Universitätsspital Basel

SteamOne
Prospective Registry Database for Rezum water vapor therapy of the prostate

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) (1).
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Risk category A acc. to ordinance HRO Art.7
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PROTOCOL SIGNATURE FORM

Study Title	SteamOne Prospective Registry Database for Rezum water vapor therapy of the prostate

The project leader (main center) and the investigator (at the local center/site) have approved the protocol version *1.3 dated 10.02.2023* and confirm hereby to conduct the project according to the protocol, the Swiss legal requirements (1,2), the current version of the World Medical Association Declaration of Helsinki (3) and the principles and procedures for integrity in scientific research involving human beings.

Project leader (lead center/site) and investigator (local center/site)

University Hospital Basel - Department of Urology – Spitalstrasse 21 – CH-4031 Basel, Switzerland

Name: Jan Ebbing, MD

Date: _____ Signature: _____

The statistician of the Clinical Trial Unit (CTU) of the Department of Clinical Research (DKF) has checked and approved the statements and data in chapters 4 and 4.1 of the protocol version 1.3 dated 10.02.2023

DKF statistician

University Hospital Basel – Department of Clinical Research (DKF) – Spitalstrasse – CH 4031 Basel, Switzerland

Name: _____

Date: _____ Signature: _____

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GLOSSARY OF ABBREVATIONS

AES	*Advanced Encryption Standard*
ASP	*Application Service Provider*
BASEC	*Business Administration System for Ethical Committees*
BCI	*Bladder Contractility Index*
BOO	*Bladder Outlet Obstruction*
BOOI	*Bladder Outlet Obstruction Index*
BPH	*Benign Prostate Hyperplasia*
BPO	*Benign Prostate Obstruction*
CNS	*Central Nervous System*
CRF	*Case report form*
CROM	*Clinical Reported Outcome Measure*
DA	*Detrusor under activity*
DO	*Detrusor over activity*
DPA	Data Protection impact Assessment
EAU	*European Association of Urology*
FOPH	*Federal Office of Public Health*
GDPR	*General Data Protection Regulation*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
IC/ICU	*Intensive Care Unit*
ICIQ-MLUTS	*International Consultation on Incontinence Questionnaire for male lower urinary tract symptoms*
ICIQ-MLUTSsex	*International Consultation on Incontinence Questionnaire Male Sexual Matters Associated with Lower Urinary Tract Symptoms Module*
ICIQ-S	*International Consultation on Incontinence - Satisfaction*
ICS	*International Continence Society*
IPSS	*International Prostate Symptom Score*
LUTS	*Lower Urinary Tract Symptoms*
MRI	*Magnetic Resonance Imaging*
MSAM	*Multinational Survey on the Aging Male*
MSHQ	*Male Sexual Health Questionnaire*
NRS	*Numeric pain Rating Scale*
PI-RADS	*Prostate Imaging-Reporting and Data System*
PROM	*Patient Reported Outcome Measure*
PROMIS	*Patient-Reported Outcomes Measurement Information System*
PVR	*Post Voiding Residual*
Qmax	*Maximum urine flow rate*
QoL	*Quality of Life*
QoR-15GE	Quality-of-Recovery-Score (German Version)
RCT	*Randomised Controlled Trials*
SaaS	*Software-as-a-Service*
UTI	*Urinary Tract Infection*

1 BACKGROUND AND PROJECT RATIONALE

Due to its minimally invasive character, the Rezum - water vapor therapy of the prostate for the treatment of lower urinary tract symptoms (LUTS) associated with benign prostate obstruction (BPO) is attracting increasing attention from both the urological experts and from patients.
Rezum is an approved treatment procedure for the treatment of BPO related male LUTS and is reimbursed by health insurance companies.
Rezum is performed transurethral by steam injections into the central or transitional zone of the enlarged prostate. The 103°C hot steam is produced by a generator and injected into the prostate tissue via a disposable handpiece with a retractable needle. About 1 injection is needed per 10ml of prostate tissue to achieve desobstruction. The single injection takes only 9 seconds. The thermal energy contained in the water vapor can develop evenly and freely in the intercellular space of the prostate by convection. This is a unique technique in the surgical desobstruction of the prostate. The steam condenses and releases the stored thermal energy to the cell membranes, which then denature. As a result, the prostate tissue shrinks about 30% in the first three months after the Rezum treatment. The shrinkage process therefore does not occur immediately, but with a time delay. The minimally invasive character results from the short operation time, the potential of Rezum to preserve sexual function (both ejaculation and erection) and the possibility to perform the Rezum procedure also in local anesthesia or analgosedation.

Data on efficacy, durability of efficacy, safety/complications and groups of indications are still limited and refer to relatively small numbers of cases in cohort studies (4–14) and one sham comparison study (15,16). The European Association of Urology (EAU) mentions Rezum under alternative ablative techniques under investigation without giving any recommendations in the use of Rezum in its guideline "Management of Non-neurogenic Male LUTS" (17). The guideline panel gives practical considerations and demands randomised controlled trials against a reference technique to confirm the first promising clinical results and to evaluate mid- and long-term efficacy and safety of water vapor energy treatment.
However, randomised controlled trials (RCTs) often examine idealized patients using outlined inclusion and exclusion criteria. Therefore, it may be difficult to draw conclusions for other patient groups or for patients in routine practice. Thus, “real life” data are just as important to determine the role of Rezum water vapor therapy in the treatment of BPO and male LUTS.
The recent development of novel minimally invasive treatment options for LUTS due to BPO, including Rezum, has increased patients´ options, and thus increased the importance of assessing and incorporating both patients´ values and preferences and physicians´ attitude and behavior towards the treatment of male LUTS, and the influence that this has on patient preferences and treatment choice. This need for considering values and preferences exits both for optimal treatment of individual patients and for the development of trustworthy clinical practice guidelines. In addition, the best or most beneficial form of anesthesia and the most beneficial form of antibiotic prophylaxis to prevent from postoperative symptomatic urinary tract infections (UTI) when performing Rezum have not yet been studied.
Furthermore, no data currently exist that show the effect of desobstruction achieved by the Rezum treatment on urodynamic pressure-flow studies.

Therefore, the study aims to record and follow-up Rezum patients prospectively in a multicenter, German-language, web-based database. We want to collect patient reported outcome measures (PROMs) and examine clinical reported outcome measures/data (CROMs) on different subgroups of patients treated with Rezum as a clinical routine treatment option for BPO related male LUTS in terms of efficacy of the procedure, outcome of sexual function and surgical safety. In addition, we want to analyse patients´ tolerance of the chosen form of anesthesia, patients´ recovery from

the chosen anesthesia, effectiveness of the chosen antimicrobial prophylaxis to prevent postoperative symptomatic UTI, physicians' and patients' preference/motivation to use Rezum in BPO and LUTS treatment, patients´ satisfaction with the Rezum treatment, patients´quality of life before and after Rezum treatment, and the effect of the Rezum treatment on urodynamic pressure-flow parameters and on magnetic resonance imaging (MRI) investigations of the prostate.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

a)
To assess the available promising clinical data of Rezum – water vapor therapy in patients with BPO and male LUTS in terms of efficacy, durability and safety in a large, prospective, multi-center cohort consisting of 1000 “real-life” patients with a follow-up of 5 years.

b)
To answer questions/endpoints of special interest in the context of a Rezum treatment (see chapter 2.2.2 and 2.2.3.1 – 2.2.3.13:

- What factors influence the effect on micturition improvement and effect duration of Rezum (e.g. prostate size, localization of injection sites, anticoagulation, comorbidities etc.)?
- How well is sexual function (erection, ejaculation, orgasm, sexual satisfaction) preserved rather influenced by Rezum?
- What factors influence periinterventional complications in Rezum treatment and what are typical side effects of a Rezum?
- How do urodynamic values in pressure-flow studies change due to the Rezum treatment?
- What changes show up in MRI scans after Rezum treatment?
- What is the rate of Rezum patients who have concurrent prostate cancer or who are diagnosed with prostate cancer during the course following Rezum treatment?
- How quickly do patients recover after Rezum treatment depending on the type of anesthesia chosen and what is the patients´ perception of pain during and after Rezum treatment?
- How does the form of antibiotic prophylaxis during Rezum treatment affect the rate of postinterventional urinary tract infections?
- What are patients' expectations of surgical treatment of BPO and of Rezum treatment and why do patients choose Rezum treatment?
- What are reasons that a practitioner uses the Rezum treatment on a patient?
- How satisfied are patients with the Rezum treatment?
- How does Rezum influence quality of life?

The majority of questions/endpoints have never been investigated in a study before.

2.2. Primary and secondary endpoints

2.2.1 Primary endpoint

The primary endpoint is change in the International Prostate Symptom Score (IPSS) five years after treatment with Rezum. IPSS is validated and available in German (18,19). The IPSS questionnaire is shown in Appendix 1. The minimal clinical difference is 5.2 points improvement.

2.2.2 Secondary endpoints in terms of efficacy of Rezum to improve micturition

- Improvement of maximum urinary flow rate (Qmax) measured by uroflowmetry.
- Decrease of post voiding residual volume (PVR) measured by ultrasound.
- Decrease of prostate size measured by ultrasound or magnetic resonance imaging (MRI).
- Retreatment rate (medical (drugs), bladder catheter and surgical)
- Improvement of International Consultation on Incontinence Questionnaire for male lower urinary tract symptoms (ICIQ-MLUTS). ICIQ-MLUTS is validated and available in German (20,21). The ICIQ-MLUTS questionnaire is shown in Appendix 2.

2.2.3 Further questions / endpoints of special interest in the context of a Rezum treatment

2.2.3.1 Efficacy of Rezum to preserve sexual function (erection, ejaculation, orgasm, sexual satisfaction)

is investigated by questionnaires for patient surveys:

- Male Sexual Health Questionnaire (MSHQ) (validated and available in German) (22–24). Erection scale, ejaculation scale and satisfaction scale are mandatory. Additional items (sexual activity and desire) are voluntary. The MSHQ questionnaire is shown in Appendix 3.
- International Consultation on Incontinence Questionnaire Male Sexual Matters Associated with Lower Urinary Tract Symptoms Module (ICIQ-MLUTSsex) (validated and available in German (25,26). The ICIQ-MLUTSsex questionnaire is shown in Appendix 4.

2.2.3.2 Surgical safety and side effects of Rezum

Surgical safety is investigated by analysing intraoperative complications classified by ClassIntra® (27–29) and 30-days postoperative complications defined by the Clavien-Dindo classification (30). The ClassIntra classification is shown in table 4, the Clavien-Dindo classification is shown in table 5.

Typical side effects of the Rezum treatment like hematopsermia, dysuria and hematuria, as well as the use of pain medication, are investigated by a self-designed patient questionnaire (Appendix 5) as part of PROMs in the first 90 days after intervention.

2.2.3.3 Anesthesia

Investigation of type of anesthesia (general anesthesia, spinal anesthesia, local anesthesia, analgosedation) incl. reason for type of anesthesia and postoperative recovery using the validated German version of the Quality-of-Recovery-Score (QoR-15GE) at the first postoperative day and two weeks after discharge from hospital.

The QoR-15 provides a valid, reliable, responsive and easy-to-use method of measuring the quality of a patient's postoperative recovery. Compared with the QoR-40 (31), it covers the same elements of quality of recovery but with fewer items and thus is more efficient in evaluating the patient's postoperative quality of recovery (32,33). The QoR-15 questionnaire is shown in Appendix 6. This endpoint has never been investigated in a study related to Rezum.

2.2.3.4 Quality of Life (QoL)

Investigation of QoL changes associated with the Rezum treatment using the PROMIS Global Health 10 questionnaire (34). This endpoint has never been investigated in a study related to Rezum. The questionnaire is shown in Appendix 19.

2.2.3.5 Patients´perception of pain during and after Rezum treatment

Investigation of patients' perception during Rezum procedure in case of local anesthesia and/or anagosedation and after Rezum treatment using Numeric pain Rating Scale (NRS) at baseline and at the first postoperative day. The NRS has the following scale: from 0 – 10 (no pain - worst pain imaginable). This is intended to query both the pain sensation during the Rezum treatment and postoperatively at day of surgery and at the first postoperative day. This endpoint has never been investigated in a study related to Rezum.

2.2.3.6 Patients´ satisfaction with clinic treatment

The ICIQ-S (International Consultation on Incontinence – Satisfaction) will be used to evaluate patient's satisfaction after urological surgery (35). The full questionnaire is answered by patients at 2 weeks, 6 weeks and 3 months. Only question 1-6 are to be answered at 6 months, 12 months and annually after surgery (Appendix 7). This endpoint has never been investigated in a study related to Rezum.

2.2.3.7 Antimicrobial prophylaxis

Investigation of the effectiveness of the chosen antimicrobial prophylaxis by analysing the rate of postoperative symptomatic urinary tract infections (UTI) within the first 30 days after surgery as part of the Clavien-Dindo classification.
Definition of symptomatic UTI is based on clinical diagnosis supported by measured bacteriuria of $\geq 10^5$ cfu/ml treated with antimicrobial agents.
This endpoint has never been investigated in a study related to Rezum.

2.2.3.8 Patients´ preferences, motivations and expectations for Rezum treatment

Investigation of patients' reasons for preference/choice of Rezum and associated expectations using self-designed questionnaires (Appendix 8 (8.1 (baseline),8.2 (follow-up 3 months), 8.3 (follow-up 6 months) and 8.4 (follow-up 1-5 years)) considering measurement tools (36–38). This endpoint has never been investigated in a study related to Rezum.

2.2.3.9 Doctors´preferences, motivations and reasons to use Rezum

Investigation of doctors´ reasons for preference/choice of using Rezum in a patient using self-designed questions. This endpoint has never been investigated in a study related to Rezum.

2.2.3.10 Influence of steam injection number and injection points

We will use a drawing in the database where practitioners can accurately draw the water vapor injection points on the prostate so that the influence of steam injection number and Injection points arrangement on outcome parameters, e.g. micturition parameters (IPSS, ICIQ-MLUTS), sexual function (MSHQ, ICIQ-MLUTSsex) prostate size, side-effects, complications can be investigated. This endpoint has never been investigated in a study related to Rezum.

2.2.3.11 Patients with pressure-flow studies (urodynamic investigations)

We like to analyse urodynamic (invasive) pressure-flow studies investigating bladder outlet obstruction index (BOOI), bladder contractility index (BCI) and detrusor (bladder muscle) overactivity (DO) before and/or after Rezum treatment in order to

1.) show the effect of Rezum on pressure-flow parameters resulting from desobstruction and investigate the relationship with PROMs (IPSS, ICIQ-MLUTS),

2.) in case of treatment failure in patients with chronic urinary retention to show that this is a result of detrusor underactivity (DU) instead of insufficient desobstruction of the prostate.

Two groups of patients are conceivable for analyzing urodynamic (invasive) pressure-flow investigations as part of study-independent routine perioperative diagnostics:

a.) Patients with available preoperative pressure-flow studies (not older than 6 months): postoperative routine diagnostics will probably not be performed in this patient group if the patient can micturate well postoperatively.
b.) Patients that might get a pressure-flow study postoperatively because of insufficient micturition (treatment failure). This group will primarily consist of patients who were preoperatively catheter dependent.

We would like to ask patients of group a), despite satisfactory micturition after Rezum treatment, to allow one further urodynamic investigation 3-6 months after Rezum therapy so that the effect of Rezum on pressure-flow values can be studied.

For patients of group b) suffering from treatment failure (unsuccessful catheter removal after surgical desobstruction of the prostate) the EAU recommends to perform urodynamic investigation (17). Therefore, urodynamics should be considered in this situation regardless of the study. Therefore, we encourage study participants to have urodynamics performed in this situation.
This endpoint has never been investigated in a study related to Rezum.

2.2.3.12 Patients with MRI investigations

MRI data not older than 12 months at time of Rezum treatment and MRI data in the follow-up period of 5 years are investigated in terms of prostate size, ablative lesions (lesions caused by Rezum) (39), PI-RADS (prostate imaging-reporting and data system) lesions (40). This endpoint has never been investigated in a study related to Rezum.

2.2.3.13 Patients with prostate cancer

Both the rate of patients under active surveillance with prostate cancer and the rate of prostate cancer detected by positive prostate biopsy in the 5 years of follow-up after treatment with Rezum is documented. This endpoint has never been investigated in a study related to Rezum.

2.3 Project design

It is a prospective, observational multicenter study recruiting patients in Switzerland, Germany and Austria.

2.3.1 Assessment of clinical and patient reported outcomes using heartbeat ONE

The study uses a web-based German-language registry database called “heartbeat ONE” by heartbeat medical solutions GmbH (Berlin, Germany) that provides both clinical reported outcome measures (CROMs) and patient reported outcome measures (PROMs). PROMs are investigated by validated questionnaires: IPSS/QoL, ICIQ-MLUTS, MSHQ, ICIQ-MLUTSsex, PROMIS Global Health 10, NRS, QoR-15GE and by home urine flow measurement (iUFlow) as well as by self-designed questionnaires to assess patients´ preferences and expectations for Rezum and for surgical therapy of the prostate, satisfaction with the Rezum therapy, side effects of the Rezum therapy, (re)medication to treat BPO and LUTS, and reoperations after Rezum therapy. The “heartbeat ONE” database is the main database of this study.

2.3.2 Kesem Health iUFlow medical uroflowmetry device

If patients have a smartphone with app function (Android or Apple), they will be provided with a certified and approved home uroflowmetry medical device (iUFlow from Kesem Health) at study entry. This should enable patients to measure their urine flow conveniently from home and thus be independent of the medical consultation (automated home bladder monitoring solution). Experience has shown that patients often do not manage to take an adequate urine flow measurement during the consultation in the clinic. Home uroflowmetry will probably improve data quality. Two iUFlow™ devices are provided for each patient in order to be able to cover the entire observation period. It is planned that the centers will be continuously supplied with devices. The devices are then handed out to the patients during the recruitment phase or hospitalization and patients are instructed by the study staff. The device-specific app, which connects to the device via bluetooth is in German language incl. the Privacy Policy (Appendix 20). When the patient opens the app for the first time, he can select the University Hospital Basel as the study clinic and insert his personal study number that he has received. The second device is shipped to the patient´s home address 24 months after the Rezum treatment and covers year 3-5 of the follow-up period. The reason for two devices is the fact that the disposable battery of the first device will be empty after two years and cannot be replaced. The devices can be disposed of via the usual battery disposal by the patient.

iUFlow™ is marketed by Kesem Health Pty Ltd, 5A Hartnett Cl, Mulgrave VIC 3170, Australia. The Device is FDA and CE approved and is approved to be used in the EU and Switzerland (see certificates in (Appendix 9). The software component of the iUFlow system is part of the medical device and is developed in accordance with the standard EN 62304:2006 / AC:2008 Medical Device Software – Software Life Cycle Processes. The development, maintenance and other relevant details are reported in SWD-002 iUFlow Software Development and Maintenance Procedure and related documents.

Every time a patient is using the device urine flow measurement data and additional voluntary parameters entered by the patient (micturition protocol, drinking protocol) will be send to the Kesem Health iUFlow study database via mobile internet or WLAN internet of the patient. The iUFlow study database is called “iUFlow Clinical Portal”, which works independently of the heartbeat ONE study database, which is the main study database that collects all CROMS and PROMS. iUFlow data is manually transferred from the iUFlow Clinical Portal to the main heartbeat ONE database by the study stuff of the University Hospital Basel (see Figure 1). Unfortunately,

an automated interface is currently not possible. If patients don't use a smartphone uroflowmetry will be performed during routine clinical follow up visits.

2.3.3 Study centers

Up to 20 Rezum centers are supposed to collect baseline data, perioperative and surgical data, clinical follow-up data (CROMs and PROMs) from the Rezum patients using the heartbeat ONE database. The data from 1000 baseline patients recruited in Switzerland, Germany and Austria are to be collected and followed up over a period of 5 years. Patients who are to be included in the database must be operated by certified urologists, that have successfully performed a Rezum training course. Clinics qualify as study sites if they have already performed more than 50 Rezum procedures and see potential to recruit 50 patients within a 12–18-months period.

In order to a) promote heterogeneity of the patient cohort and b) to increase the interest of centers to enter the study at an early stage and c) to promote centers to recruit patients quickly the following efforts are formulated beside the fact that a maximum of 20 centers can recruit 1000 patients in total:

- Study centers will get financial compensation for each patient in the study. In order to strengthen the centers' incentive to also collect the follow-up data, the compensation payments are paid out gradually.
- At least one center should recruit in each country (Switzerland, Germany, Austria).
- The number of recruiting centers per country should be equally distributed (33.3%).
- The number of patients that a single center can include is a dynamic process and is calculated on the basis of the respective number of active centers using this formula: (1000 patients − already recruited patients) ÷ number of active centers.

In order to ensure that the recruiting phase does not unnecessarily exceed the desired period of 18 months, each center is given the following minimum default values (Table 1).

Table 1 Recruitment rate

Months from initiation of site	Intended average number of recruited patients	Required minimum number of recruited patients (default values)
3	9	7
6	18	14
9	27	21
12	36	28
15	45	35
18	50	No required minimum

- If the required minimum number of recruited patients is not reached according to table 1, the site is reproved.
- If a site is reproved twice in a row, it is up to the PI to exclude a site from further recruitment.
- If a site has recruited the required minimum number of 35 patients 15 months after initiation, the site is not reproved anymore and can recruit patients until the total number of 1000 study patients is reached.
- A regular newsletter will inform the sites about the recruitment progress.

In addition to the establishment of the heartbeat ONE database at each of the participating study centers by the heartbeat company itself, each study center is planned to be initiated on site by a study nurse/coordinator and/or the PI itself. This ensures that the heartbeat database is mastered and that the responsible staff members on site are aware of the course of the study and the study protocol. The on-site training includes instruction in the iUFlow uroflowmetry, as well as in a provided tablet. Patients can use the tablet to fill out baseline and follow-up questionnaires (PROMs) at time of recruitment in the clinic, during hospitalization or during clinical follow-up visits in the clinic.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

This study recruits patients who are treated with Rezum – water vapor therapy of the prostate due to benign prostate obstruction (BPO) or male lower urinary tract symptoms (LUTS) as part of routine clinical practice. This study aims to recruit and follow-up 1000 patients prospectively in a maximum of 20 study sites in Switzerland, Germany and Austria. The follow-up time is going to be 5 years. The study is going to start in May 2022. We expect recruitment to end 18-24 months later and the trial to end a further 5 years after that (May 2029).

Inclusion criteria:

- All male patients who are treated with Rezum due to prostate obstruction and LUTS in the participating study centers can be included if certain inclusion criteria are met and some exclusion criteria are not present.
- The indication to perform Rezum needs to be made independently from the study. The decision for Rezum treatment is the responsibility of each individual practitioner and patient.
- Age ≥ 18 years
- Operated or supervision of surgery by a certified urologist
- Subgroups of special interest are e.g. catheter-dependent patients, patients with oral anticoagulation, patients with preoperative urodynamic pressure-flow investigation (not older than 6 months) or patients with prostates bigger than 80 ml

Exclusion criteria:

- Missing informed consent
- Lack of ability to answer questionnaires in German language or mentally by oneself (e.g. in dementia, mental disability).
- Patient does not have a personal email address available and the survey cannot be completed via a relative's email address and the patient is not willing to complete the survey on the tablet at the clinic.
- Known or suspected neurogenic bladder dysfunction in e.g. Parkinson's disease, multiple sclerosis or other neurological diseases with possible effects on bladder function
- History of malignant bladder tumor in the last two years (including CIS) or currently present malignant bladder tumor at time of Rezum treatment (including CIS)
- Previous operation(s) on the prostate, except prostate biopsy, if this was performed more than 4 weeks ago at time of Rezum treatment
- Previous operation(s) on the bladder neck
- Presence of bladder neck stenosis requiring treatment at time of Rezum treatment

- Planned combination of Rezum treatment concurrently with another urologic * or non-urologic procedure.

** also the combination with a planned transurethral procedure is not allowed except for bladder stone removal*

3.2 Recruitment, screening and informed consent procedure

Patients will be recruited within the participating study hospitals as part of regular patient care after an indication for Rezum treatment has been made independent of the study. According to the EAU (European Association of Urology) guideline "Non-neurogenic Male LUTS" urethrocystoscopy in men with LUTS prior to minimally invasive/surgical therapies is recommended if the findings may change treatment (17). Due to the fact that not all prostate configurations should be treated with Rezum, such as an isolated steep bladder neck, this EAU recommendation should also apply to Rezum, but is in the responsibility of each practitioner and no obligation for recruitment.

Once Rezum therapy has been determined for a patient, if all inclusion and exclusion criteria are met, the patient will be asked if he is interested in participating in the study. Since Rezum is a highly elective surgery and will be performed on a scheduled basis, the patient has ample time to read the informed consent letter and ask questions, as is customary for any elective surgery informed consent. Study participants do not receive any compensation. There are no additional costs for patients and health insurers as a result of the study.

3.3 Study procedures

The study ends with the 5-year follow-up of the last included patient out of a total of 1000 patients to be recruited. It is estimated that the 20 participating centers will each recruit an average of 50 patients in an estimated time of 18-24 months. We believe that a delay of 12 months is to take into account until initiation of the last recruiting center has been successfully finished. In summary, the study will probably end no later than 84 months (May 2029) after recruitment of the first patient (May 2022).

Patient reported outcome measures (PROMs) incl. iUFlow data will be collected during hospital stay and perioperatively, 2 weeks, 6 weeks, 3 months, 6 months, 12 months, and then annual until the 5th follow-up year (table 2).

Clinical reported outcome measures (CROMs) are collected as part of routine clinical examinations. Table 3 in Appendix 22 gives an overview about the collected CROMs and PROMs. The detailed database template with all parameters in German language is shown in Appendix 23. Fixed follow-up visits do not exist, but the study centers are encouraged to also see the study patients after completion of the perioperative phase at 3 months, 6 months, 12 months and then annually until completion of the 5th year of follow-up, or to obtain the necessary data from the physicians who continue to treat the patients.

From experience with patients who have already been treated with Rezum at the University Hospital in Basel, the time points mentioned correspond to realistic routine follow-up intervals, as they would also be carried out independently of an observational study.

3.3.1 Use of Patient Reported Outcomes Measures (PROMs) and Clinical Reported Outcome Measures (CROMs)

Patients' data, CROMs and PROMs are collected at baseline before Rezum therapy, perioperatively (at day of surgery, at first postoperative day, during hospitalization course, at day of catheter removal), 2 weeks, 6 weeks, 3 months, 6 months, and annually after surgery for 5 years using the heartbeat ONE database provided and supported by heartbeat medical solutions and the Clinical Portal supported by Kesem Health. CROMs will be assessed at baseline before Rezum is performed at day of surgery and after Rezum treatment during clinical follow-up visits. Clinical data are manually entered into the heartbeat ONE database at each study center.
Follow-up visits are scheduled according to the routine practices of the respective country/hospital. From our own practice, it can be said that routine clinical controls usually correspond to the time periods mentioned above. Since the study is intended to be observational, there are no study-dependent, strict guidelines for follow-up controls. However, practitioners are encouraged to follow up their patients on a regular basis in their own interest to check the quality of outcome of the performed Rezum treatment. The mentioned follow-up times can serve as a guideline. Table 3 in Appendix 22 shows a summarized listing of all CROMs and PROMs with corresponding time points, which are collected in the heartbeat ONE database. The detailed database template with all parameters in German language is shown in Appendix 23. However, the vast majority of study data to meet study endpoints are provided by PROMs rather than CROMs. Two important clinical outcome parameters are prostate size and post void residual urine (PVR), both of which are determined by sonography. However, both parameters are part of routine follow-up examinations.

Patient questionnaires (PROMs) will be preferred collected via the heartbeat service provider by a linked e-mail invitation, alternatively by a provided tablet (iPad) during a hospital visit if a patient does not use e-mail. Detailed data flow of PROMs via e-mail invitation into the heartbeat ONE database is described in chapter 7.2 “data recording and source data”.
Home urine flow measurement data using the iUFlow device including the smartphone App are collected by a separate study database (iUFlow Clinical Portal) provided by Kesem Health for this study. IUFlow data is manually transferred from the iUFlow Clinical Portal to the heartbeat ONE database by the study stuff of the University Hospital Basel. The exact data flow via the iUFlow device into the Kesem Health Clinical Portal is described in chapter 7.2 “data recording and source data”.

Table 2 PROMs and patient questionnaires at baseline and in follow-up

	Before Rezum	**After Rezum**									
		1 day	*2 weeks*	*6 weeks*	*3 months*	*6 months*	*1 year*	*2 years*	*3 years*	*4 years*	*5 years*
Survey point	a	b	c	d	e	f	g	h	i	j	k
Questionnaires											
IPSS/QoL	x			x	x	x	x	x	x	x	x
ICIQ-MLUTS	x			x	x	x	x	x	x	x	x
MSHQ	x			x	x	x	x	x	x	x	x
ICIQ-MLUTSsex	x			x	x	x	x	x	x	x	x
QoR-15	x	x	x								
PROMIS Global Health 10 *	x		x	x	x	x	x	x	x	x	x
Numerical pain rating scale (NRS) **	x	x									
Satisfaction with treatment (ICIQ-S) ***			x	x	x	x	x	x	x	x	x
Side effects of Rezum treatment and pain medication			x	x	x						
Patients´ preferences and expectations for Rezum treatment	x				x	x	x	x	x	x	x
BPH/LUTS medication			x	x	x	x	x	x	x	x	x
Re-operations					x	x	x	x	x	x	x
Bladder catheter					x	x	x	x	x	x	x
Completion time in minutes	31	3	16	25	31	28	28	28	28	28	28
		Home urine flow measurement									
iUFlow	x		x	x	x	x	x	x	x	x	x
Completion time in minutes	15 Min.		5 Min.	5 Min.	5 Min.	5 Min.	5 Min.	5 Min.	5 Min.	5 Min.	5 Min.

* contains a Numeric Pain Rating Scale (NRS); ** same NRS like in PROMIS Global Health 10; *** full questionnaire until 3 months; 6 months, 12 months and year 1-5 only questions 1-6

Time windows for data collection at each survey point:

a. 4 weeks prior to Rezum surgery – 1 day prior to Rezum surgery.

b. 1 day after Rezum surgery – 3 days after Rezum surgery.
c. 2 weeks after Rezum surgery – 4 weeks after Rezum surgery.
d. 6 weeks after Rezum surgery – 8 weeks after Rezum surgery.
e. 3 months after Rezum surgery – 4 months after Rezum surgery.
f. 6 months after Rezum surgery – 7 months after Rezum surgery.
g. 12 months after Rezum surgery – 14 months after Rezum surgery.
h. 22 months after Rezum surgery – 26 months after Rezum surgery.
i. 34 months after Rezum surgery – 38 months after Rezum surgery.
j. 46 months after Rezum surgery – 50 months after Rezum surgery.
k. 58 months after Rezum surgery – 62 months after Rezum surgery.

3.3.1.1 Explanation of questionnaires used in the study

Validated symptom score questionnaires for urination/draining

- IPSS/QoL = International Prostate Symptom Score / Quality of Life, completion time: 1-2 minutes

- ICIQ-MLUTS = International Consultation on Incontinence Questionnaire for male lower urinary tract symptoms, completion time: 4-5 minutes

The EAU (European Association of Urology) guideline “Non-neurogenetic Male LUTS” (17) recommends use of validated symptom score questionnaires including bother and quality of life assessment during the assessment of male LUTS and for re-evaluation during and/or after treatment. The two most widely used questionnaires are IPSS/QoL and ICIQ-MLUTS.

The IPSS is an eight-item validated questionnaire, consisting of seven symptom questions and one QoL question (18,19). The IPSS score is categorised as ‘asymptomatic’ (0 points), ‘mildly symptomatic’ (1-7 points), ‘moderately symptomatic’ (8-19 points), and ‘severely symptomatic’ (20-35 points). Limitations include lack of assessment of incontinence, post-micturition symptoms, and bother caused by each separate symptom. The IPSS/QoL questionnaire is shown in Appendix 1.

The ICIQ-MLUTS was created from the International Continence Society (ICS) Male questionnaire (20). It is a widely used and validated patient completed questionnaire including incontinence questions and bother for each symptom It contains thirteen items, with subscales for nocturia and overactive bladder (OAB). The ICIQ-MLUTS questionnaire is shown in Appendix 2.

Validated sexual function questionnaires

- MSHQ = Male Sexual Health Questionnaire (erection scale and ejaculation scale, satisfaction scale), completion time: 2-3 minutes

- ICIQ-MLUTSsex = International Consultation on Incontinence Questionnaire Male Sexual Matters Associated with Lower Urinary Tract Symptoms Module, completion time: 1-2 minutes

Epidemiological studies have also demonstrated consistent evidence for an association between lower urinary tract symptoms (LUTS)/Benign Prostatic Hyperplasia (BPH) and sexual dysfunction, regardless of age, other comorbidities and various lifestyle factors (41). The Multinational Survey on the Aging Male (MSAM-7) study - performed in the USA, France, Germany, Italy, Netherlands, Spain, and the UK - systematically investigated the relationship between LUTS and sexual dysfunction in > 12,000 men aged 50-80 years. From the 83% of men who self-reported to be sexually active, the overall prevalence of LUTS was 90%, with the overall prevalence of ED being 49%, and a reported complete absence of erection in 10% of patients. Moreover, the overall

prevalence of ejaculatory disorders was 46% (42). Effects on erectile function and ejaculation function vary according to the type of surgery performed in men with LUTS/BPH (43).

Rezum is probably currently one of the procedure with the least impact on sexual function in the surgical treatment of BPO. Currently, the rate of retrograde ejaculation is thought to be as low as 3% and no negative impact on erectile function is reported so far following Rezum treatment (15,44). However, BPO/Male LUTS drugs such as alpha-blockers are also known to negatively impact sexual function on a regular basis. However, the exact significance of sexual function preservation with Rezum remains to be systematically tested with our study.
The EAU guideline "Male Sexual Dysfunction" (45) recommends the use of validated questionnaires related to sexual dysfunction to assess all sexual function domains and the effect of a specific treatment modality.

The MSHQ questionnaire was validated in 56 men with moderate to severe LUTS and control subjects with no sexual problem and mild or no LUTS (23,24). The MSHQ long form includes 3 domains: Erection scale (3 items), Ejaculation scale (7 items), Sexual satisfaction scale (6 items) + 9 additional items (2 items measuring bothersome linked to erection and ejaculation and 7 items measuring sexual activity and desire). The 7 items on sexual activity and desire are to be filled in voluntarily. MSHQ questionnaire is shown in Appendix 3.

The ICIQ-MLUTSsex is a patient-completed questionnaire for detailed evaluation of male sexual matters associated with their lower urinary tract symptoms and impact on quality of life (QoL) in research and clinical practice. The ICIQ-MLUTSsex is derived from the fully validated ICS male questionnaire and provides robust measure to assess the impact of sexual matters on outcome. It is composed of 4 sections (erection, ejaculation, pain/discomfort during ejaculation, impact of urinary symptoms) (26). The ICIQ-MLUTSsex questionnaire is shown in Appendix 4.

Validated physical recovery questionnaire

- QoR-15 = Quality of Recovery-15, completion time: 2-3 minutes

Rezum is said to be a minimal-invasive surgical treatment for BPO related LUTS which can be performed both under general anesthesia and local anesthesia (spinal anesthesia, local prostatic bloc or analgosedation). No data exist about postoperative quality of recovery after Rezum treatment. The QoR-15 provides a valid, reliable, responsive and easy-to-use method of measuring the quality of a patient's postoperative recovery. Compared with the QoR-40 (31), it covers the same elements of quality of recovery but with fewer items and thus is more efficient in evaluating the patient's postoperative quality of recovery (32,33,46). The QoR-15 questionnaire is shown in Appendix 6. CROMs will protocol the type of anesthesia, anesthetic drugs, premedication and postoperative use of pain killers.

Validated quality of life questionnaire

- PROMIS (Patient-Reported Outcomes Measurement Information System)
Global Health 10, completion time: 2-5 minutes

The Global Health 10 Score is part of the PROMIS (Patient-Reported Outcomes Measurement Information System) and thus belongs to the latest generation of patient-related outcome measures (47). It is a measure of overall health-related quality of life based on a patient sample of 21,133 people. The questionnaire consists of a combination of 10 questions that assess both the physical and mental health status of adult patients independent of their individual medical situation. Patients subjectively rate their own health, quality of life and social aspects of their lives. It is designed to be a basic assessment of a patient's health that can be used for a variety of

conditions. Patients subjectively rate their own health, quality of life and social aspects of their lives. The items are measured using a five-point response matrix that includes physical function, fatigue, pain, emotional distress and social health (34). No data exist about changes of quality of life in the context of a Rezum treatment. The questionnaire is shown in Appendix 19.

Validated satisfaction questionnaire

- ICIQ-S = International Consultation on Incontinence Questionnaire - Satisfaction, completion time: 1-2 minutes

The ICIQ-S assesses aspects of experience, expectations, and outcomes to evaluate satisfaction after urological surgery (35). Question items consist of: outcome success, comparison of symptoms, return to 'normal life', same situation, same choice, recommend, current symptoms, preparation for surgery, satisfaction of explanation, pain after surgery, satisfaction of pain relief, current pain, complications/side effects, result of surgery and satisfaction with surgery. The ICIQ-S questionnaire is shown in Appendix 7.

Further questionnaires

- Questionnaire "Numerical Pain Rating Scale" (NRS), completion time :0.5 minutes

This is intended to query the pain sensation during the Rezum treatment and in the postoperative course. Data should be matched with the type of anesthesia and the anesthesiologic drugs used. Study results might be able to give a recommendation for the best form of anesthesia used in a Rezum procedure. The "Numerical Pain Rating Scale" questionnaire has a scale from 0 – 10 (no pain - worst pain imaginable). NRS is also part of PROMIS Global Health 10.

- Questionnaire "Rezum side effects and pain medication", completion time: 2-3 minutes

This questionnaire is self-designed. Typical side effects must be seen and investigated independently of treatment complications in order to provide patients with the best possible advice and information. The need for pain medication will be evaluated in a time context as well.
Typical side effects of Rezum treatment include discomfort (burning/stinging) in the pelvis/abdomen, hematuria, hematospermia or urinary urgency. Rezum side effects have only been studied in small cohorts, but not in a larger collective of patients. The questionnaire is shown in Appendix 5.

- Questionnaire "Preferences & expectations of Rezum treatment", completion time: 5-7 minutes (baseline questionnaire), 3 minutes (follow-up questionnaire)

The recent development of novel minimally invasive treatment options for LUTS due to BPO, including Rezum, has increased patients´ options, and thus increased the importance of assessing and incorporating both patients´ values and preferences and physicians´ attitude and behaviour towards the treatment of male LUTS, and the influence that this has on patient preferences and treatment choice. This need for considering values and preferences exits both for optimal treatment of individual patients and for the development of trustworthy clinical practice guidelines.
This self-designed questionnaire, which is currently under psychological evaluation, considers measurement tools related to BPH/Male LUTS treatment (36–38) and aims to investigate patients' motivations, expectations and preferences for surgical desobstruction of the prostate due to BPO in general but also in particular in relation to the Rezum treatment. This will attempt to better

understand patient attitudes in order to improve future counseling of patients regarding minimally invasive procedures for the treatment of BPO related male LUTS. The questionnaires are shown in Appendix 8 (8.1 – baseline, 8.2 – follow-up 3 months, 8.3 – follow-up 6 months, 8.4 follow-up 1 – 5 years).

- *Questionnaire "BPH (Benign Prostate Hyperplasia) medication", completion time: 1-2 minutes*
- *Questionnaire "Re-Operation", completion time: 1-2 minutes*
- *Questionnaire "Bladder catheter", completion time: 1-2 minutes*

All three questionnaires are self-designed. The purpose of the questionnaires is to get relevant information, not to score the questionnaires. Only one study with 197 patients has investigated the resumption of drug therapy and the reoperation rate due to BPO related LUTS over an observation period of 5 years. This study also included only patients with prostates between 30-80 ml. This study showed a reoperation rate at 5 years of 4.4% and re-treatment with BPH medications of 11.1% (15).
A very limited number of other studies have examined the efficacy of Rezum on larger prostates, but with only a very short follow-up period of one year (5,6).
Therefore, it is very interesting to prospectively observe these two outcome parameters in a larger, heterogeneous cohort of patients and with a longer follow-up. The questionnaires are shown in Appendix 15 (BPH/LUTS medication), Appendix 16 (Re-operation) and Appendix 21.

3.3.1.2 Surgical safety classifications used in the study

Surgical safety is investigated by analysing intraoperative complications classified by ClassIntra® (27–29) and 30-days postoperative complications defined by the Clavien-Dindo classification (30).

ClassIntra® - classification of intraoperative adverse events

The classification defines intraoperative adverse events as any surgery or anesthesia-related deviation from the ideal intraoperative course occurring between begin of anesthesia and end of anesthesia (Table 4).

Table 4 ClassIntra® - Classification of intraoperative adverse events

Grade 0	No deviation from the ideal intraoperative course
Grade 1	Any deviation from the ideal intraoperative course without the need for any additional treatment or intervention; patient asymptomatic or mild symptoms
Grade 2	Any deviation from the ideal intraoperative course with the need for any additional minor treatment or intervention; patient with moderate symptoms, not life-threatening and not leading to permanent disability
Grade 3	Any deviation from the ideal intraoperative course with the need for any additional moderate treatment or intervention; patient with severe symptoms, potentially life-threatening and/or potentially leading to permanent disability
Grade 4	Any deviation from the ideal intraoperative course with the need for any additional major treatment or intervention; patient with life-threatening symptoms and/or leading to permanent disability

Grade 5	Any deviation from the ideal intraoperative course with intraoperative death of the patient

The following events are not defined as intraoperative complications: sequelae, failures of cure, events related to the underlying disease, wrong-site or wrong-patient surgery or errors in indication.

Clavien-Dindo classification of postoperative complications within 30 days

The classification defines postoperative adverse events occurring after the patient has left the recovery room until 30 days after surgery (Table 5).

Table 5 Clavien-Dindo classification for postoperative complications

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological intervention. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention IIIa Intervention not under general anaesthesia IIIb Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU IVa Single organ dysfunction (incl. dialysis) IVb Multi organ dysfunction
Grade V	Death of a patient
Suffix 'd'	If the patient suffers from a complication at the time of discharge, the suffix 'd' (for 'disability') is added to the respective grade of complication.

** brain haemorrhage, ischaemic stroke, subarachnoidal bleeding, but excluding transient ischaemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit*

Note: A (re)-catheterization of the urinary bladder is not defined as a complication if it occurs due to a bladder emptying disorder. If, on the other hand, the (re)-catheterization occurs due to, for example, a symptomatic urinary tract infection or hematuria, this is to be classified at least as Clavien Dindo grade IIIa. The definition of symptomatic UTI is based on a clinical diagnosis accompanied by a measured bacteriuria of ≥10^5 cfu/ml and treated with at least one antimicrobial agent. A symptomatic UTI is classified as at least Clavien Dindo grade II.

3.3.1.3 Patients with pressure-flow studies (urodynamic investigations)

Uroflowmetry and postvoid residual urine volume (PVR) are simple tests that can raise or lower the suspicion of bladder outlet obstruction (BOO), but neither can make a definitive diagnosis. Decreased uroflow can result from impaired detrusor (bladder muscle) contractility (detrusor underactivity (DU)) or obstruction, e.g. BPO. Without the synchronous measurement of detrusor pressure (Pdet), uroflow is unable to distinguish between these two entities. Furthermore, there

are no features of the uroflow curve that allow a definitive distinction between outlet obstruction and DU. The prevalence of DU in men with LUTS is about 40% (48,49). Similarly, a normal uroflow does not exclude outlet obstruction (50). Urodynamics with pressure-flow studies remain the gold standard for diagnosing BOO, like BPO and other voiding and storage abnormalities responsible for LUTS and voiding dysfunction. Currently, no urodynamic data are published for the Rezum treatment.

Both the BOOI - Bladder Outlet Obstruction Index (former Abrams-Griffiths normogram) and BCI - Bladder Contractility Index can be simply calculated without the use of computer programs or even the nomogram for that matter:

- BOOI is represented by the equation: BOOI = P_{det} @ Q_{max} − 2 Q_{max} (P_{det} = detrusor pressure; Q_{max} = maximum flow rate)

Using the ICS - International Continence Society nomogram, men can be divided into obstructed, equivocal, and unobstructed according to their BOOI: BOOI > 40 = obstructed; BOOI 20−40 = equivocal; and BOOI < 20 = unobstructed (50)

- The BCI is represented by the following formula: BCI = P_{det} Q_{max} + 5 Q_{max}.

Using this formula, contractility can be divided into strong > 150, normal 100–150, and weak < 100 (50).

Therefore, we like to analyse urodynamic (invasive) pressure-flow studies investigating BOOI and BCI before and/or after the Rezum intervention in order to

1.) show the effect of Rezum on pressure-flow parameters resulting from desobstruction and investigate the relationship with PROMs (IPSS, ICIQ-MLUTS), and

2.) in case of treatment failure in patients with chronic urinary retention to show that this is a result of detrusor underactivity instead of insufficient desobstruction.

In addition, we like to analyse detrusor overactivity (DO) urodynamically during storage phase and correlate DO pre- and postoperatively with PROMs (IPSS, ICIQ-MLUTS).

Two patient groups are of scientific interest for the analysis of urodynamic (invasive) pressure-flow studies:

a) Patients with preoperative pressure-flow studies (not older than 6 months): postoperative routine diagnostics will probably not be performed in this patient group if the patient can micturate well postoperatively, but it is scientifically very valuable to study the effect of Rezum on the urodynamic indices for the reasons described above.
b) Patients that might get a pressure-flow study postoperatively because of insufficient micturition (treatment failure). This group will primarily consist of patients who were preoperatively catheter-dependent.

Centers should be encouraged to perform a urodynamic (invasive) follow-up pressure flow study three to six months after the Rezum intervention in patients in group a) or in case of treatment failure in group b).

Postoperative treatment failure is defined as at least two unsuccessful trials to remove the transurethral catheter with the last trial not having been performed earlier than 30 days and not later than 90 days after the Rezum intervention.

In case of treatment failure (group b) unsuccessful catheter removal, no voiding possible) the EAU recommends to perform a urodynamic pressure-flow study (17). Therefore, it should be covered by the insurance of the patient.

If postoperative urodynamic (invasive) pressure-flow studies are performed in the context of the study protocol, additional informed consent of each patient is necessary.

3.3.1.4 Patients with MRI investigations

It is assumed that some patients will have had an MRI (magnetic resonance imaging) of the prostate prior to the Rezum treatment or will get an MRI of the prostate in the follow-up years after the Rezum treatment. Reasons for this can be an investigation for the presence of prostate cancer or the fact that a patient is under active surveillance for prostate cancer.
Patients are going to be encouraged to provide MRI images in order to examine parameters that may have been changed after Rezum treatment like ablative steam lesions (39), prostate size or PI-RADS lesions (40). The MRIs are going to be reviewed in the Department of Radiology of the University Hospital Basel.
Patients will be asked to sign an additional consent form giving permission to request a copy of the MRI images of the prostate for the study, together with the written report from the radiology institute that produced the images. Any costs incurred for the requested images will be paid by the study.

3.4 Withdrawal and discontinuation

Patients participating in this research project are asked to adhere to the specifications and requirements of the research project through the PROMs protocol (Table 3).

In case of non-compliance with the protocol (Table 3), the project management or the investigator/investigator of the local institution may exclude patients from participation in the research project. If a patient's health condition no longer permits participation in the research project, the project management or the investigator/investigator of the local institution may also exclude the patient from the study project, not only in the interest of the patient's health. Data collected up to study exclusion will be analyzed.

Study participants can withdraw from the research project at any time. In this case, however, the data collected up to that point will still be analyzed in encrypted form.

After evaluation, the data are anonymized. The key allocation is destroyed so that afterwards no one can find out that the data originally came from a particular study participant. This is primarily for data protection purposes.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

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 CTU of the DKF.

4.1.1 Primary analysis

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 (18,19).

The mean difference between IPSS at five years 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.

4.1.2 Secondary analyses

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

The following secondary outcomes will also be assessed:

- Quality of life score (QoL) from the IPSS questionnaire (18,19) (Appendix 1)
- Questionnaire for male lower urinary tract symptoms (ICIQ-MLUTS) (20) (Appendix 2)
- Urinary flow rate measured using iUFlow uroflowmetry (automatic uroflow at home)
- Post voiding residual volume (PVR)
- Prostate size (in ml)
- Reoperation rate (Appendix 16)
- Remedication with BPO/LUTS drugs (Appendix 15)
- Recatherization rate (Appendix 21)
- Sexual function, including erection, ejaculation, orgasm and sexual satisfaction measured using the following questionnaires:
  - Male Sexual Health Questionnaire (MSHQ) (23,24) (Appendix 3)
  - International Consultation on Incontinence Questionnaire Male Sexual Matters Associated with Lower Urinary Tract Symptoms Module (ICIQ-MLUTSsex) (26) (Appendix 4)
- Type of anesthesia used, including reason for type of anesthesia and postoperative recovery using the following questionnaire:
  - Quality-of-Recovery-Score (QoR-15) (32,33,46) (Appendix 6)
- Quality of life from PROMIS Global Health 10 questionnaire
- ICIQ-S to evaluate patients' satisfaction with clinic treatment (46) (Appendix 7)
- In case of local anesthesia/analgosedation, the patients' perception of pain during the Rezum procedure by using a Numeric pain rating scale (NRS) from 0 to 10
- Effectiveness of the chosen antimicrobial prophylaxis (infection vs. no infection)
- Patients' preferences and expectations for Rezum treatment using self-designed questionnaires (Appendix 8) and validated preference measurement tools (36–38)
- Changes in bladder outlet obstruction index (BOOI) bladder contractility index (BCI) and detrusor overactivity (DO) among those who underwent pressure flow studies (50)
- Change of MRI investigations (ablative lesions, PI-RADS lesions, prostate size) among those who show a MRI of the prostate
- Intraoperative (ClassIntra classification, table 4) (27–29) and postoperative complications (Clavien-Dindo classification, table 5) (30)
- Rezum side-effects and need for pain medication (Appendix 5)
- Influence of steam injection number and Injection points arrangement on outcome parameters, e.g. micturition parameters (IPSS, ICIQ-MLUTS), sexual function (MSHQ, ICIQ-MLUTSsex) prostate size, side-effects, complications.

We will use both statistical models and descriptive statistics to answer our questions.

We will summarise the parameters for each time point to allow us to explore changes over time. In relation to the subgroup analyses, we will identify factors that influence the endpoints.
The endpoints described above will be assessed using the same mixed models framework that will be used for assessing the primary outcome. We will use linear mixed models for the continuous outcomes and mixed logistic regression models for the binary outcomes.
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 Rezum 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-Rezum pressure flow examination.

4.1.3 Subgroup analyses

The main subgroup analyses of interest for the outcomes “reduction of IPSS”, “reduction of ICIQ-MLUTS”, “improvement of uroflow”, “reduction of PVR volume”, “reduction of prostate size” 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).

The main subgroup analysis of interest for the outcomes “reduction of ICIQ-MLUTSsex” and “reduction of MSHQ” is the following:

- Larger prostate size of > 80 ml (expected in about 20% of the study population)

In addition, subgroups based on the following characteristics will be examined for surgical safety outcomes, i.e., intra- and post-operative complications:

- Anticoagulation
- Age ≥ 80 years
- Fragility or comorbidities identified by the Charlson Comorbidity Index (51) (making patients only eligible for local anesthesia or analgosedation)

Furthermore, we will examine the relationship between changes in the bladder outlet obstruction index (BOOI) as well as the bladder contractility index (BCI) after undergoing Rezum 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-Rezum pressure flow examination.

Determination of sample size

As alluded to above, one of the motivations behind recruiting a large cohort is the ability to conduct subgroup analyses. 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. The CTU of the DKF recommend to round 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.

4.1.4 Sample size reestimation

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, 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.

4.1.5 Safety analysis

Surgical safety will be assessed by recording intraoperative complications defined by the ClassIntra classification (27–29) as well as 30-day postoperative complications defined by the Clavien-Dindo classification (30).

4.1.6 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.

4.1.7 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.

4.1.8 Handling of patients, that will get retreatment

It may happen that during the 5-year follow-up of the patients, further therapy is carried out due to new micturition complaints. This can be drug treatment or surgical reintervention due to BPO recurrence or surgical treatment because of complications, e.g. bladder neck stenosis or urethra stricture. BPO drug or surgical retreatment rate will be described at each planed assessment point. Patients that need retreatment of BPO will continue to be followed up as part of the study, but will be statistically evaluated separately from the patients without retreatment. Factors that influence BPO retreatment will be analysed.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

5.2 Notification of safety and protective measures (HRA Art. 15, HRO Art. 20)

If, during the research project, circumstances arise which could jeopardise the safety or health of the participants or lead to a disproportionate relationship between the risks and burdens and the benefits, all the measures required to ensure protection are to be taken without delay.
The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

5.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.5 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days. After the final data analysis of the project, the data will be kept for another 10 years to have the possibility to answer further scientific questions that might arise.

5.6 Insurance

In the event of project-related damage or injuries, the Sponsor will be liable, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than would be expected in the current state of scientific knowledge (Art. 12 HRO). For sites outside Switzerland, local regulations apply.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

The study is an observational study. Common outcome questionnaires, such as the IPSS, ICIQ-MLUTS, ICIQ-MLUTSsex or MSHQ which would normally be collected during the routine medical follow-up consultation, are, however, made available to the patients in a structured manner and if wished by the patient independently of a medical consultation. The same applies to the urine flow measurement (iUFlow), which the patient can perform at home independently of a medical

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

consultation. This means that the patient is not under pressure to perform the measurement on command during a medical consultation. This often does not work (bladder already empty, micturition not possible during consultation) and data would be correspondingly incomplete. The results are accessible to both the Rezum practitioner and the study stuff via the heartbeat ONE study database. In our opinion, however, this type of data collection still corresponds to the character of an observational study; the data collection is merely shifted to the home environment, which we think will generate better and more complete data quality. In our opinion, the results provided do not influence the practitioners with regard to the treatment of their patients, as the outcome data would also be collected independently of the study during the routine follow-up visits.

Centers should be encouraged to perform a urodynamic (invasive) follow-up pressure flow study three to six months after the Rezum treatment in patients in group a) or in case of treatment failure in group b) according to chapters 2.2.3.11 and 3.3.1.3. “Patients with pressure-flow studies (urodynamic investigations)”. Although there is no benefit of postoperative pressure-flow study for patients with successful Rezum treatment (group a)), the results are scientifically very valuable to better measure the efficiency of Rezum treatment in terms of desobstruction of the prostate. However, indication for pressure-flow study in group b) is justified by the recommendation of the EAU guideline “Management of Non-neurogenic Male LUTS” (17).

The time commitment of the study participants is very manageable (table 2). Additional, study-based medical consultations in addition to routine, study-independent follow-up visits are not foreseen, except for postoperative urodynamics if necessary, despite treatment success (group a)), as described above. However, postoperative urodynamics is not a prerequisite for study participation, is purely voluntary and requires the explicit consent of the patient, who is already aware of the examination.

In the true sense, incidental findings collected via the study are not expected, as this is an observational study investigating an approved treatment.
Study patients have full right to see their study data. Participation in the study is voluntary and can be withdrawn at any time.

6.2 Risk-Benefit Assessment

In general, there are no risks involved in participation in this study. Study-related activities are restricted to filling in questionnaires, which are used via secured, well-established platforms, which have been widely used in clinical trials. Filling in questionnaires can be time consuming, what can be perceived as a burden. Furthermore, the uroflowmetry measurements (iUFlow) are also approved for usage by patients at home and bear no risks. All other data collected within this study are part of routine Rezum treatment and follow-up of patient with BPO retated LUTS. Patients with existing pressure-flow study (urodynamic investigation) before the Rezum treatment may be asked if they would allow a control pressure-flow study on a purely voluntary basis. Individual patients may not have a benefit in participating.
However, patients can have a direct benefit from participation, as they have a continuous self-assessment of their health status (PROMIS Global Health 10) in relation to their lower urinary tract (urinary bladder and prostate) and sexual function with the questionnaires on urination (IPSS/Qol, ICIQ-MLUTS) and sexual function (ICIQ-MLUTSsex, MSHQ), as well as with the urine flow measurement at home (iUFlow). This will allow patients to assess and visualize for themselves the effects of the Rezum treatment over time.

In addition, by participating, patients will help to further investigate the benefits of Rezum treatment, potential risks and side effects, and the effect on sexual function and quality of life for different groups of males. By doing so, study participants will give future patients the chance to be better advised by physicians regarding Rezum treatment with the data obtained from this study.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.
We aim to engage one full-time study nurse/coordinator (100%) for the duration of the study. The 100% will be split if necessary.

Tasks performed by study nurse(s)/coordinator(s) are as followed:

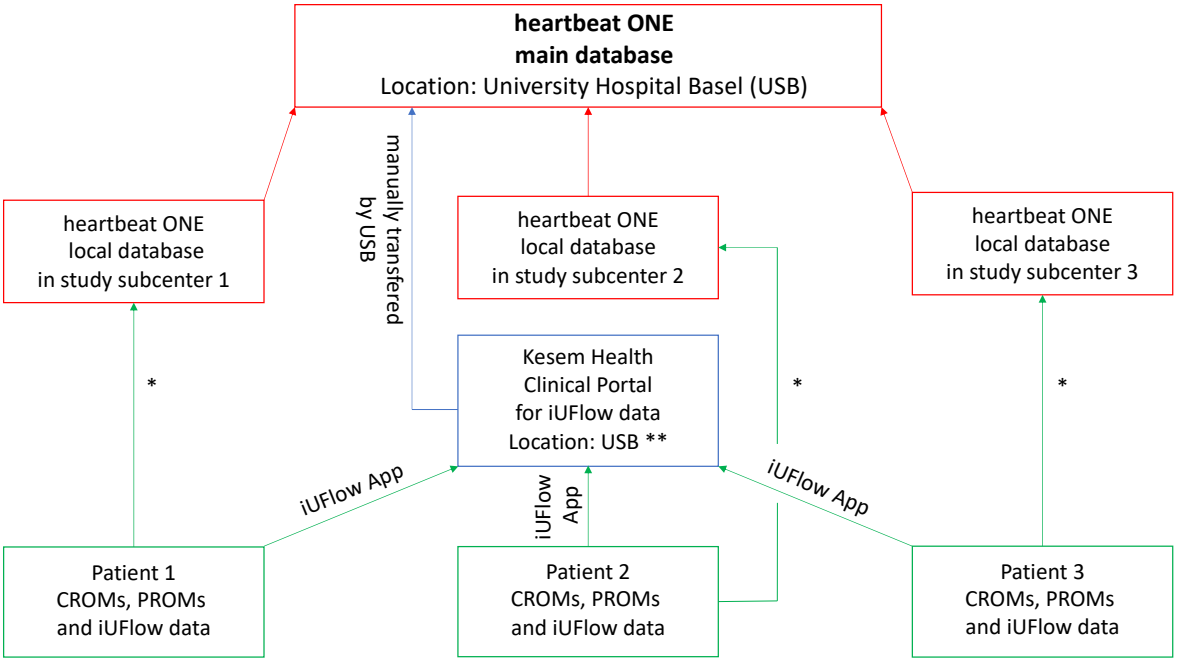
- Initiation of the study center including explanation of the heartbeat ONE database and the study protocol as well as the devices used (iUFlow, IPad tablet)
- Monitoring of recruitment at each study site
- Monitoring of the timely dispatch of uroflowmetry devices (iUFlow) to patients
- Monitoring of data entry and follow-up at each study site incl. return of clinical data, iUFlow uroflow data and questionnaires
- Ensuring continuous support for the study centers in the event of problems or queries
- Supporting patients and responding to patient queries or problems

7.2 Data recording and source data

All project data is directly recorded via the main database “heartbeat ONE” (CROMs and PROMS) except of the home uroflowmetry data which will be collected first via the Kesem Health Clinical Portal connected to the Kesem iUFlow App. Data electronically collected in the Kesem Health Clinical Portal will be manually transferred into the heartbeat ONE database by study staff of the main study center of the University Hospital Basel.
Clinical baseline and follow-up data (CROMs) are entered manually into the heartbeat ONE database by the respective study centers. The heartbeat ONE database offers a user-friendly interface so that data can be entered efficiently, in a structured and fully comprehensive but time-saving manner.
Patient questionnaires (PROMS) are basically designed so that they can be answered electronically, e.g. via a tablet or e-mail link. Each study center will be provided with a tablet that patients can use to complete the questionnaires. There is also a direct electronic way to fill in the questionnaires in the follow-up from home. If patients provide an e-mail, the questionnaires will be sent to them via an e-mail invitation with a link to the questionnaires. Alternatively, the survey can be completed via a relative’s email address or via tablet in the clinic.

Figure 1 shows the data flow. Sub-center can only see data of their own patients in the heartbeat ONE database and Kesem Health Clinical Portal, whereas the study stuff at the main study center at the University Hospital Basel can see study data from all study centers.

Figure 1: *Flow of study data*



* CROMs are entered into the local database by local study stuff (study nurses, surgeon, local PI), PROMs (questionnaires) can be answered electronically by patients via heartbeat Portal (e-mail) or via heartbeat Bridge (iPad/tablet).
** USB study stuff can authorize study stuff of local sub-centers to see iUFlow data in the Kesem Health Clinical Portal just from their study patients.

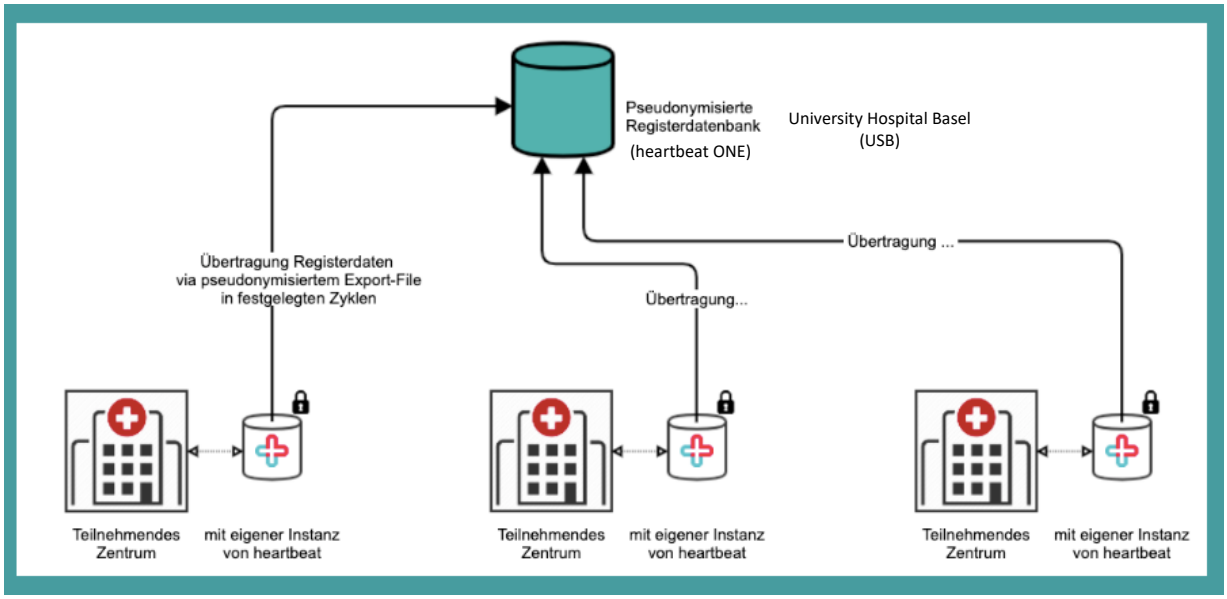
The following description contains technical, clinical and legal information about the heartbeat ONE database. heartbeat medical can provide comprehensive information material, technical system descriptions (hosting, API, etc.) and data protection-related documents (data protection impact assessment, TOMs, etc.) upon request.

7.2.1 heartbeat ONE database system description

Data entry into heartbeat ONE: All content (PROM scores and clinical documentation forms (CROMs) will be implemented into heartbeat ONE by heartbeat's medical content team according to the project specifications (Assessment Schedule_V1.0, see Appendix 23). Pathway specific task lists define survey and documentation time points according to the study/registry design. The implementation process takes into account any licensing for PRO instruments and is MDD

(Medical Device Directive) compliant, including compliance with IEC 62304, IEC 62366-1, ISO 14971 and ISO 13485.
heartbeat ONE can be used with and without an HL7-integration with the local hospitals information system (HIS). An integration allows for the automation of administrative processes (create patient, start survey processes, return data, etc.).
To collect data according to the study and/or registry protocol, each participating site receives its own instance of the platform heartbeat ONE (described as local database in Figure 1) to comply with local data and IT protection obligations (Figure 2). The preferred mode of operation is Software-as-a-Service (SaaS) but an on-Premise installation is also available upon request. heartbeat ONE SaaS instances for participants in Switzerland are operated in the Green data center in CH-5242 Lupfig, Zurich-West, certified according to ISO 5001 and ISO 27001 and for participants in Germany and Austria the instances are operated in the diva-e data center in D-60388 Frankfurt a.M. Kruppstraße 105 certified according to ISO 9001 und ISO 27001. Each customer receives a fully separated virtual machine on which the system is running.

Figure 2 *Decentralised data collection by own instances - GDPR (General Data Protection Regulation of the European Union (EU))-compliant, data can only be viewed by study staff*



Only authorised study personnel have access to the heartbeat ONE database, which is password protected. The extent of access to the heartbeat ONE database can be controlled by the PI and study stuff of the main study center of the study (USB) who have full administration rights. PI and study stuff of a local sub-center have only local administration rights. As soon as a patient's master data is entered into heartbeat ONE, he receives a personalised study number. Only study personnel who are authorised to enter data into the heartbeat ONE database have the key to the identifying master data. Data output or data viewing can be selected/set by the PI in such a way that no reference can be made between the identifying master data (key) and the study data.

Heartbeat consists of three central components (see Figure 3):

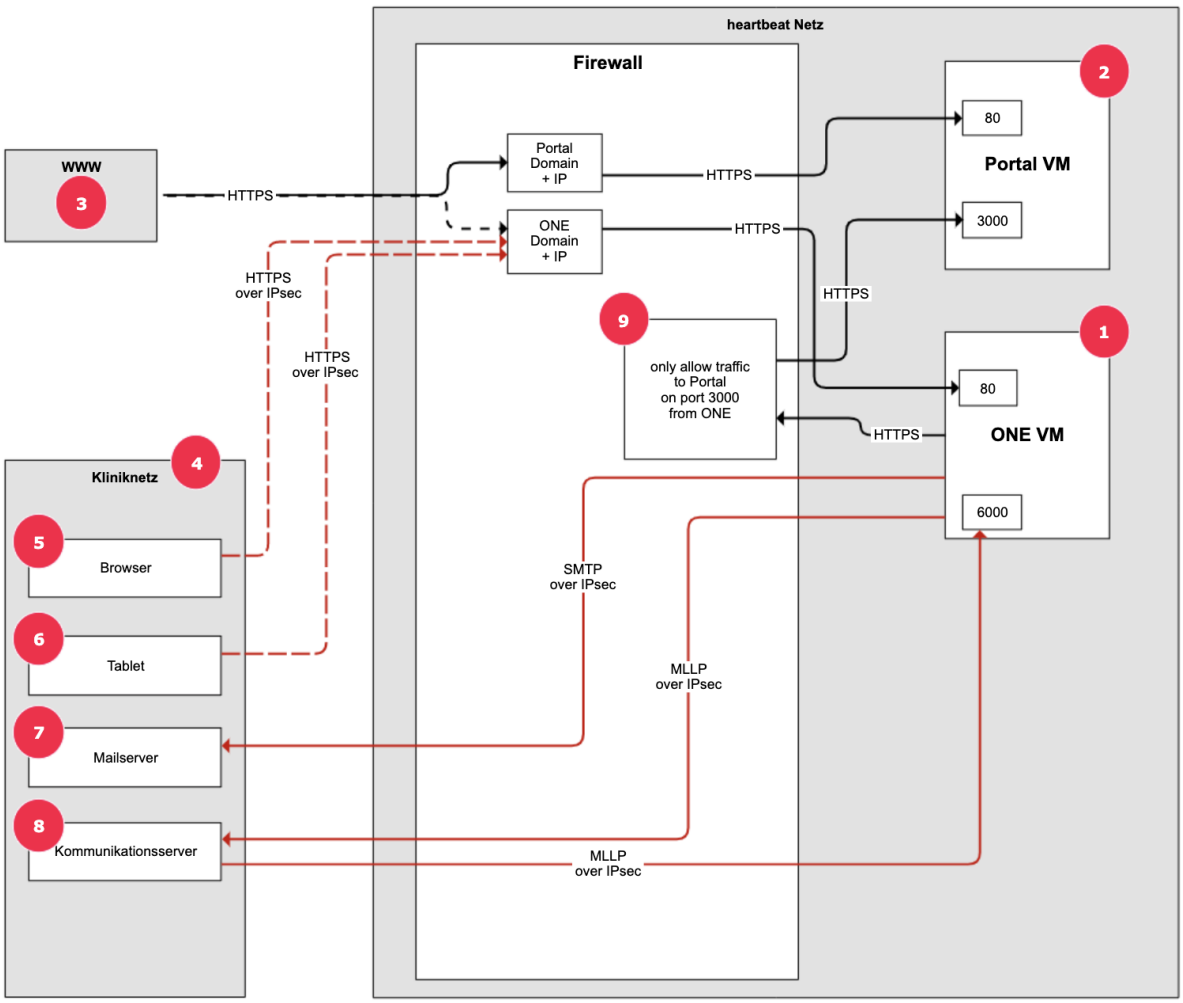
1) Heartbeat ONE is a browser application for medical staff to access and manage the data collection of their patients on an individual and group level. PRO data arriving from heartbeat Portal (e-mail) and heartbeat Bridge (iPad) is processed and stored. CROs can be entered via heartbeat ONE.

2) The patient portal provides one option for delivering patient surveys. This option is used when the patient is outside the hospital in a public network. Patients receive an encrypted link via email for their survey and, without installing an app, can answer the survey in a browser of their personal device survey after successful verification. The link itself in the e-mail has no direct reference to the person being surveyed, but links exclusively to a survey.

3) heartbeat Bridge is a tablet app, which allows patients to enter their PRO data at the study/registry site without their own device. heartbeat Bridge is integrated into the clinical network.

   The main system as well as the patient portal are separated from each other via different zones. Communication between the two zones takes place via an IPsec tunnel. All patient-identifying data is stored in encrypted form. Further detailed information about the system architecture is available on request.

Figure 3 *Heartbeat ONE SaaS setup.*



7.2.2 Entering Patient Reported Outcomes (PROs)

Study staff access heartbeat ONE database via a browser. From there, study staff can initiate patient surveys and document clinical parameters.

A patient survey can be conducted in two ways:

- iPad App - The survey via tablet app is conducted on site. After initiation, the patient receives a 4-digit verification token from the study staff. The token allows the patient to access the initiated survey on the tablet app. After a subsequent additional verification with the date of birth, the patient can conduct the survey.
- E-mail - After initiation, the patient receives an e-mail in the name of the hospital. The e-mail address and e-mail templates (logo, subject, text, contact) are configured according to study site preferences. The e-mail contains an encrypted link which directs the patient to its browser based patient portal. After verification via birth date, the patient can access the survey and enter their PRO data.

Once the patient has left the site, an automatic e-mail follow-up function helps to survey patients at defined points in time. Study staff activate these e-mail follow up (so called autopilots) by entering a reference date. The system automatically sends up to three reminders per follow up if surveys are not answered by patients.

7.2.3 Entering Clinician Reported Outcomes (CROs)

The relevant clinical parameters that are to be collected in the course of the study can be documented intuitively via documentation forms by study stuff of each sub-center (study nurse, surgeon, local PI). Dashboards and task lists remind and support study staff to keep documentation completeness and data quality at a high level.

7.2.4 Kesem Health iUFlow Clinical Portal

The purpose of the iUFlow Kesem Health Clinical Portal is to allow study staff accessing clinical iUFlow data of authorised study patients. The Clinical Portal offers a real time visibility of patients´ home uroflow tests and bladder diary. When the patient opens the device specific app for the first time, he can select the University Hospital Basel as the study clinic and insert his personal study number that he has received. Once patients connect their app to the iUFlow device, data is immediately available on the portal. The Kesem Health Clinical Portal does not contain any master data of the patient, identification is exclusively via the assigned study number. Thus, data are fully coded in the Kesem Health Clinical Portal.
The Clinical Portal supports download of data (PDF, Comma Separated Value file (CSV/Excel)) to be used for statistical analysis. Both outputs can be downloaded and used in real time. Customized messages can be sent to patients to provide real time feedback and/or reminder to perform their uroflow tests.
The Kesem Clinical Portal database has no direct connection to the heartbeat ONE main database. Data from Kesem Clinical Portal is continuously and manually transferred from the Kesem Health Clinical Portal to the heartbeat ONE main database by study stuff of the University Hospital Basel. Study stuff of the main study center of the USB will see all study patients in the Kesem Health Clinical Portal, whereas sub-centers are only authorized to see results of their patients in the Clinical Portal (Figure 1).

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require to fulfill their duties within the scope of the research project. On the CRFs and other project specific documents including the iUFlow Kesem Health Clinical Portal outside the secured heartbeat ONE database, participants are only identified by a unique participant number. PI and study staff of the main study center at the University Hospital Basel have access to all data and full administration rights for the heartbeat One database. PI and study staff of subcenters have only local access to their own patient data and have local administration rights concerning their own patients within the heartbeat ONE database. Only the main study center (USB) has administration rights for the Kesem Health Clinical Portal. Subcenters can only access the Clinical Portal to view data of their own patients without any administration rights.

Only the GCP-compliant heartbeat ONE database, secured with personalized authorization passwords, keeps the study participant identification lists. Thus, the respective PI and authorized study staff of a subcenter has access only to the subcenter specific local study participant identification list. The PI and authorized study of the main study center (USB) have access to the entire study participant identification list for all participating centers. Hence, the complete study participant identification list is kept at the University Hospital in Basel. Safety back-ups are provided on different hardware storage media within the study centers. The hardware access is always password secured.

Backups are created hourly and kept for 24 hours. In addition, it is possible to create offsite backups.

Some data will be shared with representatives and affiliates of Boston Scientific in pseudonymised/aggregated form for internal development, analysis, regulatory evidence, marketing or educational purposes. The data will be stored on a server in the USA, while obeying Swiss and European data protection regulations. The provided data includes: 1. Patient age range within 5-year bands e.g. 40-45, 46-50, 2. Prostate volume, 3. Rezum delivery parameters, as documented in the study database, 4. Relevant comorbidity, as documented in the study database, 5. IPSS, 6. Qmax, 7. Procedure-related adverse events, as documented in the study database.

7.3.1 Data security heartbeat ONE database

Heartbeat medical guarantees by contract the GCP-conformity of the heartbeat ONE database and accordingly will control the heartbeat ONE database in a validation process. An audit trail is implemented in heartbeat ONE, which will allow tracking of any user generated inputs and changes to the database.

Over the course of collaboration with more than 200 institutions, (multi-center) research projects and registries, heartbeat medical has established a comprehensive data protection concept including a mature data protection impact assessment (DPA) as well as technical and organizational measures. This concept covers all requirements in Germany, Austria and Switzerland.

Data entered by the patient is only available to system users on a read-only basis. Modification is not possible. Medical documentation can be created and edited by system users. Full access including user administration (see also User administration below) is only possible for selected system users. Access is not possible without a system account and therefore also not for

employees of heartbeat medical. Patients do not have direct access to the system, but the physician / study staff can share and discuss the results with patients.
All patient-identifying data entered or created in heartbeat ONE is secured by a password assigned by the customer using 256 bit AES encryption. Access to this data is only possible with a user account including password. Heartbeat Medical is further obligated to take appropriate precautions to prevent unauthorized access by third parties to the customer's information and data. All patient-identifying data is send and stored in encrypted form.
heartbeat ONE offers a user and permissions management system to create and manage user accounts and permissions. Individual permissions are grouped into roles and can then be assigned to the user (-groups).

7.3.2 Data security Kesem Health iUFlow App and Clinical Portal database

Kesem Health is using Amazon Web Services (AWS) as an infrastructure partner. AWS holds the following security and compliance certifications: SOC1/ISAE 3402, SOC2, SOC 3, FISMA, DIACAP, FedRAMP, PCI DSS Level 1, ISO 9001, ISO 27001, ISO 27017, ISO 27018.
Data that is collected and stored by Kesem Health is encrypted at rest. All data in transit is encrypted. Customer identifying data and clinical data is encrypted in transit using TLS 1.1 and 1.2. All Kesem endpoints support HTTPS for encrypting data in transit. In general, all identification data (in this case only the study number) is kept separate from clinical data. To further increase anonymity and data security, the user of the iUFlow app is only asked to enter his study number assigned by the study team and the location of the study "University Hospital Basel" during the initial registration in the app. No personal identifying data is necessary for registration and activation of the Kesem Health iUFlow app. The Kesem Health Privacy Policy is shown in Appendix 20. Study participants will be given the Kesem Health Privacy Policy in writing as part of the study consent process. When registering in the iUFlow app, this will be displayed again and must be confirmed.
The Kesem Health Clinical Portal database is password secured. Only study staff of the main center at the University Hospital Basel (USB) has administration rights. Study stuff of sub-centers need to get authorized by the USB to see iUFlow data of their respective patients in the Kesem health Clinical Portal, but sub-centers have no administration rights.

7.4 Retention and destruction of study data

After termination of the study, all data from the heartbeat ONE main database will be archived by Heartbeat in line with GCP-conformity criteria, which was contracted between Heartbeat and USB for a period of at least 10 years. The Kesem Clinical Portal of the study will be closed and deleted, including all data inside, after data has been monitored and fully transferred to the heartbeat ONE database.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The project is funded by Boston Scientific (BSC) International S.A. a French corporation, Parc dÀffaires Le Val Saint-Quentin, 2 rue René Caudron, 78960 Voisins-le-Bretonneux, France with a maximum total funding of 1,634,444 ONE MILLION six hundred and thirty-four thousand four hundred and forty-four euros. The basis of funding is a contract agreement (Appendix 10.1) following the principle Investigator's (PD Dr. J. Ebbing) successful application to BSC's Investigator Sponsored Research Program. Funding is distributed on a staggered basis according

to the achievement of timelines (goals). Appendix 18 shows the items in the estimated study budget in chronological order.

At least one year of follow-up data and then updates at annual intervals until the 5th follow-up year will be published in reputable peer-reviewed journals.

The study will be registered at the following study registers:

- kofam: Portal für klinische Versuche in der Schweiz (SNCTP)
- swissethics: Registry of All Reseach Projects (RAPS)
- European Clinical Trials Database (EudraCT)
- Europäische Studienregister (EU Clinical Trials Register)
- US National Institutes of Health NIH: (ClinicalTrials.gov)
- WHO: International Clinical Trials Registry Platform (ICTRP)

Collaboration with participating sub-study centers will be governed by a study sub-contract. (Appendix 14)

The following contracts form the basis of this study or are applied within the scope of the study:

1. Main contract with funder of the study, Boston Scientific International S.A. a French corporation, Parc dÀffaires Le Val Saint-Quentin, 2 rue René Caudron, 78960 Voisins-le-Bretonneux, France (Appendix 10.1).
   Chapters of the current BSC contract relating to the transfer of data to BSC and the use of data by BSC will be renegotiated by amendment. It is planned that pseudonymised data will be passed on to BSC.
   BSC would like to use this data for regulatory submissions and internal research purposes. Completely anonymised data, as required by BSC in the current BSC contract, by definition do not allow usable statistical evaluations. This contradiction will be regulated by passing on pseudonymised/aggregated data to BSC which will be contracted by amendment (Appendix 10.2).
2. Contract with manufacturer of the iUFlow (home uroflometry device), Kesem Helath Pty Ltd, 5A Hartnett Close, Mulgrave, Victoria 3170, Australia. (Appendix 11)
3. Contract with Heartbeat (HRTBT) Medical Solutions GmbH, Greifswalder Str. 212, 10405 Berlin, Germany, which provides and supports the main database “heartbeat ONE”. (Appendix 12)

3.1 heartbeat enters into a separate application service provider (ASP) contract with each participating site (Appendix 13). Those ASP contracts regulate
rights and obligations between the two parties and include a Service Level Agreement and a Data Processing Agreement.
In the course of the project, the participating centers are not charged any usage costs. These costs are borne by the central study unit (USB) and set out in a separate offer.

4. Study subcontract with participating study centers. (Appendix 14)

All contracts were reviewed and approved for contract signature by either Unitectra, Technology Transfer, Universities of Basel, Bern and Zürich, Scheuchzerstrasse 21, 8006 Zürich or by the legal department of the University Hospital Basel (USB).

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Appendix 22

Table 3: Schedule of assessments (summary) (V1.0)

Parameter	T0 (Baseline)	T – iUFlow-device	T – Dropout from study	T1 (intra-operative)	T2 (peri-operative)	T3 (1d postop)	T4 (12w postop)	T5 (day of catheter removal)	T6 (2w postOP)	T7 (6w postOP)	T8 (3m postOP)	T9 (6m postOP)	T10 (12m postOP)	T11 (2-5y postOP)
Patient Reported Outcome Measures (PROMs)														
IPSS/QoL	x									x	x	x	x	x
ICIQ-MLUTS	x									x	x	x	x	x
ICIQ-MLUTSsex	x									x	x	x	x	x
MSHQ	x									x	x	x	x	x
PROMIS Global Health 10	x								x	x	x	x	x	x
QoR-15GE	x					x			x					
NPRS (Numeric pain rating Scale)	x					x								
ICIQ-S									x	x	x	x	x	x
Rezum side effects and pain medication patient questionnaire									x	x	x			
Patients' preferences and expectations for Rezum treatment questionnaire -	x										x	x	x	x
Questionnaire BPH/LUTS medication									x	x	x	x	x	x
Questionnaire re-operations											x	x	x	x
Questionnaire bladder catheter						x			x		x	x	x	x
Questionnaire Uroflow	x										x	x	x	x

Clinical Reported Outcome Measures (CROMs)														
Study ID	x													
Demographic data	x													
Patient characteristics	x													
Comorbidities														
Urological Anamnesis														
Catheterization														
Operations/interventions of the lower urinary tract														
Prostate biopsy														
History of cancer														
Diagnostic urethrocystoscopy														
Medical imaging														
Urodynamic evaluation														
Uroflowmetry (not iUFlow)														
Micturition-related medication														
Blood and urine examination	x										x	x	x	x
Laboratory blood														
Laboratory urine														
Anticoagulation	x													
Reason for Rezum (Doctor)	x													
Surgery planning	x													
iUFlow-device		x												
Dropout from study			x											
Surgery				x										
Anesthesia				x										
Premedication				x										
Anesthetics used in the course of the intervention				x										
Hospitalization time					x									
Postoperative analgesia							x							

Postoperative catheter management								**x**						
Transurethral catheter														
Suprapubic catheter														
Follow-up											**x**	**x**	**x**	**x**
Cancer history														
Diagnostic urethrocystscopy														
Medical imaging														
Urodynamic evaluation														
Uroflowmetry (not iUFlow)														
Micturition-related medication														
Anticoagulation														
Bladder catheter														
Reoperation lower urinary tract														
Complications/ Circumstances											**x**			
Side effects														
Complications														