Stroke Genetic Research and Adults With Impaired Decision-Making Capacity
A Survey of IRB and Investigator Practices

Donna T. Chen, MD, MPH; James F. Meschia, MD; Thomas G. Brott, MD; Robert D. Brown, MD; Bradford B. Worrall, MD, MSc; for the SWISS investigators

Background and Purpose—In stroke and other brain disorders, severely affected phenotypes often impair decision-making capacity. Severity is in part under genomic control. Therefore, scientifically valid research into genetic risk may require inclusion of such impaired individuals. U.S. Federal regulations do not detail rules governing enrollment of adults with impaired decision-making capacity into genetic research. Rather, policy and practice are locally determined. This study was conducted to obtain data on how investigators and IRBs handle surrogate authorization to enroll probands into a genetic study where some may lack capacity because of ischemic stroke.

Methods—Sequential surveys of sites from an ongoing North American study investigating genetic risks for ischemic stroke (2003: 49 sites, response rate=100%; 2007: 53 sites; response rate=91%) assessed whether and how investigators enroll adults with impaired decision-making capacity and determined frequency of IRB approval for enrollment by surrogate authorization.

Results—Approximately 40% of sites report that their IRBs do not approve surrogate authorization to enroll stroke patients—43% (21/49) in 2003 and 35% (17/48) in 2007. Thirty-three percent of sites report evaluating eligible adults who lacked capacity to provide their own informed consent; 18% (9/49) in 2003 and 15% (7/48) in 2007 have enrolled these individuals. Surrogate enrollment is the most common method used. Most sites have not enrolled any individual lacking capacity to give his or her own consent.

Conclusions—Our study suggests that enrollment by surrogate authorization into stroke genetic research is often not approved by IRBs, and even when allowed is frequently not used. For disorders like stroke, this situation has significant implications for scientific validity. (Stroke. 2008;39:2732-2735.)

Key Words: research ethics | genetic research | informed consent | proxy | third-party consent

The much-heralded promise of the genomic era relies on rigorous research into common, complex diseases. In stroke as with many other neurological diseases, severely affected phenotypes are associated with impaired capacity to make informed well-reasoned decisions, and phenotypic severity may be in part genetically determined. For these disorders, research into genetic risk warrants consideration for inclusion of individuals with impaired capacity.

Investigators and investigational review boards (IRBs) lack clear guidance from federal regulations regarding acceptability of including adults with impaired capacity to consent in genetic research. Little is known about IRB and investigator practices in research not offering prospect of direct benefit to participants, as noted by the U.S. Office of Human Research Protections in a recent call for comments on this topic. We conducted sequential cross-sectional investigator surveys to determine how often IRBs allow enrollment by surrogate authorization of impaired adults as probands in “nontherapeutic” genetic research and to ascertain how often investigators enroll impaired individuals when they have IRB approval to do so.

Materials and Methods
We surveyed investigators from a multi-center North American affected sibling pair study known as the Siblings with Ischemic Stroke Study (SWISS). SWISS includes a genome-wide screen to identify novel risk factors through linkage analysis in sibling pairs concordant and discordant for ischemic stroke. For probands meeting eligibility criteria, participation includes sending letters to siblings inviting participation and providing a blood sample for genetic analysis if at least one qualified sibling also agrees to participate; samples are double-coded. Probands give their own written informed consent if able, and if unable, are enrolled through a variety of mechanisms as permitted by the local governing IRB. SWISS does not use a central IRB.
We surveyed all actively enrolling sites during the recruitment phase of the study in 2003 (n=49 centers) and again in 2007 (n=53 centers). Between surveys, 10 sites closed to enrollment, and 14 new centers started to enroll. The 2003 questions were part of a larger survey. In 2007, investigators and coordinators at the 53 sites were surveyed on experiences related to adults felt to be impaired in their capacity to provide consent; responses were collected via email, fax, and in person at investigator meetings. Survey instruments were coded to ensure nonduplication of data. No identifiers were recorded. Data were collected in an anonymized fashion precluding pair-wise statistical analysis across the two survey epochs. The University of Virginia IRB approved the study.

Results

Survey Response and IRB Position on Surrogacy Authorization
Survey response rates were excellent: 100% (49/49 centers) in 2003 and 91% (48/53 centers) in 2007. Approximately 40% of sites reported that their IRBs do not permit use of surrogate authorization to enroll probands in SWISS (43% (21/49 centers) in 2003 and 35% (17/48 centers) in 2007 (Table 1). The exact composition of participating sites differed in the two surveys, but in 2007, 4 sites reported that their IRBs changed their stance to allow surrogate authorization. No site reported an IRB rescinding approval.

Sites Experiences Encountering and Enrolling Individuals With Impaired Capacity
In 2003, 20/49 centers and in 2007, 16/48 centers reported encountering ≥1 otherwise eligible individual lacking capacity to provide informed consent (Table 2). Forty-five percent (9/20) of these centers in 2003 and 44% (7/16) of them in 2007 were successful in enrolling at least one individual who initially lacked capacity. In 2003, 4 sites enrolled these individuals only through surrogates, 2 awaited return of capacity, and 3 reported both. In 2007, 3 sites enrolled through surrogates, 3 awaited return of capacity, and 1 reported both. No center in either survey reported using research advance directives.

Among centers that both allowed surrogate enrollment and encountered otherwise eligible individuals lacking capacity, 78% (7/9) in 2003 and 50% (5/10) in 2007 enrolled at least one individual who initially lacked capacity (Table 3). Among centers not allowing surrogate enrollment that reported encountering individuals lacking capacity, 2/11 centers in 2003 and 2/6 in 2007 enrolled such individuals.

Overall, the majority of centers did not enroll individuals lacking capacity, 82% (40/49) in 2003 and 85% (41/48) in 2007. Among centers that allowed surrogate authorization, 73% (19/26) in 2003 and 84% (26/31) in 2007 did not enroll individuals lacking capacity.

Discussion
In ischemic stroke, severe outcomes cause decisional impairment and severity may have genetic determinants. In many other brain disorders like Alzheimer Disease, subarachnoid hemorrhage, and traumatic brain injury, phenotypic severity is also associated with impaired capacity and may have genetic determinants. Thus, scientifically valid research in these common brain disorders may require inclusion of decisionally-impaired individuals. This type of research would meet the "necessity" standard that decisionally-impaired individuals be considered for research if and only if their participation is necessary to ensure scientific validity of socially, scientifically, or clinically valuable research.

Genomic research in common brain disorders is a national priority. Despite its potential to advance medicine and benefit future individuals, genomic research does not offer

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<th>Survey Responses</th>
<th>2003 Survey</th>
<th>2007 Survey</th>
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<td>Sites, n %</td>
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<th>Surrogacy Authorization</th>
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<tr>
<td>Enrollment by surrogate allowed by IRB</td>
<td>26/49 53</td>
<td>31/48 65</td>
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<tr>
<td>Enrollment by surrogate not allowed by IRB</td>
<td>21/49 43</td>
<td>17/48 35</td>
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<tr>
<td>Unsure/unclear</td>
<td>2/49 4</td>
<td>0/48 0</td>
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<tr>
<td>Reporting change in IRB stance</td>
<td>NA NA</td>
<td>4/48 8</td>
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<th>Sites Experiences Encountering and Enrolling Probands With Decisional Incapacity</th>
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<tr>
<th>Report encountering 1 or more potential proband lacking decisional capacity</th>
<th>9/26 34</th>
<th>10/31 32</th>
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<tr>
<td>Report enrolling 1 or more potential proband lacking decisional capacity</td>
<td>7/26 27</td>
<td>5/31 16</td>
</tr>
<tr>
<td>Used surrogate authorization to enroll*</td>
<td>7/7 100</td>
<td>4/5 80</td>
</tr>
<tr>
<td>Used waiting for return of capacity to enroll**</td>
<td>3/7 43</td>
<td>2/5 40</td>
</tr>
<tr>
<td>Used research advance directives to enroll**</td>
<td>0/7 0</td>
<td>0/5 0</td>
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*Includes only the sites that allowed surrogate enrollment.
**Categories not mutually exclusive.
direct benefit to participants. This research underscores the challenge of simultaneously addressing the ethical requirements for “valuable research,” “scientific validity,” and “respecting persons.”15,18 Respecting persons is generally met through the processes of informed consent for individuals having capacity or use of appropriate safeguards for individuals lacking capacity. Acceptable safeguards include excluding these individuals from research if their participation does not meet the necessity requirement or enrolling them via processes such as surrogate authorization, use of research advance directives, and awaiting return of capacity.2,4,14,16,18

In SWISS, sites enrolling individuals unable to provide their own consent used both surrogate authorization and return of capacity to some extent. Research advance directives were not used. In our study, approximately 40% of IRBs do not permit surrogate authorization. Fewer than half of sites encountering potential participants lacking decision-making capacity enrolled these individuals. In both surveys, sites allowed to use surrogate authorization were more likely to enroll impaired probands than sites not allowed use of surrogate authorization. However, most sites allowed to use surrogate authorization did not enroll any impaired individuals.

IRBs can deny surrogate enrollment based on concerns over the appropriateness of the practice or an assessment of excessive risk even for research meeting the “necessity” standard. We are not aware of any statute prohibiting enrollment of decisionally-impaired individuals or use of surrogate authorization in genetic research. When there is no prospect of direct benefit, surrogate enrollment in research with minimal risk is generally permitted, following the spirit of federal regulations pertaining to research with children, as the regulations are silent on this issue with respect to adults.4,6,18 The regulations governing children also permit some research that involves a minor increment over minimal risk, even if the research does not offer prospect of direct benefit to the child-research participant, if the research is likely to yield generalizable knowledge about the subjects’ disorder.4

Granted, the federal regulations governing research involving children do not forestall continued debate over how best to determine the risks associated with research and the acceptability of various risks among children.19–21 Nevertheless, they can serve as a helpful framework when considering the enrollment in research of adults who lack the capacity to provide their own informed consent, a group currently not addressed by these regulations.18

Risks associated with genomic research are not well documented, and beliefs regarding these risks vary greatly.5,22–26 It is unlikely that risks in genomic research are always higher than in other types of research where surrogate enrollment of adults is allowed, which can carry significant risk to participants with no guarantee of benefit, though the possibility of benefit exists.27 Thus, a categorical prohibition against enrolling decisionally-impaired adults in genetic research on basis of risk seems unjustified. Nevertheless, some IRBs may judge the risk, even when minimal, to be too great to allow surrogate enrollment. In SWISS, the risk associated with participating is that of sending a letter inviting siblings to participate and of giving a double-coded blood sample for genome-wide scan and linkage analysis. More documentation of actual risks associated with genetic research overall, and with specific procedures used, would advance this debate.

In circumstances where surrogate enrollment is allowed, our results suggest that it is underutilized. We are unable to ascertain whether this results from researchers not approaching decisionally-impaired individuals, even when allowed; inability to locate a surrogate; surrogate refusal for study participation; or something else entirely. Researchers in many other brain disorders also find that use of surrogate decision-makers in research is not straightforward ethically or practically.16,28

The two other mechanisms, research advance directives and awaiting return of decision-making ability, are unfortunately not feasible alternatives. Research advance directives are difficult to implement when decline in decision-making capacity is anticipated such as in Alzheimer disease; in stroke and other unanticipated and apoplectic conditions like traumatic brain injury, implementation is even more difficult.29–31 No site in our study reported use of research advance directives. Some investigators waited for sufficient stroke recovery to obtain consent. However, because of high case-fatality or persistence of cognitive impairment in the most severe presentations of many brain disorders, awaiting return of capacity to make decisions may perpetuate enrollment bias.1 Therefore, although reasonable from the point of view of respecting informed consent, it does little to relieve concerns over scientific validity.

In general, the term consent bias is applied to the negative effect on external validity attributable to individuals declining to participate in research. Consent bias in clinical trials research has been well recognized.32,33 More recently, attention has been paid to the impact of consent bias in observational, epidemiological, and etiologic research.34–37 Data also support a negative effect of consent bias on the representativeness of DNA banks.38 These studies underscore the potential for skewing of data by requiring explicit consent and the need for strategies to address this type of bias. When the determinants of severity are some of the very factors sought in the studies or on the same causal pathways, there is potential for significant confounding and at worst may completely obscure important associations. Thus, the “consentability” bias introduced by restricting enrollment to those able to provide their own consent is more akin to survival bias, a potentially more problematic form of bias.1

Our survey addresses the issue of enrolling individuals with impaired decision-making capability in the context of a single multisite study at 2 time points. The large number of sites and the high response rates are strengths. Furthermore, rather than use hypothetical scenarios, we surveyed actual practice. Focusing on investigators at sites participating in stroke genetics research may skew our results regarding IRB approvals. However, if there is a bias in our sample, it likely favors allowing surrogate enrollment, which suggests the actual percentage prohibiting surrogate enrollment may be higher than our estimate of 40%.

Our study does not seek explanations for current IRB and investigator practices. Nonetheless, at least in practice, many IRBs appear to treat genetic research as carrying considerable risks to participants by prohibiting surrogate authorization.24 Clearly, further research to verify our findings and determine
reasoning behind IRB and investigator decisions is needed, as is further inquiry regarding level of risk and other ethical issues in enrolling decisionally-impaired adults in genetics research.

**Summary**

Currently, there are few viable strategies for enrolling decisionally-impaired adults in genetic studies, even when their enrollment may be necessary for scientific validity. Enrollment by surrogate authorization is one such strategy that is frequently allowed in other types of research. We find that use of surrogate authorization is frequently not permitted or is underutilized in genomic research. This situation has implications for scientific validity of genomic research on many brain disorders of public health significance.

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**Disclosures**

Drs Chen and Worrall had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of reporting.

**References**

6. DHHS. Request for information and comments on research that involves adult individuals with impaired decision-making capacity. Federal Register. 2007;72:50966–50970.
26. Do not ask or do not answer. The Economist. 2007;384:73–75.
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