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Statistical aspects of the study protocol

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Background

Rezūm Water Vapor Therapy is a minimally invasive treatment to reduce prostate tissue and relieve lower urinary tract symptoms (LUTS) caused by an enlarged prostate, or benign prostatic hyperplasia (BPH). Data on efficacy, the longevity of its efficacy, safety/complications and groups of indications are still limited and refer to relatively small numbers of cases in cohort studies (McVary et al., 2020; Bole et al., 2020; Johnston et al., 2020; Garden et al., 2021; Siena et al., 2021; Alegorides et al., 2020; Wong & Mahmalji, 2020; Haroon et al., 2021; Baboudjian et al., 2021; Miller et al., 2020; Ines et al., 2021) and one sham comparison study (McVary et al., 2021). Beyond randomized controlled trials that evaluate Rezūm against a reference procedure to confirm the first promising clinical results and to evaluate mid- and long-term efficacy and safety, real world data from a large cohort of patients who are treated with Rezūm in the clinic and followed up over several years are also needed to evaluate the therapy in the treatment of BPH and male LUTS.

The present study therefore aims to follow Rezūm patients prospectively in a multicenter, German-language, web-based database. Data will be collected on patient reported outcome measures (PROMs) and on efficacy of the procedure, outcome of sexual function, tolerance of the chosen anesthesia (patients' perception), surgical safety, effectiveness of the chosen antimicrobial prophylaxis, physicians' and patients' preference for using Rezūm in BPH treatment, and clinical outcome parameters for patients who underwent pressure flow studies. The number of patients that are planned to be recruited takes year-to-year dropout and the subgroup analyses into consideration.

11 STATISTICAL METHODS

Detailed methodology for summaries and statistical analyses of the data collected in this study will be documented in a statistical analysis plan. The statistical analysis plan will be finalized before database closure and will be under version control at the Clinical Trial Unit, University Hospital Basel.

11.1 Hypothesis

The primary endpoint of the study is symptom reduction from baseline to five-year follow-up as measured by the international prostate symptom score (IPSS). The IPSS is scored on a 0 to 35 scale with higher scores indicating greater frequency of BPH symptoms (Barry et al., 1995).

The investigators hypothesize that the mean difference between IPSS at five year follow-up and at baseline is different than zero:

$\mathbf{H_0}$: $\delta_{\text{IPSS}_{5\ \text{years}}-\text{IPSS}_{\text{baseline}}} = 0$

$\mathbf{H_A}$: $\delta_{\text{IPSS}_{5\ \text{years}}-\text{IPSS}_{\text{baseline}}} \neq 0$

11.2 Determination of sample size

Simulations were used to estimate the number of patients that should be recruited into the cohort. Specifically, we generated 1000 synthetic datasets for a range of potential sample sizes and possible reductions in IPSS score from baseline to five-year follow-up. We then applied the intended analysis (a linear mixed effects model with IPSS score as the outcome) to each of the simulated datasets, both for the overall study group and for subgroups of varying sizes and subgroup effect sizes. We modeled measurement time point (five-year follow-up vs. baseline) as a fixed effect and patient ID as a random effect.[1] For the subgroup analyses, we assigned varying percentages of the patients to a given subgroup and varied the difference in IPSS score expected between the two subgroups at five-year follow-up (assuming that the difference between the groups was symmetric around the overall effect)[2] and added an interaction term between measurement time point and subgroup membership.

The sample size calculations are based on the following assumptions:

- The mean IPSS score at baseline is 22 with a standard deviation of 4.8 (based on a multicenter randomized sham-controlled Rezūm trial (McVary et al., 2021))
- The minimal important difference in IPSS score is 5.2 (Blanker et al., 2019), and this is the effect that should be shown at five-year follow-up
- The standard deviation of the IPSS score is 7.8 at five-year follow-up

In addition, we assumed that the intra-patient correlation (the degree to which the two measurements for each patients are correlated with each other) is 0.7.

[1] In the actual analysis of the data, study center can be included as an additional random effect in the model.

[2] We modeled the main effect assuming a subgroup distribution of 50% in each of the two groups.

11.2.1 Overall group analysis

Assuming that Rezūm improves IPSS scores after five years by 5.2 points, 14 patients are needed to show a difference between the scores at baseline and five-year follow-up. This sample size allows detection of a reduction in IPSS scores after 5 years with 90 % probability (power), assuming that Rezūm really does reduce IPSS by 5.2 points on average.

Figure 1 shows how the sample size required from each small center depends on the true absolute decrease in IPSS from baseline to five-year follow-up.

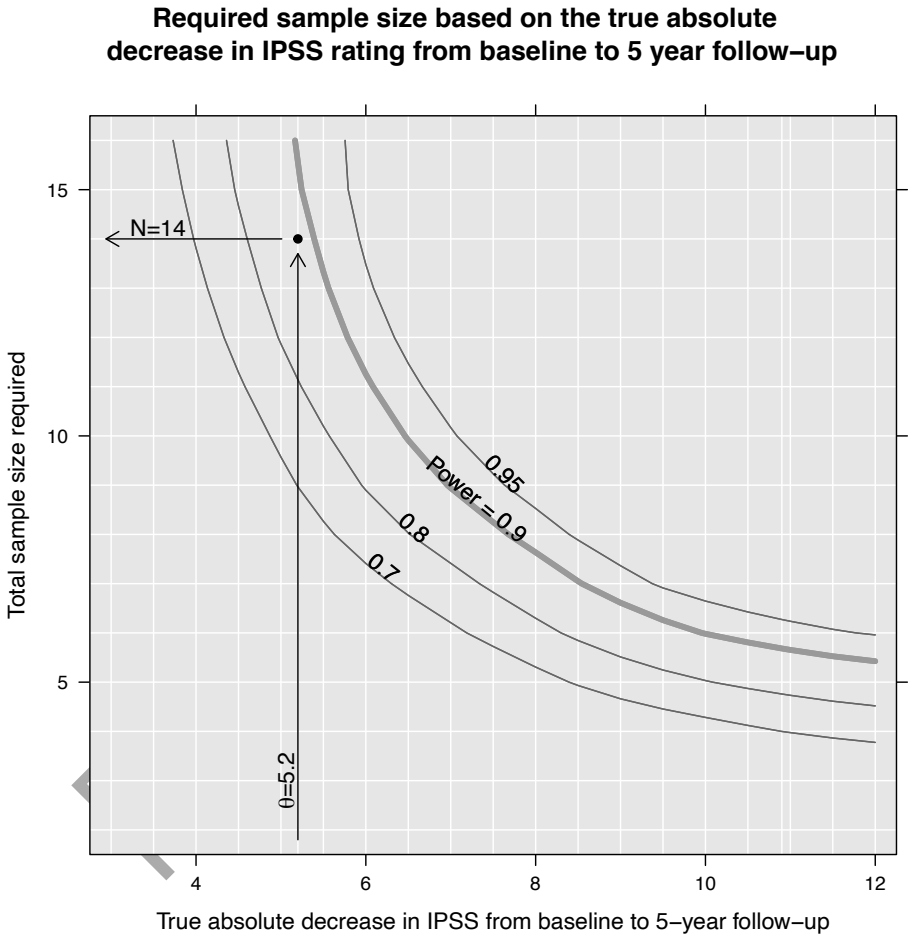

Figure 1: Sample size based on the true absolute decrease in IPSS rating from baseline to five-year follow-up. Values for power of 0.7, 0.8, 0.9, and 0.95 (i.e., 70 %, 80 %, 90 %, and 95 %) are shown. (The curves are smoothed and are shown for illustration purposes only.)

11.2.2 Subgroup analyses

We considered the subgroups of interest (described in section 11.4.3 below) and ran simulations for varying subgroup sizes as a proportion of the entire study population and possible subgroup effect sizes.

Our simulations show that if the smaller of two subgroups that are compared makes up 10% of the study population (as we expect for the subgroup of catheter-dependent patients, for example), the overall effect size is a reduction of 5.2 points and there is an absolute difference of 3 points on the IPSS between the subgroups, then 408 patients are needed to detect a subgroup effect with a power of 90 % (see figure 2).

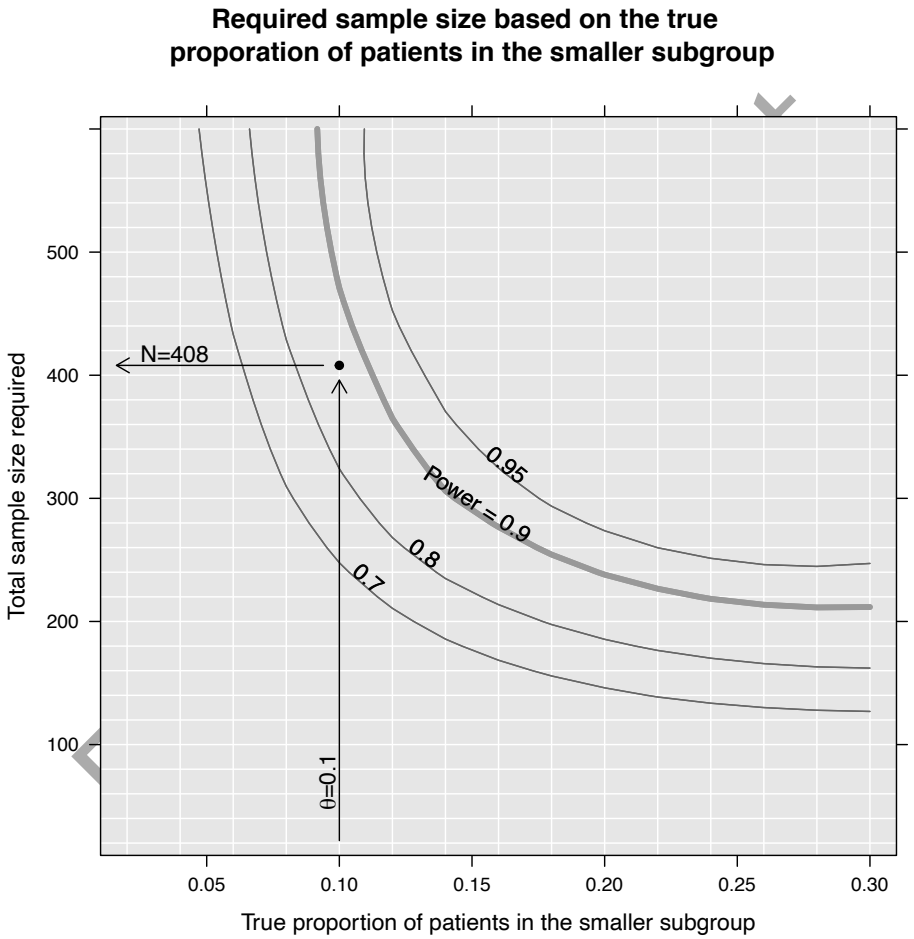

Figure 2: Sample size based on the true proportion of patients in the smaller subgroup. Values for power of 0.7, 0.8, 0.9, and 0.95 (i.e., 70 %, 80 %, 90 %, and 95 %) are shown. (The curves are smoothed and are shown for illustration purposes only.)

11.2.3 Accounting for dropout

Given that 15% of patients are expected to drop out each year, 920 patients should be recruited into the study in order to have 408 patients left after five years. We recommend rounding this number to 1000 due to uncertainty in the assumptions made and because adding center as a random effect into the model could further reduce the power.

11.3 Statistical criteria of termination of trial

None.

11.4 Planned analyses

11.4.1 Datasets to be analyzed, analysis populations

This study is a prospective, observational multi-center study with a follow-up period of five years. Data will be collected in a web-based German-language registry database designed and supported by Heartbeat Medical. Up to 20 study centers in Switzerland, Germany and Austria with experience treating patients with Rezūm will collect baseline data, clinical follow-up data and patient-reported outcome measures (PROMs) from the Rezūm patients they treat using the database. It is estimated that the participating centers can each recruit an average of 50 patients within 18 months. Patients' data and PROMs will be collected at baseline before Rezūm therapy, at day of surgery, at day of catheter removal, 1 month, 3 months, 6 months, and annually for 5 years.

Patients will be recruited who would have been treated with Rezūm independent of the study. All patients who are treated with Rezūm in the participating study centers by a certified surgeon can be included if they agree to participate in the study; otherwise, there are no specific inclusion/exclusion criteria beyond including only males ages ≥ 18.

11.4.2 Primary analysis

The mean difference between IPSS at five year follow-up and at baseline will be assessed using a linear mixed effects model with IPSS score as the outcome. The measurement time point will be measured as a fixed effect, and patient ID (possibly nested within center ID) will be included as a random effect. For the subgroup analyses, the group membership will be included as an interaction with measurement time point.

11.4.3 Secondary analyses

The primary endpoint, i.e., change in IPSS, will be assessed at each other measurement time point (after one month, three months, six months, and annually over five years) in secondary analyses.

The following secondary outcomes will also be assessed:

- Urinary flow rate measured using iUFlow uroflowmetry (automatic uroflow at home) (iUFlow, 2021)
- Post voiding residual volume (PVR)
- Prostate size (in ml)
- Quality of life score (QoL) from the IPSS questionnaire

- Incontinence measured using the International Consultation on Incontinence Questionnaire for male lower urinary tract symptoms (ICIQ-MLUTS) (Donovan et al., 2000)
- Reoperation rate
- Sexual function, including erection, ejaculation, and sexual satisfaction measured using the following questionnaires:
  - Male Sexual Health Questionnaire (MSHQ) (validated and available in German) (Rosen et al., 2004; Rosen, 2006)
  - MSHQ-EjD (Short Form for Assessing EjD) (validated and available in German) (Rosen et al., 2004; Rosen, 2006)
  - International Consultation on Incontinence Questionnaire Male Sexual Matters Associated with Lower Urinary Tract Symptoms Module (ICIQ-MLUTSsex) (Frankel et al., 1998)
- Type of anesthesia used, including reason for type of anesthesia and postoperative recovery using the following questionnaires:
  - Quality-of-Recovery-Score (QoR-15GE) (Kahl et al., 2021) at the first postoperative day
  - Questionnaire to evaluate patients' satisfaction with surgery and anesthesia at the first postoperative day
- In case of local anesthesia/analgosedation, the patients' perception of pain during the during Rezūm procedure will be assessed using a Numeric pain rating scale (NRS) from 0 to 10.
- Effectiveness of the chosen antimicrobial prophylaxis (infection vs. no infection)
- Patients' and practitioners' reasons for choosing Rezūm using self-designed questionnaires and validated preference measurement tools (Malde et al., 2021; Emberton, 2010; Bai et al., 2018)
- Changes in bladder outlet obstruction index (BOOI) and bladder contractility index (BCI) among those who underwent pressure flow studies (Nitti, 2005)

These endpoints will be assessed using the same mixed models framework that will be used for assessing the primary outcome. Patients' perception of pain in the case of anesthesia and infection status will only be evaluated at the first measurement time point (after one month). We will use linear mixed models for the continuous outcomes and mixed logistic regression models for the binary outcomes. We will present the types of of anesthesia used and reason for type of anesthesia as well as patients' and practitioner's reasons for choosing Rezūm descriptively. In addition, we will examine the relationship between changes in the bladder outlet obstruction index (BOOI) as well as the bladder contractility index (BCI) after undergoing the Rezūm intervention and changes in the clinical outcome parameters IPSS and MCIQ-MLUTS among patients who undergo pre- and post-operative pressure flow examinations using linear regression models. For these analyses, we will use the outcome measurements taken closest to the time of the post-Rezūm pressure flow examination.

Subgroup analyses

As alluded to above, one of the motivations behind recruiting a large cohort is the ability to conduct subgroup analyses. The main subgroup analyses of interest for the outcomes IPSS reduction, uroflow improvement, and reoperation rate are the following:

- Larger prostate size of > 80 ml (expected in about 20% of the study population)
- Chronic urinary retention, i.e., catheter-dependence (expected in about 10-15% of the population)

In addition, subgroups based on the following characteristics will be examined for surgical safety outcomes, i.e., intra- and post-operative complications, such as a higher incidence of bleeds:

- Anticoagulation
- Age ≥ 80 years old
- Fragility or comorbidities identified by the Charlson Comorbidity Index (Sundararajan et al., 2004) (making patients or patients only eligible for local anesthesia or analgosedation)

11.4.4 Interim analyses

After 18 months, the state of recruitment will be assessed. If the number of patients recruited is far below the 1000 patients planned, we will conduct an interim sample size reassessment. Several of the assumptions used to calculate the sample size, including size of subgroups, effect size at last time point, intra-patient correlation, variance, etc., will be examined using the patients for whom data have already been collected. The sample size simulations will be rerun using the updated assumptions. If fewer patients are required to perform the most important subgroup analyses under the updated assumptions, the sample size will be updated.

11.4.5 Safety analysis

Surgical safety will be assessed by recording intraoperative complications defined by the ClassIntra classification (Dell-Kuster et al., 2020) as well as 30-day postoperative complications defined by the Clavien-Dindo classification (Dindo, 2014).

11.4.6 Deviation(s) from the original statistical plan

If substantial deviations of the analysis as outlined in these sections are needed for whatever reason, the protocol will be amended. All deviations of the analysis from the protocol or from the detailed analysis plan will be listed and justified in a separate section of the final statistical report.

11.5 Handling of missing data and dropouts

We expect 15% dropout per year. This has been accounted for in the sample size calculation. The analyses will be conducted at each planned assessment time point using the available cases. We will quantify the dropout each year and calculate summary statistics of baseline characteristics and last measurements taken prior to dropout for those who drop out compared to those who remain in the study.

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