

## *Incompetent Persons as Research Subjects and the Ethics of Minimal Risk*

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### **Introduction**

The voluntary and informed consent of subjects has been the central focus of concern in research reviews, overshadowing the importance of all other considerations. The Nuremberg Code, with its rights-based protection of the subject's autonomy above all else, made it difficult to justify research with no intended benefit when subjects are incompetent to make a valid informed choice to participate. Subsequent codes providing for research with incompetent subjects followed the lead of Nuremberg, substituting the informed authorization of a proxy for the informed consent of the subject.

Despite substantial refinements in ethical reasoning concerning research as manifested over the past several decades in codes of research ethics, guidelines, and regulations, there remains no satisfactory ethical justification for the inclusion of incompetent adults in research with no intended personal benefit. While some disagreement remains concerning the inclusion of children in certain kinds of research, the ethical barriers to such research have been discussed extensively<sup>1</sup> and have been addressed in legislation<sup>2</sup> and recommendations.<sup>3</sup>

In this paper we trace the history of protection of incompetent adult research subjects as found in codes and guidelines regulating the conduct of research, define the gap in the ethical justification for inclusion of such subjects when there is no intended benefit for them, and develop a rationale to fill this gap based upon existing ethical and legal notions of trust, family privacy, and social responsibility. In so doing, we review the reasoning in relation to research with children insofar as it is relevant to incompetent adults.

### **A Century of Fining Gradations**

With the exception of a few early 20th century codes of research ethics (a Prussian directive in 1900 and guidelines promulgated in the Weimar Republic<sup>4</sup>), research involving human subjects was for the most part controlled only by the relationship between the research subject and the investigator, with reliance on the latter for an honest appraisal of acceptable risk. The Nuremberg Code, drafted in response to this century's most notorious research abuses, firmly established the voluntary and informed consent of the human subject as the grounding principle

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for the ethical conduct of research. The authors of the Code defined voluntary consent in the following terms.<sup>5</sup>

This means that the person involved must have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved to enable him to make an understanding and enlightened decision.

Like its German antecedents, the text provides no justification for research with individuals who are unable to make a competent choice about participation. The document is based on natural law principles<sup>6</sup>: it assumes the veracity of these principles to be self-evident.

The World Medical Association's Declaration of Helsinki, designed to address the perceived inadequacies of the Nuremberg Code, provided for research with incompetent subjects by stating that "[i]n case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation." And further: "Where physical or mental incapacity makes it impossible to obtain informed consent, or where the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation."<sup>7</sup> Like most codes and guidelines, the Declaration is a statement of ethical procedure rather than intention or justification, and thus leaves the reader ignorant of the drafter's motivation in making this major change from the Nuremberg Code's requirement for personal consent from the research subject.

### **Competency, Protection, and Risk: Finer Gradations**

The US National Commission's *Belmont Report* established the primacy of the principle of respect for persons in the regulation of research.<sup>8</sup> Respect for persons not only accords competent persons the opportunity for a fully informed, voluntary choice, it also entails an obligation to protect vulnerable persons from harm. The Commission's studies dealing with research involving children, prisoners, and the institutionalized mentally infirm elaborate upon the ethical obligation of protection for vulnerable research subjects.<sup>9</sup> Current US regulations regarding children<sup>10</sup> are based upon these reports. The regulations not only provide for proxy authorization, but they also allow it in some circumstances where there is no intended personal benefit for the child. Although the regulations themselves do not provide a specific rationale for allowing this, the circumstances under which it is allowed are circumscribed by definitions of allowable risk in order to adequately protect the young subjects. Emphasis is placed on a threshold risk level of "minimal risk," described in the regulations as "the probability and magnitude of physical or psychological harm encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons."<sup>11</sup> The National Commission also concluded that a research protocol involving nontherapeutic interventions on incompetent subjects could be approved if the risk represents "a minor increase over minimal risk" and if the intervention or procedure is "likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance."<sup>12</sup>

The categorization of risk is perhaps the most revolutionary idea to come out of the National Commission's reports. Many subsequent codes or guidelines also use this refinement of gradations of risk to allow for research with no intended benefit to subjects who are unable to consent. This is done along with other safeguards, such as review by a research ethics committee or institutional review board and the requirement of either subject assent or lack of objection to participation.

There have been a number of attempts to draw up specialized guidelines to deal with incompetent adult research subjects. The fruit of a conference sponsored by the National Institutes of Health in 1981 was "Clinical research in senile dementia of the Alzheimer's type: suggested guidelines addressing the ethical and legal issues."<sup>13</sup> This document is much more detailed and makes further distinctions with respect to recruitment of subjects than any prior code or guidelines. Some of the authors' rationale for the guidelines is found in a volume of essays published simultaneously. Much attention is paid to protecting this very vulnerable population. Yet the authors do not provide an ethical grounding for including incompetent subjects in research with no intended personal benefit beyond the dreadful nature of Alzheimer's disease and the necessity for research to overcome it for future patients. However, the authors do propose establishing a relationship between capacity to consent and the risks of research so that higher levels of competence and stringent safeguards to protect subjects are required for riskier research than would be for less risky research. This position has been taken by a number of others as well.<sup>14</sup> Although more care in assessing competency may be warranted for riskier research interventions, we question the ethical justification for adjusting competency criteria to risk level, because risk is not necessarily correlated with complexity of an intervention.<sup>15</sup>

The American College of Physicians published a series of points to consider when dealing with cognitively impaired subjects; but as with other codes and guidelines, they do not include supporting moral analysis.<sup>16</sup> Guidelines to be used in research involving subjects with dementia have been published recently that contain substantial moral analysis relating to a number of issues particular to this population. They would allow (under certain very restrictive circumstances) persons unable to consent for themselves to be enrolled in research protocols with no intended personal benefit. This is based on the assumption that when important scientific and community considerations are met, a certain amount of risk without benefit is acceptable. Our question, what makes it socially or morally acceptable, is not a subject the authors address directly.<sup>17</sup>

The above account demonstrates a gradual whittling away of the premise upon which the Nuremberg Code is based: to become a research subject, an individual must be autonomous enough to make an informed judgment about participation in a protocol. The Declaration of Helsinki substituted a proxy's informed choice for that of an incompetent subject. Proxy consent is further refined (or rationalized) when in later regulations and guidelines, the assent of the subject (along with the authorization of the proxy) becomes a surrogate for a competent and informed consent.<sup>18</sup> Substituting a prior expression of wishes to act as a research subject for a fully informed, contemporaneous, and competent consent is proposed with the use of advance directives for research.<sup>19</sup> And finally, finer gradations of competence and consent/assent are tailored to finer gradations of research risk and type.<sup>20</sup>

The question remains how to ethically justify interventions involving risk but no promise of personal benefit for incompetent subjects themselves. To date, much of the justification has been utilitarian. Some argue that the devastation of illnesses such as Alzheimer's disease forces us to find ways to conduct research even without the contemporaneous informed consent of subjects.<sup>21</sup> Others suggest that scientifically sound research can be ethically justified even without benefit to subjects on the grounds that "its anticipated knowledge will be of vital importance to the future understanding and alleviation of [Alzheimer's] disease"<sup>22</sup> or if "the knowledge to be gained from the research is relatively important and not trivial or insignificant."<sup>23</sup> One of several moral arguments put forth in the *Report on Research Involving Children* published by the Canadian National Council on Bioethics in Human Research also takes a utilitarian perspective, stating that without research, children in general will become "therapeutic orphans."<sup>24</sup> It is a powerful theme found in the research literature as well.<sup>25</sup> Without qualification, it can be a dangerous argument: a few sacrificing involuntarily for the good of their community. But is this the final, or only, moral justification for involving those unable to consent in research of no benefit to them?

### **The Role of Risk Limitation**

Current codes of research ethics place an unprecedented emphasis on the threshold of minimal risk and minor increments above minimal risk as if this limit alone provides moral justification. In many guidelines we observe minimal risk or minor increment over minimal risk as a cap for what proxies can authorize on behalf of their wards when the research has no intended personal therapeutic benefit for subjects.<sup>26</sup> Others make allowances for increases over this threshold in the extraordinary circumstance that there would be sufficient scientific benefit. They tend to demand more exacting review, for example, a national ethics board or court approval.<sup>27</sup>

Minimal risk as a real-world benchmark is a useful comparison for gauging severity. But how does it stand as an ethical threshold for acceptance or rejection? The codes are silent on this question. Freedman *et al.*<sup>28</sup> recently argued that minimal risk is a valuable threshold by which to compare a medical or research intervention. As they put it: "The concept of risks of everyday life has normative as well as descriptive force, reflecting a level of risk that is not simply accepted but is deemed socially acceptable." They have part of the answer: minimal risks are what we deem socially acceptable. They also point out that<sup>29</sup>

the risks of research are to a degree substitutive, rather than additive: research risks are undergone, but the risks of alternative activities are foregone. Normal, healthy volunteer subjects of research would otherwise be pursuing their normally risky daily lives; and ill subjects who are not enrolled in research studies may nonetheless receive treatments and diagnostic tests under the rubric of therapy that are similar to those they would have experienced in research.

An alternative way of stating this would be that research with intended *therapeutic* benefit is likely to be substitutive of conventional therapy. But in a nontherapeutic intervention this may not be the case. If the subject is institutionalized and

incompetent, for example, a patient with advanced Alzheimer's disease, then risks will probably be additive if the intervention calls for anything more invasive than mere observation.

### **Ethical Grounding for Accepting Minimal Risk**

How, then, does one ethically justify nontherapeutic interventions that inject more risk, albeit more of the same risk of daily life, in the world of an individual who cannot consent to it? On what basis have minimal risks or minor increments above them become "normative"? These risks are different from everyday life risks in important ways. The risks of everyday life for rational self-interested individuals offer some personal benefit or are simply too impractical or costly to avoid. There has been some discussion of justification in the literature. Richard McCormick argued that "the good" of healthy children can be furthered by their participation in nontherapeutic research because if they *were* able to consent for themselves, they ought to do so.<sup>30</sup> The notion of "solidarity ethics" as providing rewards "existentially and at least ideally" has been suggested as the justification for exposing very young bone marrow donors to limited risks without any personal or therapeutic benefit, a situation comparable in many ways to the case of incompetent research subjects.<sup>31</sup> The use of substituted judgment, where the proxy determines what decision an individual would make if competent, has also been considered.<sup>32</sup> All of this reasoning is based upon certain presuppositions about human nature and communities that may or may not be true, and as such, is less than satisfactory as an ethical grounding. While those required to make decisions on behalf of incompetent persons might find some comfort in bolstering a decision with this kind of narrative, we believe that a more widely recognized grounding is required to justify enrolling incompetent persons in research bearing risk of harm but no intended benefit for them.

Kennedy and Grubb reveal another dubious justification that they label "distorting the concept of 'therapy'."<sup>33</sup> This approach turns on the distinction between therapeutic research and nontherapeutic research. For example, the World Health Organization defines "health" as a state of complete physical, mental, and *social* well-being. They argue that a carefully considered proxy consent is an exercise in social responsibility that could benefit the future well-being of the volunteered subject because a child in later life can reasonably be expected to identify with the object of the research. While not based upon the same kind of presuppositions outlined above, this idea rests upon an assumption of how the research subject will feel in the future, which may or may not turn out to be accurate. The authors criticize this reasoning as "an artificial attempt to distort descriptive terminology" that uses ends to justify the means. They note as well that it is not an attractive legal argument.<sup>33</sup>

Feelings of kinship or altruism resulting from research participation have been categorized as therapeutic or at least "beneficial" by some investigators.<sup>34</sup> Yet there are protocols that involve as subjects persons who cannot now and never will appreciate their participation, such as severely cognitively impaired individuals.

Examining the powers of proxy decision makers and the protective functions they are obligated to fulfill, and notions of trust, family privacy, and family obligations of social responsibility have assisted us in elaborating an ethical ground-

ing for subjecting incompetent persons to a restricted level of risk from research when there is no intended personal benefit.

### **Powers of the Proxy**

The use of a proxy decision maker is inevitably raised in situations where the research subject is incapable of consenting. The proxy, whether a court, guardian, parent, or other individual, has historically been allowed to approve actions that would be to the benefit or welfare of the incompetent, a best interests test.<sup>35</sup> While more recently there has been support for the use of advance directives by competent persons to govern their participation in research should they become incompetent,<sup>36</sup> there will always be potential subjects who are not yet competent, who were never competent, or who gave no advance directive on the subject. Can participation by these individuals in research protocols involving risk with no corresponding personal benefit be considered as in their best interests?

To answer the question whether proxy decision makers can fulfill their ethical and legal obligations toward those under their care and at the same time authorize their enrollment in such a protocol, it is helpful to look at the legal notion of best interests and the circumstances under which legislators and courts have used the criterion. Guardianship statutes and the case law flowing from them make specific reference to the principle of best interests, which has been used in a long line of Canadian and American cases concerning the protection of assets or other material interests of an incompetent person.<sup>37</sup> How would a court view research with no intended benefit for an incompetent subject? Annas *et al.* pointed out that the issue of third party informed consent to research has been muddied in the courts "by not clearly setting forth the grounds upon which they have validated the exercise of proxy consents."<sup>38</sup> Capron called the best interests standard "vague and elastic," allowing courts to make decisions that reflect the needs of others, such as family or a social agency, more than they reflect the interests of the incompetent person.<sup>39</sup> This same view has been articulated by Gutheil and Appelbaum, among others, who have characterized the value judgments necessary for determining what is the "best" decision as "undefined, unguided, and unspecified."<sup>40</sup>

The Supreme Court of Canada noted the same difficulties in the *Eve* decision,<sup>41</sup> a case involving requested sterilization of a mentally incompetent young woman to limit reproductive capacity. Without clear legislative authorization as in the US Code of Federal Regulations for research with children<sup>42</sup> or clear and consistent court decisions, there is no objective means for deciding what is the best decision in a given case. A variety of incompatible beliefs, religious and otherwise, confound the problems.<sup>43</sup>

Yet certain facts remain clear. Proxies are obliged to perform a protective function in relation to those under their care, including protection from physical harm. In the realm of medical interventions, cases that have received judicial consideration have involved serious invasive procedures with irreversible consequences: sexual sterilization by hysterectomy,<sup>44</sup> implantation of a shunt,<sup>45</sup> surgical intervention on a Down's syndrome child,<sup>46</sup> kidney donation,<sup>47</sup> to name a few. The notion of best interests becomes very important in such instances. A court must ask whether such physical invasion is appropriate. Is it being done for the benefit of the patient or for others? It has been suggested<sup>48</sup> that a guardian's legal author-

ity does not extend to making decisions that are not for the benefit of the ward. Yet this interpretation is based on judgments that are best understood as reflecting only considerations for seriously invasive or risky procedures.

Interventions involving minor risks, or more serious risks but with a negligible probability of occurrence, are usually not litigated. However, in a 1970 British case involving a blood test for paternity proceedings where the official guardian raised an objection based on the invasive nature of the procedure, the court clearly elaborated a rationale for moving away from a strict interpretation of a parent's responsibility to act in a child's best interests<sup>49</sup>:

Surely a reasonable parent would have some regard to the general public interest and would not refuse a blood test unless he thought that would clearly be against the interests of the child . . . I would hold that the court ought to permit a blood test on a young child to be taken unless satisfied that this would be *against* the child's best interests. [emphasis added]

Using this rationale, parental obligation becomes a negative one – not to act against the interests of the child, rather than a positive one – to promote the child's best interests.

Taking a nonmedical example from Freedman and colleagues, parents may authorize their children to go on camping trips, even though there is risk involved.<sup>50</sup> Parents are expected to balance the risks and benefits and make decisions on behalf of their children without resorting to any other authority such as a court. But examples such as camping trips hold out the possibility of benefits to the children themselves. An example more relevant to the research situation where there is no intended personal benefit is where the risks are born by those for whom the decision is made, and the benefits accrue only to the decision makers or others. A practical example would be the case of engaging a professional care giver for an incompetent adult so that other family members can have an evening free for their own enjoyment.

### **Family Characteristics: Trust, Privacy, and Social Responsibility**

The right to make fundamental personal decisions has received some constitutional recognition.<sup>51</sup> The parental decision making role has been recognized as a legally protected sphere.<sup>52</sup> In Canada, the right of parents to make important decisions such as those involving medical matters is protected under Article 7 of the Charter of Rights and Freedoms.<sup>53</sup> The state may only intervene in the parent-child relationship in those exceptional cases where parents do not respect minimal socially acceptable norms. Only when these are violated may the state step in to restrain parents.<sup>54</sup>

The notion of family autonomy may be based upon a number of considerations including trust, family privacy, and obligations of social responsibility. First, while it is evident that certain everyday decisions parents and other care givers must make do expose others to risk, there is an expectation that they will fulfill their obligations to protect those under their care by minimizing the opportunities for harm. Our social structure is based on trust that parents will care for their children appropriately. This attitude is reflected in legislation aimed at protecting children. For example, the Quebec *Youth Protection Act* states that every decision made under the Act "must contemplate the child's remaining with his family."<sup>55</sup> It is only in cases where this trust is abused, or is at serious risk of being abused,

that society interferes with a parent's decision making, limiting parental discretion to make decisions by the child's right to liberty and security. The same rationale should apply when family members, guardians, or curators make decisions on behalf of adults who are unable to care for themselves.

Second, family life requires a certain amount of privacy, without interference from courts or other government agent. This privacy is only invaded when there is evidence of neglect, abuse, or other harms. Returning to the care giver example, parents or other care givers are not expected to spend every moment with their charges. Rather, they are obligated to protect their welfare and provide for their safety by choosing an individual with appropriate care and attention. This is not to say that those cared for may not be upset or bothered to have a care giver who is not a family member, or that there is absolutely no risk in hiring a care giver, particularly one unknown to the family. Even with professional references, many will feel a certain discomfort in leaving their charges in the care of a new person. Yet they are allowed to do so for their own personal benefit, so long as they are not exposing them to undue harm. Not to allow it would interfere with the daily operations of family life and would destroy the trust and privacy it requires.

Finally, families ought to be able to fulfill societal obligations of responsibility so long as they fulfill their responsibility to protect their charges from undue harm. Everyone takes risks in their daily lives. Those of us with responsibilities for others take risks on their behalf as well. These risks can be minimized but not eliminated. To set a zero risk standard could be destructive to families and we believe would be more harmful than beneficial to individuals, families, and ultimately society as a whole. Reasonable people do not (and should not) always opt for the activity that presents the least physical risk to themselves, their children, or to vulnerable adults under their care. Beyond risks taken for their own benefit or that of their charges, families ought to be allowed to act in the general public interest. An example of this is vaccination, where the medical risk is slight but the benefit may be primarily for the community in general.<sup>56</sup>

Ought these arguments apply to the case of exposing an incompetent individual to research for the benefit of others, even if there is some risk involved? Clearly the legal principle of obligation to protect vulnerable persons mandates that there must be a real and justified need for the research, that the protocols in question have scientific merit, that risks have been minimized to the greatest extent possible, and that the knowledge sought cannot be gained by using competent persons as subjects. In addition, special protection, such as outside monitoring of protocol implementation, may be required to insure that research on vulnerable persons is carried out appropriately.<sup>57</sup> When this is the case, we believe that the notions of trust, family privacy, and family obligations of social responsibility provide the necessary grounding for research with no intended personal benefit. Where care is taken to protect incompetent persons from undue harm, we believe that it is ethical for family and other substitute decision makers to enroll their charges in research protocols with no intended personal benefit so long as the risk of harm falls within the range of that commonly held to be acceptable.

### **Conclusion**

The principle of respect for persons underlying modern canons of research ethics requires society and individuals to have a responsibility to protect incompetent

persons from harm. Guardianship legislation incorporates this principle and courts have by and large fulfilled their responsibilities in this regard. But the notion is not one that should paralyze and prohibit all activities that carry limited risk. Nor should it invade family privacy or limit family autonomy. It should be interpreted to insure that decisions are not made against the interests of incompetent persons. Within the limits outlined above, promoting social or community benefit by enrolling incompetent persons in selected research protocols involving no greater than a minor increment over minimal risks should not be contrary to their best interests.

We believe that setting a limit of minor increment over minimal risks meets the ethical boundary for research on those unable to make an informed choice, even where there is no intended personal benefit for the subject.

### Notes

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11. *Code of Federal Regulations*, 5 CFR 46.303(d).
12. *Code of Federal Regulations*, 45 CFR 46.406(a)-(b).
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55. *Youth Protection Act*. R.S.Q. c. P-34. 1 s. 4, 1989.
56. See note 32. Kennedy, 1989.
57. See note 3. National Council on Bioethics in Human Research. 1992; see note 15. Keyserlingk *et al.* 1995;32:2; Weijer C, Shapiro S, Fuks A, Glass KC, Skrutkowska M. Monitoring clinical research: an obligation unfulfilled. *Canadian Medical Association Journal* 1995;152(12):1973-80.