the way that is required by their personhood-whatever way that is.” (Velleman 1999)(p616).

There is also a more general debate regarding whether there exists an obligation to participate in clinical research for all persons, and some of these arguments may apply here as well. Arguments in favour of such an obligation to participate in research include that this would form a part of a general duty of beneficence, that the failure to participate in research is a form of free-riding, and that participation in research is the condition for generating a public good: generalizable biomedical knowledge (Schaefer, Emanuel et al. 2009). Schaefer and colleagues argue that the beneficence argument and the free-riding arguments ultimately fail. The first because there are many alternative manners in which people can do good, and the second because participating in research does not diminish the burden born by others for the same goal. They do, however, convincingly defend a duty to participate in research in order to help generate a public good. Although this could in theory apply to anyone, there are limits to how far it can do so as regards patients with cognitive impairment. First, as the duty to participate rests on the fact that research results benefit everyone, this would be limited to research with the potential to benefit persons with cognitive disorders. In effect, the subsidiarity principle would still largely apply. More importantly, Schaefer and colleagues propose what amounts to an opt-out system, rather than a binding obligation to participate in research. Since opting out requires either decision-making capacity or a delegation of the power to opt out to a surrogate, their proposal will be sharply limited as regards persons with cognitive capacity. In effect, applying their conclusions to persons with cognitive impairment may not change very much to the sort of practices we would find acceptable.

5. Conclusion

In conducting research on diseases affecting cognition, it is important to remember exactly whom we are trying to protect, and why. Some special precautions will only apply when decision-making capacity is impaired, while others will apply especially when it is present, or to all patients. As with any other group for which questions of vulnerability in research and its
protection arise, the challenge is to find the right balance between protection from abuse and
the need to grant vulnerable populations access to participation in research, and to progress in
medicine’s ability to help them. In the case of persons whose decision-making is impaired by
a disease affecting cognition, as with other vulnerable subjects of research, exclusion from a
specific study will sometimes be an appropriate way to minimize patients’ risk of being
wronged in the conduct of research. This, however, will not always be the case. Studies
designed to address health problems specific to a vulnerable population are needed to improve
care for this very population, and often cannot be conducted on others. Participation in
research can hold a prospect of benefit from which it is sometimes wrong to exclude
vulnerable persons. In such cases, enrolment with special protections tailored to the sort of
wrong to be avoided is ethically preferable to exclusion.
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