How should we conduct and interpret phase III clinical trials in palliative care?

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To the Editor:

The paper by Wildiers et al\(^1\) raises some challenges in terms of ethical approaches to end-of-life phase III studies and their interpretation. Although to be commended for undertaking a large multi-site randomised controlled trial in palliative care, there are fundamental questions that do need to be addressed before the first steps can be taken to adopt these findings into practice.

There is a need to understand the natural history of secretions in the terminal stages of a life-limiting illness.\(^2\) What happens when there is no pharmacological intervention? What is the contribution of the cumulative effect of other medications with anti-cholinergic side-effects?\(^3\) What is the contribution of co-morbid illnesses such as cardiac or respiratory failure? How many people were receiving parenteral fluids? How many had widespread oedema or hypoalbuminaemia? Given the large number of observational studies that have been done in hospice and palliative care, it is disappointing that the natural history of secretions at the end of life is poorly defined.

Combining all these factors, what are the characteristics of people who do not get secretions compared to those who do, and in the light of this paper, which factors are associated more strongly with a clinically meaningful response when pharmacological therapy is introduced? This is brought into sharper focus when the data to support reduction in the volume of secretions in other settings using these medications suggests that they are relatively ineffective.\(^4\) The study by Wildiers et al\(^1\) lacked a placebo arm. Given the current state of knowledge in this field, the high risk of side effects with each of these medications, and the background evidence that intervention and placebo may have the same effect on terminal secretions in this population, the lack of a placebo is a significant omission.

Also of concern is lack of information on standardisation. Given the enormous effort to put this study together, why wasn’t the intervention blinded? How was the assessment of the primary outcome standardised across multiple sites? Nurses are an exceptionally well trained group of clinicians in hospice and palliative care, however we cannot necessarily depend upon their ability to discern, for example, pulmonary oedema requiring diuretics from terminal secretions. Re-treatment decisions were also left to nurses’ subjective decisions and could likely be influenced by worried family members or others in the room.

As this was a multi-site study, standardisation across sites is an imperative for a primary outcome measure that is inherently subjective and measured by a third party. While we commend the authors for trying to conduct a large prospective study addressing such a fundamental area to our discipline, the importance of the question increases the importance of ensuring that the study design and methods are able to be transferred across multiple sites.

These basic study design issues are magnified further by lack of informed consent in this study. Ethically, how can people not be consented when it is unknown whether the net clinical benefit of these interventions (extrapolated almost exclusively from pre-operative approaches in well people to normal physiological secretions) offer benefit that the patient or their caregivers will be able to perceive? There is sufficient equipoise to do the study. If an argument ‘that the therapy is in widespread use’ was
an acceptable yardstick, then almost any phase III study in hospice and palliative care of off-licence prescribing could be justified without prior patient or proxy consent.

Consent in this setting is not a barrier to participation but rather an invitation by a researcher to a person or his/her family to engage in a process of exploration in an open and informed way. The communities in which we live have asked all clinical researchers, irrespective of how widespread the intervention being evaluated is in existing practice, to engage in a respectful and inclusive dialogue about an individual’s involvement in research. Failure to engage in seeking consent risks compromising the community’s willingness to allow hospice and palliative care clinical research in the future, even if that research is to directly improve the quality of care. The fact that the subject is unconscious does not revoke this fundamental right unless the intervention is immediately life saving.

Options that have been demonstrated in clinical research including hospice and palliative care settings to work well, are acceptable to Institutional Review Boards and Research Ethics Committees, and include:

(i) pre-consent for someone likely to experience a condition of interest at some time-point in the future when they are unable to provide consent has been dealt with in an ethical manner without compromising the study; or
(ii) proxy consent by an adequately appointed patient advocate or next-of-kin.

How should these results be interpreted by clinicians? One could argue that the medications are equally ineffective in controlling secretions given a lack of knowledge of the natural history of the symptom and little basic science evidence to support their use in the pathological state of dying. The understanding of the natural history of secretions in this setting, appropriate consenting procedures and the inclusion of a blinded placebo is not only desirable but it is mandatory if the findings of this study are to influence practice.
References


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