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End-of-Life Research: Do We Need To Build Proxy Consent into All Clinical Trial Protocols Studying the Terminal Phase?

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Dear Editor:

Research into symptoms that occur at the end of life is paramount for ensuring we provide the best possible care for patients in the terminal phase, yet obtaining informed consent from the study participant is not possible at the time these symptoms occur. Importantly, these questions cannot be answered in any clinical population and defining the net clinical effect of medications used, for example, for noisy respiratory secretions is crucial if the quality of care is to be further improved.

Research into the pharmacological treatment of noisy respiratory secretions at the end of life is facilitated by advanced consent.^{1,2} This relies on advanced consent from potential participants, before they enter the terminal phase, when there is low likelihood the person may develop the target symptom. Studies report rates of 4 to 8 consents required for each randomization. A British study required 58 consented participants, of whom 15 were randomized and received study medication over the 7-month period.¹ The study aimed to randomize a total of 250 subjects and predicted 75–100 participants per year. Likewise in an Australian study, to randomize 10 participants, the investigators consented 80 people over a 10-month time period.² A current phase II feasibility trial of a randomized placebo controlled trial of glycopyrrolate for the treatment of the same symptom³ to date has screened 250 admissions to an inpatient palliative care unit in a 6-month period, of which 80 people were unable to give consent due to reduced capacity. Although there are defined benefits of consent ahead of time, the ratio of consents to randomization and the exclusion of those people admitted when they are too unwell to provide prior consent threatens the feasibility and generalizability of such research.

Proxy consent may provide the solution to improve the feasibility of end-of-life research. Proxy consent is sought from the person, as defined by local legislation, who is responsible for medical decision making when someone lacks capacity. In the largest study of the symptom published

to date, proxy consent was the only consent in 80% of the 333 participants.⁴

Different models exist for who can approve proxy consent to be used in clinical trials. In some jurisdictions human research ethics committees can provide this overview, and in others there is a centralized specialist agency whose entire function is to provide oversight for decision making in clinical care and research for people unable to provide their own consent.

For studies to be adequately powered and to optimize generalizability, advanced consent is not sufficient, and a more realistic approach is to ensure that proxy consent is built into every study design for symptoms in the terminal phase of a life-limiting illness.

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