Official title:

NAVIGATE – Improving Survival and Quality of Life in Vulnerable Lung Cancer Patients Through Nurse Navigation, Symptom Monitoring and Exercise: Study Protocol for a Multicenter Randomized Controlled Trial

NCT number: NCT05053997

Statistical analysis plan

December 20, 2025

Power considerations

The power calculation is based on a hierarchical composite outcome consisting of survival and Global Quality of Life (QoL) at 3 months [1], with survival prioritized over QoL as measured by the Global Health Status (a subscale of EORTC QLQ-C30). A previous randomized controlled trial included 84 older patients diagnosed with advanced pancreatic, biliary, or lung cancer who were randomized to either a control group or an exercise-based intervention [2]. The intervention group had lower baseline QoL compared with the control group, but the intervention improved QoL to a level comparable to that of the control group, with a mean difference in change of 13 point [2]. The larger sample size in Navigate is expected to result in a more balanced randomization between groups, thereby increasing our ability to detect a comparable intervention effect on QoL. With a power of 80% and a significance level of 5% (two-sided), we will be able to detect a mean difference of at least 8.7 in QoL (assuming a standard deviation of 20 of QoL at 3 months in line with previous studies [2,3], a survival rate of 86% in the control group and 89% in the intervention group at 3 months, and a dropout rate (missing QoL) of 5% at 3 months), when including a total of 250 patients (125 per group). The calculation is based on the Win Ratio [1] and performed by simulation.

Statistical Analyses

Primary Analysis

The primary outcome is a composite of 3-month survival and Global Quality of Life (QoL) measured at 3 months. In the primary analysis, we will estimate the overall effect of the intervention on the composite outcome of survival and QoL using the Win Ratio method with a hierarchical ordering where survival is prioritized over QoL [1]. The analysis will be stratified according to the randomization stratification variables [4]. Multiple imputation using baseline covariates and scores from the EORTC manual will be implemented if there is a substantial amount of missing data for QoL (survival is always observed).

Secondary and supplementary analyses

To further characterize the intervention effects, the following supplementary analyses will be conducted:

1. Survival analysis:

- o Survival probabilities up to 12 months after inclusion will be estimated using the Kaplan–Meier method.
- o Differences between groups will be assessed by the log-rank test and visualized by survival curves.

2. Causal analysis of QoL among always-survivors (SACE) at 3 months [5]:
   - o To account for differential survival, we will estimate the Survivor Average Causal Effect (SACE), which is the average intervention effect on QoL among the subset of patients who would have survived at 3 months under both intervention and control arms [5].
   - o The SACE will be estimated according to the approach by Hayden et al. (2005), providing a causal interpretation within a hypothetical population [5].
   - o Baseline QoL and other covariates will be included in the estimation process to improve precision and adjust for potential imbalances.

3. Descriptive analysis of QoL among survivors at 3 months:
   - o Mean QoL scores at 3 months will be compared between groups using a two-sample t-test.
   - o As survival differs between groups, this comparison may be biased due to selection bias ("truncation by death") and thus lacks a causal interpretation, as the groups are no longer comparable among survivors at 3 months [6].

QoL measured at 6 and 12 months, as well as other secondary outcomes, such as treatment adherence, physical and psychological symptoms, self-efficacy, and health behavior, will be analyzed using the same analytical approaches described in methods 2 and 3 above.

To explore differences in changes over time between intervention and control groups, longitudinal analyses of QoL and other quantitative outcomes may be conducted using pattern-mixture models [7] or joint models of QoL and survival [8]. These methods allow for adjustment of baseline imbalances, account for within-patient correlations and handle informative drop-out due to death or drop-out.

References

1. Pocock SJ, Gregson J, Collier TJ, Ferreira JP, Stone GW. The win ratio in cardiology trials: lessons learnt, new developments, and wise future use. *Eur Heart J*. Nov 21 2024;45(44):4684-4699. doi:10.1093/eurheartj/ehae647

2. Mikkelsen MK, Lund CM, Vinther A, et al. Effects of a 12-Week Multimodal Exercise Intervention Among Older Patients with Advanced Cancer: Results from a Randomized Controlled Trial. *Oncologist*. 2022;27(1):67-78. doi:10.1002/onco.13970

3. Bloch Z, Jensen S, Sørensen V, Langer SW, Quist M. The Effect of Exercise on Quality of Life in Patients With Advanced Lung Cancer: A Secondary Analysis of a Randomized Controlled Trial. *Clin Lung Cancer*. Nov 2025;26(7):e582-e590. doi:10.1016/j.cllc.2025.07.005

4. Dong G, Qiu J, Wang D, Vandemeulebroecke M. The stratified win ratio. *J Biopharm Stat*. 2018;28(4):778-796. doi:10.1080/10543406.2017.1397007

5. Hayden D, Pauler DK, Schoenfeld D. An estimator for treatment comparisons among survivors in randomized trials. *Biometrics*. Mar 2005;61(1):305-10. doi:10.1111/j.0006-341X.2005.030227.x

6. Colantuoni E, Scharfstein DO, Wang C, et al. Statistical methods to compare functional outcomes in randomized controlled trials with high mortality. *BMJ (Clinical research ed)*. Jan 3 2018;360:j5748. doi:10.1136/bmj.j5748

7. Pauler DK, McCoy S, Moinpour C. Pattern mixture models for longitudinal quality of life studies in advanced stage disease. *Stat Med*. Mar 15 2003;22(5):795-809. doi:10.1002/sim.1397

8. Touraine C, Cuer B, Conroy T, Juzyna B, Gourgou S, Mollevi C. When a joint model should be preferred over a linear mixed model for analysis of longitudinal health-related quality of life data in cancer clinical trials. *BMC Med Res Methodol*. Feb 10 2023;23(1):36. doi:10.1186/s12874-023-01846-3