

# Ethical Challenges and Solutions Regarding Delirium Studies in Palliative Care

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## Abstract

**Context**—Delirium occurs commonly in settings of palliative care (PC), in which patient vulnerability in the unique context of end-of-life care and delirium-associated impairment of decision-making capacity may together present many ethical challenges.

**Objectives**—Based on deliberations at the Studies to Understand Delirium in Palliative Care Settings (SUNDIPS) meeting and an associated literature review, this article discusses ethical issues central to the conduct of research on delirious PC patients.

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**Methods**—Together with an analysis of the ethical deliberations at the SUNDIPS meeting, we conducted a narrative literature review by key words searching of relevant databases and a subsequent hand search of initially identified articles. We also reviewed statements of relevance to delirium research in major national and international ethics guidelines.

**Results**—Key issues identified include the inclusion of PC patients in delirium research, capacity determination, and the mandate to respect patient autonomy and ensure maintenance of patient dignity. Proposed solutions include designing informed consent statements that are clear, concise, and free of complex phraseology; use of concise, yet accurate, capacity assessment instruments with a minimally burdensome schedule; and use of PC friendly consent models, such as facilitated, deferred, experienced, advance, and proxy models.

**Conclusion**—Delirium research in PC patients must meet the common standards for such research in any setting. Certain features unique to PC establish a need for extra diligence in meeting these standards and the employment of assessments, consent procedures, and patient-family interactions that are clearly grounded on the tenets of PC.

## Keywords

Ethics; palliative care; delirium; research

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## Introduction

Delirium is a complex neuropsychiatric disorder characterized by acute or subacute changes to mental status with impaired consciousness, attention, and cognition.<sup>1</sup> It is particularly common in palliative care (PC) settings, with prevalence estimates ranging from 13% to 42% at admission and 58% to 88% in the weeks or hours preceding death.<sup>2,3</sup> Depending on etiologic factors, delirium episodes may be reversible in 30%–50% of individuals.<sup>4,5</sup> Although delirium is a major determinant of clinical outcomes and health care costs,<sup>6,7</sup> it is often clinically under-recognized<sup>8–11</sup> and relatively under-researched, even in the PC setting. The reasons for this are complex and involve particular ethical, clinical, and methodological challenges.<sup>12–16</sup>

The aim of PC is to relieve suffering and improve the quality of life of dying patients and their relatives.<sup>17</sup> However, this cannot be achieved without solid research to support evidence-based care. There are differing views and opinions as to whether patients who are near the end of life should be involved in research studies. Some authors suggest that research in PC should be carried out and encouraged like that in other branches of medicine,<sup>12,18,19</sup> whereas others advocate that such patients never be asked to participate in research studies.<sup>20</sup> More moderate positions have proposed the need for restrictive guidelines, careful scrutiny, and oversight.<sup>21</sup>

As summarized by Duke and Bennett,<sup>14</sup> debates on the ethics of research in PC patients have centered on several key issues including the vulnerability of this patient population and their right to partake in research, as well as their capacity to consent to research. The study of delirium, a disorder that by its very nature has the potential to threaten the patient's

decision-making capacity thereby amplifying the degree of vulnerability, is further beset with unique ethical challenges when proposed in a PC setting.

In this article, we review and discuss some of these challenges in terms of the ethical principles at the heart of deciding whether such individuals should be included in research and practical matters such as consent and capacity that arise when conducting research with individuals experiencing delirium in the PC context. Some solutions regarding the matter of consent also are proposed. Finally, we briefly address the relevant cultural and international dimensions of this subject.

Our review was informed by both a literature search and a multidisciplinary input from the Studies to Understand Delirium in Palliative Care Settings (SUNDIPS) international meeting of delirium researchers and other stakeholders, held in June 2012 in Ottawa, Canada. Presentations and discussions focusing mainly on pragmatic challenges and solutions were recorded at the meeting and later transcribed. We searched MEDLINE (PubMed), Scopus and EMBASE databases using Boolean operators, and relevant key words including ethics, medical ethics, palliative care, terminal illness, and delirium. We also performed a Google and Google Scholar Internet search to identify relevant legislation and guidelines. Additional articles were identified by hand searching of initially retrieved articles. Given that this was a narrative as opposed to a systematic review, no explicit criteria were set for the inclusion or exclusion of articles.

## **Ethical Challenges, Principles, and Practical Issues**

### **Inclusion in Research**

The vulnerability of PC patients and their inclusion in research has been richly debated.<sup>14</sup> de Raeve<sup>20</sup> has assumed a radical position by arguing that any research is not morally justified in PC populations. This position is supported by a combination of Kantian philosophical perspectives and the perceived risk-benefit ratio at an individual level. She argues that the participants or “subjects” act as “means” for the researcher, and this dehumanization is unacceptable. Moreover, participation in research also is unjustified because of the absence of direct benefit for those participating who are likely to die regardless. Her position assumes that good quality care can be extrapolated from other disciplines in medicine and applied without further evaluation to the PC patient population. Although this is a pessimistic but pragmatic view, a variety of counter arguments have been offered<sup>12,13,18</sup> and systematically reviewed.<sup>14</sup> Studies report that people are excluded from delirium research in significant numbers,<sup>22</sup> which contributes to selection bias and limits the generalizability of results.<sup>23</sup> Ethically, the principles of equal moral status and autonomy are pivotal in this discussion.

Akin to the principle of justice, as espoused in the Belmont Report,<sup>24</sup> the principle of equal moral status warrants the fair distribution of benefit (direct and indirect) and burden in research.<sup>25</sup> Vulnerable individuals or groups have an equal right to have their condition represented and addressed in research. An important consideration is whether overprotective attitudes and gatekeeping practices with PC patients can actually undermine the equal moral status of these persons by automatically excluding them from research that may ultimately

bring benefit to them or their group. Furthermore, participatory deprivation may confer further risk for patients in PC, owing to the exposure of these patients to poorly recognized side effects of many medications that consequently have been understudied and, therefore, used in an off-label or unlicensed manner. On the contrary, best practice therapeutic interventions and protocols for delirium may be more beneficial than currently inadequate standard care.

Autonomy is another key principle to consider. It can be viewed along the spectrum between the Kantian categorical or moral imperative of “deciding on the basis of pure reason” and the Millian concept of individual “self-government.”<sup>26</sup> When evaluating the ethical basis of a research proposal, autonomy is most often regarded as the individual’s right to self-determination. According to the Belmont Report,<sup>24</sup> respect for persons incorporates at least two basic ethical issues: that the person should be treated as an autonomous agent and that a person with diminished autonomy is entitled to protection.

Thus, respect for human dignity implies that individuals who participate in research should do so on a voluntary basis, understanding the purpose of the research, its risks, and potential benefits. This is an expression of autonomy. Patients near the end of life may perhaps agree to participate in research, for example, to gain access to more effective symptom relief management.<sup>20,27</sup> Patients who participate in research for these reasons may not be making a choice that is truly voluntary. Voluntariness is an essential requirement of autonomy and informed consent and would arguably be diminished if patients take part in research to have secondary benefits. In addition, studies of the views of patients in PC about participation in research suggest that such patients are usually more willing to participate in research and engage altruistically than almost any other patient group, although they might not obtain direct or tangible benefit.<sup>12,28–32</sup> In a recent review of previous studies, Gysels et al.<sup>33</sup> found that patients often experienced participation as empowering and that disability, physical distress, and cognitive impairment formed barriers to individuals’ participation in research studies. Meanwhile, some studies enable patients to participate by providing assistance during the study to overcome those disabilities. However, it should be noted that patients are less willing to participate in research that has a greater risk or burden for them (e.g., studies that involve invasive procedures or clinical trials with random drug allocation).<sup>34,35</sup> The generalizability of these findings to the specific context of delirium studies in PC is not fully known, although similar attitudes and views have been found in other putatively vulnerable populations such as older adults.<sup>36</sup>

Guidelines and codes of practice are increasingly stating the need for inclusion of “vulnerable” populations in research. For instance, the Belmont Report, a seminal publication concerning ethics and health care research, under one of the three fundamental ethical principles, namely Justice, essentially involves ensuring the fair distribution of costs and benefits to potential research participants.<sup>24</sup> Similarly, the Declaration of Helsinki (as amended in 2008) Article 29 states that “Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population . . .”<sup>37</sup> In Canada, the Tri-Council Policy Statement (TCPS) outlines the principles for the ethical conduct of research with humans accepted by

Canada's three federal research agencies. It has been developed on the principles outlined in broader international documents. In Article 4 of the TCPS, the principle of justice imposes a duty on researchers "not to exclude individuals or groups from participation for reasons that are unrelated to the research." This duty is explicitly stated because groups have previously been inappropriately excluded from participation in research on the basis of attributes such as gender, race, ethnicity, age, and disability.<sup>25</sup> Taken together, these fundamental principles along with research findings indicate that the inclusion of delirious patients from PC settings in research is ethical, moral, and justifiable. Individuals should not automatically be considered vulnerable simply by virtue of being identified within a particular group. Indeed, if patients "whose mental state is both the subject of inquiry and the reason for lack of capacity are excluded from study, then knowledge cannot advance satisfactorily."<sup>38</sup> The paternalistically protective (albeit often well-intentioned) exclusion of such vulnerable populations from research may achieve precisely the opposite to what is intended and consequently a net therapeutic disadvantage; suboptimal care is received because the net clinical effect has not been evaluated in a population with unique pathophysiology.

If it is accepted that research should be conducted in PC patients who have delirium but also that the state of delirium affects the person's ability to engage with the process of consent, the imperative for researchers is *not* to disregard the interests of persons with delirium in PC but instead conduct research by upholding the principles of autonomy and equal moral status to the highest standards.

### **Informed Consent and Capacity**

The authors recognize that the terms consent and assent as obtained through an authorized representative (proxy) are used differently in certain jurisdictions. In this article, the term "consent" is used to indicate formal consent obtained from either the individual or the proxy. Assent is regarded as a behavioral expression of agreement from the participant as they engage in an activity.

Informed consent is an issue within medical ethics that is constantly in evolution and under analysis on both philosophical and empirical grounds. Historically, the incapacitating effects of illness have often been used as a pretext for paternalism in medical practice; the beneficence and nonmaleficence models of medical ethics have long dominated the approach to treatment.<sup>39</sup> Before adopting a more definitive and clearer process, consent was simply assumed if the patient did not clearly object to the treatment offered. It was not necessary for the medical practitioner to inform or explain to the patient the purpose of the treatment, the process, and the risks involved.<sup>40-42</sup> This doctrine has faced ethical and legal challenges worldwide,<sup>43</sup> and a more collaborative process is now required in most settings. The contemporary approach to consent is based on ethical principles that are not always easy to operationalize in PC research, especially when the focus is delirium.

The principles that govern the informed consent process are set out in both the Nuremberg Code<sup>40</sup> and the Declaration of Helsinki.<sup>37</sup> These principles have been incorporated into guidance documents published by medical and ethics bodies worldwide. The first international legislation for the protection of human rights in biomedicine is documented in

the Council of Europe's Convention on Human Rights and Biomedicine; although not yet universally ratified, it provides guidelines for inclusion of participants who lack capacity.<sup>44</sup>

Most ethical guidelines adhere to the principle that for consent to be truly informed, it should fulfill all three of the following conditions: 1) information must be provided about the reason for the proposed matter, its risks, its benefits, and alternative options; 2) the individual in question must understand, retain, and believe the information provided; and 3) they must deliberate, make a decision, and be able to communicate this decision. Certain individuals may not be able to fulfill all conditions and thus may be incapable of providing consent for research.

Capacity is a concept that has different ethical and legal meanings and is defined differently from country to country. Nevertheless, the basic elements required for someone to demonstrate capacity to consent include that 1) the person understands the information that is given; 2) the person can retain the information; and 3) the person can manipulate the information, appreciate the risks-benefits, and arrive at a choice or decision.<sup>45</sup> This must be done freely and without coercion.<sup>46,47</sup>

Three previous studies<sup>38,48,49</sup> have assessed capacity in delirium patients. One study,<sup>38</sup> using a capacity algorithm, found that not all delirious patients lack capacity, but those with capacity had a less severe delirium. The second study, using cognitive tests for capacity to consent for medical and surgical procedures, found that surrogates were used inconsistently, and there was a failure to obtain consent in the presence of delirium. Finally, the third study, using the MacArthur Competence Assessment Tool, found that often those with delirium may have minor impairment in their reasoning ability, but they were able to make meaningful decisions. Thus, not all people with delirium lack capacity; an important early step is to establish whether informed consent can be reliably obtained from the patient at the outset of a study. Assessing capacity is central to this issue, and it is possible to have capacity for one aspect of treatment or research participation but not for another. A central principle is that the process of reasoning—rather than the final decision alone—must be evaluated.<sup>50</sup> Although many tools are available to facilitate systematic and reliable assessment of capacity,<sup>51,52</sup> the process of assessment ultimately requires some degree of subjective evaluation of the patient's understanding and appreciation of the information. Hence, the approach used to obtain informed consent can significantly influence the representation of participants recruited to a study of delirium. Excessively stringent evaluation of capacity may overly exclude patients with delirium from studies,<sup>38,49</sup> thus rendering findings less generalizable.<sup>23,38</sup> It has been advocated, notably in circumstances with a degree of ambiguity, that the degree of certainty required about the judgment of capacity ought to be proportionate to the predicted risks of the proposed activities.<sup>53,54</sup> Procedures exist in routine clinical practice for situations in which an individual requiring urgent medical care is unable to provide consent, and delays to obtain third-party consent could compromise that individual's health. Such guidelines typically pertain only to research that addresses the emergency needs of the individual. Delirium is not usually included in this category because the risk of death is not generally perceived as immediate, and as such, the presence of delirium does not confer exemption from obtaining informed consent, although

delirium by definition is incontrovertibly a sign of acute illness and, therefore, is arguably an emergency.<sup>55</sup>

In ideal circumstances, the patient, despite suffering from a terminal illness with superimposed delirium, would still be capable of providing independent consent for research. This, however, may be the exception rather than the norm. Most jurisdictions have guidelines to follow when circumstances are such that patients lack the capacity to decide for themselves. From an international point of view, the Declaration of Helsinki (as amended in 2008), Article 29, states that "... In such circumstances (where capacity is lacking) the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative."<sup>37</sup> Similarly, provisions are explicitly stated in other guidelines such as those adopted by the three primary granting agencies in Canada (the TCPS, Articles 3.10 and 3.11).<sup>25</sup> In the provisions of the Mental Capacity Act 2005 in England and Wales, the hierarchy of people who should be consulted to obtain assent is suggested as follows: 1) a person involved in the patient's care on an unpaid basis and if this person not available and 2) a person who has no connection with the project, and if this too is impossible and the research must commence as a matter of urgency, then the researcher may take urgent action if "he has the agreement of a registered medical practitioner who is not involved in the organization or conduct of the research project." Only in the very rare circumstances that these people are unavailable may the researcher proceed simply on the basis of ethics committee approval, and this will generally only cover the first 8–10 hours. However, this authorizes the research only for as long as it is "urgent." If the research continues more than a day or so, the researcher must consult as soon as possible one of the people noted previously (i.e., a carer, a person who has no connection with the project, or an independent medical practitioner who is not involved in the research project). Although the majority of patients may willingly give retrospective consent to interventions, as few as 19% of patients actually improve to the point that they can offer consent.<sup>56,57</sup>

Delirious subjects, therefore, may lack the capacity to decide for themselves. In such cases, a suitable proxy must be identified and their consent sought on behalf of the patient, and if and when capacity is regained by the participant, free and informed consent should be sought directly from the individual. Although ethical guidelines are sometimes supported by law, such philosophical ideals may be at odds with legal criteria.<sup>58</sup> As such, researchers must be cognizant of the legislative standards in their own jurisdiction because a research study deemed to be ethical by seeking consent from third parties (proxy) for an individual who lacks capacity may not necessarily be lawful.

It is accepted that a person's capacity may vary as a function of his or her medical state or even as a function of the context or decision that must be made. The notion of capacity as a changing entity is even more prominent in delirium research. Because delirium has a highly fluctuating course that, in many cases, can be associated with prolonged disturbances, there

is a higher likelihood of fluctuation in decision-making capacity. Therefore, there may be a need to evaluate capacity at different time points throughout a study. Clearly, guidelines advocate that, wherever possible, consent should precede research and that consent is an ongoing process whereby participants can withdraw at any time without having to provide a reason. However, what happens when a participant is unable to retain information and cannot recall that he or she had consented? Chenaud et al.<sup>59,60</sup> in a longitudinal study in an intensive care unit reported that 10–12 days after informed consent had been obtained, 20% of competent participants did not recognize that they had been involved in research, and 32% could not recall the clinical trial purpose or its related risks. These studies emphasize that obtaining informed consent is a dynamic process. However, Truog<sup>46</sup> asserts that the consent process relates to a particular point in time and that subsequent inability to recall does not invalidate the original consent. This is further supported by Holt et al.<sup>32</sup> who maintain that the requirement for repeat consent should be avoided and caution that the repeated monitoring of capacity may of itself be impractical and unduly burdensome.

## **Possible Solutions to the Challenge of Consent**

Where consent poses a challenge, research efforts may gravitate toward either the use of study designs or the recruitment of subpopulations that are less challenging. Thus, there is a risk of adopting methodology that is more convenient to execute but produces less generalizable results. In the following, we discuss some possible solutions that have been proposed in the literature to resolve this dilemma. The proposed solutions are not in order of preference but are listed arbitrarily.

### **Increasing the Understanding of the Proposed Research by Potential Participants**

This can be done by shortening the informed consent form, simplifying the language, and avoiding medical terms or jargon.<sup>61–64</sup> Flory and Emanuel,<sup>65</sup> in a systematic review, analyzed interventions reported in the literature to enhance understanding. They found that extended discussions appeared to be the most effective method of improving understanding. However, this method may perhaps not apply to all PC patients as many potential participants already have cognitive impairment,<sup>66,67</sup> and thus, extensive discussion may be more confusing and burdensome to patients (see in the following sections).

### **Less Formal Capacity Assessments**

In a previous observational study in delirium, a formal test of capacity produced a demonstrable selection bias.<sup>38</sup> Lengthy assessments of capacity, especially when studies add no obvious or minimal risk to participants, may prove burdensome, irritating, increase anxiety levels, and ultimately reduce participation rates.<sup>38</sup> In the case of patients who are already delirious and possibly experiencing delusions and hallucinations, lengthy assessments of capacity also may increase the levels of psychopathology. Prior training of researchers and learning techniques of information processing for assessing capacity are valuable.<sup>68</sup>



### **Facilitated Consent**

In a facilitated consent process, a close relative (helper) asks questions on behalf of the patient, but the actual consent is provided by the patient after discussion with the physician. In cases in which the helper disagrees with the decision, the patient has the final decision. This model for obtaining informed consent has been used in stroke units to aid in the clinical decision-making process<sup>69</sup> but to our knowledge has not yet been applied to delirium research. It has been used for patients who clearly lack capacity and for patients of uncertain competence because of cognitive and/or language deficits. This model can enhance patient understanding and autonomy and is less burdensome, and it could be supported, indeed encouraged, by a research ethics board. The key issue remains one of capacity. Ultimately, the participant must make a decision, and the person obtaining consent, therefore, must have formulated an impression as to this individual's capacity, regardless of who else was additionally consulted.

### **Deferred Consent**

Deferred consent is used in emergency research and refers to the consent obtained after the treatment or intervention has commenced and when the patient has regained capacity or a proxy is engaged (deferred proxy).<sup>70,71</sup> Delirium is clearly an acute condition that can be part of a terminal process, especially in PC settings, so this could be considered an appropriate solution. However, problems arise with deferred consent when either the patient dies without being able to give valid consent or a proxy cannot be found to consent to the use of the collected data.<sup>72,73</sup> The current view generally favors using the data if there is no likelihood of any direct harm to the participant, and discarding the data may compromise the study findings.<sup>73,74</sup>

### **Experienced Consent**

This approach to consent was described by Rikkert et al.<sup>75</sup> and has been used in elderly patients. It involves a stepwise approach to consent. Initially, a verbal consent is accepted, and after a week, when the participant has been exposed to or experienced the project, written consent is sought. This method has been shown to increase the willingness of participants to give consent but does not resolve the problem of capacity. A mixture of experienced consent, deferred consent, and informal testing of capacity has been used in a previous study of delirium with minimal risk to participants and with the agreement of the local research ethics committee. An informal test of capacity was used and, in those who lacked capacity but agreed to enter in the study, consent was obtained later when or if capacity returned or a proxy was found. Reanalysis of the data after inclusion and exclusion of the initially incapacitated participants showed significant differences in the findings of the study.<sup>23</sup>

### **Advance Consent**

In this model of obtaining consent, prospective authorization by the participant for his/her future participation may be given while he or she is capable. This has been proposed in dementia and PC research, but there is a lack of consensus as to how best it might be applied.<sup>76-79</sup> Moreover, it also has been used in delirium research in medically hospitalized

AIDS patients.<sup>80</sup> In this study, informed consent was obtained from all subjects admitted to hospital who were not delirious. If they became delirious, subjects then were enrolled in a study that examined the efficacy and side effects of haloperidol, chlorpromazine, and lorazepam for the treatment of the symptoms of delirium. Although this study did not report recruitment rates, it demonstrates the feasibility of using advance consent in delirium research. However, advance consent does not apply when patients are delirious at initial presentation, as in prevalent delirium. Involving community physicians and other health care personnel and improving information sharing with this community may help to increase the accrual rate and case mix of potential subjects using advance consent procedures. Advance consent is being used as one strategy in a currently recruiting double-blind, placebo-controlled, randomized controlled trial of antipsychotics for delirium in hospice/PC.<sup>79</sup> Patients who had an episode of delirium that resolved were asked to consent to participation if it reoccurred.

### **Proxy Consent**

Although not without problems, proxy consent is a core safeguard for vulnerable participants who cannot consent on their own behalf. Nonetheless, investigators still have to obtain the assent of participants to the study<sup>81</sup> even if proxy consent is obtained. Meanwhile, both underuse and overuse of proxies have been demonstrated, overuse referring to situations where participants actually had the capacity to make decisions for themselves.<sup>48</sup> Remarkably, when it is required that the proxy be a legal representative, patient recruitment in research studies may decrease.<sup>32,82,83</sup> The decisions made by an authorized representative should be based on their knowledge of the potential participant, their known values and beliefs, and consideration for the individual's welfare. As they represent the incapable individual, representatives should strive to put forward the decisions they believe that the individuals would have made themselves if capable. This is sometimes a difficult perspective to maintain, and other factors (e.g., the representative's own beliefs or values) may come into play. Therefore, it becomes important to ensure that the representative is not in a position of conflict of interest when making this decision.<sup>25</sup> It is also incumbent on researchers to keep in mind that individuals, even if deemed incapable of making decisions related to their participation in research, can be capable of verbally or behaviorally expressing their assent or dissent from participation. These expressions must be respected, even if proxy consent has been obtained.<sup>81</sup>

Although geographic variation may occur in relation to the early use of a proxy decision maker in PC settings, it has become conventional practice in many inpatient units to establish a designated proxy or substitute decision maker in anticipation of the need arising. Furthermore, the nature of PC involves multidisciplinary team support for the family and the patient; as most proxy decision makers are family members, early engagement of and discussion with such potential proxy decision makers is fundamentally embodied in the PC model.<sup>17</sup> Early discussion regarding anticipated problems along the disease trajectory, such as delirium, may have a preparatory benefit for substitute decision makers when the need arises for them to assume this role, as in deciding whether the patient should participate in delirium research.

All the solutions described previously can potentially increase participation in delirium studies in PC. In addition, the primary research question also is key to determining how to optimally approach the process of consent. Ethically, for research that is not expected to provide direct benefit to the patient, the risk should be minimal. If the risk is higher, advance consent or proxy consent is recommended.<sup>84</sup> Ethics committees can assist researchers in identifying the degree of risk and in the choice of optimal consenting procedures in any particular situation. Similarly, consensus guidelines and criteria that come from experts and stakeholders are of valuable assistance.<sup>33,85</sup> For the delirium researcher in PC and other settings, we have included a list of potentially useful accessible web-based resources in Table 1.

## **Acknowledging Cultural and International Dimensions**

Aside from international legislative differences, culture may dictate different approaches to obtaining informed consent.<sup>86</sup> Some countries have legislation that is specific to an incapacitated participant's involvement in research, whereas in other countries, the proxy provision is more broadly defined. In a review of legislation of countries inside the European Community,<sup>82</sup> it was reported that in most countries, a relative is allowed to take on the role of proxy, but in Germany and Italy, the system of proxy is determined through the courts; in the case of Italy, this may contribute to low rates of research participation. The U.S. regulations require that research conducted by U.S. researchers or U.S. funds outside the U.S. must be reviewed by a U.S. institutional review board and by a local, regional, or national committee in the country where the research is carried out. Although international legislative differences can affect any area of research, they present particular challenges to delirium studies in PC. Delirious subjects often lack capacity, and different regulations can affect how to obtain informed consent or to involve a proxy, and in turn, this may lead to considerable variation in the accrual of subjects. Thus, results may not be comparable between different countries, and this diminishes the ability to undertake meta-analyses. Two recently formed delirium bodies, the European Delirium Association and the American Delirium Society, seek to promote collaboration in delirium research (including PC settings) among different institutions across international boundaries. Currently, compliance with the different informed consent practices between countries will inevitably complicate their efforts.

In summary, a range of challenges can arise in delirium studies in PC. Arguably, the most important is the perceived vulnerability of potential participants and the threat that delirium poses to informed consent, which must be balanced against the ethical imperative to not exclude delirious patients from studies or the management of delirium and to conduct ethically sound research that ultimately produces valid study results that can benefit all patients with this syndrome. There are various regulatory policies that can assist this process.

In international multicenter research, similar ethical standards should apply to all the contributing centers to avoid producing biased data that lack generalizability. Although multicenter ethical committees exist in some countries and also, in some cases, approval of one ethical committee does not need a second approval, international research can be

impeded by different legal requirements. Recently, the Canadian Working Committee of the Interagency Advisory Panel on Research Ethics<sup>87</sup> suggested the need for researchers to highlight the key elements that cannot be changed in a multicenter study “without invalidating the pooling of data from the participating institutions.”

## Conclusions

The ethical conduct of research in PC patients with delirium is a complex issue. It is paramount to protect participants from any harm or risk, conduct ethical and lawful research according to ethical guidelines, and produce ethical and meaningful results. This is more difficult to achieve in research on delirium and especially in PC settings, in which many patients have reduced or fluctuating capacity, and consequently, their ability to give valid informed consent is compromised. Modifications to the informed consent process are required in research with delirious patients to decrease the likelihood of ultimately obtaining invalid and thus unethical results through the exclusion of patients who lack capacity or a proxy. The nature of these modifications is dependent on the degree of risk that the research poses to the patient. When greater than minimal risk is posed by research, additional protection of the potential participants is required. Although much weight is given to the principle of autonomy and the expectation that patients can weigh risk vs. benefit, researchers have a major responsibility to evaluate risk accurately and clearly communicate it. Although robust procedures around the process of obtaining informed consent are crucial, perhaps the most important safeguard for participants is researcher behavior, which must be meticulous, responsible, ethical, and caring.

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**Table 1**  
**Web-based Ethical Resources to Assist With Delirium Research in Palliative Care Settings**

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Internationally recognized codes, declarations, guidelines, reports, and other texts

<http://www.hhs.gov/ohrp/policy/belmont.html>: Belmont Report

<http://www.hhs.gov/ohrp/archive/nurcode.html>: Nuremberg Code

<http://www.wma.net/en/30publications/10policies/b3/index.html>: World Medical Association Declaration of Helsinki—ethical principles for medical research involving human subjects

<http://www.ich.org/products/guidelines.html>: International guidelines on quality, efficacy, safety and multidisciplinary involvement mainly in relation to clinical trials

[http://www.cioms.ch/publications/layout\\_guide2002.pdf](http://www.cioms.ch/publications/layout_guide2002.pdf): International ethical guidelines for biomedical research involving human subjects. Produced by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO)

<http://www.hhs.gov/ohrp/international/intlcompilation/intlcompilation.html>: An international compilation of human research standards (2012 edition). This is a catalog of laws, regulations, and guidelines that govern human subjects' research in more than 100 countries

<http://unesdoc.unesco.org/images/0018/001895/189591e.pdf>: Report of the International Bioethics Committee on the principle of respect for human vulnerability and personal integrity

[http://ec.europa.eu/research/science-society/document\\_library/pdf\\_06/textbook-on-ethics-report\\_en.pdf](http://ec.europa.eu/research/science-society/document_library/pdf_06/textbook-on-ethics-report_en.pdf): Produced by the European Commission (2010). Chapter 3 addresses vulnerable and noncompetent subjects

National regulatory codes, guidelines, and reports

<http://bioethics.georgetown.edu/nbac/human/oversumm.html>: Ethical and policy issues in research involving human participants. US National Bioethics Advisory Commission (2001)

<http://bioethics.od.nih.gov/specific.html>: A compilation of links, including research ethics

<http://www.hc-sc.gc.ca/sr-sr/pubs/advice-avis/reb-cer/index-eng.php>: Health Canada Research Ethics Board ethics review of research involving humans

[http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS\\_2\\_FINAL\\_Web.pdf](http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf): Tri-Council Policy statement (2nd edition) on the ethical conduct for research involving humans

[http://www.gmc-uk.org/Good\\_practice\\_in\\_research\\_and\\_consent.pdf\\_52588149.pdf](http://www.gmc-uk.org/Good_practice_in_research_and_consent.pdf_52588149.pdf): Good practice in research and consent to research, published by the UK General Medical Council (updated March 2013)

<http://www.lanets.ac.uk/researchethics/4-1-intro.html>: A review of the many ethical aspects of research in vulnerable people and groups

[http://www.bps.org.uk/sites/default/files/documents/code\\_of\\_human\\_research\\_ethics.pdf](http://www.bps.org.uk/sites/default/files/documents/code_of_human_research_ethics.pdf): Code of human research ethics published by the British Psychological Society

<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002415>: Good research practice: principles and guidelines. UK Medical Research Council (2012)

[http://www.rcn.org.uk/\\_data/assets/pdf\\_file/0007/388591/003138.pdf](http://www.rcn.org.uk/_data/assets/pdf_file/0007/388591/003138.pdf): Research ethics guidance for nurses. UK Royal College of Nursing (2009)

[http://www.nhmrc.gov.au/files\\_nhmrc/publications/attachments/e72.pdf](http://www.nhmrc.gov.au/files_nhmrc/publications/attachments/e72.pdf): National statement on ethical conduct in human research published by the National Health and Medical Research Council of Australia and the Australian Research Council (2007)

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