Using Data to Improve Surrogate Consent for Clinical Research with Incapacitated Adults

Emily Abdoler and David Wendler
National Institutes of Health

ABSTRACT: current practice relies on surrogates to enroll incapacitated adults in research. Yet, it is unclear to what extent this practice protects adults who have lost the ability to consent for themselves. To address this question, we conducted two literature searches to identify articles which report empirical data on three issues central to protecting adults who have lost the ability to consent: (1) adults' willingness to participate in research should they lose the ability to consent; (2) adults' willingness to allow a surrogate to make research decisions for them; and (3) the extent to which surrogates' enrollment decisions are consistent with their charges' preferences and values. These searches identified 21 articles, representing 20 distinct datasets. The data indicate that many adults are willing to participate in research should they lose the ability to consent, and many are willing to allow their family members to make research decisions for them if they become incapacitated. The data also raise concern that surrogates may be making research enrollment decisions that, in some cases, are inconsistent with their charges' preferences and values. These findings suggest that modifications to current practice should be considered to better protect adults who have lost the ability to consent. One option would be to require, in addition to surrogate permission and subject assent, sufficient evidence that enrollment is consistent with the individual's preferences and values.

KEY WORDS: capacity, consent, research

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Many past abuses of human research subjects, including the Nazi experiments and the Tuskegee syphilis study, involved individuals who were exposed to research risks without their consent. This history has led to an emphasis on informed consent as vital to protecting research subjects. The Nuremberg Code, for example, prohibits research with those who cannot consent (Nuremberg Code). While this approach has intuitive appeal, it poses a significant obstacle to research on conditions associated with cognitive impairment. This approach also would prohibit individuals who are unable to consent from participating in research that offers the potential for clinical benefit.

These concerns raise the need for safeguards to protect adults who have lost the ability to consent without precluding research on the conditions that affect them (Secretary Advisory Committee, Recommendation 9). Most guidelines for clinical research attempt to meet this challenge by stipulating that investigators should enroll incapacitated adults only when they obtain the permission of an appropriate surrogate and also obtain the assent of those subjects who are capable of providing it (Alzheimer's Association; NBAC; Council of Europe; U.S. DHHS; Medical Research Council of Canada; NHRPAC; NIH Clinical Center; New York State Advisory Work Group; Attorney General's Working Group). In addition, many guidelines stipulate that surrogates should enroll adults who have lost the ability to consent in research only when doing so is consistent with the individual's preferences and values (Alzheimer's Association; NBAC; Council of Europe).

These requirements are important to ensure that investigators do not take advantage of individuals' incapacity to enroll them in research that is inconsistent with their preferences and values. To evaluate how well current reliance on surrogates realizes this protection, and whether revisions to current practice might provide better protection, the present paper assesses the empirical literature regarding three topics that are central to protecting adults who have lost the ability to consent: (1) adults' willingness to participate in research should they lose the ability to consent; (2) adults' willingness to allow a surrogate to make research decisions for them; and (3) the extent to which surrogates' enrollment decisions are consistent with their charges' preferences and values.

Methods

We conducted two systematic literature searches to identify empirical data on the three inclusion topics.

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The first search entered into PubMed strings of terms related to surrogate consent for research, including "surrogate(s) and research," "proxy and research," and "surrogate decision making and research." The titles of all identified articles were categorized by the first author as possibly eligible, not eligible, or of unclear eligibility. Those categorized as being of unclear eligibility were reviewed by the second author and categorized as possibly eligible or not eligible.

The abstracts of the possibly eligible articles were reviewed by the first author for terms or phrases suggesting they might include empirical data on one or more of the three inclusion topics. On this basis, the first author categorized the articles as possibly eligible or not eligible. The full texts of the articles categorized as possibly eligible were reviewed by both authors to identify those that provide empirical data on one or more of the three inclusion topics. Debates were resolved by discussion until consensus was reached. Finally, the references of the eligible articles were reviewed in the same manner. This search yielded 13 published articles, representing 13 distinct datasets.

A second search used combinations of Medical Subject Headings (MeSH) for three categories related to surrogate consent: surrogates AND impaired subjects AND clinical research (see appendix for specific terms). The titles of all 422 identified articles were categorized by the first author as possibly eligible, not eligible, or of unclear eligibility. Those categorized as being of unclear eligibility were reviewed by the second author and categorized as possibly eligible or not eligible. This step used a default of inclusion, meaning that articles were categorized as not eligible only when it was clear from their titles that they did not provide empirical data on one or more of the three inclusion topics. This process yielded 104 possibly eligible articles.

The abstracts of the 104 articles were reviewed by the first author for terms or phrases suggesting they might include empirical data on one or more of the three inclusion topics. The first author categorized the articles as possibly eligible, not eligible, or of unclear eligibility. Those categorized as being of unclear eligibility were reviewed by the second author and categorized as possibly eligible or not eligible. The full texts of the 20 articles categorized as possibly eligible were reviewed by both authors to identify those that provide empirical data on one or more of the three inclusion topics. Debates were resolved by discussion until consensus was reached. This search yielded four articles that had not been identified by the first search. The references of the four articles were reviewed in the same manner, yielding four more articles. Finally, the references of these four articles were reviewed, yielding no additional articles and, overall, 21 eligible articles, representing 20 distinct datasets.

The eligible articles surveyed a wide range of patients and healthy adults. Importantly, while some studies were limited to respondents who were competent, some others surveyed individuals who had dementia without formally assessing whether the respondents were competent to answer the questions posed. The eligible articles also used a wide range of methods and instruments. Many—including all of those investigating surrogate accuracy—employed vignettes, brief research descriptions, or hypothetical studies; several of those examining willingness to participate in research and the acceptability of surrogate consent also asked respondents questions about research in general. In addition, while many of the studies asked for yes/no/unsure responses, others used Likert scales. Finally, while most of the studies reported averages, several generated kappa statistics. Given these differences in methods, the findings of the articles could not be combined and are presented as a narrative review.

Results

WILLINGNESS TO PARTICIPATE IN RESEARCH IN THE EVENT OF FUTURE INCAPACITY

Twelve of the identified articles, representing 11 distinct datasets, provide empirical data on adults' willingness to participate in research in the event of incapacity (Table 1). Overall, the majority of respondents were willing, while a minority were not willing, to participate in clinical research should they lose the ability to consent.

Limiting the analysis to articles that involved subjects without dementia, an average of 81% of respondents were willing to participate in minimal risk research without the prospect of direct benefit. For research involving a minor increase over minimal risk, 76% were willing to participate if personal benefit was a possibility, but only 66% were willing if personal benefit was not a possibility. Finally, for research posing more than a minor increase over minimal risk and the prospect of benefit, 57% were willing to participate.

PREFERENCES REGARDING SURROGATE DECISION-MAKING

Sixteen articles, representing 15 distinct datasets, provide data on adults' views regarding surrogate decision-making for research (Table 2). Most of these studies find that a substantial majority support allowing a family member or loved one to decide whether they are enrolled in research in the event of incapacity. Limiting the analysis to studies that surveyed individuals without dementia about their preferences regarding surrogate consent for themselves, 85% would allow surrogates to make research decisions for them when the study poses no more than minimal risk. For research that

TABLE 1. Willingness to Participate in Research if Unable to Consent.

Study (Country)	Population (N)	Response Rate	Focus	Intervention	Risk Level*	Potential Benefit	Willing (%)
Berger 2005 (US)	Competent Adults ≥65 years (10)	NR	Dementia	Physical Exam Blood Draw Approved Drug: Low Risk Approved Drug: High Risk Non-approved Drug	Minimal† Minimal† Minor Increase† >Minor Increase† >Minor Increase†	No‡ No‡ Yes‡ Yes‡ Yes‡	100; 100§ 90; 100§ 80; 90§ 20; 30§ 40; 30§
Blixen 2005 (US)	Competent Stroke Survivors (12)	NR	Emergency Research	Experimental Stroke Intervention	N/S	Yes‡	92‖
Chenaud 2009 (Switzerland)	Former ICU Patients (52)	16%	Intensive Care	ICU Research	N/S	N/S	~90¶
Del Giudice 2009 (US)	Patients, Family/ Friends, & Adults (905)	NR	Intensive Care	Blood Transfusion RCT**	>Minor Increase†	Yes‡	54††
Karlawish 2009 (US)	Adults ≥65 years old (538)	51%	Alzheimer's Disease	Blood Draw Blood Draw & LP††	Minimal Minor Increase§§	No‡ No‡	82.7 48.1
Kim/Ayalon 2009 (US) ‖‖	Adults ≥51 years (374; 398; 375; 368) ¶¶	99%	Alzheimer's Disease	LP†† Drug RCT Vaccine & 2 LPs†† Gene Transfer via Neurosurgery	Minor Increase Minor Increase*** >Minor Increase >Minor Increase	No Yes Yes N/S†††	70.8 79.7 57.4 68.7
Kim 2002 (US)	Alzheimer's Patients (34) ††† & Healthy Senior Caregivers of Alzheimer's Patients (14)	NR	Alzheimer's Disease§§§	Blood Draw Drug Challenge & PET Experimental Drug Trial Brain Surgery to Infuse Experimental Drug	Minimal Minor Increase >Minor Increase† >Minor Increase	No No Yes‡ Yes	85; 100 53; 57 65; 100 21; 21
Muthappan 2005 (US)	NIH Clinical Center Inpatients' RADs‖‖‖ (216)	9%	All Research	N/S N/S N/S	N/S Minimal Minor Increase/ >Minor Increase	Yes No No	76 49 9
Sachs 1994 (US)	Healthy Seniors (60), Proxies of Dementia Patients (64), & Dementia Patients (42) ¶¶¶	77%; 73%; 49%	Dementia	Blood Draw Experimental Drug Brain Surgery to Infuse Experimental Drug	Minimal Minor Increase >Minor Increase	No Yes Yes	85; 90; 59**** 55; 70; 37**** 20; 15; 24****
Stephenson 2007 (Australia)	ED & ICU Visitors (185)	65%	Critical Illness	Clinical Trial	N/S	Yes‡	17††††

(*Continued*)

TABLE 1. (Continued)

Study (Country)	Population (N)	Response Rate	Focus	Intervention	Risk Level*	Potential Benefit	Willing (%)
Wendler 2002 (US)	Healthy Adults Involved in Research for Relatives of Alzheimer's Patients (246)	94%	Alzheimer's Disease	Computer Task	Minimal	No	99
				2 X-rays	Minor Increase	No	98
				Experimental Drug	>Minor Increase	No	80
				Experimental Drug	>Minor Increase	Yes	92
	Respondent RADs‖‖‖ (39) (Subset of 246)	16%	All Research	N/S	Minimal	No	95
				N/S	Minor Increase/ >Minor Increase	No	51
				N/S	N/S	Yes	95

* We assigned a risk category for each vignette/hypothetical study based on its description. In most cases, the studies cited did not specify a particular risk level for the vignettes used; for the few studies that did, we indicate below if we deviated from their categorization. We also indicate if we made an assumption concerning the risk level based on a very brief description of the hypothetical study.

† As the specific risks of the hypothetical study/vignette were not described in the text/supplemental material of the cited article, we assigned a risk level by making an assumption from the information provided. Unless there was reason to consider otherwise, we categorized all blood draw studies as minimal risk, all LPs as a minor increase over minimal risk, and all drug RCTs as more than a minor increase over minimal risk.

‡ As the text/supplemental material of the cited article did not state explicitly whether or not the vignette/hypothetical study entailed the prospect of direct benefit, we made an assumption based on the description provided. Unless there was reason to assume otherwise, blood draw studies were assumed not to offer the prospect of direct benefit, while drug RCTs were.

§ The first figure is based on: Subjects' "direct preferences for [dementia] research participation"; the second on subjects' "preferences for participation if their surrogate was responsible for the decision." The second figure was used in the calculation of average willingness. It is unclear if either question was asked specifically in the context of future incapacity, but the Methods section specifies that the hypothetical research focuses on moderate-severe dementia.

‖ Percent of respondents who agreed that when "a doctor could not obtain consent from the patient or family member/surrogate in sufficient time, [...] the doctor should make the decision and enroll them in the study" of emergency stroke research. We interpreted this question to represent respondents' willingness to participate if unable to consent.

¶ These data are based on responses to the question of who should consent if the patient is unconscious. We assume that all respondents who named someone else to make decisions for them in this scenario were willing to participate if not able to consent.

** Del Giudice and colleagues did not specifically ask participants about willingness to participate in research in the event of future incapacity; however, their vignette was based on a study of treatment following subarachnoid hemorrhage, which may lead to at least temporary incapacity or severe pain. In the Introduction, they propose the research because "study participants are often incapacitated," and at the beginning of the Discussion section they mention "decision-making under acute neurologic conditions that may abruptly deprive an individual of the ability to consent."

†† Respondents were asked, "If you or one of your relatives suffered rupture of a brain aneurysm would you be willing to participate in a trial to look at how best to give patients blood?" Answer choices "definitely would participate" and "probably would participate" were combined to determine percent willingness. An additional 22% chose "possibly would participate," which was the middle answer choice in the 5-point Likert scale utilized by this survey.

†† LP= Lumbar Puncture

§§ Karlawish et al. 2009 indicated that this vignette involved greater than minimal risk, but it is unclear if they specified this risk level to participants. We assigned it a level of minor increase over minimal risk based on its description.

‖‖ Kim et al. 2009 and Ayalon 2009 rely on the same data but report slightly different numbers due to methodology. We use the numbers reported by Kim et al.

¶ ¶ All survey participants were already enrolled in the 2006 Health and Retirement Survey; 1515 of 1517 approached agreed to enroll (99%) and were randomized to respond to one of the four research vignettes. The total N for this question was 1444, as 71 respondents refused to answer or answered "I don't know" to this question for their assigned scenario and were excluded from the analysis; the study did not report the exact N for each vignette. As "I don't know" responses were excluded from the analysis rather than being counted as "unwilling," the actual percentage of respondents willing to enroll in each vignette is likely somewhat lower than reported.

*** RCT of a drug for Alzheimer's Disease that can cause upset stomach and, rarely, gastric bleeding. Vignette used in Kim et al. 2005 and 2009. In Kim et al. 2005, 65.5% of respondents rated the study as minimal risk (23.6%) or a minor increase over minimal risk (41.9%).

††† This vignette involves a first in human gene transfer via neurosurgery. In this study, the vignette does not describe, nor does it preclude, potential benefit. A similar vignette is used by Kim et al. 2005, but in that vignette the possibility of benefit is specifically mentioned.

††† Alzheimer's patients in this study had an average MMSE of 23.3, with a range of 16-28.

§§§ Kim et al. 2009 did not specifically ask respondents about participation in the event of future incapacity, but they did use vignettes describing dementia research studies.

‖‖‖ RADs= Research Advance Directives

¶¶¶ It is unclear whether the healthy seniors or dementia patients were asked specifically about participation in the event of future incapacity, but the vignettes involve dementia research. The proxies were asked if they would want to be enrolled if they "were to develop memory problems or dementia." Dementia patients in this study had a mean MMSE was 16.7—with a range of 0-30—but were included based on "ability to interact with the interviewer." Many had difficulty providing a "yes" or "no" answer to this question.

**** Only 20-25 of the 42 dementia patients were able to decide "yes" or "no" for these vignettes; presumably, the others were "unsure." It is unclear if "unsure" results were included in the analysis for any of the three groups of respondents. All percentages reported are estimates based on our assessment of the bar chart in the cited article.

†††† On a 1-10 scale of willingness, 17% were 9 or 10 ("strongly in favor"); 60% were 3-8 ("neutral"); 23% were 1-2 ("strongly against").

TABLE 2. Views on Surrogate Decision-Making.

Study (Country)	Population (N)	Response Rate	Focus	Intervention	Risk Level*	Potential Benefit	Endorse Surrogate Decision-Making (%)
Ali 2006† (UK)	Stroke Patients (36) & Caregivers (15)	70%‡	Stroke	Oxygen Supplementation	Minimal§	Yes‖	75
Berger 2005 (US)	Competent Adults ≥65 years (10)	NR	Dementia	N/S	N/S	N/S	100¶
Blixen 2005 (US)	Competent Stroke Survivors (12)	NR	Emergency Research	Experimental Stroke Intervention	N/S	Yes‖	75**
Bravo 2004 (Canada)	Québec Physicians (771)	41%	N/S	N/S	Minimal††	Yes	75††
				N/S	Minimal††	No	65.5††
				N/S	N/S††	Yes	54.7††
Bravo 2003 (Canada)	Older Adults (300), Caregivers (434), Researchers (98), IRB Members (136)	61.5%	N/S	N/S	Minimal††	Yes	~50-82††
				N/S	Minimal††	No	~30-84††
				N/S	N/S††	Yes	~11-54††
Chenaud 2009 (Switzerland)	Former ICU Patients (52)	16%	Intensive Care	ICU Research	N/S	N/S	75§§
Del Guidice 2009 (US)	Patients, Family/ Friends, & Adults (905)	NR	Intensive Care	Blood Transfusion RCT	>Minor Increase§	Yes‖	96‖‖
Karlawish 2009 (US)	Adults ≥65 years (538)	51%	Alzheimer's Disease	Blood Draw	Minimal	No‖	96.3
				Blood Draw & LP¶¶	Minor Increase***	No‖	96.1
Karlawish 2008 (US)	AD Patients††† in Research (58) & Their Proxies (59)	80%; 80%	Alzheimer's Disease	RCT of Simvastatin	>Minor Increase§	Yes‖	86; 85†††
Kim/Ayalon 2009†, §§§ (US)	Adults ≥51 years old (374; 398; 375; 368) ‖‖‖	99.9%	Alzheimer's Disease	LP¶¶	Minor Increase	No	72.0
				Drug RCT	Minor Increase¶¶¶	Yes	82.5
				Vaccine & 2LPs¶¶	>Minor Increase	Yes	70.5
				Gene Transfer via Neurosurgery	>Minor Increase	N/S****	67.5
Kim 2005 (US)	Competent Adults at Risk for Dementia and Enrolled in AD Prevention Research (229)	88%	Alzheimer's Disease	Observation	Minimal††††	No	97††††
				Interview	Minimal††††	No	95.6††††
				Blood Draw	Minimal††††	No	95.2††††
				MRI	Minimal††††	No	86††††
				LP¶¶	Minor Increase††††	No	69††††
				Drug Challenge	Minor Increase††††	No	80.3††††
				Brain Biopsy	>Minor Increase††††	No	57.6††††
				Drug RCT	Minor Increase††††	Yes	89.5††††
				Vaccine & 2LPs¶¶	>Minor Increase††††	Yes	69.4††††
				Gene Transfer via Neurosurgery	>Minor Increase††††	Yes	54.5††††

(*Continued*)

TABLE 2. (Continued)

Study (Country)	Population (N)	Response Rate	Focus	Intervention	Risk Level*	Potential Benefit	Endorse Surrogate Decision-Making (%)
Sachs 1994 (US)	Healthy Seniors(60) & Dementia Patients (42) §§§§	49%; 77%	Dementia	Blood Draw	Minimal	No	97; 60-67
				Experimental Drug	Minor Increase	Yes	83; 60-67
				Brain Surgery to Infuse Experimental Drug	>Minor Increase	Yes	77; 60-67
Stephenson 2007 (Australia)	ED & ICU Visitors (185)	65%	Critical Illness	Clinical Trial	N/S	Yes‖	26‖‖‖‖
Stocking 2006 (US)	Dementia Patients (149) ¶¶¶¶	NR	Alzheimer's Disease/ Dementia	Blood Draw for AD Test	Minimal§	No‖	≤ 91.5*****
				Blood Draw for Genetic Marker	Minimal§	No‖	≤ 91.5*****
				LP¶¶ for AD Marker	Minor Increase§	No‖	≤ 81.8*****
				Experimental Medication	>Minor Increase§	Yes‖	≤ 83.9*****
				Intracranial Stem Cell Implant	>Minor Increase§	Yes‖	≤ 73.5*****
Wendler 2002 (US)	Healthy Adults Involved in Research on Relatives of Alzheimer's Patients (246)	94%	Alzheimer's Disease	N/S	N/S	N/S	88†††††

* We assigned a risk category for each vignette/hypothetical study based on its description. In most cases, the studies cited did not specify a particular risk level for the vignettes used; for the few studies that did, we indicate below if we deviated from their categorization. We also indicate if we made an assumption concerning the risk level based on a very brief description of the hypothetical study.

† These studies asked respondents about the acceptability of surrogate consent from a societal, rather than self, perspective. For the Kim/Ayalon studies, respondents indicated whether they think society should allow families to make research enrollment decisions on behalf of incompetent patients. Ali and colleagues asked, "Do you think it would be appropriate to ask a member of the patient's family or a close friend to assent to the study on behalf of the patient?"

‡ 70% of focus group participants completed the survey. It is unclear how many individuals were approached and refused to participate in the focus groups.

§ As the specific risks of the hypothetical study/vignette were not described in the text/supplemental material of the cited article, we assigned a risk level by making an assumption from the information provided. Unless there was reason to consider otherwise, we categorized all blood draw studies as minimal risk, all LPs as a minor increase over minimal risk, and all drug RCTs as more than a minor increase over minimal risk.

‖ As the text/supplemental material of the cited article did not state explicitly whether or not the vignette/hypothetical study entailed the prospect of direct benefit, we made an assumption based on the description provided. Unless there was reason to assume otherwise, blood draw studies were assumed not to offer the prospect of direct benefit, while drug RCTs were.

¶ In this study, "subjects were asked whether or not their health surrogate should also make decisions about research." The authors do report that some respondents made comments suggesting that they would restrict their surrogate's decision-making ability based on the risk-benefit profile of studies.

** Seventy-five percent may represent the minimum level of endorsement of surrogate decision-making, as the respondents were asked whether they thought "it would be important for a family member/surrogate to give consent before being entered in the trial" of emergency stroke research. Arguably, those respondents who disagreed might still support surrogate decision-making.

†† Bravo and colleagues' description of research as involving "no serious risk" was interpreted to mean minimal risk research, while "some risks" could not be interpreted to represent a given risk level.

‡‡ If no legal guardian had been appointed to represent the respondent.

§§ These data indicate the percentage of respondents who were willing to allow their surrogate to give consent "in 2 steps" if the individual was unconscious.

‖‖ 88% indicated that they would have a family member or friend make research decisions for them; others (7%) would allow a health care professional, or someone else (1%). Only 4% of respondents chose "no one" in response to this question.

¶¶ LP= Lumbar Puncture

*** Karlawish and colleagues indicated that this vignette involved greater than minimal risk, but it is unclear if they specified this risk level to participants. We assigned it a level of minor increase over minimal risk.

††† AD patients enrolled in the CLASP trial had MMSE scores of 12-26, although two had MMSEs <12 by the time they entered the Karlawish study. Overall, the percentage of patients in the very mild, mild, and moderate stages of dementia by MMSE was 31%, 32%, and 37%, respectively.

‡‡‡ This study asked whether respondents endorsed surrogate decision-making for themselves (AD patients) or their AD patient relative (proxies), as well as whether they endorsed the practice in general. Karlawish and colleagues reported the percent agreeing with both statements (self and in general for AD patients, charge and in general for proxies).

(*Continued*)

TABLE 2. (Continued)

§§§ Kim et al. 2009 and Ayalon 2009 rely on the same data but report slightly different numbers due to methodology. We use the numbers reported by Kim et al.

‖‖‖ All survey participants were already enrolled in the 2006 Health and Retirement Survey. 1515 of 1517 approached agreed to enroll (99%) and were randomized to respond to one of the four research vignettes. The total N for this question was 1463, as 52 respondents refused to answer or answered "I don't know" to this question for their assigned scenario and were excluded from the analysis; the study did not report the exact N for each vignette. As "I don't know" responses were excluded from the analysis rather than being counted as not endorsing surrogate decision making, the actual percentage of respondents endorsing the practice for each vignette is likely lower than reported.

¶¶¶ RCT of a drug for Alzheimer's Disease that can cause upset stomach and, rarely, gastric bleeding. Vignette used in Kim et al. 2005 and 2009. In Kim et al. 2005, 65.5% of respondents rated the study as minimal risk (23.6%) or a minor increase over minimal risk (41.9%).

**** This vignette involves a first in human gene transfer via neurosurgery. In this study, the vignette does not describe, nor does it preclude, potential benefit. A similar vignette is used by Kim et al. 2005, but in that vignette the possibility of benefit is specifically mentioned.

†††† Kim et al. asked respondents to categorize the risk level of each vignette employed in their study. For the most part, we follow the categorizations they report, although we use one less risk level. In their study, a majority of respondents categorized the observation study, interview, and blood draw as minimal risk (78%, 68%, and 58%, respectively). While 41% rated the MRI study as minor increase over minimal risk, 31% rated it minimal risk. The highest percentage of respondents thought that the drug RCT involved a minor increase over minimal risk (42%). The majority characterized the LP and drug challenge as either moderate risk or a minor increase over minimal risk (79.5%, 79%, respectively), while most respondents thought that the brain biopsy, vaccine, and gene transfer were either moderate (50%, 52%, 42%, respectively) or high (31%, 23%, 47%, respectively) risk.

†††† Percent willing calculated by adding the % "definitely yes" and "probably yes."

§§§§ The dementia patient proxies enrolled in this study did not answer this question. Dementia patients in this study had a mean MMSE of 16.7—with a range of 0-30—but were included based on "ability to interact with the interviewer." The authors report that some of the patients answering "no" to this question "appeared to have difficulty understanding the conditional nature of the question."

‖‖‖‖ On a 1-10 scale of willingness, 26% were 9 or 10 ("strongly in favor"); 55% were 3-8 ("neutral"); 19% were 1-2 ("strongly against").

¶¶¶¶ Dementia patients had a mean MMSE score of 19.8, with a range of 2-29.

***** Stocking et al. only reported the percentage not endorsing surrogate decision-making. The values listed here were calculated by subtracting the percentage who did not endorse surrogate decision-making from 100% ; accordingly, they include those respondents who answered "unsure." The actual number endorsing surrogate decision-making is likely lower.

††††† In the event respondents do not have an RAD.

poses a minor increase over minimal risk, the percentage of capacitated adults willing to rely on a surrogate was 88% for studies that offer the prospect of benefit and 86% for studies that do not. Finally, 84% of capacitated adults would accept surrogate decision-making for research that offers the potential for clinical benefit and poses more than a minor increase over minimal risk.

SURROGATE ACCURACY

Five articles, representing five distinct datasets, provide empirical data on the extent to which surrogates' enrollment decisions are consistent with the decisions their charges would make (Table 3). Two of these datasets enrolled patients with dementia. One of the three articles assessing capacitated adults and their surrogates found that surrogates' predictions of what decisions their charges would make were no more accurate than random guessing (Muncie et al., 1997). Surrogate accuracy in the other two articles that assessed capacitated adults ranged from 55% to 73% (Ciroldi et al., 2007; Coppolino & Ackerson, 2001).

These studies assessed surrogate accuracy by comparing the decisions made by the respondents, to the decisions made by their surrogates, in hypothetical scenarios. Hence, it is unclear precisely how closely these data reflect the accuracy of actual surrogate decisions. Recognizing this limitation, the data raise concern that surrogates may be making research enrollment decisions that are inconsistent with the decisions their charges would have made for themselves, if they had been competent. Specifically, the data suggest that approximately 10% of the cases in which surrogates enroll an incapacitated adult in minimal risk research may involve subjects who would, if competent, have chosen not to enroll. For greater than minimal risk research, the present data suggest that the percentage who may be enrolled against their competent wishes is approximately 15–20% (Ciroldi et al., 2007; Coppolino & Ackerson, 2001). Conversely, these data suggest that 17% of individuals willing to participate in minimal risk research, and 14–20% of those willing to participate in greater than minimal risk research, may not be enrolled by their surrogates (ibid.).

Limitations

The present findings are subject to several important limitations. First, most of the studies were conducted in the United States. Second, many of the studies surveyed a small number of respondents and some had low response rates. It is unclear whether this might have influenced the results. Third, several of the studies surveyed adults who were ill, including some who had dementia. As a result, some of the data might represent the views of individuals who were not competent at the time they were interviewed. Fourth, the data on surrogates' predictive accuracy are limited and based on

TABLE 3. Surrogates' Predictive Accuracy.

Study (Country)	Population (N pair)	Response Rate	Risk Level*	Potential Benefit	Agree† (%)	Enrolled Against Preferences/ Total (%)	Not Enrolled Despite Willingness/Total (%)
Ciroldi 2007‡ (France)	Competent ICU patients at discharge (100)	NR	Minimal	No	67	11/100 (11)	17/100 (17)
			> Minor Increase§	Yes‖	55	20/100 (20)	20/100 (20)
Coppolino 2001 (US)	Cardiac Surgery Patients (100)	34%	Minimal	Yes	73	10/100 (10)	17/100 (17)
			> Minor Increase§	Yes	71	15/100 (15)	14/100 (14)
Muncie 1997¶, ** (US)	Individuals ≥65 years old, either living independently or in nursing homes‡‡ (315)	NR	Minimal	No	No specific data. Kappa values indicated (0.05 - 0.15) that "the agreement between the proxies' and charges' decisions was not significantly different from random agreement."		
			Minimal	No			
			Minimal	Yes‖			
			Minimal	Yes			
			> Minor Increase	No			
			> Minor Increase	No			
			> Minor Increase	Yes			
			> Minor Increase	Yes			
Sachs 1994‡‡, §§ (US)	Dementia Patients (40) ‖‖	47%	Minimal	No	No specific data. Kappa value across all trials indicated only modest agreement***		NR
			Minor Increase	Yes			NR
			> Minor Increase	Yes			7/40 (17.5)
Stocking 2006 ‡‡, §§, ††† (US)	Dementia Patients (149) †††	NR	Minimal§§§	No‖	91.5	4/130 (3)	7/130 (5)
			Minimal§§§	No‖	85.45	6/110 (5)	10/110 (9)
			Minor Increase§§§	No‖	61.8	26/76 (34)	3/76 (4)
			> Minor Increase§§§	Yes‖	69.2	11/104 (11)	21/104 (20)
			> Minor Increase§§§	Yes‖	81.8	13/99 (13)	5/99 (5)

* We assigned a risk category for each vignette/hypothetical study based on its description. In most cases, the studies cited did not specify a particular risk level for the vignettes used; for the few studies that did, we indicate below if we deviated from their categorization. We also indicate if we made an assumption concerning the risk level based on a very brief description of the hypothetical study.

† Calculation of a single accuracy rate was impossible, as the studies use different statistical methods.

‡ While "Unsure" was a possible answer choice, it is unclear how it was included in the analysis.

§ The authors categorized these vignettes as "greater than minimal risk" in the article text, but we assigned them a more nuanced level of "more than a minor increase over minimal risk" based on vignette risk descriptions. The risk level was not categorized in the vignette for respondents.

‖ As the text/supplemental material of the cited article did not state explicitly whether or not the vignette/hypothetical study entailed the prospect of direct benefit, we made an assumption based on the description provided. Unless there was reason to assume otherwise, blood draw studies were assumed not to offer the prospect of direct benefit, while drug RCTs were.

¶ It is unclear whether "Unsure" was a possible answer choice.

** Here, we report the comparison between what the charge would decide and the proxy's prediction of what the charge would decide, rather than what the proxy would actually decide for the charge. Thus, these data represent the substituted judgment standard.

‡‡ Participants were screened for competence using 10-item Mental Status Questionnaire, and only those scoring ≥ seven were included in the analysis.

‡‡ Surrogates were not instructed to use substituted judgment in making their decisions. While this was not specified in the text of the Stocking article, the authors confirmed this fact through personal correspondence.

§§ While "Unsure" was a possible answer choice, it was excluded from analysis.

‖‖ Dementia patients in this study had a mean MMSE of 16.7—with a range of 0-30—but were included based on "ability to interact with the interviewer." Only 20-25 were able to decide "yes" or "no" for these vignettes; presumably, the others were "unsure."

*** Generalized kappa was 0.31, which included a post-mortem brain autopsy vignette that was excluded from this analysis given the fact that it did not involve research on living human subjects. The brain autopsy vignette had the largest kappa at 0.35, so the average kappa for the three included vignettes is likely lower than 0.31.

††† Stocking et al. published the number of pairs disagreeing on one, two, three, or four vignettes (46, 19, 7, and 2, respectively), as well as how many total pair disagreements entailed patient willingness/proxy unwillingness and vice versa. They graciously shared their raw data with us so that we could report the percent agreement for each vignette.

‡‡‡ Dementia patients had a mean MMSE score of 19.8, with a range of 2-29.

§§§ As the specific risks of the hypothetical study/vignette were not described in the text/supplemental material of the cited article, we assigned a risk level by making an assumption from the information provided. Unless there was reason to consider otherwise, we categorized all blood draw studies as minimal risk, all LPs as a minor increase over minimal risk, and all drug RCTs as more than a minor increase over minimal risk.

individuals' responses to hypothetical scenarios. It is unclear to what extent these data reflect the predictive accuracy of surrogates in actual practice. Fifth, some of the articles did not report the precise vignette or question used for a given dataset. This limited our ability to accurately assign a risk and benefit level and may have resulted in the miscategorization of some vignettes. Sixth, several of the articles did not specify that, in the vignettes or scenarios assessed, the individual was not able to provide their own informed consent. For example, several studies assessed individuals' views regarding their participation in research on dementia without specifying that, in the case being considered, the individual was not able to consent for themselves.

Discussion

Clinical research with adults who have lost the ability to consent is vital to improving the understanding of, and the treatment for, a number of devastating conditions. This research also raises concern that subjects' inability to consent might be exploited for the benefit of others. In particular, this research raises concern that investigators might take advantage of individuals' inability to consent to enroll them in research that conflicts with their preferences and values.

Most guidelines stipulate that adults who have lost the ability to consent should be enrolled in research only when they agree, or assent. While this is an important protection, the agreement of an adult who is cognitively impaired and unable to consent does not imply that enrolling them in research is appropriate. Recognizing this, most guidelines further mandate that adults who have lost the ability to consent should be enrolled in clinical research only when it is consistent with their preferences and values. Current practice relies on patient-designated and next-of-kin surrogates to implement this safeguard (Alzheimer's Association; NBAC; Council of Europe; U.S. DHHS; Medical Research Council of Canada; NHRPAC; NIH Clinical Center). Data published over the past decade provide the opportunity to evaluate this practice of relying on research surrogates to protect those who have lost the ability to consent.

The published studies consistently find that many adults are willing, and a minority is not willing, to participate in clinical research should they become incapacitated. Further, individuals' willingness to participate decreases as the risks increase, and as the potential clinical benefits decrease. It follows that blanket policies—those that prohibit, as well as those that allow, the enrollment of *all* adults who cannot consent—are inconsistent with the preferences and values of many individuals.

Current reliance on surrogates provides a more individualized approach, basing research enrollment decisions on the surrogate's best estimate of what decision the patient would have made, if the patient were capacitated. This strategy gains support from data that most adults endorse allowing their family members or loved ones to decide whether they are enrolled in research in the event of incapacity. Yet, the studies also find that, when presented with hypothetical scenarios, surrogates often make enrollment decisions that are inconsistent with the decisions their charges would make for themselves. Although these data on surrogate accuracy in the research setting are limited, they are consistent with more extensive data from the clinical setting, which find that surrogates frequently make decisions that conflict with the decisions their charges would make for themselves (Shalowitz, Garrett-Mayer, & Wendler, 2006).

Because the data on surrogate accuracy were collected in the context of hypothetical scenarios, it is unclear to what extent they provide an accurate measure of surrogate accuracy in practice. It may be that, when making actual decisions, surrogates take their task more seriously, which in turn may increase their ability to predict accurately what decisions their charges would have made. Alternatively, surrogate accuracy may be lower when making actual decisions for loved ones who are ill and incapacitated. While the existing data do not provide a definitive answer, this latter possibility seems more likely given the complexity and stress of making actual decisions for ill and incapacitated loved ones. In addition, surrogates who actually make such decisions are often further removed in time from exposure to their charge's competent preferences and values than hypothetical surrogates who are trying to guess their competent loved one's preferences. Accordingly, the existing data may represent—if anything—a somewhat inflated estimate of surrogate accuracy. The existing data thus suggest that, under current practice, 10–20% of incapacitated adults who are enrolled in research by a surrogate may be enrolled in research that they themselves would have opposed. On the assumption that the decisions individuals make for themselves in this context provide evidence of their relevant preferences and values, this conclusion raises concern that incapacitated adults may be getting enrolled in research that conflicts with their preferences and values.

This conclusion might not be too troubling if competent adults were willing to grant their surrogates significant leeway when making research decisions. Specifically, individuals might be willing to accept the decisions their surrogates make for them, even when the surrogates' decisions conflict with the decisions the individuals

would have made for themselves. The data do suggest that a majority of individuals are willing to give their surrogates at least some leeway when making research decisions. That is, many individuals endorse their surrogates making the decision that seems best to the surrogate at the time, independent of the extent to which it is consistent with the individual's previously expressed wishes. Unfortunately, the same studies find that many others are not willing to give their surrogates leeway (Karlawish et al., 2009; Kim et al., 2009; Wendler et al., 2002; Stocking et al., 2006). One study found that 17–26% of older Americans would allow their surrogates complete leeway, 38–41% would allow some leeway, and 33–45% would allow no leeway at all (Kim et al., 2009). These data suggest that over one third of individuals want their surrogates to make decisions based on the individual's own preferences and values, not based on which option the surrogate prefers in the situation.

Taken together, the empirical data, while limited, suggest that current practice may result in research enrollment decisions that are consistent with the preferences and values of approximately two thirds of incapacitated adults, and inconsistent with the preferences and values of approximately one third of incapacitated adults, in a context where a substantial minority of individuals think that their surrogates should have no leeway when making decisions. This conclusion suggests that the best response may be to maintain current practice, while evaluating ways to supplement it to increase the extent to which it protects those who have lost the ability to consent.

One option would be to try to supplement current practice in ways that improve surrogates' ability to predict what decisions their charges would have made if competent. The empirical data find that the two most plausible strategies for increasing surrogates' ability to predict what decisions their charges would make are ineffective. Perhaps the most widely endorsed strategy—encouraging competent adults to discuss their research-related preferences with their surrogates (Wendler et al., 2002; Coppolino & Ackerson, 2001; Shalowitz, Garrett-Mayer, & Wendler, 2006; Stocking et al., 2006; Chen, Miller, & Rosenstein, 2002)—appears to not improve surrogates' predictive accuracy (Coppolino & Ackerson, 2001; Shalowitz, Garrett-Mayer, & Wendler, 2006). An alternative, endorsed by the Secretary's Advisory Committee on Human Research Protections (SACHRP), would be to stipulate that "only certain categories of surrogates may provide consent, for example, those specified by advance directives" or next of kin (SACHRP). This approach might provide better protection if next-of-kin and/or personally appointed surrogates were better able to predict their charges preferences, or if individuals were more willing to grant their next-of-kin or personally appointed surrogates greater leeway. Yet, the existing data find that personally appointed and next-of-kin surrogates are no more accurate than other surrogates (Shalowitz, Garrett-Mayer, & Wendler, 2006). Additionally, while many individuals are willing to grant their next-of-kin surrogates at least some decisional leeway, up to 45% are not (Kim et al., 2009).

Perhaps the most important finding from the empirical data is that competent adults have a range of preferences and values regarding enrollment in research in the event of incapacity. This finding points to the possible alternative strategy of supplementing current practice by stipulating that incapacitated adults may be enrolled in research only when there is sufficient evidence that enrollment is consistent with the preferences and values of the specific individual being enrolled.

Individuals could provide such evidence in a formal advance directive which specifies the types of research in which they are willing to participate and/or designate whom they want to make decisions for them and the amount of leeway their surrogate should have in making decisions. While this approach makes sense, a high percentage of adults, including those who are willing to participate in research, do not complete advance directives. For example, two studies found that only a small percentage (28% and 16%, respectively) of capable adults who were participating in clinical research completed a formal advance directive documenting their research preferences (Muthappan, Forster, & Wendler, 2005; Wendler et al., 2002). These studies argue that requiring a formal advance directive would prohibit significant research, including research with many individuals who were willing to participate (ibid.). This suggests that more informal types of evidence, including knowledge gained from discussions with the individual and decisions the individual made while competent, should be considered in determining whether or not an incapacitated adult should be enrolled in research. The "Sufficient Evidence Framework" (Table 4) provides one way to implement this approach.

Sufficient Evidence Framework

Given the importance of protecting vulnerable subjects, one might argue that incapacitated adults should be enrolled in research only when it is *certain* that enrollment is consistent with their preferences and values. The problem with this suggestion is that absolute certainty is unobtainable. This suggests that the ethical requirement is for investigators to use due diligence, not for them to achieve certainty, in evaluating whether

TABLE 4. Sufficient Evidence Framework.

Benefit	Risk Level	Evidentiary Standard	Example
In Subject's Medical Interests	All	No Contrary Evidence	Subject not opposed to research or to facing level of risks involved
Not in Subject's Medical Interests	Minimal Risk	Attitudinal Evidence	Volunteered to help others
	Minor Increase over Minimal Risk	Research-Related Evidence	Expressed willingness to be in 'non-beneficial' research
	More than Minor Increase over Minimal Risk	Category-Specific Evidence	Expressed clear willingness to be in risky 'non-beneficial' research

enrollment conflicts with an individual's preferences and values. To implement this standard, investigators could enroll adults who have lost the ability to consent in research only when there is sufficient evidence that enrollment is consistent with the individual's preferences and values.

The data reveal that fewer individuals are willing to participate in research as the risks increase and as the potential benefits decrease. Although enrolling individuals in any research that conflicts with their preferences is problematic, the harms associated with studies that have less favorable risk-benefit profiles warrant a higher degree of protection. For example, many guidelines allow research to be conducted without any consent at all when the risks are sufficiently low, but require consent for riskier research. These considerations suggest that what is needed is a framework which requires more evidence as the risk-benefit profile becomes less favorable for the subjects.

Much of the empirical data on adults' willingness to participate in research in the event of incapacity is based on the framework used in the U.S. pediatric regulations, which divides research into four categories: minimal risk, prospect of direct benefit, minor increase over minimal risk without a prospect of direct benefit, and more than a minor increase over minimal risk without a prospect of direct benefit. Individuals' willingness to participate seems sensitive to these four categories, and many review committees are familiar with applying them. Hence, it seems reasonable to incorporate these categories, rather than devising entirely new ones.

Most individuals want to promote their medical interests. Thus, when research offers a potential for clinical benefit that justifies or outweighs the risks, and the risk/benefit profile is at least as favorable as that of the available alternatives (including not participating in research at all), a reasonable default would be to enroll incapacitated adults. The exception would be cases in which there is good evidence that the individual would not want to be enrolled. For example, this standard might be met by an individual who consistently opposed clinical research. In addition, the data suggest that at least a minority of adults are unwilling to participate in research that poses very high risks, even when it offers a compensating potential for clinical benefit. Thus, for higher risk studies, surrogates should consider whether, despite the compensating potential for clinical benefit, there is good reason to think that their charges would not want to be exposed to the level or kind of risks in question.

Research that does not offer a prospect of direct benefit conflicts with individuals' medical interests. In these cases, incapacitated adults should be enrolled only when there is positive evidence that enrollment is consistent with the individual's preferences and values. A large majority of individuals are willing to be enrolled in minimal risk, nonbeneficial research in the event they lose capacity (Berger & Majerovitz, 2005; Karlawish et al., 2009; Kim, Cox, & Caine, 2002; Muthappan, Forster, & Wendler, 2005; Sachs et al., 1994; Wendler et al., 2002). Moreover, such research poses a very small chance of harm. This suggests that a low level of evidence should be required in these cases—the "Attitudinal Evidence" standard. This standard could be satisfied by evidence of the character and general preferences of the potential subject (Karlawish et al., 2009; Bravo et al., 2004), such as the individual's willingness to donate blood (Kim et al., 2005) when they were competent or willingness to spend time helping others.

For studies presenting a minor increase over minimal risk, more positive evidence should be required—"Research-Related Evidence." This standard requires specific knowledge of the individual's preferences and values. For instance, enrollment in this category could be justified if the individual had expressed a willingness to participate in research that poses risks and offers no potential for clinical benefit. Knowledge that a subject was supportive of research on a given disease and willing to contribute to its advancement might also satisfy this standard.

There is significant debate over whether nonbeneficial research involving more than a minor increase over minimal risk is ever appropriate with incapacitated adults. SACHRP argues that, in exceptional circumstances, research which offers no prospect of direct benefit and "moderate" risks might be acceptable (SACHRP). Empirical studies find that some individuals are willing, and many individuals are not willing, to participate in such research. Accordingly, enrollment of incapacitated adults should be prohibited in this category unless there is absolutely *compelling* evidence that enrollment is consistent with the specific individual's preferences and values.

The requirement for "Category-Specific Evidence" might be satisfied by individuals stating repeatedly, while competent, their willingness to be enrolled in a specific study or, more broadly, research in this category. For example, individuals with psychotic disorders might document the types of studies in which they would be willing to participate at times when they are incapacitated. Similarly, individuals with mild dementia might document and reiterate their willingness to be in certain studies once they lose the ability to consent. Given the concerns raised by this category of research, it might make sense to require that an independent party certify that the category specific evidence standard has been satisfied.

Best Practices

Reliance on surrogate decision-makers is the prevailing standard for research with incapacitated adults. However, the published data raise concern that surrogates may be enrolling their charges in research studies that conflict with the charge's preferences or values. One way to address this shortcoming might be to supplement current reliance on surrogates with a stipulation that adults who have lost the ability to consent may be enrolled in research only when there is sufficient evidence that enrollment is consistent with the individual's preferences and values—the Sufficient Evidence Framework. This approach has the potential to ensure incapacitated adults receive appropriate protection without precluding research that is needed to find better treatments for the conditions that affect them.

Research Agenda

The present study did not address how best to implement the present recommendations, nor what impact their implementation might have on clinical research. Before the present recommendations are adopted, it will be important to consider and evaluate these questions. Additional research might also consider ways to increase the evidence regarding individuals' research preferences and values, including the possibility and feasibility of developing research advance directives.

Educational Implications

This study has important implications for the education of those who are conducting clinical research with adults who have lost the ability to consent. Investigators who are conducting such research should be urged to consider what evidence exists that the individuals would want to participate in the research in question. In some cases, such as longitudinal studies of Alzheimer disease, investigators might encourage adults to discuss and document their preferences prior to becoming unable to consent. Ethics committee members who are evaluating research projects that are intending to enroll adults who have lost the ability to consent should be instructed to consider this issue and how it should be evaluated in practice.

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Author Note

Address correspondence to: David Wendler, Department of Bioethics, NIH Clinical Center, Building 10, Room 1C118, Bethesda, MD 20892-1156. Phone: 301-496-2429; Fax: 301-496-0760; E-MAIL: dwendler@nih.gov.

Authors' Biographical Sketches

Emily Abdoler was a fellow in the Department of Bioethics at the National Institutes of Health in the United States, where she trained in conducting conceptual and empirical research related to ethical issues in clinical research. She is currently a student at the University of Michigan Medical School.

David Wendler trained as a philosopher. He heads the unit on vulnerable populations in the Department of Bioethics at the National Institutes of Health in the United States.

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Appendix: Literature Search

Search terms: proxy [mh] or surrog* [tw] or legal guardians [mh] or third-party consent [mh] or ((caregivers [mh] or family [mh]) AND decision making [mh]) AND Search dementia [mh] or mental competency [mh] or cognition disorders [mh] or vulnerable populations [mh] AND Search biomedical research [mh] or human experimentation [mh] or patient participation [mh] or research subjects [mh] or patient selection [mh] or refusal to participate [mh] or treatment refusal [mh] or advance care planning [mh]