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Incorporating death in longitudinal PRO analyses: SISAQoL-IMI Best practice recommendations for oncology clinical trials

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Abstract

Purpose:

Patient-reported outcomes (PROs) are central to evaluating treatment benefit-risk in oncology randomised clinical trials (RCTs). However, high mortality rates impact PRO data analysis and interpretation. Current methodologies often inadequately account for death as an intercurrent event (ICE), leading to potential biases. This manuscript explores strategies for addressing death using the estimand framework to ensure clarity and consistency in PRO analyses.

Methods:

A motivating example is used to provide examples of potential strategies for addressing death as an ICE when estimating treatment effects in the context of a RCT, and a case-study example illustrates details of three strategies for addressing death as an ICE: hypothetical, while alive, and composite.

Results:

The different strategies can produce markedly different treatment effects, particularly as the proportion of deaths increases. The case study emphasized the importance of defining the timeframe of interest for the analysis when selecting the appropriate method to account for hypothetical timepoints after death.

Conclusion:

Robust PRO analysis requires clear research objectives, pre-specified estimands, and transparent incorporation of ICEs like death. SISAQOL-IMI acknowledges that there is no single optimal strategy for addressing death in PRO analyses in RCTs and recommends justifying the chosen strategy, which should match the predefined PRO objective of the clinical trial. Clear estimands, aligned statistical analyses, and transparent presentation of death events over time are essential to enhance credibility and impact of PRO data in oncology trials.

Plain language summary

In cancer clinical trials, patient-reported outcomes (PROs) provide important information about the effect of new cancer treatments from the patients' perspective. Currently, when results of clinical trials are reported, it is not always clear how to interpret reported average changes in PROs over time in the presence of mortality. This study provides guidance and a framework on how to improve clarity of the analysis and reporting results of PRO data in cancer clinical trials, aligning with international standards for clinical trials. The study includes a pictorial motivating example and a clinical trial case-study to illustrate the use of different possible approaches for statistical analysis. The study provides recommendations about how to present changes in PRO over time data together with mortality rates to improve clarity of results and interpretation of PRO data in oncology clinical trials.

Introduction

Patient-reported outcomes (PROs) are increasingly integral to benefit-risk evaluations and comparative effectiveness analysis in oncology clinical trials.[1–3] PROs directly capture patients' symptoms, functioning, and health-related quality of life (HRQoL), [4] Yet concerns persist regarding variability in study design, data collection, analysis, and interpretation, which can limit their impact in regulatory and clinical decision-making.[5,6 7] Standardized and harmonized guidance for analysis and interpretation of PROs in randomised clinical trials (RCTs) is of utmost importance.[8]

The SISAQOL-IMI initiative has recently published consensus guidelines to design, analyse, interpret and present PROs in cancer clinical trials, [9] adding to the previously published guidelines from SISAQOL[8 10] and SPIRIT-PRO Extension to guide the inclusion of PROs in clinical trial protocols[11] and CONSORT-PRO for reporting [12] as well as PROTEUS consortium for PROs in grant applications. {Snyder, 2021 #55}

The SISAQOL-IMI recommendations relied on the estimands framework as guided by ICH E9 (R1), the addendum to ICH E9 ("Statistical principles for clinical trials"),[13] to map RCT study PRO objectives with the PRO analyses to obtain the treatment effect of interest. For each PRO objective, the target population, variable, population-level summary, and especially the approach to intercurrent events (ICEs) must be prospectively defined. ICEs are events occurring after treatment initiation that affect interpretation or observation of outcomes and are common in oncology, where disease progression, treatment discontinuation, or death often occur. [14–16] Data absent due to ICEs is not an issue of data collection or measurement error; the data is unavailable because it did not exist (e.g., after the patient has died) or was not part of the assessment plan (e.g., data after progression not considered relevant or feasible to collect). Therefore, data absent due to ICE must be distinguished from regular missing data, which is absent while the data was intended to be collected, for example, due to a missed clinic visit or a patient forgetting to complete a questionnaire. Possible ICE strategies described in ICH E9 include treatment-policy, hypothetical, and composite strategies; the general application of these strategies to PRO endpoints has been discussed elsewhere. [7,17–21]

In RCTs, longitudinal PRO data, collected repeatedly over time, are particularly susceptible to the occurrence of missing data and ICEs. In cancer RCTs, where sadly patient deaths often occur within the timeframe of the RCT, when considering appropriate statistical analysis of PRO endpoints, patient death represents a specific challenge. Patients who have died will obviously have no PRO assessments after death, whereas patients with better survival outcomes will have PRO assessments for longer during the RCT. For analytical purposes, death constitutes a "terminal" ICE because no meaningful PRO value exists after the event.[22] SISAQOL guidance and ICH E9 highlights that this warrants thoughtful consideration. [8,23] Assumptions underlying how death is incorporated can substantially influence results and the interpretation of treatment effects on both efficacy and tolerability PRO endpoints. [7,17,19]

Consequently, interpreting mean changes in PRO scores from standard statistical models that do not incorporate survival status. is methodologically challenging. Many statistical methods implicitly assume the same number of observations over time per patient[17]. When standard longitudinal models are applied without explicit consideration of death, they generally treat post-death assessments as randomly missing data. If no distinction is made between potentially informative missing or unobservable data, then death is treated in the same way as randomly missing data, e.g., data missing due a technical issue with an ePRO device, would be considered randomly missing. An assumption that all unobserved data is missing at random and can be ignored is rarely plausible in oncology, particularly in non-curative settings. This assumption is, however, often implicit in common analysis methods, which can seriously bias estimates and may lead to the wrong conclusions about the treatment effect.

Literature Review

As part of a literature review conducted by the SISAQOL-IMI, 29 published protocols and 14 European public assessment reports (EPARs) of authorised medicines for phase III RCTs were reviewed. HRQoL outcomes were reported as secondary endpoints in most of these documents (86%). The most frequently applied endpoint type was the magnitude of change from baseline at specified time points (84%). [24] To inform this publication, SISAQOL-IMI conducted a further review of cancer trial publications presenting PRO results. A common approach to addressing death as an ICE in the reviewed documents was to rely on the available data only, an approach mentioned in about 49% of the sources, while around 22% of the documents did not specify how death was addressed at all. [24] Overall, the key findings were that the PRO research questions and estimands were poorly specified and that strategies for incorporating death events in the analysis were either unclear or not explicitly stated. The statistical analyses were not aligned with clear research questions; in many cases longitudinal statistical models were used for analysing magnitude of change, but the implicit modelling as related to death events (relating to hypothetical assumptions) was not acknowledged (see Appendix A).

From the literature reviews, we concluded that analysis of magnitude of change in a PRO score is context dependent and therefore, careful consideration of the estimand and intercurrent event (ICE) strategy is needed to select the appropriate approach to address missing data due to death. Discussion among SISAQOL-IMI members identified several acceptable approaches, each appropriate for different clinical and analytical scenarios, including expected mortality patterns, the PRO domain and the clinical setting for the trial.

The aim of this manuscript is to build on the SISAQOL-IMI recommendations for incorporating death in longitudinal PRO analyses by highlighting scenarios where each strategy may be suitable to aid planning for the analyses. We present a motivating example and a synthetic case study demonstrating how the choice of strategy for addressing death can directly affect the interpretation of differences between treatment groups.

Recommended strategies for incorporating death in longitudinal PRO analyses

Rather than prescribing a single optimal method, the SISAQOL-IMI recommendations recognize that no single strategy for ICE of death is universally optimal. Instead, the recommendation is to keep all options open, with the choice of ICE strategy determined by the specific clinical context, research question, and disease setting. The recommendations from SISAQOL-IMI on addressing death as an ICE in RCTs with PRO endpoints are published on the SISAQOL Toolkit website [25]. Here, we focus on detailed examples for the three most common strategies: hypothetical, while alive, and composite (See Fig. 1 for worked example). We note that a key consensus from SISAQOL-IMI was that completely removing all data from those patients who died on-study is rarely justifiable; this consensus view was particularly strongly endorsed by the patient representatives.. SISAQOL-IMI recommendations describe that a principal-stratum strategy may also be appropriate for PRO endpoints, which relates to the selection of a subgroup of patients who would be alive regardless of treatment assignment. This method does pose several challenges as such subgroups may not be uniquely defined and relies on unverifiable assumptions. A detailed discussion of this approach is outside the scope of this manuscript. We also note that a treatment-policy strategy for death is not recommended as this approach attempts to ignore the event. The approach requires collecting data after death, which is not feasible. The post-death unobserved data would be considered randomly missing data and lead to biased results.[26,27].

Table 1 summarises the different research questions and characteristics of each proposed strategy considered in this manuscript, with considerations for trial scenarios where each may be suitable.

Table 1
Examples of ICE strategies for deaths; research questions and methods for estimation

Research question	**Hypothetical**	**While Alive**	**Composite**
	What is the mean difference in PRO score between treatments, had there been no deaths during the time period of interest?	**What is the mean difference in PRO score between treatments while the patient is alive?**	**What is the mean difference in PRO score, where patients who died are assigned a PRO score that plausibly reflects death or the impact of death on the PRO**
How is death incorporated?	Uses linear mixed model likelihood approach or multiple imputation. Flexible modelling can allow for different assumptions.	Patients who have died on or before the timepoint of interest will be excluded from the analysis.	Directly incorporates mortality rate into the endpoint by replacing unobserved PRO score with a fixed value. Often, the worst possible PRO score is used after death.
Is the ITT (Intention- to-treat) principle preserved?	Yes	No	Yes
What is the assumption regarding the relationship between death and PRO score?	Death is not expected to be related to the PRO variable of interest.	Death and PRO are part of a bivariate outcome (i.e., two separate outcomes evaluated together). In a simplistic analysis, that ignores death, it is not expected to be related to the PRO variable of interest.	Death is expected to be related to the PRO variable of interest.
Notes of caution	Interpretation of results is difficult. The correctness of any imputation or estimation cannot be empirically verified.	PRO results need to be supplemented with mortality figures to allow for joint interpretation of both endpoints.	The result is a mix of real PRO scores with post-death imputations. The choice of the imputed value is subjective. The data does not solely represent actual PRO values observed over time. Use of worst score can cause disproportionate impact on mortality and mask PRO effect in the observed data.
When might the strategy be suitable?	It may be appropriate when deaths are unrelated to the PRO endpoint (e.g. a symptom not expected to change during the RCT) or when the number of deaths is limited	May be reasonable for descriptive purposes or in single-arm studies. Formal treatment comparisons are not recommended as ITT is not preserved (i.e., selection bias may be introduced over time due to death); unless limited	Allows for population-based comparison and may be suitable when death represents the worst possible state for the PRO domain (e.g., physical functioning). Interpretation mixes observed and imputed values and should be complemented by

Research question	Hypothetical	While Alive	Composite
	What is the mean difference in PRO score between treatments, had there been no deaths during the time period of interest?	**What is the mean difference in PRO score between treatments while the patient is alive?**	**What is the mean difference in PRO score, where patients who died are assigned a PRO score that plausibly reflects death or the impact of death on the PRO**
	during the time period of interest.	mortality with similar pattern across the two arms	mortality figures to understand this impact of deaths.

A motivating example (Fig. 1) illustrates that identical observed PRO data can yield markedly different treatment effects depending on the chosen strategy to account for death. The motivating example shows PRO data for 10 patients (5 on Treatment A; 5 on Treatment B) with PRO assessments at baseline and 3 post-baseline timepoints. For each patient, their PRO data did not change over time (i.e., no effect of treatment on PRO scores). Patients with lowest baseline PRO scores died earliest; overall, patients in treatment A survived longer.

Despite identical PRO trajectories, the estimated treatment effect differs across strategies. A hypothetical approach showed no difference in mean change in PROs between treatment arms; while-alive analyses favoured treatment B due to selective survival of fitter patients. The composite analyses favoured treatment A by “penalising” the patients in treatment B for greater mortality. These diverging results stem not from differences in PRO trajectories but from different conceptualisations of the role of death in the research question.

From a statistical perspective, none of these approaches is inherently “correct”; rather, each corresponds to distinctly different estimands reflecting different objectives. The hypothetical strategy concludes that PRO scores remain stable over time, but this only holds when ignoring observed differences in mortality. The while-alive approach captures the evolving composition of the surviving population, implicitly incorporating diverging selection driven by the relationship between survival and PRO. The composite strategy combines survival and PRO into a single endpoint, such that results reflect the treatment effect within the overall randomised population instead of the PRO experience among individuals over time.

Case Study

A synthetic dataset of 200 patients with lung cancer, derived from an actual randomised controlled clinical trial provided to SISAQOL-IMI, was generated and used to illustrate how different estimands varying their approaches to death can yield different results at different timepoints. Further details of the synthetic dataset creation and programming code are provided in Appendix B. Patients were randomised equally (1:1) to Experimental vs Control arms, with physical functioning (EORTC QLQ-C30) assessed monthly until death. PRO assessments were collected until death, regardless of treatment

discontinuation or disease progression. The dataset included some missing data due to logistical reasons, as might be observed in a real clinical trial.

The PRO research question is to define the treatment effect on the magnitude of change in longitudinal PRO score (patient reported physical function). We pre-specified the threshold for a meaningful between-group difference in change from baseline in physical function score at ≥ 5 points. [28]

We defined three timepoints of interest (6, 12, and 24 months) and illustrated three potential approaches related to the ICE of death at each timepoint (hypothetical, while alive, and composite), yielding nine different estimands. Example estimands at the 12-month time point are shown in Table 2.

Table 2
Potential estimands for magnitude of change in longitudinal PRO score at 12 months

RESEARCH QUESTION	**Research Question 1**	**Research Question 2**	**Research Question 3**
	Mean change in PRO score for all patients (assuming that patients did not die before the timepoint)	**Mean change in PRO score for patients alive (alive at timepoint)**	**Mean change in PRO score, assuming that, after patients die, they have worst possible PRO score**
	Estimand 1: Hypothetical	**Estimand 2**: While alive	**Estimand 3**: Composite
ESTIMAND			
Population	All patients fulfilling study eligibility criteria and randomised to treatment		
Treatment	Experimental vs Control until death		
Variable	Patient reported EORTC-QLQ C30 physical function change from baseline score at **12 months**		
Population level summary measure	Difference between treatments in mean change from baseline PRO score		
ICE - Death	Hypothetical: PRO scores after death extrapolated from observed data	While alive: Only patients alive at timepoint of interest included	Composite: A PRO score of “0” is assigned for all timepoints post death

Analysis Method: hypothetical estimands

Three analysis datasets were created – one dataset for PRO monthly assessment data from baseline up to and including 6 months only, one dataset for PRO data up to and including 12 months, and one dataset for data up to and including 24 months. For each analysis dataset, a longitudinal repeated

measures mixed model (MMRM) of change from baseline in PRO score over time was used to estimate the treatment effect. This model included time (visit) as categorical, treatment and treatment-by-visit interaction as fixed effect; patient was fitted as a repeated effect, and a heterogeneous compound symmetry (CSH) covariance structure was used. The LSmean change from baseline and LSmean difference between treatments at the timepoint were reported. For illustrative purposes, the MMRM was adjusted for baseline PRO score only; in a pre-specified RCT analysis, stratification factors and key prognostic covariates would typically be included as additional fixed effects.

Analysis Method: while alive

Three separate analyses were conducted, using patient change from baseline PRO score at each time point (6 months, 12 months and 24 months). Patients' mean change from baseline score for only patients alive at the single timepoint was summarised; a single-timepoint t-test was used to estimate the difference between mean scores at the time point.

Analysis Method: composite

Three separate analyses were conducted, using patient change from baseline PRO score at each time point (6 months, 12 months and 24 months). At each time point, for any patients who had died by that time point, their PRO score was imputed as zero, the worst possible value for the EORTC QLQ-C30 physical functioning measurement. Following imputation, patients' mean change from baseline score was summarised; a single-time point t-test was used to estimate the difference between mean scores at the time point.

Case study: Results

The mean change from baseline scores in each treatment arm for each time point and ICE strategy is shown in Fig. 2; the number of deaths and the difference between treatments in means in each scenario are presented in Table 3. At 6 months, the mortality was relatively low (7.5% = 15/200) and the three methods provided similar results. As the number of deaths increased at 12 months (30.5%=61/200) and at 24 months (67%=134/200), this increased mortality impacted the observed results. This is illustrated at the 24-month time point, where mortality was 57% (n = 57/100) in the experimental arm and 77% (n = 77/100) in the control arm. At 24 months, the results varied across the methods; using the hypothetical approach, the experimental arm showed stable physical functioning, while physical functioning in the control arm declined, producing a significant between-group difference (difference in means 6.86 points; 95% CI -0.22, 13.93). However, interpretation is limited because high mortality undermines the credibility of the hypothetical scenario. In the subset of patients alive at 24 months, mean PRO scores in both arms decreased, but no difference between mean scores was observed (0.15 points 95% CI -14.75, 15.06); the CI are much larger due to the use of a small subset of data, which excludes data from many of the randomised patients. With the composite approach, both arms showed declining mean scores, driven

largely by the assigned post-death minimum values; a larger decline in control led to a significant between-group difference favouring experimental arm (difference 17.14 points (95% CI 6.00, 28.28).

Table 3
Case study: Mean change from baseline and difference between treatment arms in EORTC QLQ-C30 physical function score

Timepoint	**6 Months**		**12 Months**		**24 Months**	
Treatment	Experimental	Control	Experimental	Control	Experimental	Control
N randomised	N = 100	N = 100	N = 100	N = 100	N = 100	N = 100
N died	**Died: 9**	**Died: 6**	**Died: 27**	**Died: 34**	**Died: 57**	**Died: 77**
Hypothetical LSmean (95% CI)	2.15	-5.01	-0.55	-7.41	-1.53	-8.39
LSmean Difference (95% CI)	7.17 (3.79, 10.55)		6.86 (1.65, 12.07)		6.86 (-0.22, 13.93)	
While Alive	72	74	49	41	26	10
n with PRO score Mean (95% CI)	0.58	-3.72	-2.38	-3.01	-3.85	– 4.00
Mean Difference (95% CI)	4.29 (-062, 9.21)		0.63 (-6.93, 8.18)		0.15 (-14.75, 15.06)	
Composite	81	80	75	74	81	85
n with PRO score Mean (95% CI)	-5.82	-9.35	-26.44	-38.60	-54.16	-71.29
Mean Difference (95% CI)	3.53 (-4.16, 11.22)		12.16 (-1.15, 25.46)		17.14 (6.00, 28.28)	

[1]Hypothetical – MMRM model – change from baseline PRO score at all timepoints up to and including timepoints of interest included in the longitudinal model

[2] While alive – mean of change from baseline score for only patients alive at the timepoint (difference from t-test).

[3]Composite – after occurrence of death, assigned PRO score as “0” and recalculated change from baseline score, mean change of baseline scores at that timepoint (difference from t-test)

LSmean = least squared mean. CI = confidence interval

To illustrate the longitudinal analysis using the hypothetical strategy for ICE of death at 12 months, the Least Squares mean (LSmean) change from baseline over time until 12 months from the linear mixed model is presented in Fig. 3 using the recommendations from SISAQOL-IMI for figures, showing the number of patients included in the analysis and number of deaths over time, which allows for a transparent review of the impact of deaths over time on the conclusions. In this example, one can identify that less than half of the patients contribute a PRO score at month 12 (45.5% = (49 + 42)/(100 + 100) with the majority of the unobserved data stemming from deceased patients, casting doubt on the hypothetical strategy.

Physical function as measured with the EORTC QLQ-C30 (score range 0-100, higher scores indicating better physical functioning). The specified time point of interest is 12 months. Linear repeated measures model (MMRM) of change from baseline scores included baseline score as covariate,time as a discrete variable and a treatment by time interaction.

At each time point: Sample size (n) = patient observed data included in analysis. Intercurrent events (deaths, n) = patient data not observed due to death. Missing (n) = patient data excluded from analysis due to any other reason.

CI = confidence interval. N = all randomised patients. Dotted horizontal reference lines = threshold for within-group change over time (+ 6 improvement, -6 worsening).[28] Overall Diff = difference in mean change between groups at 12 months. Applied significance level = $p < 0.05$. Applied meaningful between-group difference in change threshold: ≥ 5 points.[28]

In summary, at 6 months, when mortality was low, the three ICE strategies produced comparable results. At 12 and 24 months, increasing mortality substantially altered the treatment effect estimates and interpretation, depending on the method selected. This divergence was most pronounced at 24 months, where mortality reached 57% in the experimental arm and 77% in the control arm. The hypothetical strategy yielded a statistically significant treatment difference favouring the experimental arm. The hypothetical approach, however, attempts to extrapolate beyond death, a questionable strategy given the high mortality rate. The while-alive approach resulted in a null finding, but with wide confidence intervals reflecting increased uncertainty due to the small remaining sample. The composite approach produced a significant treatment difference, favouring the experimental arm, though this was predominantly driven by the post-death imputation strategy rather than observed changes in PRO scores among survivors.

Discussion

The endpoint comparing treatment groups with respect to changes in PRO data over time is often a key endpoint of interest for patients, clinicians, and regulators, particularly in the context of oncology RCTs.[1–6] The statistical treatment of death in these analyses, however, represents a fundamental, yet often inadequately addressed, consideration. SISAQOL-IMI has published recommended strategies for

addressing death in RCTs within an estimand framework in the SISAQOL Toolkit, accessible online.[25] This manuscript builds on the SISAQOL-IMI recommendations by presenting further considerations for the choice of strategy to aid with the implementation of the recommendations in practice.

The motivating example and synthetic case study in this manuscript highlight the fact that the choice of strategy matters: different strategies yield variations in the size of the treatment effect, including whether these are statistically significant between treatment groups or not. In our case study, when mortality was low, the three ICE strategies produced comparable results. With higher mortality, the choice of strategy substantially altered the estimates of treatment effects and their interpretation.

In settings where deaths are expected to be uncommon or balanced in each treatment arm in the timeframe of interest specified, and deaths were unrelated to the PRO outcome of interest, the hypothetical approach may be an appropriate choice. A hypothetical strategy would thus provide a treatment effect estimate unconfounded by these incidental deaths, allowing valid inference regarding the relative treatment effect on PRO outcomes. A hypothetical strategy also aligns closely with the observed PRO data. In cancer clinical trials, this scenario of uncommon or balanced deaths that are unrelated to the PRO outcome is exemplified by early-stage disease settings where patients are often treated curatively, where deaths are relatively uncommon over the whole trial period and are attributable to causes unrelated to cancer or its treatment. The hypothetical strategy is also particularly applicable for analyses of PRO change at sufficiently early timepoints in a clinical trial, e.g., timeframes intended to identify acute treatment toxicities.

A while alive strategy is an appealing and apparently straightforward strategy and can be most appropriate in situations in RCTs where deaths are very uncommon in the timeframe of interest, such as in adjuvant treatment settings, as this maximises use of data from the majority of patients and reduces the risk of biases between the number of patients in each treatment arm included in the analysis. The results of an analysis using a while alive strategy reflects the observed PRO outcome for patients surviving over a given time period. While producing results that are subject to selection bias, and therefore biased for direct comparative treatment effects, the approach can be useful to communicate realistic estimates for PRO experience under specific conditions (e.g., what is the expected change in a symptom for a patient surviving until a specific timepoint?).

The composite strategy recognizes that death inherently represents a severely negative health state. This approach may be particularly relevant when treatment toxicity directly contributes to death and when analysing PRO endpoints such as physical functioning that is conceptually related to being alive or dead. However, when analysing disease- or treatment-specific symptoms or side effects (such as nausea or vomiting), death may not be directly associated with the PRO concept. Attributing the most severe level of a PRO score to all patients who died may therefore introduce an exaggerated mortality-driven effect and misrepresent the actual patient experience. In certain clinical ,settings, particularly a palliative care settings where the treatment aim is symptom relief and not intended to prolong life, a

composite strategy for a patient-reported symptom relief endpoint could be excluded as the strategy implies that death equals failure of symptom relief.

In most scenarios, particularly those with moderate (especially when absolute rates differ between the arms) to substantial mortality as in our example, a single analytical approach is insufficient. Instead, to properly interpret the PRO data collected in a RCT, sensitivity analyses (targeting the same estimand) and supplementary analyses (employing different estimands with alternative ICE strategies) are required to assess the plausibility of results across are range of assumptions and approaches to address the ICE of death. Care should be taken, that a difference in outcome due to different strategies is not interpreted as statistical instability, but rather as reflecting different objectives, as we have illustrated in the motivating example.

For the estimation of the treatment effect, linear mixed models, such as a MMRM are an established method and commonly used for longitudinal PRO analyses. [24,29–31] However, the underlying assumptions, including an implicit approach to addressing unobserved data due to death, should be clearly stated. In our case study, we illustrate a hypothetical approach for ICE of death using a MMRM without any explicit imputation of PRO scores (a method that implicitly treats post-death measurements as missing at random). Alternatively, hypothetical approaches could explicitly impute PRO scores after death using a multiple imputation approach (e.g., delta adjustment to assume a decrement in PRO scores after death). Other longitudinal statistical models warrant consideration depending on the estimand and context. For example, in single-arm trials settings, SISAQOL-IMI recommendations include the use of a while alive approach using a generalized estimating equation (GEE) longitudinal data analysis model and accounting for the probability of survival in the statistical analysis [20] and similar approaches could be adapted for RCTs where appropriate [21]. In addition, competing-risk analysis or truncation of follow-up at death represent conceptually distinct alternatives to other linear model approaches. [32,33]However, these methods require careful specification of the target estimand, and their application to PRO endpoints in RCTs is currently limited. Further investigation is needed to determine their practical value and implications for the interpretation of resulting treatment effects.

This work builds on the initial recommendations from SISAQOL-IMI and provides further pragmatic advice on the suitability and consequences of various strategies to account for death. We made use of a synthetic case study, informed by an actual cancer clinical trial, and further work on trial datasets would supplement this work. There is a recent example in the literature utilising a trial dataset to demonstrate strategies with up to 40% of data truncated due to death, providing a complementary look at each of these proposed approaches to account for unobserved data due to death.[33] This work supports our observation that estimated treatment effects differ with strategy and therefore, consideration of the plausibility of approaches in the specific trial setting is required.

Regardless of the choice of strategy and analysis methodology applied to account for mortality, for correct interpretation of the treatment effect on the PRO endpoint, the incidence of death over the time period should be presented transparently, distinguished from other ICEs or missing data. SISAQOL-IMI

has provided graphical templates for presenting change from baseline over time, including these elements, as used in this manuscript. [34]

Conclusions and recommendations

Robust PRO analysis requires clear research objectives, pre-specified estimands, and a transparent approach to ICEs like death. SISAQOL-IMI acknowledges there is no single optimal strategy for addressing death in PRO analysis in RCTs and recommends that such a strategy be pre-planned and justified, matching the pre-defined PRO objective of the clinical trial. Clear estimands, aligned with the study objectives, must define the timeframe of interest and explicitly specify how intercurrent events, including death, affect the outcomes.

All assumptions made in statistical models and any implicit or explicit imputations applied in the analysis must be clearly stated. The incidence of death must be distinguished from incidence of other ICEs (such as disease progression) and from missing data. Where the mortality rateis either common or imbalanced between treatment arms in the time period of interest, for appropriate interpretation of PRO endpoints, sensitivity and supplementary analysis should be conducted to assess the robustness of the results. Also, for an appropriate interpretation PRO endpoints, itis also crucial to present the incidence of death over the time period of interest aligned with changes in PRO scores, to ensure that death events are not ignored. Taking these steps are essential for enhancing the credibility and impact of PRO data in oncology clinical trials.

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Competing interests

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[9]**SISAQOL-IMI Work Package 2 Members to be listed in PubMed**

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Author Contributions

All authors contributed to the study conception and design and interpretation. Literature review was conducted by Ahu Alanya and Abigirl Machingura. Creation of the motivational example was led by

Michael Schlichting and Corneel Coens. Statistical analysis of the case study data was conducted by Rachael Lawrance, with Kim Cocks, Ahu Alanya and Corneel Coens review. The first outline draft of the manuscript was written by Rachael Lawrance and Corneel Coens; all authors contributed to authoring sections of the manuscript as well as commenting on versions of the manuscript during development. The SISAQoL-IMI WorkPackage 2 members reviewed early versions of the manuscript. All authors read and approved the final manuscript.

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Consent to Participate N/A

Consent to Publish N/A

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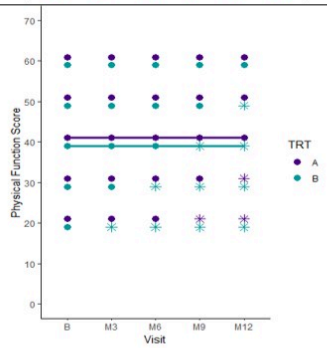
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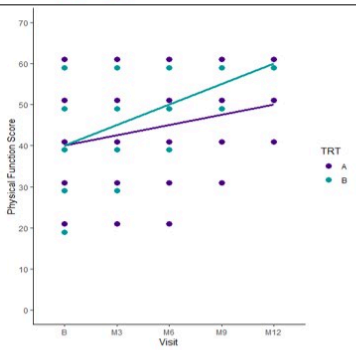
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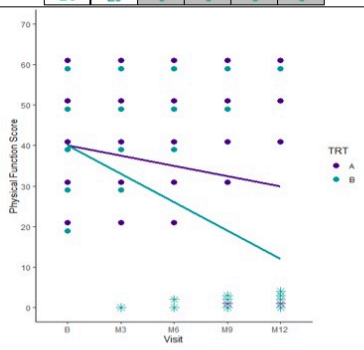
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Figures

<table>
<tr><td>Strategy for ICE death:</td><td>Hypothetical –extrapolate</td><td>While-alive</td><td>Composite – assign score “0” post death</td></tr>
<tr><td>Physical function (PF) scores
(0-100)
Higher score = better physical functioning</td><td>
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<tr><th>Trt A</th><th>B</th><th>M3</th><th>M6</th><th>M9</th><th>M12</th></tr>
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<tr><td>Mean Change from baseline to Month 12</td><td>Trt A: 40 - 40 = 0 points
Trt B: 40 - 40 = 0 points
Difference: 0 points</td><td>Trt A: 50 - 40 = 10 points
Trt B: 60 - 40 = 20 points
Difference: -10 points</td><td>Trt A: 30 – 40 = -10 points
Trt B: 12 – 40 = -28 points
Difference: 18 points</td></tr>
<tr><td>Conclusion</td><td>No change in PF
No effect of treatment on PF</td><td>PF improves in Trt A and Trt B
Greater improvement in Trt B</td><td>PF decreases in Trt A and Trt B
Greater decreases in Trt B</td></tr>
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Footnote for Figure 1: ICE = intercurrent event; PF = physical function PRO score; Trt = Treatment

Figure 1

Motivating Example: Mean changes from baseline in PRO score using different approaches for ICE of death

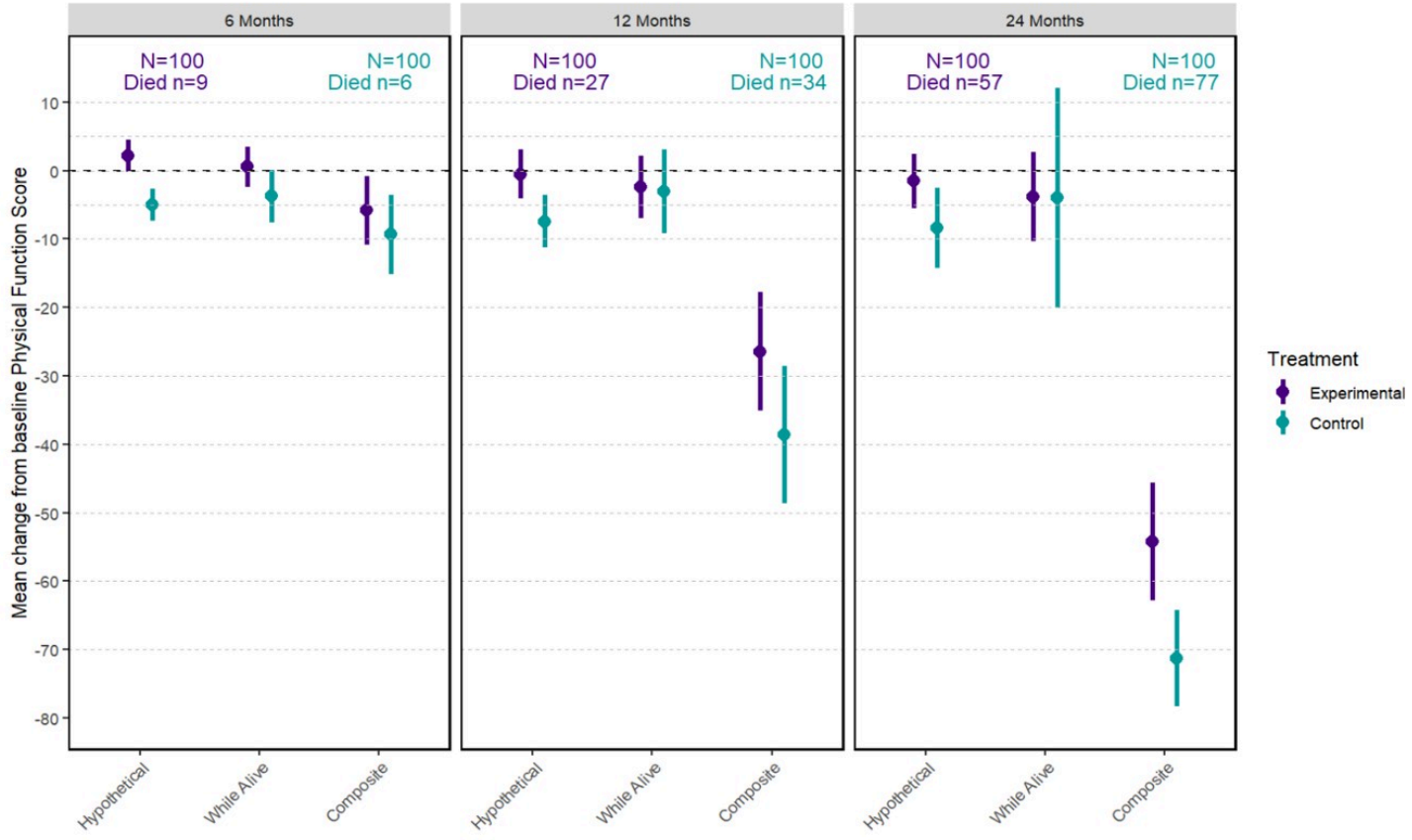
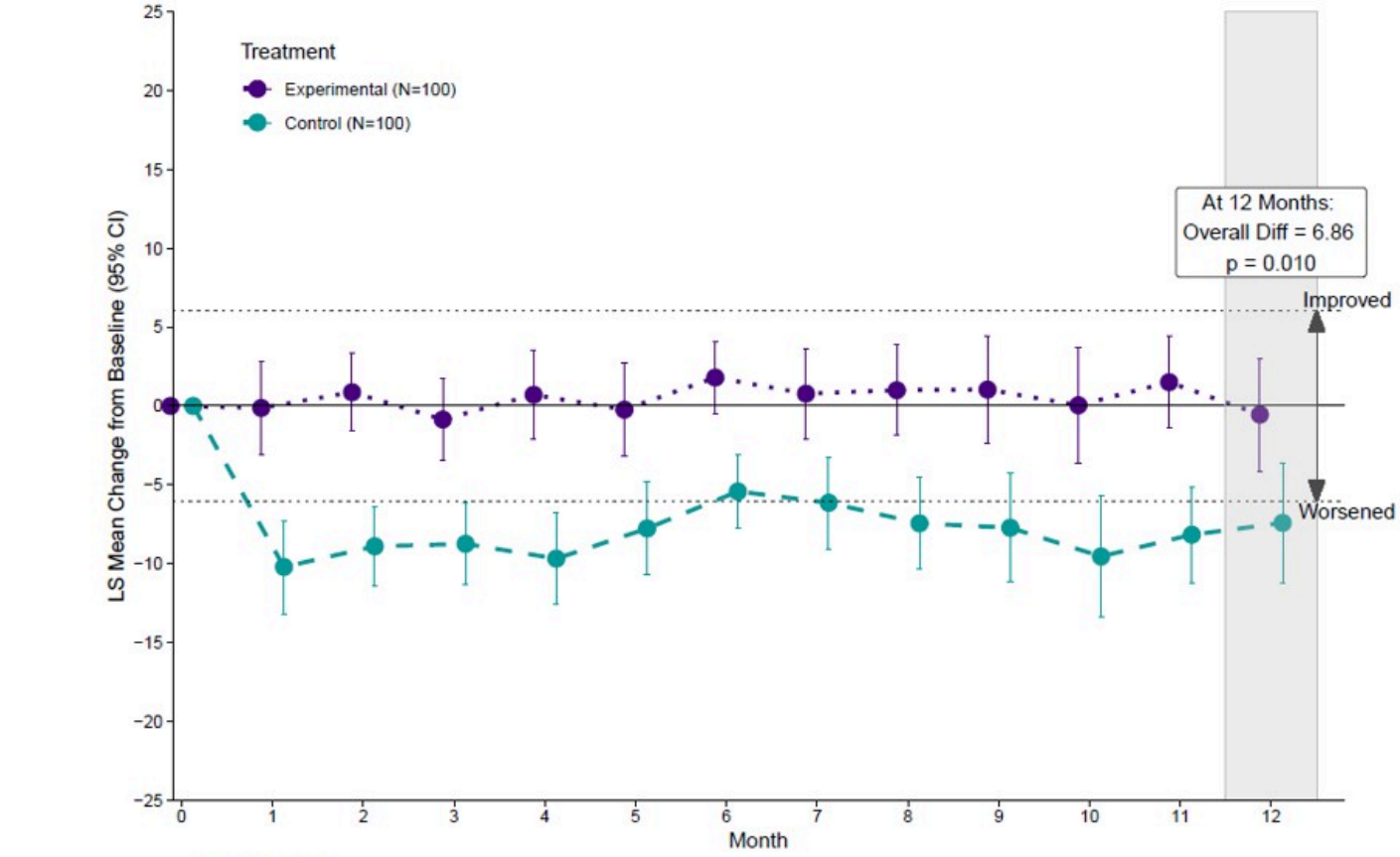


Figure 2

Case Study: Mean change from baseline in EORTC QLQ-C30 Physical Function Score (95% CI)



Sample size (n)													
Experimental	97	94	92	86	83	79	72	72	67	62	61	54	49
Control	98	97	88	88	81	79	75	69	65	63	54	48	42
Intercurrent events (deaths, n)													
Experimental	0	0	0	1	2	6	9	11	15	19	20	25	27
Control	0	0	0	0	2	4	6	11	15	18	23	30	34
Missing (n)													
Experimental	3	6	8	13	15	15	19	17	18	19	19	21	24
Control	2	3	12	12	17	17	19	20	20	19	23	22	24

Figure 3

Case Study: Timepoint: 12 months, ICE death – hypothetical strategy; LSmean Change from baseline in EORTC-QLQ C30 physical function score

Physical function as measured with the EORTC QLQ-C30 (score range 0-100, higher scores indicating better physical functioning). The specified time point of interest is 12 months. Linear repeated measures model (MMRM) of change from baseline scores included baseline score as covariate,time as a discrete variable and a treatment by time interaction.

At each time point: Sample size (n) = patient observed data included in analysis. Intercurrent events (deaths, n) = patient data not observed due to death. Missing (n) = patient data excluded from analysis due to any other reason.

CI = confidence interval. N = all randomised patients. Dotted horizontal reference lines = threshold for within-group change over time (+6 improvement, -6 worsening).[28] Overall Diff = difference in mean change between groups at 12 months. Applied significance level = p <0.05. Applied meaningful between-group difference in change threshold: ≥ 5 points.[28]

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AppendixAandB.docx