



Nontherapeutic research with imminently dying and recently deceased study populations: addressing practical and ethical challenges

Nicholas B. Murphy, PhD · Charles Weijer, MD, PhD · Saptharishi Lalgudi Ganesan, MBBS, MD, DM · Sonny Dhanani, MD · Teneille Gofton, MD, MSc · Marat Slessarev, MD, PhD

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Because of a paucity of high-quality evidence, the updated Canadian Death Determination Guidelines featured in this month's Special Issue of the *Journal* include several recommendations based on low to moderate certainty of evidence or expert opinion.¹ In generating its recommendations, the guideline development group identified numerous knowledge gaps.² Many of these suggest research questions answerable only through nontherapeutic studies involving imminently dying or recently deceased adult and pediatric patients in controlled intensive care unit environments.

While advancing the science of death determination is in the interest of patients, families, health care providers, health care institutions, and society, there are currently no dedicated Canadian ethical guidelines addressing the substantial

challenges of research with imminently dying or recently deceased patients (Table 1). Indeed, to our knowledge, nor are there authoritative international guidelines for research with these populations, perhaps owing to the novelty of these areas of research. Uncertainty regarding the ethics of research with the imminently dying and recently deceased has hindered research into important scientific questions. Accordingly, below we explore the ethical and practical challenges of research with these populations, highlight existing guidance where available, and point to areas where further guidance is needed.

Ethical lacunae

The principles of respect for persons, justice, and beneficence guide all research with human participants.³ These principles ground moral rules to which researchers must adhere (Table 2).

N. B. Murphy, PhD (✉)
Department of Medicine, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada

Department of Philosophy, Western University, 1151 Richmond St, London, ON N6A 3K7, Canada

C. Weijer, MD, PhD
Department of Medicine, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada

Department of Philosophy, Western University, 1151 Richmond St, London, ON N6A 3K7, Canada

Department of Epidemiology and Biostatistics, Western University, London, ON, Canada

S. Lalgudi Ganesan, MBBS, MD, DM
Department of Paediatrics, Western University, London, ON, Canada

S. Dhanani, MD
Pediatric Critical Care, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada

T. Gofton, MD, MSc
Department of Clinical Neurological Sciences, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

M. Slessarev, MD, PhD
Department of Medicine, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada

Trillium Gift of Life Network, London, ON, Canada

Table 1 Ethical and practical challenges of research with imminently dying and recently deceased study populations

	Imminently dying patients	Pediatric patients	Recently deceased patients
Ethical and practical challenges	Participant vulnerability; exacerbated in the pediatric setting		Unclear ethical status
	Surrogate informed consent based on prior expressed wishes and values	Surrogate informed consent based on child's best interest; surrogates may be reluctant to include the patient in nontherapeutic studies	Surrogate authorization based on prior expressed wishes and values
	Limited time window for providing informed consent while dealing with emotional and psychological burden or grief		
	Potential resistance from RECs or attending staff due to the novelty of the research	Well-intended protectionism from RECs and attending staff due to the vulnerability of the patient	Uncertainty regarding acceptability among RECs and health care providers
	Risk minimization: nontherapeutic study interventions must be "minimal risk"		Minimization of invasiveness is advisable
	Potential for interference with routine care		Potential for interference with death rituals and grief processes
	Potential for therapeutic misconception		Families may have difficulty accepting DNC when the deceased is maintained with somatic support
	Family distress and anxiety; particularly acute in the pediatric setting		
	Mitigating research impacts on families and attending staff		

DNC = determination of death by neurologic criteria; REC = research ethics committee

Nevertheless, there is no consensus on the application of these moral rules to studies involving imminently dying or recently deceased patients. Nontherapeutic studies do not benefit participants medically, and uncertainties concerning the permissible limits of such research and the protection owed to participants therefore persist.⁴ Moreover, the ethical status of recently deceased patients has been debated, with international variation regarding whether they ought to be afforded research participant protection.⁴

Additionally, recent scholarship has illuminated how nonparticipant "bystanders" can be impacted by research activities.⁵ Studies involving imminently dying or recently deceased patients will impact families facing emotional burdens and health care providers concerned that patient participation will negatively affect patient care or family grief.⁶ Measures to support families and health care providers are therefore warranted in research of this kind.^{7,8} Just what these supports should be, however, has not been determined.

Research with imminently dying patients

Research enrolling patients expected to die within hours or minutes is critical to improving practices for death determination in the interest of future patients. For example, a study to document cerebral blood flow and cerebral electrical activity in relation to arterial pulse pressure following withdrawal of life-sustaining measures is needed to determine when cessation of brain function occurs during the dying process.²

While the prospect of research with imminently dying patients provokes unease because of participant vulnerability, there is no compelling reason why this population should be excluded from research, provided they are afforded adequate protection. Indeed, exclusion would unjustly deny patients and families the opportunity to altruistically contribute to science and deprive future patients of the benefits of scientific knowledge.⁷

Table 2 Ethical principles and normative entailments

Principle	Definition	Normative guidelines
Justice	The potential benefits, risks, and burdens of research participation must be distributed equitably	Fair procedures must be in place for the selection of research participants Vulnerable research participants are entitled to additional protection
Respect for persons	Candidates for research participation must be treated as autonomous agents, and those with diminished autonomy are entitled to protection	Informed consent must be obtained from prospective research participants When prospective participant autonomy is lacking, informed consent must be obtained from an authorized surrogate decision-maker Protect the confidentiality of private information
Beneficence	Research participants must be protected from harm and their welfare must be promoted	Therapeutic procedures must satisfy equipoise Any risks of nontherapeutic procedures must be minimized consistent with sound scientific design, and reasonable in relation to the knowledge to be gained

Table adapted from Murphy *et al.*⁷

Ethical issues

Nontherapeutic studies like that described above—which will involve physiologic monitoring of dying patients purely for research purposes—test the limits of existing ethical guidance.⁷ While research involving the imminently dying has been successfully undertaken,⁹ it poses significant ethical challenges.⁶ These include participant vulnerability, difficulties obtaining informed consent, the possibility that research could interfere with routine care and the dying process, potential effects on families, and the reservations of health care providers and research ethics committees.^{6,7,10} These ethical challenges—and the practical difficulties attending them—are principal obstacles to achieving important scientific ends.

Available guidance

Imminently dying patients generally lack decision-making capacity and are therefore vulnerable. Vulnerable participants are entitled to protections beyond what is typical for competent participants.¹¹ Below, we outline these protections and their implications. Table 3 describes strategies for ensuring these requirements are met (Table 3).

The ethical principle of justice demands that answering a study's research question necessitates the inclusion of the vulnerable population. This will usually require that the study aims to produce knowledge of benefit to future members of the study population—in this case, imminently dying patients.

As imminently dying patients are typically incapable of consenting to study participation, the ethical principle of

respect for persons requires that consent be obtained from surrogate decision-makers. Obtaining surrogate consent to research in the context of an intensive care unit is challenging, particularly because of surrogate distress, confusion, or decisional burden.⁷ Nonetheless, it is critical to ensuring that research participation aligns with the patient's prior expressed wishes or values.^{7,10}

The ethical principle of beneficence prescribes that the risks of research participation stand in reasonable relation to knowledge benefits for imminently dying patients. First, risks of nontherapeutic procedures must be minimized consistent with sound scientific design. This involves prioritizing patient care over research goals, minimizing the risks of nontherapeutic interventions, and avoiding alterations to routine care as far as possible.⁷ Second, the risks of nontherapeutic study interventions must not exceed a “minimal risk” threshold, defined in Canada as the risks of daily life for the study population.¹¹ While this may appear to permit highly risky interventions given the risks facing imminently dying patients, in practice “minimal risk” is considered synonymous with the risks involved in routine clinical care.¹²

Finally, while not mandated by research ethics guidelines, studies with the imminently dying ought to consider “bystanders” affected by the research.⁵ Strategies for minimizing impacts on participants' families and health care providers should be included in study protocols.⁷

Although it does not amount to authoritative guidance, a recent article coauthored by several of us outlines the major ethical challenges of research with the imminently dying and further identifies strategies for their resolution.⁷ The user-friendly ethical checklist we advance in this paper

Table 3 Additional ethical requirements for nontherapeutic research with imminently dying patients and strategies for ensuring these requirements are met

Requirement	Suggested strategies
Study hypothesis must require participation of the vulnerable population	<p>Ensure the study question could not be answered using a population less vulnerable than the imminently dying</p> <p>Ensure the study stands to benefit the patient population in future</p> <p>Ensure scientific rigor (e.g., sample size must be sufficient to answer the study question)</p>
Study must have a favorable risk-benefit ratio	<p>Ensure risks are reasonable in relation to the knowledge benefits</p> <p>Ensure the study has social value insofar as it will benefit the study population in future</p>
Study interventions must be minimal risk	<p>Ensure nontherapeutic interventions pose risks no higher than those typically experienced by the study population as part of their routine care (e.g., blood draws, imaging, etc.)</p>
Risks and intrusiveness must be minimized and consistent with sound scientific design	<p>Ensure adequate protection is in place for storage of data and biological samples</p> <p>Follow standard of care so far as is possible, and mitigate interference with routine care</p> <p>Minimize obtrusiveness of study personnel and equipment</p> <p>Make use of clinically indicated monitoring for data collection where feasible</p> <p>Combine nontherapeutic imaging with indicated imaging where feasible</p> <p>Account for risks of patient transport (e.g., for imaging)</p> <p>Account for risks and inconveniences associated with any delays to withdrawal of life-sustaining measures</p> <p>Include plans for dealing with participant distress in study protocol</p>
Surrogate informed research consent is required	<p>Consult attending staff regarding surrogate's emotional and psychological state before approaching for consent to ensure distressed family members are not overburdened</p> <p>Ensure surrogates understand their role as surrogate decision-makers</p> <p>Ensure surrogates are aware that refusal will not impact patient care</p> <p>Ensure surrogates are aware the withdrawal from the study will not impact patient care</p> <p>Mitigate risk of therapeutic misconception by having a third party who is not part of the care team make the approach when feasible</p> <p>Ensure surrogates have adequate time to consider the patient's participation and ask questions</p> <p>Repeat information at intervals if necessary</p> <p>Discuss participation in a private setting where possible</p> <p>Consider the use of multimedia educational instruments for detailing study rationale and procedures</p> <p>Ensure consent discussion and documents are in lay terms</p>
Impacts on families and surrogates must be minimized and opportunities for benefits must be maximized	<p>Include patient and family partners in protocol design to ensure responsiveness to family perspectives</p> <p>Prepare families for study processes using visual aids and discussion</p> <p>Minimize intrusiveness of study procedures and personnel</p> <p>Ensure supports are available (e.g., spiritual care providers, social workers)</p> <p>Promote meaning-making by communicating the social value of the study</p> <p>Plan to provide summary findings to families</p>
Healthcare workers must be supported	<p>Include health care providers who care for patients at the end of life in protocol development</p> <p>Offer workshops on study processes and aims before participant enrollment</p> <p>Provide informational pamphlets/printouts and ensure health care providers are aware of the study before commencing enrollment</p> <p>Acknowledge concerns and incorporate suggestions for mitigating interference with routine care</p> <p>Communicate the social value of the study</p> <p>Discuss the study regularly with health care providers to assess perspectives and address concerns</p>

may prove useful to researchers when designing study protocols.

Roadmap

While the above requirements for research with the imminently dying are instructive, we caution that they may fall short of what is needed to support stakeholders. Dedicated guidelines for research with this population are therefore urgently needed. Importantly, guideline development must involve those stakeholders who will be most impacted: patients, families, and health care providers who care for patients at the end of life.

Pediatric considerations

Due to a dearth of high-quality research, the updated Canadian Death Determination Guidelines include several pediatric-specific recommendations based on low certainty of evidence.¹ Answering important questions regarding the physiology of the dying process in pediatric populations will require studies involving imminently dying children. For example, a study to document the incidence of autoresuscitation following circulatory arrest is needed to inform the appropriate “hands-off” period prior to organ recovery in pediatric donation after the determination of death by circulatory criteria.²

Ethical issues

The practical and ethical challenges to research involving imminently dying children cannot be overstated.^{13–16} Foremost among these is a “well-intended protectionism” by health care providers and research ethics committees.¹⁴ Critically ill children are vulnerable. They are typically unable to voice assent or dissent, and younger children have yet to develop the capacities required to express an autonomous interest in research participation. Parents and guardians are distraught, profoundly concerned for the welfare of the child, and strive to be “the good parent” by focusing on the child’s quality of life.¹⁷ Hence, there is an understandable reluctance to impose potential research burdens on the patient.^{13–15}

Moreover, parents of critically ill children frequently seek to make decisions that the rest of the family accepts,¹⁷ complicating surrogate consent to research. Further, parents are prone to emotionally driven decision-making,¹⁸ and may therefore be susceptible to therapeutic misconception—a mistaken belief that research interventions are administered with therapeutic warrant.¹⁹ Finally, given the uniquely tragic circumstances attending

a child’s critical illness or injury, parents are themselves vulnerable, meaning that impacts on research bystanders could be more substantial than in research with adult populations.

Available guidance

Researchers, attending staff, and research ethics committees should not assume that research opportunities will be unwelcome to the patient-family unit. Indeed, families may benefit from meaning-making by contributing to the advancement of science.^{7,13,14} While it is important to acknowledge stakeholder reservations regarding nontherapeutic research with critically ill children, research with this population can also be ethically justifiable provided protocols include adequate protection for patients and families.¹⁶ Nonetheless, further discussion and debate are warranted.

Roadmap

The challenges to nontherapeutic research with critically ill children are immense, and it is advisable to proceed with caution while awaiting dedicated ethical guidance. Guideline development should follow consultation with health care providers, youth advisors, and families of children who have suffered critical illness or death to determine under what circumstances—if any—nontherapeutic research with critically ill children is perceived to be acceptable.

Research with recently deceased patients

Filling some knowledge gaps identified by the guideline development group will require studies involving recently deceased patients.² For example, most recommendations regarding ancillary tests were based on studies that did not include children; the validity of these tests for neonates and pediatric patients is unknown.² Studies involving nonindicated ancillary tests following clinical determination of death by neurologic criteria may therefore be undertaken to assess the sensitivity of ancillary tests in children.

Ethical issues

Dedicated Canadian guidelines for research with the deceased are lacking. While Canadian research ethics guidelines suggest that deceased patients involved in research are research participants and owed the full range of standard protection,¹¹ there are compelling reasons to

dispute this. The dead are not moral persons. They are neither vulnerable nor subject to welfare harms. It is therefore unclear what would underpin requirements such as risk minimization. Indeed, the contention that deceased patients are research participants is out of step with influential guidelines from jurisdictions that stipulate only living persons meet the criteria for participant status.⁴

Nevertheless, there are independent reasons to afford deceased patients some protection.^{8,20} For example, doing so reflects the dignity accorded human bodies, shows respect for the deceased and their family, and maintains public trust in research.⁸ Such reasoning suggests that one credible rationale supporting protection for the deceased is to mitigate effects on the living.⁴

Available guidance

To our knowledge, there are no authoritative international guidelines for whole-body research with recently deceased study populations. That said, the high-level recommendations issued by the North American Consensus Panel on Research with the Recently Dead are likely to be useful to Canadian researchers.²⁰ Importantly, while the panel rightly emphasizes that “cadavers should be treated in a manner that is consistent with respect for the value and dignity of the once-living person,” it also acknowledges that research procedures “need not be identical to those used with the living.”²⁰ This observation highlights the uniqueness of research in this domain and suggests that what constitutes an ethically permissible intervention may be determined by a calculus different than that used for living participants.

In the absence of dedicated Canadian guidelines for research with the recently deceased, researchers should adhere to stipulations in Canada’s regulatory framework for the time being by affording the deceased participant protections.¹¹ Involving family partners and health care providers in study design will help to ensure that research procedures are sensitive to the needs of recently bereaved families.²

Roadmap

The ethics of research with the recently deceased currently lack a sound foundation, meaning that—here again—dedicated Canadian guidelines are needed. Further thinking is required to establish what protection the deceased and their families are owed in the context of postmortem research. Sensible measures may include scientific oversight, confidentiality protection, clear protocols for storage of biological materials (where appropriate), an

approved plan for final disposition of remains, and surrogate authorization to ensure that the use of the body is compatible with the deceased’s values.^{8,20} Other protection, such as research ethics committee oversight and risk minimization, should be explored, but it is currently unclear what would justify its applicability to this setting.

Conclusion

Strengthening the evidence base supporting guidelines for death determination in Canada requires studies that test existing research ethics frameworks. Although research with imminently dying and recently deceased populations is ethically justifiable, further discussion and debate are warranted. Indeed, given the importance of public trust for the research enterprise, it is advisable to approach research with the imminently dying and recently deceased cautiously. While some relevant guidance is available,^{7,8,10,20} dedicated Canadian guidelines for research with these populations are urgently needed. In the interim, we encourage researchers undertaking studies with these populations to reflect on the above considerations when designing study protocols, and to consult the references cited in this article for further nuance.

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