East and North Hertfordshire
NHS Trust

Statistical Analysis Plan:

Robotic Prostatectomy Artificial Intelligence Low Pressure Pain Study Trial - "The monitoring of patients outcomes intraoperatively and perioperatively using the Airseal and Stryker insufflator undergoing Robotic Assisted Laparoscopic Prostatectomy at a pressure and stability of pneumoperitoneum of 8 mmHg".

Short Title: Robotic Prostatectomy Artificial Intelligence Low Pressure Pain (RALP) Trial

Version number: 1

Version date: 15/11/2024

IRAS ID: 346481

Data Analysis Plan

The data analysis plan has been planned in order to conform to best current statistical practice and the reporting of analyses in accordance with the relevant sections of the CONSORT 2010 Statement and Checklist (Schulz et al., 2010). It is anticipated that it will also enable reporting to conform to the updated CONSORT 2024 Statement (when that is released) or will be enhanced in response to it. Analysis will be on a "per protocol" basis as departures from the randomised allocation (which will be fully reported) are not a matter of participant adherence to study protocol.

Descriptive Statistics

Summary statistics regarding the conduct of the trial will be presented, including the numbers of participants randomly assigned, drop-outs and exclusions, separately for each arm of the trial, along with dates of recruitment and follow-up.

Baseline demographic and relevant clinical characteristics will be presented for participants in each arm of the trial. The number of participants in each group in subsequent analyses will be given, along with details of any changes of groups that might have occurred since the original assignments.

Primary Outcomes

The primary effectiveness outcome is the pain associated with use of the two insufflator devices. Pain will be measured during and immediately after surgery in the recovery room and then by 6-hour increments, measured by a 0 – 10 Numeric Rating Scale (NRS) and a PMD-200 nociception monitor.

Summary descriptive statistics for these outcomes will be given for each arm of the trial and modelling undertaken, as described below. Confidence intervals and both absolute and relative effect sizes will be reported where appropriate.

For the measure of pain obtained using the PMD-200 nociception monitor, longitudinal analysis of covariance will be used as the method of analysis. Incorporation of a baseline measure into the analysis will be undertaken in accordance with the recommendations contained in Twisk et al. (2018), including the use of a random effect to allow for the correlation between the baseline and non-baseline measurements at the individual level. Random effects will also be included to allow for different surgeons undertaking operations.

For the NRS, it is the intention to again used longitudinal analysis of covariance with the pain measure as a continuous variable. However, if the distribution of the pain measure is such that it is more appropriate to treat it as an ordinal categorical variable, then the analysis will take that approach.

For both analyses, adjustment for differences between the two arms of the trial will be undertaken by the inclusion of potential confounding covariates.

For testing of significance, the residuals of the fitted models will be examined to assess the reasonableness of assumptions. In the event of assumptions being untenable, robust methods such as bootstrapping will be used.

Secondary Outcomes

Secondary measures relate to the procedure being undertaken (e.g. procedure time, number of times insufflator settings adjusted) and post-operative measures (e.g. length of recovery room stay, length of hospital stay, severity of postoperative nausea/vomiting).

Summary descriptive statistics for these outcomes will be given for each arm of the trial and modelling undertaken, as described below. Confidence intervals and both absolute and relative effect sizes will be reported where appropriate.

For variables which can be regarded as continuous in nature, analysis of covariance will be carried out, including the use of a random effect to allow for different surgeons undertaking operations. Adjustment for differences between the two arms of the trial will be undertaken by the inclusion of potential confounding covariates.

While some secondary outcomes (e.g. procedure time) may clearly be regarded as continuous, it will be necessary to explore the distribution of others (e.g. length of recovery room stay, length of hospital stay) to ascertain whether it might be more appropriate to derive ordered categorical variables and analyse these. In this case, the analysis of covariance will again be used, employing methods suitable for an ordered category response.

Secondary measures which are counts (e.g. number of times insufflator settings adjusted) will be analysed using methods for count data, with these methods being chosen in a manner recommended by Jakobsen et al. (2015).

For testing of significance, the residuals of the fitted models will be examined to assess the reasonableness of assumptions. In the event of assumptions being untenable, robust methods such as bootstrapping will be used.

Other variables which are categorical in nature will be analysed using methods appropriate to the variables under consideration, such as chi-square tests and/or exact tests.

Ancillary analyses

Where ancillary analyses of undertaken of other outcomes or where subgroups are analysed, it will be made clear that these are not pre-specified. The rationale for undertaking these analyses will be given.

Software

It is anticipated that R statistical software will be used to undertake the analyses for the trial. The individual R packages and version numbers that are used for analyses will be reported.

Departures from protocol, exclusions and serious adverse events

Any departures from protocol which occur will be fully reported, as will the reasons for any exclusion of participants and any serious adverse events.

References

Jakobsen, J.C., Tamborrino, M., Winkel, P., Haase, N., Perner, A., Wetterslev, J. & Gluud, C. (2015) "Count data analysis in randomised clinical trials", *Journal of Biometrics & Biostatistics*, 6, 227.

Schulz, K.F., Altman, D.G., Moher, D., CONSORT Group (2010) "CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials". *PLoS Medicine*, 7, 3, pp1-7.

Twisk, J., Bosman, L., Hoekstra, T, Rijnhart, J., Welten, M. & Heymans, M (2018) "Different ways to estimate treatment effects in randomised controlled trials", *Contemporary Clinical Trials Communications*, 10, pp80-85.