INFORMED CONSENT, EXPLOITATION AND WHETHER IT IS POSSIBLE TO CONDUCT HUMAN SUBJECTS RESEARCH WITHOUT EITHER ONE

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ABSTRACT

Clinical research with adults who are unable to provide informed consent has the potential to improve understanding and care of a number of devastating conditions. This research also has the potential to exploit some of society’s most vulnerable members. Recently, a number of task forces and individual writers have proposed guidelines to ensure that such research is both possible and ethical. Yet, there is widespread disagreement over which safeguards should be adopted. In the present paper, I consider to what extent these disagreements can be resolved by appeal to a general account of the interests of subjects who are unable to consent and the conditions that must be satisfied for research enrollment to constitute exploitation of their inability to make their own decisions.

INTRODUCTION

Regulations governing clinical research tend to rely heavily on subjects’ informed consent. As long as those participating in research provide informed and voluntary consent, one need not worry, at least not so much, about what is being done to them, or why. Leaving aside the extent to which this approach succeeds in the standard cases, it, like the contractarian theories from which it derives, provides no guidance on how to treat individuals who are unable to consent. To address this gap, a number of writers and task forces have developed guidelines for research with these

1 I bracket emergency research and research with minors and focus on non-emergency research with adults.
individuals.\textsuperscript{2,3,4,5,6,7,8} In addition, several existing guidelines, most notably the Canadian Tri-Council and Council of Europe regulations, already include such guidelines.\textsuperscript{9,10}

There is no widely accepted analysis of what safeguards these guidelines should include. As a result, the recent proposals and existing guidelines have been developed based primarily on the authors’ intuitions of which safeguards make the most sense. Not surprisingly, this reliance on bare intuitions has produced conflicting recommendations. In this article, I consider to what extent these disagreements might be resolved by appeal to a more general conceptual framework.

In developing this framework, I use the terms ‘protections’ and ‘safeguards’ in a specific way. A protection corresponds to one of the potential harms raised by research with individuals who are unable to consent: since exploitation is a potential harm of research with individuals who are unable to consent, one of the needed protections is shielding individuals from exploitation. Safeguards are the specific requirements or stipulations that guidelines incorporate to implement the necessary protections. For instance, to shield individuals from exploitation, some writers argue that these individuals may be enrolled in

\begin{itemize}
\item \textsuperscript{2} National Bioethics Advisory Commission. \textit{Final Report: Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity.} December 1998.
\item \textsuperscript{3} New York State Advisory Work Group on Human Subject Research Involving Protected Classes. \textit{Recommendations on the oversight of human subjects research involving the protected classes.} (State of New York Department of Health, Albany, 1998)
\item \textsuperscript{7} American College of Physicians. ‘Cognitively impaired subjects’, \textit{Ann Intern Med} 1989; 111: 843–848.
\item \textsuperscript{9} Canadian Tri-Council Report on the Ethical Conduct for Research Involving Humans. \url{www.ethics.ubc.ca/code}
\item \textsuperscript{10} Council of Europe. \textit{Convention for the Protection of human rights and dignity of the human being with regard to the application of biology and medicine.} The Council of Europe guidelines, which have been signed by 24 member states, are currently under revision.
\end{itemize}
research only when it offers them the potential for medical benefit.

The present suggestion is that a good deal of the disagreement over the appropriate guidelines for research with individuals who are unable to consent traces to the urgency of the issue, not irresolvable differences in moral intuitions. Given the need to develop guidelines for on-going research, most writers have proposed specific safeguards without a prior analysis of what protections are needed. After developing such an analysis, I consider whether two key proposed safeguards – the ‘necessity’ and ‘subject’s condition’ requirements – help to implement the needed protections.

WHY ARE ADDITIONAL SAFEGUARDS NECESSARY?

It is widely agreed that individuals who are unable to consent need additional safeguards to protect them from exploitation. Research participation places subjects at risk for the purpose of benefiting society in general. For this reason, all research subjects face some risk of exploitation. They face the possibility that researchers may regard them purely as a means to benefit society or, more subtly, enroll them when the societal benefits to be gained from the research do not justify the risks that subjects face. Several widely accepted human subjects regulations address this potential for exploitation of subjects qua persons. Most regulations stipulate that subjects should be placed at risk only when the research addresses an important scientific question and offers a reasonable chance of answering that question. Individuals who are unable to consent also face the risk that investigators may exploit their inability to understand and make their own decisions. To determine what additional safeguards are needed to protect these individuals, one needs to clarify this form of exploitation and then determine what safeguards address it.

Taking advantage of subjects’ inability to consent does not, in itself, constitute exploitation of that inability. For instance, one can imagine a study that proposes to examine the psychological importance of autonomy by enrolling individuals who have lost the ability to make their own decisions and assessing what impact this loss has on them. In the morally neutral sense of the term, this study takes advantage of individuals’ inability to make their own decisions in order to learn more about the psychological importance of autonomy. However, all clinical research takes advantage of certain characteristics that subjects possess in order to advance medical knowledge. Although one could regard all
such taking advantage as unethical, this view suggests that all clinical research is morally suspect and should be limited or prohibited altogether. Here we are concerned with the narrower task of clarifying the special form of exploitation that, it is assumed, is a concern only when investigators enroll individuals who are unable to consent. Put generally, this concern is not that investigators will take advantage of individuals’ inability to consent to advance scientific knowledge, but that investigators will take advantage of their inability to enroll them in research. The question, then, is when does enrolling individuals who are unable to consent involve exploiting their inability?

The determination of whether a particular instance of taking advantage of some state of affairs is inappropriate requires a comparison between the course of events in question and the course of events that we would expect in a fair exchange. (The threat of circularity in such accounts will be less of a concern here since there is an independent account of what constitutes fair research enrollment.) The clearest examples of this comparison between the actual and expected course of events involve economic relationships in which one compares what individuals earn against what we would expect them to earn in a fair exchange. To take a related example considered by Wertheimer, imagine that a tow truck driver earns his living pulling cars out of snow banks.\textsuperscript{11} In one sense, the driver takes advantage of his clients’ misfortune – he makes money because these individuals are stuck and, let us assume, have no other means of extricating themselves. However, whether the truck driver thereby exploits his clients’ misfortune depends, in large part, on what he charges. If he charges wildly in excess of the baseline fair price for the service he provides, then he is exploiting his clients’ misfortune. In contrast, if he charges a fair price, he is not, despite the fact that he takes advantage of their misfortune to make a living.

The potential to inappropriately take advantage of research subjects’ inability to consent first arises when investigators do not need to enroll them.\textsuperscript{12} Thus, imagine that an investigator


\textsuperscript{12} There is a lot more that would need to be said to make this a complete account of exploitation in the research setting. In particular, it is not clear whether fairness is the right way to construe inappropriate forms of taking advantage in this setting. For present purposes, I shall bracket these questions since they do not substantively influence the determination of which safeguards are appropriate for those unable to consent.
studying rheumatoid arthritis could equally well enroll individuals who can consent, but instead chooses to enroll individuals who are unable to consent. Such enrollment raises the concern that the investigator is exploiting these individuals in the sense of enrolling them because they are unable to consent and, hence, less able to protect themselves. To address this possibility, almost all writers support the ‘necessity requirement’: individuals who are unable to consent should not be enrolled unless their participation is scientifically necessary. For instance, the Council of Europe’s guidelines require that: ‘research of comparable effectiveness cannot be carried out on individuals capable of giving consent.’\textsuperscript{13} One might be less concerned with the enrollment of individuals unable to consent in research protocols that offer them the potential for important medical benefit. In such cases, excluding those unable to consent may seem more like discrimination than protection. I return to this concern when I consider the proper scope of the necessity requirement.

In addition to running a risk of exploitation, investigators who enroll individuals who are unable to consent, when they could enroll those who can consent, create the appearance of exploitation. The appearance of exploitation has moral significance here because society supports and benefits from human subjects research. Thus, society incurs a special obligation to ensure that individuals unable to consent are not exploited. To meet this obligation for public accountability, simply conducting research without exploitation is not enough; it must be clear that this is the case. This need to avoid even the appearance of exploitation also supports the use of the necessity requirement. Finally, as I argue below, the necessity requirement is supported by the ethical concerns that arise in conducting research with individuals unable to consent.

In some cases it might not be clear whether the participation of individuals who are unable to consent is necessary. For instance, Xeraderma Pigmentosum (XP) is a rare form of skin cancer which, for unclear reasons, leads to severe cognitive impairments in a subset of individuals with the disease. Imagine that an investigator develops a potential treatment for XP and, after the appropriate initial tests, proposes to enroll 100 people with the disease to test the potential treatment’s effectiveness. Further imagine that the investigator has enough money to keep

\textsuperscript{13} Council of Europe, \textit{Convention for the Protection of human rights and dignity of the human being with regard to the application of biology and medicine}, Article 27.iii.
the study open for three years during which time she can enroll
75 people with XP who can consent and 25 who cannot consent.
Whether the necessity requirement would allow this investigator
to enroll the 25 individuals who are unable to consent depends
upon which aspects of the study one holds constant in making
this determination. If one holds the investigator’s budget
constant, she must enroll those unable to consent to obtain the
information sought. Alternatively, one could argue that she does
not need to enroll those who are unable to consent, she simply
needs to increase the study’s budget and keep it open longer.

The necessity requirement is intended to protect individuals
who are unable to consent from being enrolled when it is in the
institution’s or investigator’s control to enroll those able to
consent. The key question, then, is whether the investigator or
institution could alter the aspects of the study that result in
these individuals being necessary. Could the institution supply
more money? Could the institution conduct the study at a
different site with faster enrollment? If so, these changes should
be made as opposed to enrolling individuals who are unable to
consent. Of course understanding the relevant ethical con-
siderations does not imply that the necessary ethical judgements
will always be clear. Imagine that the institution could supply
the money needed to keep the study open for an extra year, but
only by reducing the power of a different study. In such cases,
IRBs will have to weigh the relative importance of the possible
changes.

What happens to the potential for exploitation when the
enrollment of individuals unable to consent is necessary?
Presumably the potential for exploitation traces to the fact that
individuals cannot consent. And this fact does not change simply
because the alternative of enrolling those able to consent is no
longer available. On this basis, one could argue that even the
necessary enrollment of individuals unable to consent is
exploitative. At the other extreme, one might argue that as long
as the enrollment of individuals unable to consent is necessary,
their enrollment is not exploitative, hence, no other safeguards
are needed. In this case, they are being enrolled because their
enrollment is necessary to obtain important scientific infor-
mation, not because they are unable to consent.

This latter argument fails to distinguish between the
expectation that investigators will enroll the population of
individuals who are unable to consent versus the expectation
that they will enroll specific individuals who cannot consent. It is
appropriate to enroll individuals who are unable to consent when
the information being sought cannot be obtained by enrolling individuals who can consent. However, necessity alone does not imply that, in a fair exchange, the necessary individuals would be enrolled. Instead, we expect that in a fair exchange the decision to enroll specific individuals will be guided by their preferences and values. On this understanding, investigators take unfair advantage of individuals’ inability to consent when they enroll them in research that conflicts with their preferences and values. This enrollment is unfair because, we assume, if the individuals had been able to make their own enrollment decisions they would have recognized the conflict between the research and their preferences and values and declined to enroll. Since the need to enroll individuals unable to consent does not imply that such enrollment is consistent with specific individuals’ preferences and values, the necessity requirement alone is not sufficient to address the potential for exploitation.

Assessing whether a particular enrollment decision is exploitative by comparing it to the decision we expect the subject would make if competent allows one to assess degrees of exploitation. In the previous example, the extent to which the tow truck driver exploits his clients depends upon how much he charges them over the fair price. Overcharging by a little does not constitute the same degree of exploitation as overcharging them by a lot. In the research example, one could assess the degree of exploitation by considering to what extent an enrollment decision conflicts with an individual’s preferences and values. However, the present goal is to develop safeguards that protect individuals unable to consent from all exploitation, not just exploitation that exceeds some threshold. Thus, the question of degrees of exploitation will receive little attention.

An account of what decision we would expect subjects to make if they were competent should not assume that individuals always make the right decisions. Even competent individuals misconstrue their preferences and values and fail to fully understand the decision in question. As a result, they sometimes end up making choices that conflict with their preferences and values. This possibility is important. For it reveals that in developing an account of the potential exploitation of individuals’ inability to

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14 In addition to unfair taking advantage, exploitation typically requires that the exploiter gains some benefit and the exploitee is put at some kind of risk. Since these two conditions do not substantively affect the safeguards that are needed to protect individuals unable to consent, I will not consider them here.
consent, we should not set our baseline expectations too high. We do not expect individuals to always make the research enrollment decision that, in fact, is most consistent with their preferences and values. Rather, we expect them to make the decision that appears, given all they know about their preferences and values and the decision in question, to be most consistent with their preferences and values.\(^{15}\)

What individuals know about their relevant preferences and values, and the decision in question, depends, in large part, upon how much they ‘investigate’. Importantly, even a decision as simple as whether to cross the street could be investigated endlessly. How much do I really want to get to the other side? How much do I care about the opportunities foregone if I do? Is there a greater chance a meteor will strike where I am standing or where I am headed? Despite these possibilities, individuals do not investigate every decision endlessly. Instead, individuals roughly tailor their depth of investigation depending upon the risks and potential benefits presented by the various options. If the risks are very low, one investigates for a moment; if the risks are great, one investigates more thoroughly.

What decision we expect individuals would make if competent depends upon what they would know about the decision in question and their relevant preferences and values. And what they would know if competent depends upon how much they would investigate which, in turn, depends upon the risks and potential benefits involved. This account suggests that whether investigators exploit individuals’ inability to consent depends upon how much evidence they have that the individuals want to enroll. If there exists overwhelming evidence that enrollment in the study in question is consistent with the individuals’ preferences and values, then enrolling them is not exploitative: if the individual had been able to make their own enrollment decision, the expectation is that they would have chosen to enroll.

On the present account, protecting individuals who are unable to consent from exploitation requires ensuring that they are enrolled in research only when there is sufficient evidence they want to enroll. And what constitutes sufficient evidence depends upon the protocol in question. When the risks are very low, investigators need on balance only minimal evidence of the

\(^{15}\) Depending upon one’s analysis of knowing, it might be more accurate to talk in terms of what the individual is consciously aware of at the time of the decision.
subjects’ relevant preferences and values. Thus, even a spouse’s sense that the individual wants to enroll based on the fact that he likes to help others in general would be sufficient for minimal risk research.\textsuperscript{16} For riskier research, investigators should have more explicit evidence, such as written or verbal statements, that the individual is willing to participate in the research. Finally, for research that presents a real concern of serious harm, investigators must have evidence that establishes beyond any reasonable doubt that the individual wants to enroll.

The fact that every research protocol presents some, however remote, risk of serious harm does not imply that investigators need overwhelming evidence to enroll individuals unable to consent in every protocol. Recall the decision to cross the street. There is a very small chance that I could be struck by a meteor on the other side. This remote chance of serious harm does not lead me to investigate for hours whether I really want to walk over there. Thus, on the present account, investigators do not need overwhelming evidence that individuals unable to consent want to enroll in a blood draw study, say, even though it presents some risk of a clot that could lead to a heart attack.\textsuperscript{17} The focus on the decision individuals would make if competent underscores the importance of evaluating risks from the subject’s perspective. If the subject regarded piercing of the skin as seriously immoral then, our own evaluation of the risks of blood drawing notwithstanding, one would have strong evidence against enrolling her in a blood draw study.

One may wonder to what extent it makes sense to appeal to the preferences and values of individuals who are unable to consent. If individuals cannot understand the decision in question, the

\textsuperscript{16} Obviously, the appeal here is to all the available evidence. Having some evidence that an individual would want to enroll is not sufficient if there is more evidence that the individual would not want to enroll.

\textsuperscript{17} The analysis of risks and potential benefits depends heavily on psychological factors. For instance, we tend to be more averse to unfamiliar risks than familiar risks. This raises the question of whether investigators should abide by clearly irrational decisions that an individual would make while competent. For instance, imagine that a person has the irrational belief that any piercing of the skin presents a high risk of death. Most such people would not consent to research protocols that involve a blood draw even when they recognize the fear as irrational. Now imagine that in the process of losing the ability to consent, such a person also loses their irrational fear of blood draws. On the present account, enrolling them in a simple blood draw study involves exploiting their ability to consent because they would not have consented if they were competent. Taking account of this kind of example would require a modification of the present account to refer to an idealized account of what the person would decide if competent.
argument might go, how can they have preferences relevant to that decision? For present purposes, it will be important to distinguish two questions: Do these individuals possess relevant preferences and values? Can others determine what their relevant preferences and values are? To provide informed consent, research subjects must: a. understand the nature of the protocol in question; b. appreciate their own personal situation; c. make a voluntary decision whether to enroll based on this understanding, and in light of their own preferences and values; and d. communicate this decision.\textsuperscript{18,19,20,21} Individuals who fail any one of these conditions are unable to provide informed consent. However, the fact that individuals lose one or more of these abilities does not, in itself, imply that they have thereby lost all relevant preferences and values.

If I am rendered unconscious as the result of being struck on the head, I temporarily lose the abilities to understand and communicate. As a result, as long as I remain unconscious, I am unable to consent to any research protocols for which I might be a candidate. Nonetheless, I may retain strong preferences about the research protocols for which I am a candidate: the average knock on the head, even those severe enough to render the sufferer unconscious, typically does not eliminate one’s preferences and values. Individuals do not lose all their preferences and values the moment they lose consciousness and then suddenly regain them upon awakening. Instead, absent evidence to the contrary, we assume, and it is typically the case, that individuals retain their competent preferences and values during periods of incapacity. For this reason, individuals’ competent preferences and values provide the default as to their competent preferences and values when they are unable to consent.

Of course not all incapacitating insults are like knocks on the head. Alzheimer’s Disease, to take a prominent example, involves a gradual dementing process by which the plagues and tangles that characterize the disease alter the architecture of sufferer’s brains. Obviously such neuroanatomical changes could affect

individuals’ preferences and values. Granting this possibility, there needs to be evidence that this is the case. The assumption that the debilitating insults of Alzheimer’s Disease do not necessarily, at least immediately, wipe out one’s preferences and values is not simply a conceit of bioethicists; it is supported by what we know about neuroanatomy. In particular, it is supported by the fact that brain functions are relatively compartmentalized, so that an insult can destroy one function, such as memory, but not others, such as valuing.

To stay with the present example, Alzheimer’s Disease first affects the hippocampus which is crucial for the ability to turn short term declarative memories into long term memories. For this reason, Alzheimer’s Disease begins with impairment in one’s ability to remember recent facts and events, even though one can vividly remember events from long ago. As the disease spreads it takes in the medial temporal lobes and then the amygdala which is crucial for the development of nondeclarative memories. At this point, individuals begin to lose the ability to name every day objects and perform familiar tasks such as preparing dinner and dressing themselves. However, there is strong evidence that feelings, emotions and reasoning are not localized in the regions that are first affected by Alzheimer’s Disease. As a result, even severe impairment to the hippocampus, say, does not necessarily eliminate one’s preferences and values. Thus, individuals who are unable to consent due to Alzheimer’s Disease may have preferences and values relevant to whether they are enrolled in research protocols that they cannot fully understand. A similar story could be told about other debilitating conditions. For instance, schizophrenia can affect one’s ability to understand the world without affecting ones preferences; severe depression can affect one’s ability to make decisions without affecting one’s preferences or ability to understand.

One might assume that determining the preferences and values of impaired research subjects is most difficult with respect to those with the severest impairments. In fact, the most severely impaired often cannot understand or communicate at all. As a result, to the extent one cannot develop any evidence that the individual’s preferences have changed, one continues to follow their competent preferences and values. Of course the longer the impairment goes on, and the more severe it becomes, the less

confidence one should have that the individual’s competent preferences reflect his present preferences.

Individuals with moderate impairments present a different challenge. Imagine that an individual is morally opposed to any research involving fetal tissue. However, after developing moderate Alzheimer’s Disease, the individual expresses a desire to enroll in a research study that involves the use of fetal derived cells. Should we say that the individual has changed his mind and no longer opposes such research? Or should we say that this individual’s expressed preferences do not reflect his actual preferences. These cases raise two related concerns.

First, they press the question of to what extent an individual’s competent preferences and values reflect the preferences and values of the individual in front of us – to what extent are these two time slices of the same individual. Others have written on this question and I won’t try to answer it here except to point out that it is not peculiar to research with individuals who are unable to consent. This question arises whenever one is presented with evidence that an individual’s preferences have changed. In such cases, one needs to determine who is the person in front of one – does this expression represent a real change or mere confusion?

These cases also raise the question of to what extent the expressed preferences of those who are unable to consent should be respected simply in virtue of the fact that a person is expressing them. Does respect for autonomy provide a reason to respect an individual’s competent preferences only? Or does it also require that we give moral weight to expressed preferences of the individual in front of us even if the preferences they are expressing might not represent their competent preferences? We will come back to this question when we consider the autonomy interests of individuals who are unable to consent.

Granting that individuals who are unable to consent have preferences and values, presses the question of how an investigator might determine what they are. The fact that individuals’ competent preferences and values provide the default as to their present preferences and values implies that the first source of evidence involves statements made while they were competent. It is for this reason that research advance directives have gained so much attention. For present purposes, I will not consider in depth the various ways in which investigators might gain evidence of individuals’ preferences and values. This is in equal part because the question is not directly relevant to the present analysis and because I do not think, in the end, these differences
make much of a difference. It is what the investigator knows, not how she knows it.

It is important to note that competence is task specific. One is unable to consent when one cannot understand the specific protocol(s) in question. Despite this inability, one may still be able to understand a great deal and, based on this understanding, develop new preferences and values. For this reason, one should not assume that there is some clear line in an individual’s life prior to which one’s preferences and values are competent and after which any new preferences and values that the individual develops must not be competent.

Finally, the appeal to subject’s competent preferences and values in order to determine what choice they would make if they were able to make a choice raises the question, which I will not attempt to answer here, of how the present account applies to individuals who were never competent, such as those who were born with severe mental retardation. Does the fact that some individuals never had competent wishes imply that they should not be enrolled in research? Or does it imply that the potential to exploit them must be judged on other grounds, such as whether the research is consistent with their stable, albeit never competent, preferences?

THE SCOPE OF THE NECESSITY REQUIREMENT

While there is widespread support for the ‘necessity requirement’, there is a good deal of disagreement over its scope. Some argue that individuals who are unable to consent should be barred whenever their participation is scientifically unnecessary. On this view, the necessity requirement should bar unnecessary enrollment even when it offers the potential for important medical benefit. The American College of Physicians supports this broad version, arguing that if ‘it is possible to answer the research question by studying competent patients, only competent patients should be studied’.

In support of this approach, proponents argue that the potential medical benefits of research participation are inherently speculative. Thus, they can never justify enrolling individuals who are unable to consent unless their participation is scientifically necessary. These writers conclude that the necessity requirement should be applied to all research protocols. For instance, Robert Veatch writes:

I believe they [individuals unable to consent] should be considered for human experimentation only in cases where research on the first group [those capable of consent] is impossible … because, by definition, therapeutic research proposes experimental treatments about which there is no consensus as to benefits, it is never possible to justify such experiments on general patient-benefit grounds.24

Critics respond that research participation sometimes offers subjects the potential for important medical benefits that are unavailable outside of the research context. To this extent, the broader necessity requirement goes against the current emphasis on using regulations to guarantee access to research’s benefits, rather than protection from its risks.25, 26, 27, 28, 29 To avoid barring individuals from pursuing important medical options, including last chance treatments for otherwise fatal diseases, these writers conclude that the necessity requirement should not be applied to protocols that, in Dresser’s words, offer ‘a strong possibility of direct benefit to decisionally incapable subjects’.30

Despite this disagreement, both sides choose their preferred version of the necessity requirement based on which one is thought to most benefit individuals who are unable to consent. Approached in this way, the debate over the necessity requirement reduces to a debate over whether research is ever in the medical best interests of these individuals. However, since most human subjects research is conducted precisely to determine the risk/potential benefit profile of the treatment under investigation, it is impossible to determine which version of the

27 J.D. Moreno, ‘Ethical Issues Related to the Inclusion of Women of Childbearing Age in Clinical Trials‘ in Mastroianni, Faden, Federman op cit.
necessity requirement would provide more overall benefit to individuals who are unable to consent. Fortunately, this deadlock is the result of a misunderstanding over the nature of human subject regulations.

The goal of clinical research is to develop generalizable knowledge that can be used to improve overall health and well-being.\textsuperscript{31,32,33} This goal shapes almost every aspect of research protocols, including who may enroll in them. Individuals with brain tumors are prone to seizures, and it is often impossible to determine whether these seizures are due to drugs the individuals are taking or the physiological effects of their tumors. Given this ambiguity, individuals with brain tumors are routinely excluded from phase 1 cancer trials, even when such exclusions bar them from last chance treatments for otherwise fatal conditions. These ‘scientific’ exclusions are widely accepted because they promote the development of generalizable knowledge. However, barring individuals with brain tumors from last chance protocols is not ethically acceptable because knowledge per se is more important than these individuals’ lives. Rather, excluding individuals with brain tumors is ethically acceptable because the added scientific knowledge furthers research’s goal of improving overall health and well-being.

Since overall health and well-being includes the health of present individuals as well as the health of future individuals, human subjects regulations should try to minimize the aggregate harms and maximize the aggregate benefits to research subjects. To do this, clinical investigators and IRBs must assess the effect on particular research protocols of enrolling different classes of subjects. To take an extreme example, excluding subjects who face a risk of death, when there are equally suitable subjects who do not face any serious risks, helps to improve overall health and well-being by reducing the extent to which research harms subjects.

Because clinical investigators, who tend to be physicians, typically make these judgements without the need of an explicit policy, the justification for these exclusions is rarely considered and their policy implications largely ignored. Most importantly, the practice of excluding individuals whose enrollment would


\textsuperscript{33} United States Federal Regulations. ‘Protection of Human Subjects. 45 Code of Federal Regulations 46.102 d.’
detract from research’s goal of improving overall health and well-being implies that human subjects regulations should exclude ‘riskier’ subjects – subjects whose research enrollment would introduce significantly greater personal risks, but no compensating potential for scientific or personal benefit, as compared to other candidates for the same protocol. With that said, only regulations that do not violate subjects’ rights should be adopted. Therefore, before concluding that ‘riskier’ subjects should be excluded, it needs to be considered whether doing so violates their rights.

Although there is no right to be in research per se, one might argue for a right to enroll in protocols that offer the potential for personal benefit from a more general right to health care. Such a right could be construed in either of two ways. First, subjects might possess a right to have access to experimental treatments that offer a potential for personal benefit with a corresponding societal obligation to provide such treatments. Understood in this way, the claim that investigators should exclude ‘riskier’ subjects does not violate a right to be in research. If potential subjects possess such a right, then there is a corresponding societal obligation to provide enough research slots for everyone who wants to enroll. Thus, it is the decision to limit the number of subject slots that violates subjects’ right, not the decision as to who should be enrolled once the number of slots has been limited.

Alternatively, subjects might possess a right to have fair access to research participation – the right not to be excluded from research participation without good reason. Although this is a more plausible understanding of subjects’ right to be in research, the claim that ‘riskier’ subjects should be excluded does not violate this right any more than the claim that subjects who present increased scientific risks should be excluded. Enrolling either type of subject conflicts with research’s goal of improving overall health and well-being. As a result, both claims offer non-arbitrary, non-discriminatory methods for excluding potential subjects.

The conclusion that ‘riskier’ subjects should be excluded does not imply that their medical needs should be ignored. The challenge of research is to gain the most information while doing the least harm. Excluding subjects who introduce significantly increased risks, but no compensating potential for scientific or


personal benefit, helps to accomplish this goal. These exclusions only highlight – they do not settle – the very different question of when ‘riskier’ subjects should have access to appropriate medical care. In cases where ‘riskier’ subjects should have access to medical care, it is the decision to limit the number of research slots, or the decision to restrict available medical care to the research context, that is problematic.

By highlighting the impact of these decisions, the exclusion of ‘riskier’ subjects may force a more systematic analysis of their medical needs. Should the number of research slots be expanded to accommodate all potential subjects? Should alternative sources, such as compassionate exemptions or expanded access programs, be developed? These questions raise complex issues concerning access to health care and resource allocation. They should be addressed directly and systematically at the policy level, not left to clinical researchers whose job it is to improve overall health and well-being, not provide clinical care.

I next argue that individuals who are unable to consent face significant ‘moral’ risks not faced by individuals who are able to consent. Thus, individuals who are unable to consent qualify as riskier, hence, should be excluded from research enrollment, except when their enrollment would introduce a compensating potential for scientific or personal benefit.

THE MORAL RISKS OF PROXY ENROLLMENT

Clinical investigators have an obligation to protect subjects’ well-being and respect their autonomy. For competent subjects, investigators discharge both obligations by allowing them to make their own enrollment decisions. However, individuals who are unable to consent must have a proxy decision maker enroll them in research. This practice, albeit ethically mandated, poses moral risks of its own.

To start with those most clearly unable to consent, individuals with profound cognitive impairments, such as those with severe Alzheimer’s Disease and those in coma, are unable to determine the course of their own lives. Since these individuals have no autonomy interests, enrolling them in research based on the permission of a proxy decision maker does not pose any risks to their autonomy.36 At the same time, individuals with severe cognitive impairments retain a number of interests, including an

interest in their own well-being. Since proxy decision makers may make enrollment decisions that conflict with these remaining interests, the enrollment of individuals with severe cognitive impairments based on the permission of a proxy decision maker poses a risk of exploitation.

As argued previously, regulations should minimize this risk by stipulating that individuals unable to consent may be enrolled only when there exists sufficient evidence that they want to enroll. When there is not enough evidence to make a substituted judgement, proxy decisions should be based on what is in the subject’s best interests.\(^{37}\) While this solution reduces the risk of exploitation, it does not eliminate it. Profoundly impaired subjects cannot communicate their interests to their proxies who, without any guidance from subjects, are poor good judges of subjects’ interests.\(^{38,39,40}\) In most cases, then, reliance on a proxy poses a risk of subjects being enrolled in research that conflicts with their interests.

It is important to note that having individuals indicate their research preferences in advance does not eliminate this potential for exploitation. Individuals often do not accurately anticipate their future preferences, particularly with respect to situations that are fundamentally worse than their present circumstances.\(^{41}\) Furthermore, as noted earlier, the fact that individuals undergo fundamental psychological changes, as occurs when they develop profound cognitive impairments, brings into question the extent to which statements made prior to these changes are relevant to their present state.\(^{42,43}\) For these reasons, the research enrollment of individuals with profound cognitive impairments, even by


an appropriate proxy decision maker, poses a risk of exploitation compared to the research enrollment of competent adults.

Adults who are unable to consent due to mild to moderate cognitive impairments differ from adults with profound cognitive impairments in two important ways. First, most adults with mild to moderate cognitive impairments are able to understand aspects of their research participation and communicate their relevant preferences. Given that understanding comes in degrees, the level of understanding of some individuals with mild to moderate cognitive impairments will not be significantly less than the understanding of some individuals who are able to consent. In particular, individuals just below the cutoff for the minimum level of understanding required to give informed consent understand only slightly less than those just above this cutoff. Thus, as long as clinical investigators solicit the views of individuals with mild to moderate cognitive impairments, they will know almost as much about these individuals’ interests and preferences as they know about the interests and preferences of individuals just above the cutoff for minimum understanding.

In addition, the enrollment of individuals just below the understanding cutoff also requires the permission of a proxy decision maker. Even if this individual provides only minimal added protection, the enrollment of individuals just below the cutoff for minimum understanding will pose no greater, and perhaps even lower, risks of exploitation compared to the enrollment of individuals just above the cutoff. For this reason, focusing only on the risks of exploitation would imply that there is no reason to treat individuals unable to consent due to mild to moderate cognitive impairments differently from individuals of below average, but sufficient, understanding. However, adults with mild to moderate cognitive impairments differ from adults with profound impairments in a second way.

Many individuals with mild to moderate cognitive impairments can make their own decisions. They can conceive of alternative courses of action and make a decision based on what they want their future to include. For this reason, the use of a proxy decision maker, while necessary to protect these individuals’ well-being, poses a risk to their autonomy interests. To minimize the risks to individuals’ autonomy interests, most proposals stipulate that either adults unable to consent must assent when capable or their

dissent must be respected.\textsuperscript{46} To take one example, recommendation 7 of the U.S. National Bioethics Advisory Commission report states: ‘Any potential or actual subject’s objection to enrollment or to continued participation in a research protocol must be heeded in all circumstances.’\textsuperscript{47} By requiring assent or lack of dissent, these policies ensure that adults who are unable to consent due to mild to moderate cognitive impairments have some say in their research futures. However, by also requiring surrogate consent, these policies give another person veto power over whether these individuals enroll in research. For this reason, these individuals’ ability to control their own lives is constrained in the research context. Given that autonomy interests are central to one’s status as a person, this constraint represents a significant moral risk.\textsuperscript{48} It follows that adults who are unable to consent face serious moral risks from research enrollment compared to individuals who are able to consent. To determine whether these individuals thereby qualify as ‘riskier’, it needs to be determined whether their research enrollment ever offers a compensating potential for personal or scientific benefit.

WHEN DO INDIVIDUALS UNABLE TO CONSENT QUALIFY AS ‘RISKIER’?

In rare cases, individuals who are unable to consent may face significantly fewer personal risks. For instance, individuals with Alzheimer’s Disease might face drastically lower risks from an experimental drug whose side effects are limited to the hippocampus. Similarly, individuals who are unable to consent could face a significantly greater potential for benefit. For instance, trials of a potentially curative drug might offer a dramatically increased potential for medical benefit to individuals with severe Alzheimer’s Disease compared to individuals with mild Alzheimer’s Disease. However, even in these rare cases, the decreased personal risks or increased personal benefits faced by individuals who are unable to consent will typically be outweighed by the decreased potential for scientific benefit that their enrollment introduces.

The scientific value of many protocols is influenced by the cognitive capacities of their subjects. For instance, the scientific value of many drug studies is affected by how well subjects report side effects and comply with a protocol’s requirements. Subjects who are unable to sufficiently understand the protocol in question often will be less able to meet these demands. Given that any reductions in the scientific value of a protocol affect all those who might have benefited from the information lost, almost any increased scientific risk will cancel out even a substantially increased potential for personal benefit or dramatically decreased personal risks. Thus, the only realistic possibility for compensating for the significant moral risks faced by individuals unable to consent is with a sufficiently increased potential for scientific benefit.

Taking into account the impact that enrolling individuals who are unable to consent has on research’s goal of improving overall health and well-being reveals that they should be excluded unless their participation is necessary to obtain the scientific information being sought. It follows that the necessity requirement should apply to all research protocols, even those that offer a potential for personal benefit that is unavailable outside of the research context. The present approach also reveals that the proposed versions of the necessity requirement should be amended in three ways.

First, the necessity requirement is a rule of thumb, not an absolute principle. In rare cases, individuals who are unable to consent will face dramatically greater personal benefits or dramatically lower personal risks without introducing increased risks to the scientific value of the protocol. In such cases, individuals unable to consent should not be excluded even when their participation is not necessary to obtain the scientific information being sought. Of course, whether individuals unable to consent should actually be enrolled in these cases will depend upon whether they meet the appropriate additional requirements, including the permission of a proxy decision maker.

Second, given the seriousness of the moral risks, individuals unable to consent should not be enrolled in research simply because their participation is necessary to answer the scientific question being posed. They should be enrolled only when the question being posed is of sufficient scientific importance to justify these risks.

Individuals who are unable to consent introduce significant risks and no compensating potential for benefit across a broad range of protocols. For this reason, the present approach resolves
the deadlock over the necessity requirement and allows investigators and IRBs to determine whether individuals unable to consent should be enrolled in most cases. However, since it is impossible to provide a quantitative estimate of the moral importance of individual autonomy, there will still be unclear cases. In particular, in the rare cases where individuals who are unable to consent face a greater potential for personal benefit or reduced personal risks, but do not pose greater risks to the value of the science, it will not always be possible to determine definitively whether these differences compensate for the increased moral risks they face.

Finally, it is not protocols per se, but the procedures they involve, that pose risks to research subjects. Thus, the necessity requirement should also bar individuals who are unable to consent from undergoing risky research procedures when their doing so is not necessary to obtain the scientific information being sought. For instance, investigators often obtain biological samples and research data from individuals participating in clinical drug trials. To ensure that individuals who are unable to consent undergo such procedures only when scientifically necessary, a consensus policy should stipulate that their participation must be necessary for both the protocol as a whole, and for all additional procedures they undergo during research participation that present more than minimal risk.

To take a specific example, both versions of the necessity requirement would allow individuals with severe Alzheimer’s Disease to participate in a drug trial when their participation is scientifically necessary. However, the present version, but not the standard version would prohibit the individuals in this protocol from undergoing a PET scan with arterial line for independent research purposes when this data could be obtained from individuals with mild Alzheimer’s Disease who are able to consent.

**THE SUBJECT’S CONDITION REQUIREMENT**

A number of proposals attempt to supplement the necessity requirement with the ‘subject’s condition’ requirement. The idea is that perhaps the most obvious scientific reason to enroll individuals who are unable to consent is that the research in question concerns a condition associated with their incapacity.

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For instance, it makes sense to enroll individuals who suffer from severe Alzheimer’s Disease in a study of a potential treatment for severe Alzheimer’s Disease. This intuitive plausibility leads many writers to argue that individuals unable to consent should be enrolled in clinical research only when it concerns a condition associated with their impairment. The final report of the Maryland Attorney General’s Working Group on Research Involving Decisionally Incapacitated Subjects argues that: ‘researchers should seek to enroll decisionally incapacitated individuals as research subjects only if the research is expected to yield generalizable knowledge important to the understanding or amelioration of the subject’s disorder or condition.’

According to the U.S. Office for the Protection from Research Risks (OPRR): ‘It is now generally accepted that research involving persons whose autonomy is compromised by disability ... should bear some direct relationship to their condition or circumstances.’

The ‘subject’s condition’ requirement was first articulated in 1969 by Hans Jonas in one of the classic papers in research ethics. Jonas, like many recent proponents, assumes that restricting individuals who are unable to consent to research on conditions associated with their cognitive impairments ensures that they will be enrolled only when there is good scientific reason to enroll them rather than individuals who are able to consent. This view is based on the implicit assumption that there is good scientific reason to enroll individuals who are unable to consent when the research concerns a condition associated with their cognitive impairments. Although plausible, this assumption fails to distinguish between investigators having a scientific reason to enroll particular individuals versus their having a scientific reason why they must enroll these individuals.

Most diseases do not produce cognitive impairments uniformly. For instance, Alzheimer’s Disease leads to severe cognitive impairment, but only during its later stages, while Xeroderma Pigmentosum is associated with severe cognitive impairments, but only in a subset of individuals affected with the disease. Given this variability, research on diseases associated with

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cognitive impairment can sometimes be conducted with individuals who are able to consent, such as individuals in the early stages of Alzheimer’s Disease. For this reason, the subject’s condition requirement would allow enrollment of individuals who are unable to consent in some protocols that could be conducted by enrolling individuals who are able to consent.

Perhaps in recognition of the present difficulties, some proponents endorse a broader version of the subject’s condition requirement that limits the enrollment of individuals unable to consent to research that concerns any condition from which they suffer, not just conditions associated with their cognitive impairments. For instance, a Canadian group argues that the enrollment of individuals who are unable to consent should ‘be restricted to that relevant to their own condition, whether dementia or another condition’.53 Similarly, the New York task force proposes that research with individuals unable to consent may concern any ‘condition from which they suffer’.54

The fact that this broader version would allow enrollment in protocols on conditions not associated with individuals’ cognitive impairments suggests that it is intended to ensure that they are enrolled only when they face a potential for medical benefit. And, since individuals unable to consent retain an interest in their own well-being, this version might be defended on the grounds that it ensures these individuals are enrolled only when it is consistent with their preferences and interests. However, many protocols do not offer the prospect of medical benefit, even to individuals who suffer from the condition under study. As a result, the broader version does not ensure that individuals unable to consent are enrolled only when it is consistent with their preferences and interests.

Taking a slightly different approach, one might argue that individuals are more likely to support research on conditions from which they suffer, not because they might benefit from such research, but because they identify with its goals. If this were right, satisfaction of the broader version would increase the chances that individuals are enrolled only when it is consistent with their preferences and interests. Against this, individuals support the goals of research studies for a number of reasons.

In particular cases, it may be because the research concerns a condition from which they suffer. However, even in this case,


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individuals may not want to enroll in the research. There are many more individuals who support the goals of cancer research than are willing to enroll in cancer protocols. Thus, the subject’s condition requirement would allow many individuals to be enrolled in research that conflicts with their preferences. Furthermore, individuals may identify with the goals of a protocol for other reasons, for instance, because it concerns a condition that affects their grandchildren. This possibility is plausible given that cognitive impairments often strike late in life, at a time many individuals are more concerned with their family’s future than their own. When these preferences are known, the broader version of the subject’s condition requirement conflicts with the widely accepted principle that investigators and proxy decision makers should make enrollment decisions based on individuals’ known preferences.

To avoid this conflict, supporters might argue that investigators should follow the subject’s condition requirement only when there is no other evidence of an individual’s research preferences. Against this suggestion, there is no reason to think that the presumed preference for research on conditions from which individuals suffer should be privileged over other presumed preferences, such as the preference for research that affects subjects’ grandchildren. In addition, the fact that a protocol concerns a condition from which the individual suffers does not, on its own, provide sufficient evidence that enrollment is consistent with her preferences and interests. To ensure that individuals unable to consent are enrolled in research only when it is consistent with their preferences and interests requires an explicit evidence requirement: individuals unable to consent may be enrolled in research only when there is sufficient evidence that enrollment is consistent with their preferences and interests. Before considering this requirement explicitly, consider the suggestion that the subject’s condition requirement should be included along with the necessity and sufficient evidence requirements as supplemental protection.

THE SUBJECT’S CONDITION REQUIREMENT AS SUPPLEMENTAL PROTECTION

In some cases, there will be sufficient evidence that individuals want to enroll in research on a condition from which they do not suffer; in others there will not be sufficient evidence that they want to enroll in research on conditions from which they do suffer. In both cases, the subject’s condition safeguard does not
further, but actually conflicts with, the sufficient evidence protection. The subject’s condition requirement may also conflict with the necessity requirement.

When two related conditions are strongly correlated with cognitive impairment, research studies may need to enroll individuals unable to consent for comparison purposes even though their incapacity may not be associated with the disease under study. As the expert panel reporting to the NIMH points out: ‘Comparing individuals suffering from one neurobiological disorder with other diagnostic groups’ is crucial for certain kinds of research.\(^55\) To take a concrete example, postmortem exams reveal that individuals with Down’s Syndrome invariably develop neuropathological and neurochemical abnormalities strikingly similar to Alzheimer’s Disease.\(^56\) For this reason, individuals with Down’s Syndrome provide a unique opportunity to assess the preclinical stages of Alzheimer’s Disease.

One study asked whether glucose metabolism in the neocortical parietal and temporal regions is abnormal prior to onset of Alzheimer’s Disease.\(^57\) Since it is not possible to identify individuals in the preclinical stages of Alzheimer’s Disease itself, this study could not be conducted by enrolling individuals with Alzheimer’s Disease. In contrast, it is possible to identify individuals with Down’s Syndrome, and individuals with Down’s Syndrome inevitably develop abnormalities similar to Alzheimer’s Disease. Hence, the enrollment of individuals with Down’s Syndrome was scientifically necessary to conduct the study.

Determining whether the subject’s condition requirement would allow the enrollment of individuals with Down’s Syndrome in protocols on Alzheimer’s Disease requires determining whether individuals with Down’s Syndrome develop Alzheimer’s Disease itself or only changes very similar to Alzheimer’s Disease. If the former, then it seems that these individuals’ cognitive impairments are not associated with the condition under study. If the latter, it will have to be determined whether, in some sense, individuals with Down’s Syndrome have Alzheimer’s Disease before they develop the related neurological changes and

whether, under the subject’s condition requirement, having Alzheimer’s Disease in this (genetic?) sense is sufficient to enroll them in research on Alzheimer’s Disease.

Application of the subject’s condition requirement requires an understanding of how medical conditions ought to be individuated. Does the ‘subject’s condition’ cover necessary sequelae of the disabling condition? Possible sequelae? Under the subject’s condition requirement can someone impaired by a meningioma of the frontal lobe be enrolled in research on any CNS disease, or only CNS cancers, or only brain cancers, or only meningiomas? Unfortunately, the answers to these kinds of questions often will not be clear. Alternatively, IRBs could answer them by appeal to the necessity requirement: in the particular case, is the individuals’ enrollment scientifically necessary. This strategy reveals that the necessity requirement does all the work, while the subject’s condition adds confusion without additional protection.

Finally, the ethical principle that it is better to enroll individuals in research on conditions from which they suffer can conflict with the principle that individuals should understand the nature of their research participation. This possible conflict traces to the much discussed ‘therapeutic misconception’. The therapeutic misconception refers to the possibility that individuals might fail to distinguish between research participation and clinical care. This possibility is worrisome because it can jeopardize an individual’s informed consent. It is reasonable to assume that the ‘therapeutic misconception’ is more likely to occur when subjects are enrolled in research on conditions from which they suffer. Thus, in a study where there is a high likelihood of the therapeutic misconception, an IRB might stipulate that the investigators should enroll individuals who do not have the condition under study, hence, are less likely to think that the research is being conducted for their benefit. Presumably it is with this possibility in mind that the Declaration of Helsinki requires that ‘non-therapeutic’ research be conducted on normal volunteers or patients ‘for whom the experimental design is not related to the patient’s illness’.58

There is very little data on the therapeutic misconception, including the extent to which it can be altered by investigators’ intervention. As a result, it is impossible to gauge the extent to which barring individuals with the condition under question is

appropriate. Of course, one might think that this possibility is irrelevant to persons who are unable to consent. However, as mentioned previously, individuals who are unable to consent should be required to provide assent when capable. Although the paucity of data renders any claims tentative, in theory the therapeutic misconception could jeopardize individuals’ assent in the same way that it jeopardizes others’ consent. Individuals who cannot consent may provide assent because they think the research is intended to help them.

SUFFICIENT EVIDENCE REQUIREMENT

The first step toward ensuring sufficient evidence of the subject’s preferences and values is to require that individuals unable to consent have a proxy decision maker, usually a family member or close friend. Proxies make decisions based on what individuals would decide in the situation that obtains if they were competent (the substituted judgement standard), and based on what is in the individuals’ best interests when their preferences and interests are unclear or unknowable.  

Barring evidence to the contrary, it is assumed that individuals’ preferences and interests endure over time. Thus, in making research decisions, proxies should consider individuals’ competent preferences and interests the default as to their preferences and interests once incapacitated. Some individuals may express their research preferences while competent, either orally or in writing. In the absence of explicit statements, proxies can derive evidence of individuals’ preferences from past behavior, as well as general character. When there is not sufficient evidence of the subject’s preferences and values, enrollment decisions should be based on what is in the individual’s best interests.

As argued previously, what constitutes a sufficient level of evidence to enroll someone who is unable to consent depends upon the risks and potential benefits. As a general rule, more evidence should be required as risks increase and potential medical benefits decrease. A proxy’s belief that an individual would want to enroll, based on a close acquaintance with the individual, provides sufficient evidence to enroll her in a minimal risk protocol. It is important to note that the need for some evidence embodied in the substituted judgement standard implies that proxies should not enroll individuals in even minimal risk protocols without some evidence that the individual wants to enroll.


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Some contend that individuals who are unable to consent should be barred from research that presents greater than minimal risks without a compensating potential for medical benefit. Although this approach is reasonable, and has been incorporated into the Council of Europe’s guidelines, the sliding scale approach would allow enrollment in riskier research when there is clear and convincing evidence that it is consistent with the individual’s preferences and interests. When there is, it is not clear why individuals unable to consent should be barred. On the present account, the existence of overwhelming evidence supports the expectation that the individual would have chosen to enroll if competent. Thus, enrolling the individual when incompetent does not exploit her inability to make her own decision. It follows that any argument for a risk ceiling will have to be made on grounds other than the potential for exploitation of subjects’ inability to consent.

Most proposals assume that riskier research that offers subjects a potential for medical benefit does not present as great a potential for subject exploitation, hence, does not require as many additional safeguards. However, the proposals overlook the fact that the mere presence of some potential for benefit does not, in itself, affect the potential for exploitation much. As we have seen, the operative question is what choice the person would make: the fact that there is some chance for potential benefit might not affect their choice at all. For instance, an experimental drug trial that presents a risk of kidney damage, but only a very small chance of minimal clinical benefit, requires greater safeguards than a protocol that presents the same risk of kidney damage, but a real chance for a cure of metastatic cancer.

To mark this distinction, and ensure that subjects are protected appropriately, the category of potential for medical benefit research should be defined clearly. The NBAC reference to research that ‘may’ benefit the subject, and the Maryland and New York accounts of research that has a ‘realistic possibility’ of improving the subject’s condition, are insufficient. Instead, a consensus policy should stipulate that the potential for medical benefit must outweigh the risks, and the protocol’s risk/benefit profile must be at least as favorable as all available alternatives.

60 A. Capron. ‘Ethical and Human-Rights Issues in Research on mental Disorder that may Affect Decision-Making Capacity.’ New England Journal of Medicine, 1999; 340 p. 1433.
CONCLUSION

I have argued that it is possible to conduct human subjects research without informed consent or exploitation. To do so, two protections must be in place: individuals unable to consent should be enrolled only when there is good reason to enroll them rather than those who can consent; individuals who cannot consent should be enrolled only when there is sufficient evidence that such enrollment is consistent with their preferences and values. To ensure these protections, any final policy should include a necessity requirement and a sufficient condition requirement.

To ensure sufficient evidence, individuals unable to consent should be required to have a proxy decision maker who makes research decisions based on the individual’s preferences when known and otherwise based on what is in the individual’s best interests. In addition, more evidence should be required as the risk/benefit profile becomes less favorable to subjects. With these safeguards in place, the widely supported subject’s condition requirement should not be adopted. Doing so would conflict with the substituted judgement standard and may block important research without reason. Finally, while it is important to protect individuals who are unable to consent from exploitation, investigators and IRBs must recognize that some individuals who are unable to consent retain some autonomy interests. To ensure that these interests are respected, those who are capable should be required to provide a positive agreement to participate (assent) prior to research enrollment and during research participation.

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