To the editor

The authors thank Drs Grobler and Lee for their comments in response to the article on intention-to-treat analyses for randomised controlled trials in frail populations such as hospice / palliative care patients.

Withdrawals between randomisation and first exposure to the intervention occur in a larger proportion of the study population in hospice / palliative care than almost all other clinical trial settings (2.34%; range 0%-10.00%). Hospice / palliative care clinical trial investigators currently include the data of people who withdraw between randomisation and first exposure to the intervention as treatment failures in the analysis of intervention arm(s).

At the same time, in absolute terms, hospice / palliative care randomised controlled trials (RCTs) have relatively small populations because the difference sought between arms in symptom control studies needs to be clinically significant, translating to large deltas for between-arm differences and hence relatively modest sample sizes in comparison to many other trial settings.

This leaves investigators with relatively small datasets and no data from exposure to the intervention from which to impute. The suggestion that more sophisticated imputation is the simple solution to this particular circumstance of missing data fails to take into account key factors that distinguish the hospice / palliative care population from other study populations. The only data from which imputation can occur are their data at screening for eligibility. The higher the percentage of such withdrawals and the smaller the sample size, the less stable even the most sophisticated imputation methods will be.

Ultimately, this is *not* about missing data. The proposal in the original paper was about avoiding missing data in total adherence to the International Committee on Harmonisation – Good Clinical Practice (ICH GCP) guidance: study participants / investigators are still blinded, and both arms of the intervention are available simultaneously. Essentially, this is an argument to have the safety population as the intention-to-treat (ITT) analysis, while keeping the ITT principle. Its focus is to *avoid* missing data, a step prior to handling missing data. Cautions around this argument have been placed with the proposed criteria in the original paper's Discussion section.

In terms of the attrition rate, inflation of the sample size during the planning stage is a common practise and still valid under the new argument. Actually, excluding withdrawals between randomisation and first exposure has two advantages:

1. It will lead to a smaller overall attrition rate and hence smaller inflation in sample size calculation; and

2. It will potentially be easier to assume a reasonable overall attrition rate, which is a common challenge at the design stage.

Analyses assume that data in RCTs are missing at random (i.e. the missing data depend on the observed responses but are unrelated to the missing values). If missing data are related to specific missing values (i.e. the data are not missing at random), and this correlation is

ignored, this can bias the results. To further minimise bias associated with withdrawal, a sensitivity analysis should also include a comparison of all the available primary and secondary outcomes for the participants who withdraw from each arm between randomisation and first exposure to the intervention with those remaining in the study. The comparison between the groups will help identify when withdrawal does not appear to be random.

Largely unrelated to the paper by Kochovska *et al*, Grobler and Lee also suggest using proxy assessments (rather than participant reported ones) for primary end-points to reduce missing data in hospice / palliative care clinical trials. Proxy measures of symptoms or quality of life (which are by definition subjective) by health professionals or family members have consistently been shown to under-estimate symptom burden. When considering prevalent and distressing symptoms such as pain and breathlessness, health professionals systematically under-estimate symptom burden in simultaneously collected assessments, including non-clinical domains such as the daily activities or overall quality of life. The primary outcomes for all of the RCTs cited in the paper by Kochovska *et al* were (and should be) subjective measures. It therefore seems that Grobler and Lee are proposing a trade-off that is fundamentally unacceptable in hospice / palliative care clinical research: quality of data to be diminished in order to increase the quantity of data available (less missing data). Participant-reported outcome measures should be carefully selected so as not to be too burdensome to participants, whilst still being appropriate for the trial outcomes.

Hospice / palliative care is a difficult population in whom to design and conduct clinical trials in order to refine the quality of the care that we offer. Continuing discussions about managing the unique challenges presented by trials in this population are important to ensure the quality of these trials.

References

Grobler AC, Lee K. Intention-to-treat Analyses for Randomized Controlled Trials in Hospice/Palliative Care enhanced by principled methods to handle missing data. J Pain Symptom Manage 2020 [in press]

Klinkenberg, M., Smit, J.H., Deeg, D.J.H., Willems, D.L., Onwuteaka-Philipsen, B.D. and Van Der Wal, G., 2003. Proxy reporting in after-death interviews: the use of proxy respondents in retrospective assessment of chronic diseases and symptom burden in the terminal phase of life. *Palliative Medicine*, *17*(2), pp.191-201.

Kochovska S, Huang C, Johnson MJ, Agar M, Fallon M, Kaasa S, Hussain JA, Portenoy RK, Higginson IJ, Currow DC. Intention-to-treat analyses for randomised controlled trials in hospice/palliative care: the case for analyses to be of people exposed to the intervention. J Pain Symptom Manage 2020;59(3):637-645.

Lewis JA. Statistical principles for clinical trials (ICH E9): an introductory note on an international guideline. Stat Med 1999;18:1903e1942.

Nekolaichuk CL, Bruera E, Spachynski K, MacEachern T, Hanson J, Maguire TO. A comparison of patient and proxy symptom assessments in advanced cancer patients. Palliative medicine. 1999 Jun;13(4):311-23.

Tamim H, McCusker J, Dendukuri N. Proxy reporting of quality of life using the EQ-5D. Medical care. 2002 Dec 1:1186-95.