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Please cite this as: Agar, M., Ko, D.N., Sheehan, C., Chapman, M. and Currow, D.C., 2013. Informed consent in palliative care clinical trials: challenging but possible. *Journal of Palliative Medicine*, 16(5), 485-491.

doi:10.1089/jpm.2012.0422

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Informed Consent in Palliative Care Clinical Trials: Challenging but Possible

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Abstract

Obtaining informed consent is a key protection that should be afforded universally to people using health services and the basis around which any participation in clinical trials is built.

Randomized controlled effectiveness studies are necessary to answer key questions in hospice and palliative care, in order to help systematically improve the quality of care. In order to be properly generalizable, such trials need to have broad inclusion criteria to reflect the population most likely to be affected by the condition. The inclusion of patients who are seriously ill, and therefore potentially vulnerable, requires careful exploration of ethical and legal principles that underpin informed consent.

Specific challenges in obtaining informed consent for randomised clinical trials (RCTs) in clinically unstable populations such as hospice and palliative care include higher rates of people with impaired cognitive capacity as well as interventional studies in clinical situations which may present as a sudden change in condition. None of these challenges is unique to hospice and palliative care research, but the combination and frequency with which they are encountered require systematic and considered solutions.

This article outlines five different ethically valid consent approaches and discusses their applicability to hospice and palliative care research trials. These include: consent by the patient (at the time of enrolment, in advance of the study, or delayed until after the study has commenced); a proxy (or legally authorised representative); or a consent waiver. Increased use of the less traditional modes of informed consent may lead to greater participation rates in hospice and palliative care trials, thereby improving the evidence base more rapidly in part by better reflecting the population served and hence improving generalizability.

Introduction

OBTAINING INFORMED CONSENT IS a key protection that should be afforded universally to people using health services and the basis around which any participation in clinical trials is built. Randomized controlled effectiveness studies are necessary to answer key questions in hospice and palliative care, in order to help systematically improve the quality of care. In order to be properly generalizable, such trials need to have broad inclusion criteria to reflect the population most likely to be affected by the condition. The inclusion of patients who are seriously ill, and therefore potentially vulnerable, requires careful exploration of ethical and legal principles that underpin informed consent. Challenges in obtaining informed consent for randomized clinical trials (RCTs) in clinically unstable popula-

tions such as hospice and palliative care include higher rates of people with impaired cognitive capacity as well as interventional studies in clinical conditions that arise suddenly. Neither of these challenges is unique to hospice and palliative care research, but the combination and frequency with which they are encountered require systematic and considered solutions. This paper outlines five different ethically valid consent mechanisms and discusses their applicability to hospice and palliative care research trials. These include consent by the patient (at the time of enrollment, in advance of the study, or delayed until after the study has commenced); a proxy (or legally authorized representative); or a consent waiver. Increased use of less-traditional modes of informed consent, such as proxy or early consent, may lead to greater participation rates in hospice and palliative care trials, thereby

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Accepted December 12, 2012.

improving the evidence base more rapidly, in part by better reflecting the population served and hence improving generalizability.

Research in hospice and palliative care is essential to inform improvements in the quality of the care offered to those with serious and life-limiting illnesses. People in palliative care and hospice (inpatient, ambulatory, and community) services are keen to participate in clinical research at rates far higher than other clinical disciplines¹ as part of a legacy, to help to make sense of their current condition, and to improve care for people in the future.² Palliative care researchers must be especially vigilant not to exploit such good will.¹

Ethical and legal frameworks must be incorporated into trial design and conduct. Even with these in place, sound clinical research is required to enhance scientific knowledge, and must be methodologically rigorous, ensure fair subject selection, have a favorable risk-benefit ratio, be independently reviewed, and guarantee respect for the enrolled subjects.³

Ethical Frameworks of Informed Consent

The key goal of clinical research is to improve the quality of medical care by developing generalizable knowledge gained from studying a small sample of subjects. In the pursuit of this knowledge, research subjects are inevitably exposed to some risks they otherwise would not encounter. It is therefore important that any potential harm is minimized and any findings used as widely as possible.

Informed consent is one of the most important ways persons are afforded protection; such consent is underpinned by respect for participants' autonomy. Cases of unethical research performed on human subjects without their knowledge or consent have been well documented.^{4,5} Informed consent allows the subject with decision making capacity to weigh up the potential personal risks and benefits in the context of the purpose of the research to determine whether involvement is acceptable and personally meaningful.

The International Conference on Harmonisation Good Clinical Practice (ICH GCP)⁶ provides consensus guidelines on the design, conduct, safety, and reporting of clinical trials. The guidelines outline the responsibilities and expectations of all participants involved in the conduct of a clinical trial. The process of obtaining informed consent as outlined in ICH GCP guidelines ensures (1) the potential participant gets objective information from the investigator or trial staff without coercion or undue influence to participate; (2) the investigator or trial staff have appropriate credentials and skills relevant to the potential participant and his or her concerns; (3) information delivered is in an appropriate setting and in an unhurried manner; and (4) ample opportunity for the potential participant to ask questions.

Though not mandated by ICH GCP, the participant may have a family member or support person present who can ask questions or take information away to discuss with a family member or primary care doctor before deciding whether or not to participate.^{7,8}

Challenges in Palliative Care Research

There are no consent issues unique to palliative care and not found in other clinical research settings, for example in

emergency medicine or geriatric medicine. However, there are scenarios that occur more frequently than in other clinical disciplines or are otherwise amplified by clinical research in the hospice and palliative care setting. Obtaining informed consent for participation in hospice and palliative care clinical trials is an ongoing challenge faced by researchers.^{9,10} The reasons for this are complex and multifaceted and influenced by the nature of the research itself as well as by patient/participant, provider, and systems issues.

In terms of research topics, palliative care research may focus on specific times in a person's illness when consent is unable to be obtained, e.g., investigations into terminal respiratory secretions or the development of delirium, or on unpredictable events, e.g., first presentation of a bowel obstruction.⁹ There are sensitivities around introducing a study that is exploring a symptom or clinical condition in people with a life-limiting illness if the participant may not have full knowledge of his or her condition or prognosis, does not acknowledge his or her condition,⁶ or does not currently have the condition being studied but is quite likely to develop it in the foreseeable future.

At the patient/participant level, challenges in providing informed consent may include, but are not limited to (1) impaired or fluctuating decision making capacity (in the hospice and palliative setting this can occur due to the illness itself, e.g., brain tumors, delirium, psychoactive medications); (2) decreased levels of consciousness in the terminal phase (last hours or days of life); or (3) a sense of being in an increasingly dependent relationship with health professionals in general because of progressive frailty.

In more advanced disease, participants fatigue easily and can find it difficult to concentrate for long periods on processes like consent, especially if the information is new and complex.⁹ This population is predominantly comprised of older adults whose mentation and physical well-being may be deteriorating.

At the provider level, clinicians may facilitate engagement or create barriers. Ways in which clinicians become gatekeepers include where the clinician makes the decision not to inform the patient/participant that a trial is available or fails to provide a patient with objective information regarding a study in an effort to "protect" him or her. This creates a situation where the patient/participant who still is autonomous and has decision making capacity is unable to make an informed choice for his or herself.^{11,12}

Informed Consent in Palliative Care Research

There are different mechanisms for informed consent that can potentially be applied to palliative care research to ensure nonexploitation and protection of subjects. In this paper, five mechanisms of consent are discussed. The paper is limited to studies of interventions that aim to impact symptom control and quality of life for someone utilizing a palliative care service. The paper does not consider studies of medications unrelated to a person's condition, such as phase I studies of a new medication's first use in patients for a condition they don't have. Such studies require more detailed data, given the greater possibility of harm, where the person participates simply because he or she is dying but does not have the index condition.¹³

The five consent mechanisms under consideration involve the participant (1) at the time of enrollment, (2) in advance of having the index condition or commencing the study, or (3)

deferred to a time after the study has commenced; another person, (4) 'person responsible' or 'proxy;' or no consent, (5) waived consent.

Participant's informed consent at the time of enrollment

This mechanism should be utilized wherever possible and can be achieved in the majority of palliative care clinical studies immediately prior to the time of enrolment in the study. A key principle is that complexity and presentation of information has to be in the context of this person's ability to make decisions (competence), with a view to ensuring that his or her key concerns are addressed in providing information. This is largely independent of age but not of education.¹⁴ The ability to make informed decisions about participating in clinical research is generally deemed to be present if an individual possesses all of these characteristics:

- understanding of the issues involved in the decision including the research protocol and the risks and benefits of participation or nonparticipation
- rational ability to manipulate this information
- appreciation of the information in the context of patient's situation
- demonstrable consistency in this process
- evidence of a voluntary and uncoerced choice¹⁵

A number of tools have been validated in an attempt to refine and standardize the processes of determining a patient's capacity to consent to participate in research. An example is the MacArthur Competence Assessment Tool.¹⁶ However, recent reviews of such instruments have found that, while they can aid clinicians to make decisions regarding capacity, the results are variable and in the end, capacity decisions are largely a matter of clinical judgment. Unfortunately, determining decisional capabilities in many mildly cognitively impaired people remains challenging and is approached with a high degree of variability.¹⁷⁻²⁰

During the consent process, the researcher is continually determining the potential participant's understanding of the information and his or her capacity then to provide fully informed consent. Consideration should be given to allowing the consent process to occur over several short sessions rather than one longer session. Additionally, as the life-limiting illnesses progress and a potential participant's performance status declines, the researcher should regularly assess the person's willingness to continue to participate in the research throughout the entire research project, and not just prior to the commencement of the study.

In any clinical setting, participants may be eager to please their clinicians, creating a milieu where exploitation could potentially occur, despite the fact that the person obtaining consent is a third party. In palliative care there may be a perception that a clinical trial brings hope for improved health, which may be an unrealistic expectation. Despite these difficulties, a participant's own informed consent remains the gold standard.

Participant's informed consent in advance of having the index condition

Advanced consent here is defined as the consent of subjects prior to a predictable or potential loss of capacity²¹ or where

there may be a need to initiate therapy rapidly without the ability to engage meaningfully in a conversation about the trial. Informed consent takes place before the onset of either cognitive decline or the emergence of the condition of interest, yet close enough to enrollment to allow information that is relevant and salient to the condition of interest to be discussed.²¹ Advanced consent can facilitate research in palliative care without the reliance on surrogate or proxy decision making at the time an emotionally distressing event has occurred and has been used in studies of critical care management after planned surgery whereby patients are consented prior to induction of anaesthesia.² Advanced consent for autopsy has also been used, especially to advance research into dementia, which aids relatives in knowing the prior wishes of the deceased.^{3,24}

After advanced consent has been obtained, asking the patient/participant to nominate a person to act as his or her proxy during the study period further enhances processes to safeguard the best interests of the participant. The proxy can continue to act on the patient/participant's behalf if testamentary capacity is lost between consent and initiating the study or during the course of the study. Some researchers have had this person also sign a consent form at the same time as the potential participant and confirm the participant's advanced consent at the time of trial participation if the patient/participant is unable to. Indeed, given that capacity may change during a study, it has been suggested that the relevant proxy be involved in all palliative care research.²⁵

Advanced consent may also be used where a person is at high risk of a condition and there is the need to begin therapy without delay. In a study of delirium in hospitalized people with AIDS, advanced consent was used to recruit subjects who were not delirious but allowed participation if they subsequently developed delirium.²⁶ People who have had an episode of delirium are at high risk of another episode and could provide advanced consent. Advanced consent has also been used in studies of terminal respiratory secretions when the person is most likely unconscious.^{27,28} Such an approach necessitated informed consent to be obtained from a relatively large number of people compared with those eventually randomized.

Malignant bowel obstruction. It is possible to identify a high-risk group (patients with previous subacute bowel obstruction or patients with widespread peritoneal cancer) who could potentially participate in a phase III study of pharmacological management if a bowel obstruction occurred.²⁹ Given that the majority of patients/participants in this setting are likely to present to the emergency department, at which time discussion about potential study participation may be difficult, this is a group appropriate for considering advanced consent. Only on presentation would the person be randomized to a particular intervention arm. This allows rapid initiation of therapy in the trial protocol. In cases of bowel obstruction the participant will likely be able to confirm consent. In a recently completed study of such patients, 112 people were randomized, of whom 21 were among the 63 people who had given advanced consent.

Concerns have been raised regarding a patient's ability to truly consider the implications of research when he or she does not have a firsthand understanding of the condition. This is an overwhelming issue, and one way to resolve it is limiting consent to people who have had the index condition resolve

TABLE 1. MECHANISMS OF INFORMED CONSENT AND THEIR ABILITY TO MEET PRINCIPLES OF ETHICAL INFORMED CONSENT

<i>Consent process</i>	<i>Objective information, including research protocol, risks and benefits, in context of patient situation</i>	<i>Information delivered in appropriate setting and in unhurried manner</i>	<i>Ample opportunity for participant to ask questions</i>	<i>Voluntary and uncoerced choice</i>
Participant consent at time of enrollment	Consent processes include direct information on risks and benefits to participant, in context of current situation	Yes, main concern is where clinical situation needs management quickly	Yes, the opportunity to ask questions should be highlighted on the informed consent documents and in discussion	Information regarding voluntary choice is provided
Advanced consent by participant	Yes, main concern is lack of firsthand understanding as yet to have the index condition	Yes, information can be provided well in advance	Yes, information can be provided well in advance, hence sufficient time for questions	information regarding voluntary choice is provided
Deferred consent	Participants receive information after study participation only	Not achievable	Not achievable	Not achievable
Person responsible or proxy consent	Not for participant, but is provided to proxy	Yes, achievable for proxy	Yes, achievable for proxy	Yes, achievable for proxy who is provided information about voluntary choice
Waived consent	No information provided to participant	Not achievable	Not achievable	Not achievable

and yet are at high likelihood of recurrence of delirium or bowel obstruction.

Participant’s informed consent deferred to a time after the study has commenced

Deferred consent is where the participant is enrolled in the study without consent and then, when able, may provide consent. The data collected until that time point may then be utilized as the person commences to participate in the study.^{30,31} This is an approach used in emergency and critical care research,^{32,33} where there is a higher probability that study procedures will have been completed prior to an ability to obtain consent. In emergency and critical care research, excluding people from whom consent could not earlier be obtained will jeopardize the conduct of the study.³⁴ There are probably few palliative care research scenarios in which deferred consent has a place, as this consent mechanism fails to afford protection from overinclusion in research and may jeopardize the voluntary nature of participation.

‘Person responsible’ or ‘proxy’ consent

When a potential participant is unable to give informed consent, a proxy or person responsible can be used. National guidelines in the United States, United Kingdom, other parts of Europe, and Australia guide how such consent can be given.³⁵⁻⁴² A proxy may not necessarily be the person’s next of kin; this is a statutory concept. In the United States a proxy is defined in federal regulations as a Legally Authorized Representative (LAR) who is “an individual or judicial or other body authorized under applicable law to consent on behalf of the prospective subject to the subject’s participation in the procedure(s) involved in the research.”⁴³ Complementary state-based laws outlining who can serve as an LAR and the circumstances under which this can occur are often not clear.⁴³ The European Directive relating to good clinical practice in clinical trials states that the vulnerable should “be included in clinical trials only where there are grounds for expecting the administering of the medicinal product would be of direct benefit to the participant, thereby outweighing the risks.”³⁷ However, the sign-off for the European Directive has not been completed by all countries and, even with sign-off, individual countries’ legislative frameworks define proxy consent and conditions differently, or are not clear.

Proxy consent has been utilized in dementia research and has been determined to be acceptable to both participants and their proxies.^{21,39} Delirium research is also suited to consideration of proxy consent given absent or fluctuating capacity to consent. Delirium research that is unable to utilize a ‘person responsible’ consent results in participant populations that don’t represent delirium patients as a whole and hence limit generalizability when translating into clinical practice.⁴⁴ A successful use of proxy consent was in an RCT using best evidence pharmacological management of delirium and comparing risperidone with haloperidol or placebo.⁴⁵ This study acknowledges delirium is potentially reversible and if testamentary capacity is regained, participant consent is actively sought before continued participation in the study.

In the setting when the participant may not have capacity to consent, it is important to consider whether the research question has sufficient merit and whether the risks involved are justified by the proposed benefits.³⁹ The thresholds

considered appropriate by ethics committees or institutional review boards may differ from those for research where the participants can consent for themselves. Another key principle to consider in this setting is that it is not possible to conduct effective research only in adults who have capacity to consent for conditions such as delirium, as such findings could not be generalized.^{35,37,41}

To successfully undertake studies utilizing 'person responsible' consent, systems must be in place that can objectively determine capacity, consider the merits of the question, and have a local institutional review board or ethics committee skilled in its consideration—or a specific independent tribunal that reviews trials of this nature.¹ There also remains the need to ensure that if a 'person responsible' or 'proxy' is used, he or she is even more informed than a competent potential participant, given what is asked of the proxy.

Waived consent

Much debate has occurred about conducting a clinical trial without consent, with approval of the study as a whole by the local ethics committee only. Precedents exist for waived consent, including studies to evaluate interventions for cardiac arrests and acute brain injuries.⁴⁶ There is unlikely to be a study in palliative care that warrants waiving consent by either the potential participant or his or her proxy.

Table 1 provides a comparison of the five mechanisms of consent and their ability to meet the principles required for valid informed consent. Participant consent either at the time of enrollment or in advance can meet all the principles, with the one concern being with individuals yet to experience the condition having a different understanding from those who are consented having experienced the index condition. Because of this concern, advanced consent should be reserved for situations where patient/participant consent at time of enrollment would not be possible for the index condition for the reasons outlined in detail above.

Deferred and waived consent do not meet most of the requirements for informed consent and are unlikely to be valid mechanisms in palliative care research, as the clinical scenarios that warrant their use don't occur, and alternative consent approaches can be applied in most study situations.

Proxy consent meets the principles of informed consent in relation to the proxy, but not by the participant who lacks the ability to exercise autonomy at this time in his or her illness. On balance, it is important that high-quality evidence is available for conditions where the participant is unable to provide consent at the time or in advance such as with new-onset delirium, that clear guidelines exist to inform the design of clinical trials utilizing proxy consent, and how proxy consent can best be obtained.

Legal Frameworks that Complement the Ethical Frameworks

Consideration of the mechanisms of informed consent that meet internationally recognized legal principles is crucial to match the ethical underpinnings of research. Failure to obtain proper informed consent for participation in research has been grounds for common law negligence and malpractice claims.⁴⁷ There is general agreement that there is a legal duty to properly inform potential research participants of the risks and benefits of the research; the scope and extent of this duty

vary depending on jurisdiction. In the United States three different standards exist. There are two material risk standards: one requires physicians to provide all the information that a hypothetical reasonable patient would consider significant in making a decision; the other material risk standard defines duty to disclose information by reference to what an actual specific patient would consider material. The third material risk standard, the malpractice standard, requires physicians to provide information that a reasonably prudent physician would disclose in the same circumstances. The malpractice standard is based therefore on the accepted practice of the medical profession.

In Australia and the United Kingdom, recent case law has seen a shift from the standard of the prudent physician (Bolam Principle) to what a reasonable patient would expect.⁴⁸ To establish a malpractice case in addition to establishing breach of the duty of disclosure, research participants need to show injury and causation. Had the researcher engaged in a satisfactory informed consent process in which a reasonable person would have consented to the research? While litigation brought by research participants is rare, the incidence has been increasing with utilization of novel claims of actions and class actions, apart from the common law grounds.⁴⁹

Conclusions

The challenge of research in palliative care amplifies several aspects of informed consent, given the nature of the populations and the studies, that can inform better quality of care. As well as the legal issues, the knowledge, attitudes, and beliefs of patients/participants, their families, and health care providers influence informed consent. These challenges are not insurmountable, but have for too long contributed to the limited number of controlled clinical trials in palliative care. Participant consent at time of enrollment, advance consent by participant, and "proxy" consent all meet the ethical requirements of informed consent and can be used in palliative care clinical trials.

Author Disclosure Statement

The authors declare that they have no competing interests.

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