Intention-to-treat analyses for randomised controlled trials in hospice/palliative care: the case for analyses to be of people exposed to the intervention.

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ABSTRACT

Introduction

Minimising bias in randomised controlled trials (RCTs) includes intention-to-treat (ITT) analyses. Hospice/palliative care RCTs are constrained by high attrition unpredictable when consenting, including withdrawals between randomisation and first exposure to the intervention. Such withdrawals may systematically bias findings *away from* the new intervention being evaluated if they are considered non-responders. This study aimed to quantify this impact within ITT principles.

Methods

A theoretical model was developed to assess the impact of withdrawals between randomisation and first exposure on i) study power and ii) effect sizes. Ten reported hospice/palliative care studies had power recalculated accounting for such withdrawal.

Results

In the theoretical model, when 5% of withdrawals occurred between randomisation and first exposure to the intervention, change in power was demonstrated in binary outcomes (2.0-2.2%), continuous outcomes (0.8-2.0%) and time-to-event outcomes (1.6-2.0%), and odds ratios were changed by 0.06-0.17. Greater power loss was observed with larger effect sizes.

Withdrawal rates were 0.9%-10% in the ten reported RCTs, corresponding to power losses of 0.1%-2.2%. For studies with binary outcomes, withdrawal rates were 0.3-1.2%, changing odds ratios by 0.01-0.22.

Discussion

If blinding is maintained and all interventions are available simultaneously, our model suggests that excluding data from withdrawals between randomisation and first exposure to the intervention minimises one bias. This is the safety population as defined by the International Committee on Harmonisation.

When planning for future trials, minimising the time between randomisation and first exposure to the intervention will minimise the problem. Power should be calculated on people who receive the intervention.

Key words: Intention-to-treat analyses, palliative care, randomised controlled trials, good clinical practice, study withdrawal, imputation, missing data, International Committee on Harmonization

Running title: ITT Analyses in Palliative Care

Introduction

The International Committee on Harmonization Statistical Principles for Clinical Trials (ICH E9) guideline has been adopted internationally as the authoritative document on the conduct and analysis of clinical trials.[1] Included in the ICH E9 guideline is a section on the study populations to be included in the analyses, and the reasons for choosing one population over another, depending on circumstances.[1] For example, it outlines the times at which one should use an intention-to-treat (ITT) analysis and contrasts that with when it may be appropriate to use a *per protocol* analysis.[1]

ITT analyses aim to evaluate the primary outcome in randomised controlled trials (RCTs) to minimise bias and ensure that the point estimate is as close to the "truth" as possible.[1 2] With an ITT approach in mind, the sample size is calculated using the parameters related to the primary endpoint, attempting to only include the number of participants required to answer the question in the most robust way. This also ensures an ethical approach as studies should be no bigger than required to answer the question (as estimated from pre-specified power) so that participants are not unnecessarily enrolled and exposed to harms or not offered benefits that may have already been defined by the study.

Two time points are crucial when considering the design, conduct and analysis of RCTs within an ITT context: randomisation and first exposure to the intervention. The ICH E9 guideline recognises that sub-groups of people might withdraw from RCTs at different stages of study engagement, including eligible people who were randomised:[1]

(1) but
  a) were not exposed to the intervention; *and*
  b) provided no further post-randomisation data; *while*
  c) participants, clinicians and other research staff were still blinded to their allocated arm;

(2) and were not exposed to the intervention, but provided no further data;

(3) and were exposed to the intervention, and provided further data, but withdrew prior to the primary endpoint.

This current study deals entirely with this first group where people withdrew between randomisation and first exposure to the intervention.

For most RCTs, participants who withdraw between randomisation and first exposure to the intervention constitute an extremely small proportion of participants and their withdrawal consequently makes little difference to the power of the studies or its conclusions. By contrast, this proportion is appreciable in hospice / palliative care studies.

In hospice/palliative care RCTs, there are three issues that suggest a strict application of the ICP E9 guidance be applied in order to ensure that this source of bias away from the new intervention is minimised:

- Hospice/palliative care studies tend to seek a clinically significant difference between groups requiring a large delta between groups.[3-6] Because of this, sample sizes tend to be smaller, potentially leading to a greater loss of power when people withdraw.[2]

- Withdrawal of study participants cannot be predicted at enrolment or it would be unethical to enrol those persons in the first instance. A proportion of these people will withdraw between randomisation and first exposure to the intervention.

- The proportion of subsequent withdrawals after intervention commencement at any point prior to the primary endpoint is also higher,[7] even when the trial measures the endpoint at the earliest clinically appropriate time for the intervention under study. In some hospice/palliative care RCTs, total withdrawals any time between randomisation and the endpoint can be as high as 50%,[8] and sufficient to introduce bias.[7] Importantly, most withdrawals will be unrelated to the intervention(s) being tested.[2 7 9]

An unnecessary bias may be avoided if withdrawals between randomisation and first exposure to the intervention are excluded from the analysis. Currently, they are assumed to be non-responders (a conventional view of ITT as they are post-randomisation), potentially introducing a systematic bias away from the intervention being evaluated. However, ICH E9 directly addresses such a situation, offering an alternative. It states that: 'The intention-to-treat principle would be preserved despite the exclusion of [*people who withdraw between randomisation and first exposure to the intervention*] provided, for example, that the decision of whether or not to begin treatment could not be influenced by knowledge of the assigned treatment.'[1[p.1929]] Crucially, there is no indication that the *interpretation* and *applicability* of the ITT principle changes with such exclusions from the data sets. The ICH E9 considers such analyses to be unambiguously ITT; therefore, analyses that exclude the data of participants between randomisation and first exposure to the intervention should ***not*** be seen as 'modified' ITT.

The unanswered question is whether applying the conventional interpretation of ITT to the primary analysis (which assumes withdrawals before exposure to the intervention are non-responders) may introduce bias against the finding of effectiveness and therefore justify exclusion of these patients from the analysis. Conversely, if data from such participants are excluded, there will be a modest but at times appreciable loss of power and potential to underestimate the adverse event rates.

Given concerns about potentially higher rates of attrition between randomisation and first exposure to the intervention, which contributes to attrition that occurs in hospice/palliative care RCTs, this paper sought to explore this problem through three approaches:

1. Demonstrate theoretically how inclusion of the data from consented participants who withdraw between randomisation and first exposure to intervention (with the assumption that they are non-responders in primary analyses) reduces the power and effect size of a study using three different types of primary outcome measures (binary, continuous and time-to-event data);
2. Quantify these rates in a convenience sample of ten completed double-blind, placebo-controlled phase III hospice/palliative care studies while evaluating the impact on the power and effect size on these selected ten phase III studies; and
3. Offer recommendations for future conduct and analyses of all hospice/palliative care phase III studies.

If power is affected appreciably, a strong case could be made for a change to the approach to analyses without compromising the interpretation and applicability of the ITT principle as first outlined by ICH E9.

Methods

Phase 1. Theoretical model

Illustrative hypothetical models were developed reflecting hypothetical studies with three different effect sizes (small, medium and large) and three types of outcome measures (binary, continuous and time-to-event). For the purpose of these theoretical models, the authors assumed that: 1) the hypothetical studies had already closed for recruitment, and 2) all withdrawals were only between randomisation and first exposure to the intervention. The sample size calculation package nQuery (version 8.0) was used to generate these three theoretical models corresponding to the type of primary outcome measure:

1. *Binary outcome data.* The authors assumed the proportion of responders in the theoretical control group was 30% while in the intervention group responders accounted for 40% (small effect size (10%)), 50% (moderate effect size (20%)) and 60% (large effect size (30%)) of participants. This corresponded to odds ratios of 1.56, 2.33 and 3.50, for small, medium and large size, respectively.
2. *Continuous data.* The standard deviation was set at 1.0, and mean differences between groups of 0.2, 0.5 and 0.8 (to reflect small, medium and large effect size, respectively) were used.[10]
3. *Time-to-event data.* Assuming hazard ratios of 0.8, 0.6, and 0.4 (for small, medium and large effect size, respectively), event rates by the primary endpoint were 50% and 42% (in the control group), and 31.5% and 17.7% (in the intervention group).

Impact on power

For each type of outcome measure, we first generated the sample size with appropriately fixed 0.05 significance level and 80% power reflecting levels most frequently used in hospice/palliative care trials to ensure the models reflected current practice. We then calculated a revised sample size and power calculation based on the assumption that 5% of study participants withdrew between randomisation and first exposure to the intervention, and were excluded from the analysis.

Impact on odds ratio

Studies with binary primary outcomes were employed to assess the theoretical impact of 5% withdrawals between randomisation and first exposure to the intervention on the studies odds ratios. Assuming 0.05 significance level, 80% power and three study effect sizes (small, medium and large), we first calculated the odds ratios of the studies assuming these withdrawals were included in the analysis as non-responders. We then repeated the calculations assuming these withdrawals were excluded from the analysis.

For continuous or time-to-event analyses, withdrawal between randomisation and first exposure to the intervention do not allow imputation given the lack of data. If the study includes such people in the overall *a priori* recruitment total, the study will again be at risk of being underpowered.

Phase 2. Assessing the model using phase III hospice/palliative care studies

A convenience sample of ten RCTs published in the hospice/palliative care literature between 2003 and 2018 were used to evaluate the problem. The selected trials were led by four clinical research teams from around the world, and were double-blind, placebo-controlled

randomised trials testing pharmacological interventions for symptom control in people with advanced life-limiting illnesses. Crossover and parallel-arm studies were included.

Study characteristics retrieved from study protocols and published articles included: study design (randomisation, blinding, and treatment/control intervention), the primary outcome, number of sites involved, days between successful screening and first exposure to the study intervention, sample size, number of participants randomised, and number of participants withdrawn before first intervention.

Study characteristics were summarised using counts, percentages, medians, interquartile ranges, standard deviation, and means as appropriate. Descriptive statistics were used to present the types of withdrawal.

For each study, we calculated the proportion of participants who withdrew between randomisation and first exposure to the intervention. We then calculated changes in the power that would have occurred if these people's data were excluded from the analysis. For studies with binary primary outcomes, the impact on changes in odds ratio was also examined for these same exclusions.

Ethics

The use of secondary, de-identified data did not require additional ethics approval. Approvals for primary data collection were obtained from all relevant Human Ethics Research Committees before each study commenced.

Results

1. Results of the theoretical modelling

Impact on power
For hypothetical studies with binary outcomes, a 5% rate of withdrawal between randomisation and first exposure to the intervention lead to 2.0-2.2% difference in power depending on the inclusion or exclusion of these data from the analysis (Table 1). For studies with continuous outcomes, a 5% attrition caused 0.8-2.0% power loss, depending on the study effect sizes; greater power loss was observed in studies with smaller effect sizes. For studies with time-to-event outcomes, the power loss associated with 5% attrition ranged from 1.6% to 2.0%; again, greater loss of power was observed in studies with smaller effect sizes.

Impact on odds ratio
For hypothetical studies with binary outcomes, the impact of counting withdrawals as non-responders on odds ratios ranged from 0.06 to 0.17 (Table 2). Excluding the withdrawals changed the odds ratios; greater loss of power was seen with larger effect sizes.

2. Assessing the model using phase III hospice/palliative care studies

Study characteristics
Ten studies were conducted across 85 sites in Australia, Norway, and the UK (Table 3). The total number of participants randomised to the studies was 1710. The median time to primary endpoint was 7 days (IQR 4-16). In seven studies,[11-17] median time from screening to first exposure to the study intervention was 1 day, while for three studies,[18-20] these data were not

available). In three studies,[12 14 17] there was a run-in period prior to receiving the first study intervention for a median of 1 day. The *a priori* power calculations for seven studies were set at 80%,[11-15 17 19] one study was powered to 85%[16] and two were powered to 90%.[18 20]

The total number of participants who were randomised but were not exposed to the intervention was 40, which was 2.34% of the 1710 patients randomized in all ten studies.

Table 3 presents the impact of withdrawals between randomisation and first exposure to the intervention on power loss and odds ratio changes for all phase III studies. Primary outcomes were binary (four studies);[12-14 16] continuous (five studies);[11 18-20] or time-to-event (one study).[15]

Only one study had no withdrawals between randomisation and first exposure to the intervention.[12] For all other studies, this proportion ranged from 0.9% to 10.0%, which corresponded to 0.1-2.2% power loss reflecting increasing loss of power with and increasing proportion of such withdrawals.[13-20] The exception to this was Agar et al.[11] where a 4.4% rate corresponded to a 0.1% loss of power; with the power loss being mitigated because of the baseline and follow-up outcome correlation was considered in the sample size calculation.

For studies with binary outcomes,[12-14 16] withdrawal between randomisation and first exposure to the intervention ranged from 0.9% to 2.6%, with corresponding 0.01-0.22 changes in odds ratios when the withdrawals were excluded from analysis.

Discussion

Our theoretical model demonstrated that an ITT population that excluded participants who withdrew between randomisation and first exposure to the intervention resulted in a loss of power of approximately 2% compared to an analysis that included these participants, irrespective of the primary outcome measures employed. Effect size did not impact on this loss of power in studies with binary outcomes although, as expected from first principles, power loss was relatively less in trials with continuous or time-to-event outcomes with moderate or large effect sizes. In studies with binary outcomes, excluding withdrawals changed the odds ratio; the loss of power was greater with larger effect sizes. In studies with large effect sizes, the odds ratio changed by approximately 17%.

Across ten trials conducted in people with advanced life-limiting illnesses, 2.34% of consented participants withdrew between randomisation and first exposure to the intervention. One study experienced no withdrawals and one study had a withdrawal rate of 10%. The loss of power paralleled the rate of withdrawal and was similar to the theoretical model, ranging between 0.1%-2.2%. The expected power loss was not seen in Agar et al.[11] in which a 4.4% rate of withdrawals led to only 0.1% loss of power because the method of sample size calculation mitigated the impact of withdrawals. By contrast, in the studies that used a binary outcome, excluding withdrawals between randomisation and first exposure to the intervention changed the odds ratio by as much as 22%.

Although attrition between randomisation and first exposure to the intervention represents a relatively small proportion of participants in studies in general, the phenomenon is relevant to RCTs in people with advanced life-limiting illnesses given that overall sample sizes in symptom control studies are often relatively small because of the large delta required for clinically relevant differences of effect size between groups. This impact is further amplified

because most hospice/palliative care RCTs are powered to 80% (including seven of the ten studies in our convenience sample). The smaller the trial, the greater the loss of power with withdrawals as each individual carries more "power".

Withdrawals between randomisation and first exposure to the intervention from binary outcome trials affect the odds ratio if included in the analysis as non-responders, especially in the typically large effect size trials in palliative care. A 22% change in odds ratio represents a clinically relevant difference potentially. Participants who withdraw between randomisation and first exposure to the intervention from trials using continuous or time-to-event outcome as their primary powered endpoint will not contribute to the analysis unless missing data are imputed. Yet, they provide no data for imputation as they have not been exposed to the intervention. Including the population who have no exposure to the intervention (or control) and treating their data in the same way as any participants who has been exposed to the intervention does not help to minimise a potential bias.

Implications for trial conduct and analysis

Excluding people who withdraw between randomisation and first exposure to the intervention effectively means that the population described for the primary analysis in hospice/palliative care RCTs (subject to certain caveats) would be both the ITT population but also the *safety population* – i.e. those who have had exposure to the intervention and can exhibit treatment emergent adverse events. The theoretical model and its application to our convenience sample of ten studies suggest that this use of the 'safety population' (defined as '[…] *those…who received at least one dose of the investigational drug*'[1[p.1934]]) may pose advantages for RCTs in hospice/palliative care and other frail populations.

However, in order for this argument to be valid, there are four criteria that must be met. In order to exclude study participants who withdraw between randomisation and first exposure to the intervention from an ITT analysis data set, criteria include:

1. As noted in the ICH E9 guideline, *the study must still be blinded at the time of withdrawal.*[1] This is to ensure that any decisions about the start of the intervention are not influenced by knowledge of the assigned intervention.[1] This may preclude some cluster-randomised studies that are single-blinded or unblinded.
2. *Access to each arm must happen simultaneously.*[2] There can be no delay to the access to one arm, or unblinding will have occurred. (This was a principle that led to the ITT principle being articulated in the first place.)
3. As a check on reverting to the original ITT principles, *the drop-out rate per arm should be of the same order of magnitude.*[2] This is to ensure that the withdrawal is due to natural disease progression or sudden death, rather than the study intervention.[2]
4. The impact of excluding the data from such participants should be evaluated as a sensitivity analysis.[2]

Recognising that attrition between randomisation and first exposure to the intervention is a potential problem in hospice/palliative care RCTs suggests that the design of such studies should be reconsidered. The following is a proposed hierarchy of changes that may help investigators to reduce this risk.

1. Closed studies

If the conditions for excluding participants between randomisation and first exposure to the intervention are met, it is reasonable to consider excluding these data from the primary analysis. The requirements for ITT will be maintained (and therefore the resultant analysis should not be labelled a modified ITT), and the effect of the new intervention will not be under-estimated. This will, however, lead to a loss of power.

2. Studies currently open to recruitment
Additional recruitment to reach the original sample size may be possible if participants withdraw between randomisation and first exposure to the intervention (and this is stipulated in the protocol). The withdrawals should not be counted towards the proposed optimal study recruitment.

3. Designing future studies
Ideally, participants should not be randomised until they are ready to be exposed to the intervention, although this is not always practical. If there is a run-in period, randomisation should occur at the end of that period. Alternative sample size calculation can also be used, such as the one in Agar et al.,[11] which seems to mitigate against loss of power due to withdrawals between randomisation and first exposure to the intervention.

Implications for future research

Prediction of eligible participants most likely to withdraw prior to any exposure to the intervention would enable refinement of eligibility criteria. End-of-study attrition rates in supportive/palliative oncology studies have been shown to be associated with higher baseline symptom burden (among other factors).[21] Determining any relationship between participants' overall performance status, disease status and co-morbidities at baseline and their withdrawal before they can be exposed to the intervention, may help to refine recruitment strategies in future hospice/palliative care studies and aid generalisability.

Limitations

A priori estimates of withdrawal proportion were not available nor were detailed breakdowns of withdrawal between first exposure to the intervention and the primary endpoint for the ten included phase III studies. Understanding in more detail study withdrawal rates in phase III hospice/palliative care studies between randomisation and each study's primary endpoint will further develop this work.

Conclusions

Excluding withdrawals between randomisation and first exposure to the intervention from the primary analysis in hospice/palliative care RCTs still fully honours the principles of ITT, formed from the population that is best described as the safety population – those people who have been exposed to the intervention at least once. Although the loss of power may be modest, the impact of withdrawals between randomisation and first exposure to the intervention can be minimised or even eliminated by attention to trial design for new studies, and managing loss of power by additional recruitment for studies currently open. Exclusion of data from these participants would minimise one small but appreciable bias in reporting clinical trial outcomes.

Declaration of conflicting interests

The authors declare no competing interests.

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Table 1. The impact of withdrawals between randomisation and first exposure to the intervention in ITT analyses on losing study power

	Binary outcomes (e.g. response rate, etc.)					
	Small effect size		Medium effect size		Large effect size	
	No withdrawals	5% withdrawals	No withdrawals	5% withdrawals	No withdrawals	5% withdrawals
Proportion in control group	30%	30%	30%	30%	30%	30%
Proportion in intervention group	40%	40%	50%	50%	60%	60%
Effect size	10%	10%	20%	20%	30%	30%
Odds ratio	1.556	1.556	2.333	2.333	3.500	3.500
N per group	356	338	93	88	42	40
Power	80%	77.9%	80%	77.8%	80%	78.0%
Power loss	2.1%		2.2%		2.0%	
	Continuous outcomes (e.g. quality of life, etc.)					
	Small effect size		Medium effect size		Large effect size	
	No withdrawals	5% withdrawals	No withdrawals	5% withdrawals	No withdrawals	5% withdrawals
Mean difference	0.2	0.2	0.5	0.5	0.8	0.8
SD	1.0	1.0	1.0	1.0	1.0	1.0
Effect size	0.2	0.2	0.5	0.5	0.8	0.8
N per group	394	374	64	61	26	25
Power	80%	78.0%	80%	78.2%	80%	79.2%

Power loss	2.0%		1.8%		0.8%	
	Time-to-event outcomes (e.g. overall survival, etc.)					
	Small effect size		Medium effect size		Large effect size	
	No withdrawals	5% withdrawals	No withdrawals	5% withdrawals	No withdrawals	5% withdrawals
Event rate at primary endpoint in control group	50%	50%	50%	50%	50%	50%
Event rate at primary endpoint in intervention group	42%	42%	31.5%	31.5%	17.7%	17.7%
Hazard ratio	0.8	0.8	0.6	0.6	0.4	0.4
N per group	589	560	106	101	33	31
Power	80%	78.0%	80%	78.1%	80%	78.4%
Power loss	2.0%		1.9%		1.6%	

Table 2. The impact of counting withdrawals between randomisation and first exposure to the intervention as non-responders on changing odds ratio

	Binary outcomes (e.g. response rate, etc.)					
	Small effect size		Medium effect size		Large effect size	
	No withdrawals	5% withdrawals	No withdrawals	5% withdrawals	No withdrawals	5% withdrawals
Responders in control group	30%	25%	30%	25%	30%	25%
Responders in intervention group	40%	35%	50%	45%	60%	55%
Odds ratio	1.556	1.615	2.333	2.455	3.500	3.667
Odds ratio difference	0.059		0.122		0.167	

Table 3. The impact of withdrawals between randomisation and first exposure to the intervention on potential power loss and odds ratio changes for 10 randomised controlled trials in hospice/palliative care

Study	Primary outcome	Sample size (per arm)	Median days: Successful screen to receiving first exposure to the intervention	Withdrawals between randomisation and first exposure to the intervention	Corresponding power loss[a]	Corresponding odds ratio difference[b]
	Binary outcomes					
Currow et al.[13]	Treatment response	190 in total; megestrol acetate (n=61) or dexamethasone (n=67) or	1	5/190 (2.6%)	1.2%	0.22

		placebo (n=62)				
Hardy et al.[16]	Response rate	187 in total; ketamine (n=93) or placebo (n=92); deleted from analysis (n=2)	1	4/185 (2.2%)	0.5%	0.06
Fallon et al.[14]	Treatment response	233 in total; pregabalin & radiotherapy (n=116) or placebo &	1	2/233 (0.9%)	0.3%	0.01

		radiotherapy (n=117)				
Currow et al.[12]	Treatment response	223 in total; sertraline (n=112) or placebo (n=111)	2	0/223 (0%)	0%	0
	Continuous outcomes					
Klepstad et al.[18]	Time needed to achieve pain relief	40 in total; immediate release morphine (n=19) or sustained release	Not available	4/40 (10%)	2.2%	Not applicable

		morphine (n=21)				
Oxberry et al.[19]	NRS breathless severity score	39 in total; cross-over: oramorph / oxynorm / placebo (n=39)	Not available	2/39 (5.1%)	1.8%	Not applicable
Paulsen et al.[20]	Pain intensity	50 in total; methylprednisolone (n=26) or placebo (n=24)	Not available	1/50 (2%)	1.0%	Not applicable
Currow et al.[17]	Breathlessness change	287 in total; morphine (n=146) or	1	8/287 (2.8%)	0.7%	Not applicable

		placebo (n=141)				
Agar et al.[11]	NuDESC score	249 in total; risperidone (n=82) or haloperidol (n=81) or placebo (n=86)	0	11/249 (4.4%)	0.1%	Not applicable
	Time-to-event outcomes					
Fallon et al.[15]	Duration of analgesic benefit	214 in total; ketamine (n=107) or placebo (n=107)	1	3/214 (1.4%)	0.6%	Not applicable

[a]The power loss calculation corresponds to Table 1; [b]The odds ratio change is applicable to studies with binary primary outcome (response rate, etc.) and corresponds to Table 2; [c]CIBP – Cancer-Induced Bone Pain; HF – Heart Failure; NRS – Numerical Rating Scale; NuDESC – Nursing Delirium Screening Scale.