NICO Final Statistical Analysis Plan Addendum

The trial was stopped early and given the sample size it would not be appropriate to conduct the specified statistical analyses in the current final statistical analysis plan (v2.0).

The following will not be performed/included:

1. The methods described in Section 4.3 'Identification and handling of outliers' will not be performed, data will be summarised and extreme values will be identified from summary statistics.
2. There will be no quality of life analyses carried out that require adjustment for covariates as described in Section 4.4 'Adjustment for covariates'.
3. Missing data will be summarised in tables and the methods described in Section 4.6 'Multiple imputation', will not be performed.
4. Analysis of the data will be conducted using an 'Intention to Treat' approach and no Per-protocol analyses as described in Section 4.7 will be conducted.
5. Given the sample size it would not be appropriate to conduct 'Subgroup analyses' as described in Section 4.8 (univariate and multivariate):
    - Logistic regression models for one-year disease free survival rate.
    - Cox Proportional Hazards models for disease free survival and overall survival.
    - Logistic and Poisson regression models for surgical outcomes. Instead the infection, free-flap failure and peri-operative mortality rates and 95% confidence intervals will be presented for each cohort separately. For length of hospital admission, the mean length and 95% confidence interval will be presented.
6. Testing of the proportional hazards assumption using Schoenfeld residuals (Section 4.12) due to the fact that Cox PH models are not being considered.
7. There will be no statistical testing procedures performed – no hazard ratios and p-values will be presented; no log rank and chi-squared tests will be performed.
8. Joint modelling of quality of life and disease-free survival will not be conducted.
9. Integrated quality of life and time-to-event product method will not be conducted.

The following will be added to the report:

1. The mean and 95% confidence interval for the change from baseline to end of treatment for each of the symptom scales/ items of the EORTC QLQ-H&N35.
2. So that information required for the upload of results to EudraCT is available the following will be presented:
    - Age categorised into '18-64 years', '65 to 84 years' and '85 years and over' will be added to the baseline characteristics table.
    - Adverse events (AE) and serious adverse events (SAE) will be presented using MedDRA coding rather than CTCAE short term.

- All AEs not just those that are Grade 3+ will be presented. All SAEs will be presented not just those that are the worst SAE for each type for each patient. In particular, the number of patients affected by and occurrences of each AE and SAE will be reported.
- Additionally, for each SAE the number of occurrences that were related to Nivolumab will be reported.
- Deaths – total number of deaths (all causes) and total number of deaths resulting from serious adverse events.

3. The minimum and maximum disease-free survival time, overall survival time and length of hospital admission will be presented.

Clarifications:

1. Overall survival is defined as the time from recruitment until death by any cause. In Section 4.9.2, the formulae for calculating OS time should be:

- OS Time (Death) = (Date of Death – Date of Registration)/30.44
  OS Time (Alive) = (Date of End of Study/Date last known alive – Date of Registration)

Approval:

Trial Statistician

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Signed*: 

Date: 28 Feb 2023

Senior Statistician

Name: Dr Ashley Jones

Signed*: 

Date: 28 Feb 2023

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Date: 2 Mar 2023

*Signature should be evidenced via physical signature (wet-ink or electronic).