Economic evaluation of Prostatic Urethral Lift (Urolift)
ECOLIFT

Sponsor code: CHUBX 2019/12

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING THE HUMAN PERSON

(Category 2 - minimal risks and constraints)

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HISTORY OF PROTOCOL UPDATES

VERSION	DATE	REASON FOR UPDATE
1.0	16/DEC/2019	Initial version
2.0	05/JAN/2021	Substantial amendment N°1
3.0	19/APR/2021	Substantial amendment N°2
4.0	19/JAN/2022	Substantial amendment N°3
5.0	25/JUL/2022	Substantial amendment N°4
6.0	31/JAN/2023	Substantial amendment N°5

PROTOCOL SIGNATURE PAGE

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANSM	French National Agency for Medicines and Health Products Safety
ASA	Amélioration du service attendu
ATC	Drug classification (*Anatomique, Thérapeutique et Chimique*)
BOO	Bladder Outlet Obstruction
BPE	Bordeaux PharmacoEpi, the Pharmacoepidemiology research platform of the University of Bordeaux - INSERM CIC1401
BPH	Benign Prostatic Hyperplasia
CNAM	French national health insurance fund for salaried worker (*Caisse Nationale de l'Assurance Maladie*)
CNIL	French data protection commission (*Commission Nationale de l'Informatique et des Libertés*)
CPP	Committee for the Protection of Persons
CepiDC	Centre d'épidémiologie sur les causes médicales de décès
CEREES	Committee in health data research (*Comité d'Expertise pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé*
DEP	Data Extraction Plan
DRG	Diagnosis-Related Groups (or GHM for *Groupes Homogènes de Malades*)
EGB	1/97th random sample of the national health insurance database (*Echantillon Généraliste de Bénéficiaires*)
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D	Euroqol questionnaire-5 dimensions
HAS	Haute Autorité de Santé (French National Health Authority)
hDRS	high dimensional Disease Risk Score
HUI3	Health utility index
ICD-10	International Classification of Diseases, 10th classification
ICIQ-UI SF	International Consultation on Incontinence questionnaire for urinary incontinence – short form
IPSS	International Prostate Symptom Score
ISI	Incontinence Severity Index
LPLV	Last Patient Last Visit
LTD	Long-Term Disease (registration for major chronic diseases with full insurance coverage of all claims related to disease)
LUTS	lower urinary tract symptoms
MSHQ EjD	Male Sexual Health Questionnaire for Ejaculatory Dysfunction
PMSI	National hospital discharge summary database (*Programme de Médicalisation des Systèmes d'Information*)
PUL	Prostatic Urethral Lift
QALY	Quality adjusted life year
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SARe	Statistical Analysis Report
SNDS	National healthcare insurance system database (*Système National des Données de Santé*)
SRG	Stay-Related Groups (or GHS for *Groupes Homogènes de Séjours*)
TURP	Trans Urethral Resection of the Prostate

SUMMARY OF THE RESEARCH

SPONSOR	Centre Hospitalier Universitaire de Bordeaux
COORDINATING INVESTIGATOR	Prof. Grégoire ROBERT
METHODOLOGY AND DATA MANAGEMENT CENTRE	Bordeaux PharmacoEpi (BPE) Plateforme de recherche en pharmaco-épidémiologie INSERM CIC1401 Université de Bordeaux
ACRONYM AND TITLE	ECOLIFT: Economic evaluation of Prostatic Urethral Lift (Urolift)
SIMPLIFIED TITLE	Economic study of PUL
JUSTIFICATION / CONTEXT	Transurethral surgery (transurethral resection of the prostate (TURP), holmium laser enucleation, or GreenLight laser vaporisation) is the first line surgical treatment for bladder outlet obstruction (BOO) secondary to benign prostatic hyperplasia (BPH). Even if bipolar and laser surgery have dramatically improved surgical outcomes in terms of length of hospital stay and post-operative complications, these procedures remain associated with a significant amount of infectious and bleeding complications, as well as with some persistent side effects such as sexual dysfunction and urinary incontinence. Prostatic urethral lift (PUL) has been developed as a minimally invasive alternative to TURP with no need of general anaesthesia, less need of urinary catheter and less exposure to post-operative complication. Its efficacy and safety have been assessed by two clinical randomized trials. In summary, PUL resulted in urinary symptom improvement that remained inferior to TURP but that were durable for 5 years. PUL preserved overall quality of life better than TURP especially with regard to sexual quality of life and quality of recover. Given these results, Urolift has been recommended by the EAU guidelines and has been recognized by the French authorities (HAS). In the French health care system, the cost of the implants could not be financed by the hospital itself, as it would be more costly than the incomes related with the hospital stay. Very few patients would be willing to pay for it. Reimbursement of the implants by the healthcare system is therefore needed for the distribution of PUL in France. To ensure reimbursement of the implants in addition to the tariff of the hospital stay, Urolift should obtain ASA 3 statement by the HAS. To date there is very little clinical experience of Urolift in France; real-life data are not sufficient and economic evaluation of Urolift in the setting of the French healthcare system is missing. ECOLIFT study will be conducted in two phases: a field study will first compare patients treated with PUL to those treated with TURP/laser during one year follow-up, and, an additional study will then compare healthcare consumptions during 3 years of follow-up between each treatment group using data of the French National Claims Database (*Système National des Données de Santé*, SNDS). These data are needed to support the reimbursement file at the HAS.

HYPOTHESIS	To assess if PUL (Urolift) could be a cost-effective therapeutic strategy compared to transurethral surgery (TURP/laser) for selected patients, from the French healthcare system point of view.
OBJECTIVES	**Primary objective:** To assess the incremental cost-effectiveness ratio of PUL compared with transurethral surgery 4 months after initial hospitalization **Secondary objectives:** To assess the incremental cost/effectiveness ratio of PUL compared with transurethral surgery at 12 months. The secondary objectives will be also to compare between the PUL and the transurethral procedures: ● The real cost of hospitalization related to each surgery procedure from the hospital point of view; ● The overall and specific urogenital healthcare consumptions at 4 months, 1 and 3 years after surgical procedures ● The BPH retreatment rate (including medical and surgical treatments) at 1 and 3 years after surgical procedures ● The urinary symptoms at 4 months and 1 year after surgical procedure ● The global quality of life, including sleep comfort at 4 months and 1 year after surgical procedures ● The time to complete recovery and to return to normal professional activities during the 4 months and 1 year after surgical procedures; ● The sexual side effects at 4 months and 1 year after surgical procedures ● The complications associated with the surgical procedures at 4 months after surgical procedures.
STUDY DESIGN	ECOLIFT is an observational multicenter cohort study conducted on the 3 following cohorts: ● **The PUL cohort:** 80 patients with a PUL surgery in first line treatment for BOO with a 1-year follow-up, for which, clinical data will be enhanced with data from SNDS with 2-year history before BPH surgery and a follow-up of 3 years. ● **The TURP/laser cohort**: 80 patients with a TURP or laser (HLE or GLV) surgery in first line treatment for BOO with a 1-year follow-up, for which clinical data will be enhanced with data from SNDS with 2-year history before BPH surgery and a follow-up of 3 years. ● **The SNDS cohort:** patients from the SNDS with any transurethral surgery (TURP, HLE or GLV) in first line treatment for BOO randomly matched to patients of the PUL cohort using a high dimensional disease risk score (hDRS) based on the one-year SNDS information before transurethral procedure.
STUDY POPULATION	● **The PUL and TURP/LASER cohorts:** **Inclusion criteria**: male patients affiliated to a French health insurance system aged over 50 years who experienced a PUL or TURP/Laser surgery in first line of treatment for a symptomatic BPH, with an International Prostatic Symptom Score ≥14, a Peak urine flow rate ≤ 15ml/sec on a bladder repletion volume ≥150ml a Prostate volume >30cc to <80 cc per ultrasound or RMI (within 6 months before patient inclusion). **Exclusion criteria**: Patients with current urinary retention, post void residual urine > 250ml, active urinary tract infection at time of treatment, previous BPH procedure, urethral conditions that may prevent insertion and delivery of device system into bladder, previous

	pelvic surgery or irradiation, history of neurogenic or atonic bladder, biopsy of the prostate within the past 6 weeks, life expectancy estimated to be less than 1 year, history of prostate or bladder cancer, PSA>10ng/ml unless prostate biopsy is negative, person guardianship or curatorship will not be included in the cohorts. Patients intending to move abroad within 1 year after inclusion will not be included either. Person participating to another interventional study on benign prostatic hyperplasia during the study. Patients of the PUL and TURP/LASER cohorts will be identified in the SNDS through their NIR national identifier (if possible) or using a probabilistic linkage with age, hospital identifier (FINESS), date of hospitalization for the procedure and ICD-10 discharge diagnosis. Only patients with a 2-year history before the procedure and a 3-year follow-up after the procedure will be analysed. ● **The SNDS cohort:** **Inclusion criteria**: male patients affiliated to a French health insurance system aged over 50 years who experienced a TURP/Laser surgery in first line of treatment for a symptomatic BPH in the same period as patients of the PUL and TURP/LASER cohorts. **Exclusion criteria:** Patients hospitalized in one of the 7 investigational centers and patients with a previous BPH procedure, a previous pelvic surgery or irradiation, history of prostate or bladder cancer within the 2 previous years, a biopsy of the prostate within the past 6 weeks, or with a short life expectancy will not be included in the cohort. **Matching criteria:** A total of 5 patients will be matched to 1 patient of the PUL cohort for each procedure (TURP, HLE, GLV) according to age, date of the procedure (same month) and a high dimensional disease risk score (hDRS) based on the one-year SNDS information before the transurethral procedure.
RESEARCH PROCEDURES/ STRATEGIES	The studied procedures are: ● The experimental procedure: PUL, consisting in transurethral placement of permanent UroLift implants into the lobes of the prostate. The intent of PUL procedure is to retract the lobes of the prostate in order to reduce prostatic obstruction. ● The comparison procedure: classic prostatic endoscopic surgery (TURP or laser).
OUTCOMES	**Primary outcome:** Incremental cost per avoided complication (based on Clavien Dindo classification) of PUL compared to classic transurethral surgery (TURP or laser) 4 months after the surgical procedure **Secondary outcomes measures:** ● The incremental cost/QALY of PUL compared with transurethral surgery at 12 months. ● The real cost of hospitalization related to each surgery procedure from the hospital point of view (€) ● The overall and specific urogenital healthcare consumptions at 4 months, 1 year and 3 years following the surgical procedures; ● The BPH retreatment (including medical and surgical treatments) at 1 and 3 years after surgical procedures; ● The urinary symptoms at 4 months and 1 year after surgical procedure; ● The global quality of life, including sleep comfort at 4 months and 1

	year after surgical procedures; ● The time to complete recovery and to return to normal professional activities evaluated at 1, 2, 3 and 4 months; ● The sexual side effects at 4 months and 1 year after surgical procedures; ● The complications associated with the surgical procedures at 4 months after surgical procedures.
DATA SOURCE	Clinical and economic data will be collected within the scope of a prospective interventional study and then will be enhanced by data from the SNDS database. The SNDS is the French nationwide healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims linked to the national hospital-discharge summaries database system (PMSI) and the national death registry (CépiDC), using a unique national pseudonymised identifier. It currently includes 98.8% of the French population, more than 66 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires (Bezin 2017). The SNDS contains individual pseudonymised information on (Tuppin 2010, Bezin 2017): ● General characteristics; ● Date of death for those concerned and cause of death; ● Long-term disease (LTD and associated ICD-10 codes) registration for full insurance coverage (with start and end dates); ● Outpatient reimbursed healthcare expenditures with dates and codes (but not the medical indication nor result); ● Hospital-discharge summaries from PMSI.
STUDY SIZE	● 80 patients in the PUL cohort ● 80 patients in the TURP/laser cohort ● 1200 patients in the SNDS cohort: 400 transurethral resection, 400 laser enucleation, 400 laser vaporization
INVESTIGATIONAL CENTERS	7investigational centers ● CHU de Bordeaux – G. ROBERT ● CHU de Lyon – A. RUFFION ● CHU de Montpellier – T. MUREZ ● CHU de Lille – A. VILLERS ● Hôpital Cochin, APHP – N. BARRY DELONGCHAMPS ● CHU de Tours – F. BRUYERE ● Clinique La croix du Sud – B. PRADERE
DURATION OF THE RESEARCH PROJECT	● For the PUL and TURP/Laser cohorts (prospective interventional study) ○ Recruitment: 32 months ○ Clinical follow-up: 12 months

	○ SNDS database follow-up: 3 years ○ SNDS database history: 2 years ● For the SNDS cohort ○ Inclusion date: date of the surgical procedure completion ○ Follow-up: 3 years ○ History: 2 years ● Regulatory aspects Q4 2019 – Q2 2020 ● Inclusion period of PUL and TURP cohorts Q2 2021-Q2 2023 ● Clinical data analysis ○ Primary endpoint data (4 months after surgical procedure) Q4 2023 ○ Data management and statistical analysis for primary endpoint Q1-Q2 2024 ○ Data management and statistical analysis for clinical data Q3-Q4 2024 ● SNDS data extraction and analysis ○ Statistical Analysis Plan Q1 2023 ○ 1st Data extraction (1-year follow-up) Q4 2025 ○ Data management and interim statistical analysis Q1-Q2 2026 ○ Interim study report Q3 2026 ○ 2nd Data extraction (3-year follow-up) Q4 2027 ○ Data management and final statistical analysis Q1-Q2 2028 ● Final study report Q3 2028
DATA ANALYSIS	The analyses will be performed for each cohort, according to the matched treatment group and will include: ● A description of study populations ● A comparison of baseline characteristics between the PUL and the TURP cohorts ○ A comparison of baseline characteristics between the PUL and the SDNS cohorts before and after hDRS matching (flow-chart, baseline characteristics); ○ An Estimation of cost effectiveness ratios between the PUL and TURP/laser cohorts at 4 months and 1 year. ○ An estimation of the cost of hospitalization related to each surgery procedure during hospital stay ○ A description of the overall and specific urogenital healthcare

	consumptions ; ○ a description of BPH retreatments; ○ a description of urinary symptoms; ○ a description of the quality of life; ○ a description of the time to recovery after surgery and to return to normal professional activities; ○ a description of the sexual side effects; ○ a description of the associated complications. Comparisons between the PUL and the TURP/Laser cohorts and between the PUL and the SNDS cohorts will be performed after 1 year and 3 years of follow-up in a intention-to-treat analysis using: ○ a linear regression model when it involves quantitative variables, ○ a logistic regression model adjusted on potential confounding when it involves qualitative variables.
EXPECTED IMPACTS	Results of the study will be used to support French market release, reimbursement, and clinical acceptance of the Urolift system in France.

1. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

1.1. CURRENT STATE OF KNOWLEDGE

1.1.1. ON THE PATHOLOGY

Benign prostatic hyperplasia (BPH) is a common condition, as men get older. It causes lower urinary tract symptoms (LUTS), such as blocking the flow of urine out of the bladder. It can also cause bladder or kidney damages.
According to French population based studies, about 21% of men between 50 and 80 years have moderate to severe urinary symptoms associated with benign prostatic hyperplasia and could need surgical treatment. (1)
Transurethral surgery using bipolar or laser resection is the first line surgical treatment for bladder outlet obstruction (BOO) secondary to BPH.

1.1.2. ON THE STRATEGIES/PROCEDURES AND THE STUDY

1.1.2.1. Transurethral surgery

In France about 60.000 transurethral procedures for BOO are performed each year. However, even if bipolar and laser surgery have dramatically improved surgical outcomes in terms of length of hospital stay and post-operative complications, these procedures remain associated with a significant amount of infectious and bleeding complications, as well as with some persistent side effects such as sexual dysfunction and urinary incontinence (2, 3).
The incidence of post-operative complications has been evaluated in many RCTs comparing different surgical procedures. Clavien Dindo complications grade 2 and higher were experienced by 20 to 40% of patients depending on the surgical technique. Most of complications related with surgery are occurring within 3 months after surgery. After the first 3 months, delayed complications such as urethral strictures, bladder neck sclerosis and urinary incontinence may lead to additional surgical treatments. LUTS recurrence may also lead to restarting medical treatment or secondary surgical treatment .

1.1.2.2. UROLIFT

Prostatic urethral lift (PUL) has been developed as a minimally invasive alternative to TURP with no need of general anaesthesia, less need of urinary catheter and less exposure to post-operative complications. Two randomized studies have been conducted to assess the efficacy and safety of this procedure.
The LIFT study is a randomized controlled trial (North America and Australia) comparing Urolift with sham procedure. Roehrborn et al. reported rapid improvement in urinary symptoms, quality of life (QoL) and flow rate that was durable to 5 years. IPSS and QoL improvements in this study were respectively 36% and 50% and surgical retreatment rate was 13.6%. Sexual function was stable over 5 years with no de novo, sustained erectile or ejaculatory dysfunction. (4)
The BPH6 study is a European multicentric randomized controlled trial comparing Urolift with TURP. After one year follow-up, Sonksen et al. reported better improvement of the composite quality of life endpoint in the Urolift group. Gratzke et al reported the 2-year outcomes of the same study. Change in IPSS and Qmax in the TURP arm were superior to the PUL arm but PUL resulted in a superior quality of recovery and ejaculatory function preservation. It resulted in better performance of Urolift on the composite BPH6 index (including IPSS, Sexual Health Inventory for Men (SHIM), Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD), Incontinence Severity Index (ISI), Quality of Recovery visual analogue score (QoR VAS), and the Clavien–Dindo classification of adverse events. (5)
In summary, PUL resulted in urinary symptom improvement that remained inferior to TURP but that were durable for 5 years. PUL preserved overall quality of life better than TURP especially with regard to sexual quality of life and quality of recover.
Given these results, Urolift has been recommended by the EAU guidelines (EAU guidelines for management of non neurogenic male LUTS; https://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/) and has been recognized by the French authorities (HAS) (Appendix 1).

1.1.2.3. PUL (Urolift) in the French market

In France, the cost of each PUL implant is about €500 and a mean of 4 implants are needed in each surgical procedure. In the French healthcare system, these costs could not be financed by the hospital itself, as it would be more costly than the incomes related with the hospital stay (the mean income of hospitalization for this kind of treatment is about €2253 in 2019). Very few patients would be willing to pay for it. Reimbursement of the implants by the French healthcare social insurance is therefore needed for the distribution of PUL in France. To ensure reimbursement of the implants in addition to the tariff of the hospital stay, Urolift should obtain ASA 3 statement by the HAS. To date there is very little clinical experience of Urolift in France; real life data are not sufficient and economic evaluation of Urolift in the setting of the French healthcare system is missing. These data are needed to support the reimbursement file at the HAS.

1.2. RESEARCH HYPOTHESES AND EXPECTED RESULTS

In real life practice, transurethral surgery implies a general anaesthesia, a long hospital stay and length of surgery. Furthermore, complications and side effects associated with transurethral surgery of the prostate are quite frequent and lead to high healthcare costs. In this context, we assume that costs related to PUL implants and surgery could be covered by a reduction in healthcare expenses related to these transurethral surgery events.

Our hypothesis is that from the French healthcare system point of view, PUL (urolift) is a cost-effective strategy compared to classic transurethral surgery (TURP/laser) for selected patients treated for BOO.

1.3. JUSTIFICATION OF THE METHODOLOGICAL CHOICES

A two-phases economic evaluation
Randomized controlled trials were yet conducted and the remaining question is the cost effectiveness of PUL compared to other transurethral procedure in French daily practice. That's the reason why, we decided to propose an economic evaluation as the primary objective of this study.
In order to provide all pertinent clinical and economical information comparing PUL and TURP/laser surgery over a long-term follow-up period in the French context, we propose to conduct a study in two phases.
1-In the first phase we will prospectively compare a cohort of patients treated with PUL to another cohort of patients treated with TURP/laser during one year follow-up. This part of the study will enable us to gather real-life unknown information on the use of Urolift in French hospitals daily practice and organisation (number of implants needed, length and cost of surgery, length of hospital stay…) and to collect quality of life and clinical data from French population.
2- As some consequences of the surgery, as well as differences between healthcare consumptions, can occur even after 4 months and 1 year, and because it is difficult to pursue the clinical trial over 1 year without too many lost for follow-up patients, we decided to work on health databases for the second part of this study. This second phase will cover a 3-years follow-up by analysing healthcare resources utilization in each cohort using the French nationwide claims database, the SNDS. The comparison between PUL and TURP/Laser procedures will be strengthened by a complementary analysis performed between the PUL cohort and a matched cohort of patients identified in the SNDS database with the same baseline characteristics but treated with transurethral procedures. The matching process (based on a hdDRS) and the statistical methods of adjustment will overcome the absence of randomization in the initial process of patients' assignment to the PUL or TURP cohort.
In addition to provide exhaustive information on the costs of all healthcare consumptions supported by the national healthcare system during the 3-year follow-up, which is very challenging by using conventional methods, the SNDS analysis will provide accurate statistical power to compare the PUL cohort to patients treated with each transurethral procedure. The SNDS analysis will also increase the generalizability of the study results by considering TURP/laser patients randomly selected from all French hospital centers, contrary to the clinical part of the study which will be focused on 7 investigational centers. The SNDS database will however not provide any clinical information on the functional results of the interventions thereby justifying to combine it with a conventional clinical study.

Incremental cost per avoided complication as main evaluation criterion
In this study, we propose an incremental cost / avoided complication at 4 months as the primary result for the following reasons:
- The incremental cost/Qaly is difficult to assess in our context: in France, only EQ-5D and HUI3 questionnaires have utility index that are validated in the French population. However, according to the literature and some experts, these questionnaires are too "generic" to really capture differences in quality of life between both groups of patients in the context of BOO. These questionnaires are not enough discriminating to propose a relevant cost/Qaly ratio as the main objective. However, this ratio will be provided as a secondary objective as it remains necessary for public decisions makers to know it in our French context.
- In our case, on a clinical point of view, avoided complication represent one of the most relevant criteria to discuss the place of PUL in the therapeutic strategy of BOO in comparison with transurethral surgery. We therefore chose the incremental cost / avoided complication at 4 months as the main evaluation criterion in this study.

1.4. RISK/ BENEFIT RATIO

PUL surgery is a mini-invasive alternative to BPH standard surgery, which is intended to avoid post-operative complications and some long-term side effects, while keeping a reasonable efficiency to treat LUTS. The post-operative complications are mainly related to infections and bleeding, and are responsible of the morbidity of the BPH surgery. The persistent complications as urinary incontinence strongly affect the long-term quality of life.

Performing PUL surgery may decrease the risk of post-operative complications related with infections and bleeding.
Performing PUL surgery may decrease the risk of the persistent urinary and sexual side effects and preserve quality of life.
Performing PUL surgery may be less effective than standard surgery in terms of LUTS treatment.
Performing PUL surgery may lead to earlier relapse of LUTSs compared to standard surgery.

1.5. EXPECTED BENEFITS

PUL surgery is a mini-invasive alternative to BPH standard surgery, performed under local anaesthesia in a day-care surgical unit, which need less operating time, less use of urinary catheter, and less length of stay. The procedure consists of implanting devices and does not involve resection of prostatic tissue, which should avoid some complications.
BPH standard surgery is associated with a significant amount of post-operative complications, as well as with some persistent side effects such as sexual dysfunction and urinary incontinence. Moreover, those persistent side effects may decrease urinary and sexual comfort, which strongly affect the quality of life.

As the procedure does not involve resection of prostatic tissue, we can expect less bleeding complications.
As we expect less use of urinary catheter, infectious complications should be reduced.
This procedure does not involve risk of urinary sphincter lesion so we can expect at least not worse and probably less urinary incontinence.
For men who maintain regular sexual activity, the procedure should preserve ejaculation.
For the type of patient selected in the clinical trial, we think that PUL surgery could achieve acceptable functional improvements compared to baseline and to those of standard surgery.

If our assumptions are confirmed, PUL surgery could be an efficient alternative to standard surgery, with a reduced time and amount of care and fewer complications, as well as an improvement of the overall long-term quality of life by avoiding persistent side effects.

1.6. JUSTIFICATION OF THE LOW LEVEL OF INTERVENTION

In 2017, the CNEDiMTS (HAS) performed a review of all available publications regarding Urolift device in order to assess its relevance in France in comparison with available standard of care (TURP).
The CNEDiMTS (HAS) performed a comprehensive review of the results of the LIFT study with 3 years follow-up data, of the BPH-6 Study, of an economic evaluation performed by the NICE in the UK, and of all the previously published data. At the end of this process, the experts of the CNEDiMTS (HAS) concluded that Urolift had an entire place in the therapeutic strategy of BOO treatment in France and could be used in daily practice. They assorted this statement by an ASA IV ranking corresponding to a minor improvement compared to standard treatment. They also asked the company (NEOTRACT, INC) to follow-up patients receiving Urolift in France by collecting their clinical characteristics, the number of implants used, the mid-long term functional results, and the need for any kind of retreatment.
Since then, Urolift has been sparsely used in France mainly due to the fact that the price of this single-use device is not covered by the hospitalization and that Urolift is still not reimbursed by the French Healthcare System.

In the setting of the ECOLIFT study, the Urolift device will be used following the exact recommendations of the HAS (same inclusion/exclusion criteria). The ECOLIFT protocol strictly reproduces the clinical use of Urolift without any additional clinical visit or any invasive procedure due to the research protocol as compared to French standard of care (TURP).
Additionally, the aim of our study is not to assess again its clinical effectiveness but to measure its economical value in the setting of the French Healthcare System to support the need of its reimbursement.
Finally, surgeons participating to the ECOLIFT study will have to be experienced with this procedure or to be specifically trained upfront any participation to the ECOLIFT study. Experience of at least 15 cases will be required. If the selected surgeon does not have sufficient experience, specific assistance will be provided by the company for his/her training (visit in an expert center for case observation, surgical mentoring for at least 5 cases, and 10 additional cases performed alone with possible critical review of a recorded video by an expert).

Considering that Urolift will be used in the exact setting of its recommended clinical usage (CNEDiMTS HAS recommendations) with no additional procedure compared to the standard of care, that our main objective is to perform an economic evaluation without any new clinical usage investigation and that the surgeons will have

sufficient experience before entering the study, we assume the fact that this protocol must be considered at low level of intervention with minimal risks and constraints.

2. STUDY OBJECTIVES

2.1. MAIN OBJECTIVE

To assess the incremental cost-effectiveness ratio of PUL compared with transurethral surgery 4 months after initial hospitalization.

2.2. SECONDARY OBJECTIVES

To assess the incremental cost/effectiveness ratio of PUL compared with transurethral surgery at 12 months.

The secondary objectives will be also to compare between the PUL and the transurethral procedures:

- The real cost of hospitalization related to each surgery procedure from the hospital point of view
- The overall and specific urogenital healthcare consumptions at 4 months, 1 year and 3 years following the surgical procedures;
- The BPH retreatment (including medical and surgical treatments) at 1 and 3 years after surgical procedures;
- The urinary symptoms at 4 months and 1 year after surgical procedure;
- The global quality of life, including sleep comfort at 4 months and 1 year after surgical procedures;
- The time to complete recovery and to return to normal professional activities evaluated at 1, 2, 3 and 4 months;
- The sexual side effects at 4 months and 1 year after surgical procedures;
- The complications associated with the surgical procedures at 4 months after surgical procedures.

3. STUDY OUTCOMES

3.1. PRIMARY OUTCOME

The primary endpoint will be the incremental cost per avoided complication (based on Clavien Dindo classification) of PUL compared to transurethral surgery 4 months after the surgical procedure.

3.2. SECONDARY OUTCOMES MEASURES

Secondary endpoints will be:

- **The incremental cost/Qaly** of PUL compared to transurethral surgery at 12 months
- **The total hospital cost** of each surgery procedure based on a top down micro-costing method performed during hospitalization stay
- **Overall and specific urogenital healthcare consumptions** at 4 months, 1 year and 3 years following the surgical procedure
  - Dispensed medications identified using the corresponding codes of the Anatomical Therapeutic Chemical (ATC) Classification;
  - In- and out-patient visits;
  - Hospitalisation and their corresponding discharge diagnoses coded according to International Classification of Disease, 10th revision;
  - Medical procedures;
  - Nursing acts and physiotherapy;
  - Medical imageries and lab tests;
  - Transport;
  - Sick allowances;
  - At 4 months: all healthcare consumptions which are not reimbursed, but payed by the patient (e.g.: urinary incontinence products).
- **BPH retreatment,**
  - Any dispensing of the following medications at 1 and 3 years after surgical procedure: alpha-blockers (ATC code G04CA) or 5-alpha-reductase inhibitors (ATC code G04CB);

- Hospitalization at 1 and 3 years after surgical procedure, with the main diagnosis of BPH (ICD-10 code N40) and the surgical procedure codes JGNE003, JGNE171, JGNJ001, JGFA005 JGFA009, JGFA015, JGFE023, JGFE365.

- **Urinary symptoms,**
  - Urinary incontinence evolution between inclusion and 4 months after surgical procedure (Incontinence Severity Index (ISI));
  - International consultation on Incontinence questionnaire for Urinary incontinence short form (ICIQ-UI SF)
  - Hospitalization with a discharge diagnosis ICD-10 code related to an urinary infection (code N41 for acute prostatitis or code N10 for acute pyelonephritis) at 1 and 3 years after surgical procedure;
  - Hospitalization with a discharge diagnosis ICD-10 code related to urinary retention (R33) at 1 and 3 years after surgical procedure;
  - Hospitalization with a discharge diagnosis ICD-10 code and/or medical procedure related to urethral stricture at 1 and 3 years after surgical procedure.
- **Global quality of life,**
  - IPSS and IPSS-Q8 evolution between inclusion, 4 month, and 1 year after surgical procedure;
  - Jenkins sleep questionnaire between inclusion, 4 months, and 1 year after surgical procedure;
  - EQ-5D-5L questionnaire (appendix 2) evolution between inclusion, 4 months, and 1 year after surgical procedure;
- **The time to complete recovery and to return to normal professional activities**
  - Recovery after surgery (Quality of Recovery visual analogue score (QoR VAS)) at 1, 2, 3 and 4 months after surgical procedure;
  - Time before returning to professional activities.
- **Sexual side effects,**
  - Sexual quality of life evolution between inclusion, 4 months and 12 months after surgical procedure (IIEF15, Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD).
- **Associated complications,**
  - Clavien Dindo classification of adverse events at 4 months after surgical procedure.

4. STUDY DESIGN AND METHODOLOGY OF ECONOMIC EVALUATION

4.1. STUDY DESIGN

ECOLIFT is a multicenter cohort study conducted on 3 cohorts as follows:

- **The PUL cohort:** a sample of surgeons from the 7 investigational centers will prospectively include 80 patients with a PUL surgery in first line treatment for BOO with a 1-year follow-up. Clinical data will be enhanced with healthcare consumptions and hospitalizations from SNDS with 2-year history before BPH surgery and a follow-up of 3 years.
- **The TURP/laser cohort**: a sample of surgeons from the 7 investigational centers different from those who will perform the PUL procedure (if not possible, it can be exceptionally the same surgeon) will prospectively include 80 patients with a TURP or laser (HLE or GLV) surgery in first line treatment for BOO with a 1-year follow-up. Clinical data will be enhanced with healthcare consumptions and hospitalizations from SNDS with 2-year history before BPH surgery and a follow-up of 3 years.
- **The SNDS cohort:** will include patients from the SNDS with any transurethral surgery (TURP, HLE or GLV) in first line treatment for BOO randomly matched to patients of the PUL cohort; For each transurethral surgery (TURP, HLE or GLV), 5 patients will be matched to 1 PUL patient using a high dimensional disease risk score (hDRS) based on the one-year SNDS information before transurethral procedure. The Disease Risk Score (DRS) estimates the probability of complications occurrence in the absence of the surgery of interest (PUL). DRS will be computed from a multivariable logistic regression model using a large set of variables collected during the one-year period among the SNDS cohort.

4.2. METHODOLOGY OF ECONOMIC EVALUATION

The economic evaluation will be conducted from the French Healthcare System point of view. This means that all healthcare expenditures and costs assumed by the French Healthcare Insurance, hospitals and patients will be taken into account in the analysis.

The incremental cost/avoided complication at 4 months between the PUL and TURP/laser cohorts, will be based on the following criteria:

- **Differences in costs between both strategies:**
  - A micro-costing measurement will be performed in both groups during hospital stay to provide the total cost of each procedure. To identify costs, we will directly observe the resources used during the hospital stay that are related to each surgical procedure including human resources, materials, consumables and equipment…. Because it will not be possible to perform micro-costing for all items over the whole hospital stay, we will also use gross-cost hospital databases for some items (laundry, bedrooms, catering, general daily care, hospital equipment). Although it would be relevant to carry out a multicentric analysis on all recruiting centers, we prefer to restrict this analysis to the patients participating in the study in 3 hospitals: Bordeaux, Lyon and Lille University Hospitals and one clinic, the clinic la Croix du Sud at Quint Fonsegrives . This is justified because this kind of surgery seems to be standardized and doesn't vary a lot from one surgeon to another. Furthermore it will be easier to organise data collection in these centers, which are very used to economic studies. We intend to collect data for 5 patients/surgeries in each group, which means a total of 30 patients/surgeries included in the costing study. This choice could induce a lack of representativeness that we will study carefully by 2 ways before drawing our conclusions in the final report: 1- during collection data: we will study the variability of surgical practices through the filling of micro-costing questionnaires. If, at the end of the 30 observations, the questionnaires are very heterogeneous, we will continue to collect data in order to ensure representativeness of our costing study 2- during statistical analysis, we will perform sensitivity analyses on cost data.
  - During the first 4 months after hospital discharge all expenses related to healthcare consumptions, reimbursed and not reimbursed, will be systematically collected at each follow-up visits by the participant of the study. Follow-up visits will be scheduled every month (including phone call with clinical research assistant and medical appointments).
- **Differences in complications:**
  - Complications will be classified according to the Clavien Dindo classification of adverse events.

The incremental cost/Qaly at 1 year between the PUL and TURP/laser cohorts will be based on the following criteria:

- **Differences in costs between both strategies:**
  - The total cost of hospitalization assessed by the micro-costing method described before.
  - During the 12 months after hospital discharge all reimbursed expenses related to healthcare consumptions of each participant in each cohort will be gathered using SNDS claims databases.
- **Differences in Qaly:**
  - The EQ-5D-5L questionnaire (appendix 2) will be fulfilled by the participants at the inclusion, at 4 months and at 1 year after initial surgery.

Statistical methods associated with this economic evaluation are described in chapter 11.

5. ELIGIBILITY CRITERIA

5.1. PUL AND TURP/LASER COHORTS

5.1.1. INCLUSION CRITERIA

- Male Gender
- Diagnosis of symptomatic BPH requiring a surgical procedure by PUL or TURP/laser
- Age > 50 years
- International Prostatic Symptom Score ≥14
- Peak urine flow rate ≤ 15ml/sec on a bladder repletion volume ≥150ml

Prostate volume >30cc to <80 cc per ultrasound or RMI (within 6 months before patient inclusion).

- Affiliated to a French health insurance system

5.1.2. EXCLUSION CRITERIA

- Current urinary retention
- Post void residual urine > 250ml
- Active urinary tract infection at time of treatment

- Previous BPH procedure
- Urethral conditions that may prevent insertion and delivery of device system into bladder (i.e. urethral strictures, meatal stenosis, bladder neck contracture)
- Previous pelvic surgery or irradiation
- History of neurogenic or atonic bladder
- Biopsy of the prostate within the past 6 weeks
- Life expectancy estimated to be less than 1 year
- History of prostate or bladder cancer
- PSA>10ng/ml unless prostate biopsy is negative
- Person intending to move abroad within 1 year after inclusion
- Person placed under guardianship or curatorship
- Person participating to another interventional study on benign prostatic hyperplasia during the study

Patients of the PUL and TURP/LASER cohorts will be identified in the SNDS through their NIR national identifier (if possible) or using a probabilistic linkage with age, hospital identifier (FINESS), date of hospitalization for the procedure and ICD-10 discharge diagnosis. Only patients with a 2-year history before the procedure and a 3-year follow-up after the procedure will be analyzed.

5.2. SNDS COHORT

5.2.1. INCLUSION CRITERIA

- Male Gender
- Patients hospitalized for transurethral surgery for first line treatment of symptomatic BPH in the same period as patients of the PUL and TURP/LASER cohorts (i.e. hospitalisation with the main diagnosis ICD-10 code N40 and the surgical procedure codes JGFE023 for TURP, JGFE365 for HLE and JGNE171 for GLV);
- Affiliated to a French health insurance system

5.2.2. EXCLUSION CRITERIA

- Patients hospitalized in one of the 7 investigational centers
- Patients with a previous BPH procedure previous pelvic surgery or irradiation, history of prostate or bladder cancer (2-year database history and/or Long term disease registration)
- Patients with biopsy of the prostate within the past 6 weeks
- Patients with short life expectancy based on a Charlson Comorbidity Index ≥ 10 (this threshold reflects the presence of metastasis or an equivalent health condition) (cf. Bannay and al., 2015).

5.2.3. MATCHING CRITERIA

A total of 5 patients will be matched to 1 patient of the PUL cohort for each procedure (TURP, HLE, GLV) according to age, date of the procedure (same month) and a high dimensional disease risk score (hDRS) based on the one-year SNDS information before the surgical procedure. The Disease Risk Score (DRS) estimates the probability of complications occurrence in the absence of the surgery of interest (PUL). DRS will be computed from a multivariable logistic regression model using a large set of variables collected during the one-year period among the SNDS cohort.

5.3. FEASIBILITY AND RECRUITMENT PROCEDURES

Investigational centers have been chosen based on their large experience in conducting clinical trials in the field of BPH.
All sub-investigators also have been chosen based on their significant clinical activity in the field of BPH (at least 80 trans-urethral procedures a year).
Recruitment is planned to last 24 months and will be dispatched as follows between participating centers:

Center	Cohort PUL	Cohort TURP/Laser
Bordeaux	12	12

Paris Cochin	12	12
Lille	11	11
Tours	11	11
Montpellier	11	11
Lyon	11	11
Quint Fonsegrives	12	12
Total	**80**	**80**

In order to ensure quick and equal recruitment in both groups the following measures will be applied:

- Recruitment will be competitive after the first 6 months of inclusion;
- Recruitment will be stopped if not equally dispatched between groups (if a participating center does not recruit equally in both groups recruitment in the first group will be stopped until patients have been recruited in the other group). A difference of 3 cases between groups will be tolerated.

6. THE SNDS

The nationwide healthcare insurance system database, the SNDS (*Système National des Données de Santé*) contains individual anonymous information on all reimbursed outpatient claims (SNIIRAM) linked to the national hospital-discharge summaries database system (PMSI) and the national death registry (CépiDC), using a unique national pseudonymised identifier. It currently includes 99% of the French population, more than 66.6 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. Both EGB and SNDS contains individual pseudonymised information on (TUPPIN 2010, BEZIN 2017):

- General characteristics: gender, year of birth, affiliation scheme, area of residence;
- Date of death for those concerned and cause of death with a lag of 2-3 years;
- Long-Term disease registration (LTD – ALD: "*Affection longue durée*" in French) and associated ICD10 codes, including most of chronic diseases with long term and/or expensive treatment. Registration with a LTD is obtained at the request of a patient's practitioner and must be validated by the health insurance system physician. Once registered, patients receive full (i.e. 100%) reimbursement for expenditure related to the LTD, as defined by the health authorities. The LTD information is specific for the diagnosis (very low risk of false positives), but not sensitive because not all patients with the disease ask to benefit from a LTD;
- Outpatient reimbursed healthcare expenditures: visits, medical procedures, nursing acts, physiotherapy, medical imageries, lab tests, drugs with dosage and number of boxes dispensed, medical devices, transports, sick leaves… with prescriber and professional caregiver information (medical or paramedical specialty, private/public practice), dates (prescription and dispensing), and codes (e.g. ATC codes for drugs, LPP codes for medical devices), but not the medical indication nor result;
- Hospital-discharge summaries from the PMSI: ICD10 diagnosis codes (primary, related and associated diagnosis) for all private and public medical, obstetric and surgery's hospitalizations, with the date and duration of the hospital stay, medical procedures, and cost coding system, as well as most of very costly drugs. The hospital discharge summary includes the medical unit summaries when the patient is hospitalized successively in several medical units.
    - Primary diagnosis is the health problem that motivated the admission in the hospital. It is determined at hospital discharge. For patients hospitalized successively in several medical units, the primary diagnosis of the hospitalization, as well as for all medical unit primary diagnosis, are generally taken into account to define the occurrence of an outcome in a pharmacoepidemiology study.
    - A related diagnosis can exist only if the primary diagnosis is a care procedure with a code Z of the ICD10 classification (e.g. chemotherapy session) for a chronic or LTD disease. It indicates the pathology at the origin of the care procedure.
    - Associated diagnoses are specified mainly if they represent specific healthcare resources. They are mainly underlying chronic diseases. Associated diagnoses can be used to define chronic diseases but are generally not taken into account to define the occurrence of an outcome in a pharmacoepidemiology study (many being false positives for the studied outcome).

Access to SNDS is regulated and needs approval from the National Institute of Health Data (*Institut National des Données de Santé* - INDS), the committee in health data research (*Comité d'Expertise pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé* - CEREES), and the French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL).

7. STUDY INTERVENTION

7.1. INVESTIGATIONAL PROCEDURE: PROSTATIC URETHRAL LIFT

Prostatic urethral lift (PUL) consists in transurethral placement of permanent UroLift implants in both lateral lobes of the prostate. PUL intends to retract the lateral lobes of the prostate in order to reduce prostatic obstruction.
Based on clinical studies, between four to six implants are needed to treat one patient (based on the results of the Lift study) but the number of implants needed to treat each patient will be left at the discretion of the surgeon inside clinical study.
All procedures will be performed under local anaesthesia. Nitrous oxide inhalation use will be permitted, but we won't use oral or intravenous sedation.

In order to avoid complications related with the learning curve a proper training of the surgeons will be organized upfront starting of clinical study: a minimum of 15 cases performed under local anaesthesia in a day-care surgical unit will be required before entering clinical study.
One surgeon per investigating center will be trained and qualified to include patients in the PUL group.

Cases with obstructive median lobe of the prostate will not be excluded as was done in the precedent PUL studies (LIFT and BPH6), but will be treated only by advanced users as in the recently published MedLift study.

7.2. COMPARATIVE PROCEDURE: CLASSIC PROSTATIC ENDOSCOPIC SURGERY

Patients included in the TURP/Laser cohort will be treated following the habits of each investigating center (TURP, laser enucleation or laser vaporization will be allowed).
One surgeon per investigating center will be allowed to include patients in the trans-urethral surgery cohort. This surgeon will be different from the one including in the PUL group (if not possible, it can be exceptionally the same surgeon).

In order to avoid complications related with the learning curve this surgeon will have to be sufficiently experienced with transurethral surgery (experience of more than 100 trans-urethral surgical treatment will be required for entering this clinical study).

8. ASSOCIATED/ PROHIBITED TREATMENTS AND PROCEDURES

Our aim in this research project is to compare the cost-effectiveness of 2 surgical procedures in the real life practice. Therefore there will not be any prohibited treatment but we will systematically collect the use of any medication that could interfere with the assessment of the primary or secondary evaluation criteria. In particular we will systematically collect the use of any medication related with lower urinary tract symptoms.

9. STUDY PROCEDURE

9.1. STUDY CALENDAR

- Duration of the inclusion period: 32 months
- Participation duration of each participant: 12 months
- Total duration of the research: 44 months
- Follow-up in the SNDS database: 3 years
- History in the SNDS database: 2 years

9.2. SUMMARY TABLE OF ASSESSEMENTS

Assessments carried out as part of the care (C) or specifically for research (R).

	Inclusion	**Intervention**	**V1** Month 1 (+/- 7 days)	**V2** Month 2 (+/- 7 days)	**V3** Month 3 (+/- 7 days)	**V4** Month 4 (+/- 7 days)	**V5** Month 12 (+/- 14 days)
Patient information (R)	✓						
Informed consent (R)	✓						
Verification of eligibility criteria (R)	✓						
Medical and surgical history (R)	✓						
Drugs whether or not related to BPH (R)	✓	✓	✓	✓	✓	✓	✓
Recovery after surgery (R)			✓	✓	✓	✓	
Clinical examination (C)	✓					✓	✓
Biological examination [1] (C)	✓					✓	✓
Urinary flowmetry (C)	✓					✓	✓
Urinary tract ultrasound (C)	✓						
Urine microscopic examination (C)	✓	✓					
Functional and quality of life questionnaires[2] (R)	✓					✓	✓
Complications and adverse effects (R)		✓	✓	✓	✓	✓	✓
Cost of hospitalization (R)		✓					
Health care consumptions (declared by the patient) (R)			✓	✓	✓	✓	

[1] Blood sample tests: total PSA and creatinine dosage
[2] IPSS, IPSSQ8, IIEF15, MSHQEJD, ISI, ICIQ-UI SF, QoR VAS, EQ-5D-5L, Jenkins sleep scale

9.3. INCLUSION VISIT

9.3.1. COLLECTION OF CONSENT

During the inclusion visit, the investigator will inform the participant and answer all questions regarding the purpose, nature of constraints, foreseeable risks and expected benefits of the research. The investigator will specify the participant's rights in the context of the study and the collection of the individual national healthcare identifier (Numéro d'Inscription au Répertoire, NIR) required to link clinical and economic data to those of the SNDS database. The investigator will also check patients eligibility criteria.

A copy of the information package and the consent form will then be given to the participant by the investigator. After this information session, the participant will be given a period for reflection. If the participant agrees to participate, the participant and the investigator will clearly enter their names and surnames and date and sign the consent form. This must be signed BEFORE ANY CLINICAL OR PARA-CLINICAL EXAMINATION REQUIRED BY THE RESEARCH IS CONDUCTED.

If the participant gives his consent to participate, he and the investigator will clearly write their names and surnames and date and sign two original copies of the consent form.

The copies of the briefing note and the consent form will subsequently be allocated as follows:

- The investigator will give a copy of the briefing note and the signed consent form to the participant.
- The investigator will keep the other original copy (even in the event of a change in the participant's address during the course of the research project) in a safe place that is inaccessible to third parties.

9.3.2. CONDUCTING THE VISIT

The investigator will perform the inclusion visit. The inclusion visit will take place between 1 day and at the most 90 days before the surgery. Prior to any research-related examination, the investigator will collect the participant's free, informed and written consent (or that of his legal representative, if applicable).
Clinical examination: general physical examination, digital rectal examination, abdominal palpation, lumbar percussion
Para-clinical examination: urinary flowmetry, urinary tract ultrasound
Blood sample: PSA and creatinine dosages
Auto-questionnaires: IPSS, IPSSQ8, IIEF15, MSHQEJD, ISI, ICIQ-UI SF, QoR-VAS, EQ-5D-5L, Jenkins sleep scale

9.4. INTERVENTION

The surgical procedure will be performed during hospitalisation in an operating theatre. The micro-costing data will be collected during the time of intervention, on the basis of a micro-costing questionnaire developed by the project team.
By the end of hospitalisation for the surgical procedure, participant will be provided with a participant diary/book to self-report of healthcare consumptions (medications, hospitalizations, out-patient visits, radiology and biology exams, not reimbursed treatments …) and QoR-VAS until Visit 4.

9.5. VISITS 1, 2 AND 3

Visit 1, 2 and 3 will be phone call visits performed by the Clinical Research Assistant.
It will be collected according to participant notification:

- All medication in relation with BPH or with the intervention
- All healthcare consumption between two visits
- The QoR-VAS completed by the participant at home
- Any complication or adverse effect will need to be confirmed by a medical doctor and classified according to the Clavien Dindo classification

9.6. VISIT 4

Visit 4 will be performed at the outpatient clinic by a certified urologist at month 4 (+/- 7 days).

- Participants will undergo urinary flowmetry
- Participants will undergo standard physical examination including digital rectal examination, abdominal palpation and lumbar percussion.
- Participants will complete the following standard questionnaires (part of care):
    - IPSS score
    - IPSS Q8
    - ISI (Incontinence symptom index)
    - ICIQ-UI SF
    - MSHQ-Ejd
    - IIEF15
    - QoR-VAS
    - EQ-5D-5L
    - Jenkins sleep scale
- Investigator will collect:
    - Any adverse effect and complications based on Clavien Dindo classification
    - All medication in relation with BPH or with the intervention
    - All healthcare consumptions since visit 3

9.7. VISIT 5

Visit 5 will be performed at the outpatient clinic by a certified urologist at month 12 (+/- 14 days).

- Participants will undergo urinary flowmetry
- Participants will undergo standard physical examination including digital rectal examination, abdominal palpation and lumbar percussion.
- Participants will complete the following standard questionnaires (part of care):
    - IPSS score
    - IPSS Q8

  - ISI (Incontinence symptom index)
  - ICIQ-UI SF
  - MSHQ-Ejd
  - IIEF15
  - QoR-VAS
  - EQ-5D-5L
  - Jenkins sleep scale
- Investigator will collect:
  - Any adverse effect and complications based on Clavien Dindo classification
  - All medication in relation with BPH or with the intervention

Visit 5 is the end of study visit for participant.

9.8. SNDS ASSESSMENTS

For each patient identified in the SNDS cohort, the following settings will be defined:

- **Inclusion date:** date of the surgical procedure completion
- **Look-back period:** 2 years preceding the inclusion date;
- **Follow-up period:** 3 years following the inclusion date.

9.9. RULES FOR STOPPING THE RESEARCH

9.9.1. END OF STUDY

The end of the study corresponds to the end of the participation of the last subject (cf. Articles L.1123-11, R.1123-59 of the Code of Public Health), also called the Last Patient Last Visit (LPLV).
When the study reaches its expected term, the end of the study must be reported to the CPP and ANSM within 90 days.

9.9.2. PREMATURE DISCONTINUATION OF RESEARCH

This is particularly the case when the sponsor decides:

- Not to begin the study, despite obtaining the favourable opinion of the CPP to do so.
- Not to resume the research after temporarily discontinuing it or after its suspension by the ANSM.

When the study is definitively discontinued in advance, the end of the study must be reported to the ANSM within 15 days with an explanation of the reasons for doing so.

9.9.3. TEMPORARY DISCONTINUATION OF RESEARCH

The temporary interruption of clinical research (cf. Article R.1123-55 du CSP) consists of:

- Stopping the inclusion of new subjects;
- And/or discontinuation of the medical acts specified in the research protocol.

The ANSM and the CPP must be informed immediately of any decision by the sponsor to end this study. Thereafter, and within a maximum of 15 days following the date of this interruption, an application for authorisation to make substantial modifications to the temporary suspension must be requested from the ANSM and the opinion of the CPP must be sought.

9.10. PROTOCOL DEVIATIONS

Deviations can affect all aspects of a research protocol: inclusion, monitoring, measurement of endpoints, and the treatment process. All deviations must be documented by the investigator and discussed by the steering committee.
Even in the event of deviation from the protocol, participants must be monitored until the date planned in the protocol.

9.10.1. PREMATURE AND DEFINITIVE DISCONTINUATION OF THE EVALUATED TREATMENT

A participant must be considered as stopping the study when he/she no longer follows the study procedure but he/she is still followed in the study (visits, blood samplings…). Everything must be done to collect the information regarding the primary criteria variables in the time lapse expected in the protocol.
Premature **discontinuation** of the study procedure has to be notified to the coordinating investigator. The reason for, and the date of, the end of the study procedure must be documented. Any patient who stops the study procedure must be cared for as well as possible according to his health status and medical knowledge.

9.10.2. PARTICIPANTS WRONGLY INCLUDED

A participant will be considered wrongly included if all eligibility criteria are not validated. Participants wrongly included should be discussed with the steering committee.

9.10.3. PARTICIPANT LOST TO FOLLOW UP

The coordinating investigator must be informed of any patient lost to follow up.

9.10.4. OTHER DEVIATIONS

Protocol deviations should be documented and justified.
Violations are considered major deviations in:

- regulatory aspects,
- the primary endpoint.

All major violations are subject to a presentation to the steering committee to decide whether the patient's data can be exploited.

9.11. CONSTRAINTS RELATED TO THE RESEARCH AND POSSIBLE COMPENSATION OF PARTICIPANTS

As ECOLIFT study does not require any additional clinical visit or any additional invasive examination than normal clinical practice, there won't be any compensation for participants.

10. MANAGEMENT OF ADVERSE EVENTS AND NEW DEVELOPMENTS

10.1. DURING THE CLINICAL TRIAL

Adverse events / undesirable effects / incidents will be declared to the various circuits of health vigilance applicable to each product or practice concerned (care vigilance, pharmacovigilance, materiovigilance, haemovigilance, cosmetovigilance ...) in accordance with the regulations in force.

Registrants should specify that the participant is included in a clinical trial and accurately identify the clinical trial concerned.

If the investigator becomes aware of a breach of patient safety in the course of the research, he must inform the sponsor without delay.

10.2. FROM THE SNDS

The SNDS is a database using anonymous individual information without any spontaneous reporting. Study outcomes will be reported in aggregate in the final study report, and no individual or expedited reporting is required, according to the EMA Guideline on good pharmacovigilance practices cited above (GVP VI*), as well as the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.
* The latest revision of the Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2) from EMA (coming into effect 22 Nov 2017) specifies: *For Non-interventional post-authorisation studies based on secondary use of data (VI.C.1.2.1.2): "The design of such studies is characterised by the secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses. For these studies, the submission of suspected adverse reactions in the form of ICSRs is not required. All adverse events/reactions collected for the study should be recorded and summarised in the interim safety analysis and in the final study report unless the protocol provides for different reporting due to justification*".

11. STATISTICAL ASPECTS

11.1. CALCULATION OF STUDY SIZE

In the SNDS, the study size will depend on the number of patients initially recruited. The expected number of patients will thus be for:

- **PUL Cohort:** 80 patients with PUL;
- **TURP/Laser Cohort:** 80 patients for the TURP or laser surgery
- **SNDS Cohort:** 1200 patients distributed between 400 matched TURP patients, 400 matched HLE patients and 400 matched HLV patients.

80 patients (in each of the PUL and TURP cohorts) will allow 95% confidence intervals with a precision:

- between 7% and 11% for observed proportions between 10% and 50%
- between 13% and 26% for observed means with coefficient of variation between 0,6 and 1,2.

Furthermore, 80 patients in each PUL and TURP cohorts is largely enough to answer to the primary economic objective (cost-effectiveness ratio, expressed as incremental cost/avoided complications) with a power of 80% and an alpha risk of 5%. In fact, according to the Glick formula[1], the needed number to treat to answer this question is about 40.

400 patients in each of the 3 subgroups of the SNDS cohort will allow 95% confidence intervals with a precision:

- between 3% and 5% for observed proportions between 10% and 50%,
- between 6% and 12% for observed means with coefficient of variation between 0,6 and 1,2.

11.2. STATISTICAL METHODS EMPLOYED

11.2.1. GENERALITIES

Statistical analysis will be performed using SAS® software (SAS Institute, latest current version, North Carolina, USA). Qualitative and ordinal variables will be summarized by frequencies and proportions of each modality, taking into account missingness as a modality. Continuous variables will be summarized by size, number of patients with missing data, arithmetic mean, standard deviation, median, interquartile ranges and extreme values. Confidence intervals will be estimated using Normal approximation for quantitative and qualitative relevant parameters, or bootstrapping method for costs when count < 100 patients.

Standardized mean differences *(Rosenbaum, Rubin, 1985)* will be estimated to measure the effect size of quantitative and qualitative baseline characteristics between groups (PUL and TURP cohorts, matched patients of PUL and SNDS cohorts).

For confidence intervals, 2-sided confidence level of 95% will be used. For all tests, a 2-sided significance level of 5% will be used:

- Proportions will be compared between two independent groups using Pearson's Chi-2 test (or Fisher's exact test when expected counts are < 5)
- Means will be compared between two independent groups using Student's t-test when normal distribution is followed (or Mann-Whitney's test when normal distribution is not followed)
- Occurrence of events (retreatment, urinary symptoms) will be estimated across time using Kaplan-Meier estimator and compared between groups with logrank test.
- Adjusted comparisons between PUL and the TURP/Laser cohorts and between PUL and SNDS cohorts will be performed in intention-to-treat analysis using linear regression model when it involves quantitative variables, and using logistic regression model adjusted on potential confounders when it involves qualitative variables.

A Statistical Analysis Plan (SAP) will be developed and will be validated before the analyses.

11.2.2. POPULATION DESCRIPTION

The following analyses will be performed:

- A flow chart depicting the number of patients available in the database satisfying each cohort criteria;
- A description of baseline characteristics for each cohort;
- A comparison of baseline characteristics between the PUL cohort and the TURP cohort with mean standardized differences (significant difference at the threshold of 10%) and p-value (significant difference at the threshold of 0.05);
- A comparison of baseline characteristics between the PUL cohort and the SDNS cohort according to the treatment group with mean standardized differences (significant difference at the threshold of 10%) before and after hDRS matching;
- The hDRS will be estimated using a multivariable logistic regression model including a large set of variables collected within the one year preceding surgical procedure.

[1] Glick HA. Sample size and power for cost-effectiveness analysis. 2011;29(3):189/98, Pharmacoeconomics, 2011

11.2.3. COST-EFFECTIVENESS CRITERIA

We will assess the cost-effectiveness ratio as following: $\Delta C/\Delta E = (Ceval - Cref)/(Eeval-Eref)$ where

- ΔC = cost differences between both surgery
- ΔE = effectiveness differences between both surgery
- Ceval = Cost of PUL surgery
- Cref = Cost of classical surgery (TURP/laser)
- Eeval = Complications observed at 4 months in the PUL group
- Eref = Complications observed at 4 months in the TURP/laser group

The ratio assessment for the second economic criteria (incremental cost/Qalys at 12 months) is the same.
First an unadjusted estimate of the cost-effectiveness ratios will be made. Their 95% confidence interval of the ratio will be estimated by bootstrap. We will then estimate the net monetary benefit of each surgical procedure (BNM = E λ - C), where λ is the differential cost - effectiveness threshold. The distribution of each BNM will be determined by boostrap. This will allow us to develop an acceptability frontier, a curve representing the probability that the BNM of each surgical treatment will be highest for each value of λ between 0 € and 30000 € per avoided complication (or Qaly in the secondary criteria).

11.2.4. SECONDARY CRITERIA

The following analyses will be performed for each cohort, according to the matched treatment group:

- An estimation of the total hospital cost of each surgery procedure based on a top down micro-costing method performed during hospitalization stay;
- A description of the overall and specific urogenital healthcare consumptions during the 3 years of follow-up;
- A description of BPH re-treatment over the 3 years of follow-up (number of patients with a new BPH medication, number of patients hospitalized for BPH surgical procedure);
- A description of urinary symptoms (value of the IPSS, ISI, ICIQ-UI SF scores during the 1st year of follow-up and number of patients with hospitalization for urinary infection, for urinary retention, or for urethral stricture during the 3 years of follow-up);
- A description of the quality of life during the 1st year of follow-up using the IPSS-Q8 score, the Jenkins sleep questionnaire, the EQ-5D-5L questionnaire;
- A description of the recovery after surgery using the Quality of Recovery visual analogue score and the time before returning to normal professional activities;
- A description of the sexual side effects during the 1st year of follow-up using the IIEF15 and MSHQ-EjD questionnaire;
- A description of the associated complications (number and types).

A detailed analysis plan will be defined and will be validated by the steering committee of the study. Subsequent modifications must be made before the blinding is lifted on the database and will be systematically validated by the Scientific Council.

12. STUDY SUPERVISION

12.1. STEERING COMMITTEE

12.1.1. COMPOSITION

A steering committee will supervise the running of the study. The steering committee will be responsible for monitoring the progress of the study towards its objectives, and ensuring adherence to the protocol and local regulations as well as subject safety. The steering committee will include the Project Coordinator (Pr Grégoire Robert), the Scientific Coordinator (Pr Nicolas Bary Delongchamps), methodologist (Dr Patrick Blin), economist (Antoine Benard), representatives from relevant fields according to the nature of the research, and sponsor representative.

12.1.2. FREQUENCY OF MEETINGS

The Scientific Research Council will meet to be defined according to the needs of the study and at least once per year.

12.1.3. FUNCTION

Its goal is to make all important decisions at the request of the coordinating investigator concerning the proper implementation of the research and following protocol.
It checks that ethics are respected.
It keeps up to date with the research progress, possible issues and available results via the coordinating team and coordinating investigator research center.
It makes decisions on all necessary protocol amendments for the research project, in particular:

- Measures facilitating recruitment for the research project,
- Changes to the protocol prior to their presentation to the CPP and the competent health authority,
- Decisions to open or close sites participating in the research,
- Measures that guarantee the highest level of safety of the participants (including changes in information sheets and consent documents),
- Discussion of the results and the approach to their publication.

The steering committee can suggest prolonging or interrupting the research if the recruitment rate is too slow, the loss to follow-up is too high, or major protocol violations have occurred, as well as for medical and/or administrative reasons. The steering committee specify the possible terms for prolonged monitoring of the participants included in the research.
If the participating individuals suggest carrying out new biological research studies using the research material and when these have not been laid out in the protocol, the Scientific steering committee studies them and sets the information conditions of the participants, data access and result publication rules.
At the conclusion of the meeting, the president of the steering committee must inform the sponsor of the decisions that have been made. Decisions concerning a major change to the science or budget change must be approved by the sponsor.

13. RIGHTS OF ACCESS TO DATA AND SOURCE DOCUMENTS

13.1. ACCESS TO DATA

Agreeing to participate in the protocol implies that the investigators will make the documents and personal data that are strictly necessary for the monitoring, quality control and auditing of the research, available in accordance with the laws and regulations in force.

13.2. SOURCE DATA

All information contained in original documents, or in authenticated copies of these documents, relating to clinical examinations, observations or other activities conducted as part of a research study and necessary for the reconstitution and evaluation of the research. The documents in which the source data are saved are called the source documents.

13.3. DATA CONFIDENTIALITY

In accordance with the legislative provisions in force, persons having direct access to source data will take all the necessary precautions to ensure the confidentiality of information relating to investigational medicinal products, research, participants, especially as regards their identity and the results obtained. These people, like the investigators, are subject to professional secrecy.

During or at the end of the research, the data collected on the participants and sent to the sponsor by the investigators (or any other specialised contributor) will made anonymous. The data must never explicitly mention the names of the persons concerned or their addresses.

Each patient will be assigned a confidential identification code, consisting of the number of the investigation center (2 digits) and a patient number (3 digits) and a code letter (3 letters). The code letters may be constructed from the initials of the name and surname of the patient.

The sponsor will ensure that each participant has given his/her written agreement for access to the individual data concerning them and strictly necessary for the quality control of the research.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. GUIDELINES FOR COLLECTING DATA

All the information required by the protocol must be recorded in case report forms and an explanation must be provided for any missing data. The data must be collected as and when they are obtained, and transcribed in these notebooks in a clear and legible way.
Clinical and economic data, all data will be collected on electronic CRF (e-CRF), and specific auto-questionnaire.

14.2. QUALITY CONTROL

A clinical researcher appointed by the sponsor will regularly visit each center investigator, during the implementation of the research, one or more times during research according to the frequency of the inclusions and at the end of the research. During these visits, and in accordance with the risk-based monitoring plan (participant, logistics, impact, resources), the following elements will be reviewed:

- informed consent,
- compliance with the research protocol and the procedures defined therein,
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the source documents (medical records, appointment books, originals of laboratory results, etc.).

All visits will be the subject of a monitoring report by written report.

14.3. DATA MANAGEMENT AND SNDS LINKAGE

For each included patient, all clinical and economic data will be collected by the BPE research platform using an e-CRF and a self-administered questionnaire. A specific database will be developed for this study using standard tools (input dataset using MySQL, and data entry web application via Grails) in accordance with the General Data Protection Regulation (GDPR). It will allow an on-line data entry and remote by internet. This database will be tested before any data input. Database access will be restricted to authorized personnel, using state-of-the-art security techniques. A data validation plan will be developed and will describe in detail the controls to be made for each variable (coherence of dates and intervals, coherence of conditional variables, invalid values, boundaries, missing data, respect of criteria predefined in the protocol, etc.).
All clinical and economic data will constitute the dataset [Prostatic_Surgery], which will also include the confidential identification number allocated to each patient, as described in the §13.3.
Two methods may be used to link data from the dataset [Prostatic_Surgery] to those of the SNDS: the direct linkage, for which patient NIR national identifier is required, and the probabilistic linkage, which allows identifying eventually patients not found with the previous method.

i. Direct linkage

To link directly patient data to SNDS data, the patient NIR national identifier will be requested directly to the patient through the consent form. Once the NIR recovered, the BPE research platform will create a table separate from the dataset [Prostatic_Surgery], which will include the NIR, the confidential identification number, the birth date and the sex of each patient of the study. The BPE research platform will transmit this table to the CNAM using the online SAFE application. Based on the data forwarded, the CNAM will generate a pseudo anonymized SNDS identification code through it own 3-step anonymization procedure to make possible the extraction of the required SNDS data for the patients concerned.

ii. Probabilistic linkage

For probabilistic linkage, the BPE research platform will create a table separate from the dataset [Prostatic_Surgery], which will include for each patient, the confidential identification number and the data that are common to the dataset [Prostatic_Surgery] and the SNDS database. These data are listed below:

- birth date;
- city of residence;
- hospital identifier (FINESS);
- date of hospitalization for the prostatic procedure;

- procedure codes of the prostatic procedure performed during the hospitalization.

This table will be encrypted and deposited on the secured platform of the CNAM, according to the CNAM or Health DataHub procedures in force.
Based on data of the table provided by the BPE research platform, the CNAM will search in the SNDS the corresponding patients and will develop a targeting algorithm relevant for answering the study requirements. This algorithm will require applicant approval before any extraction.

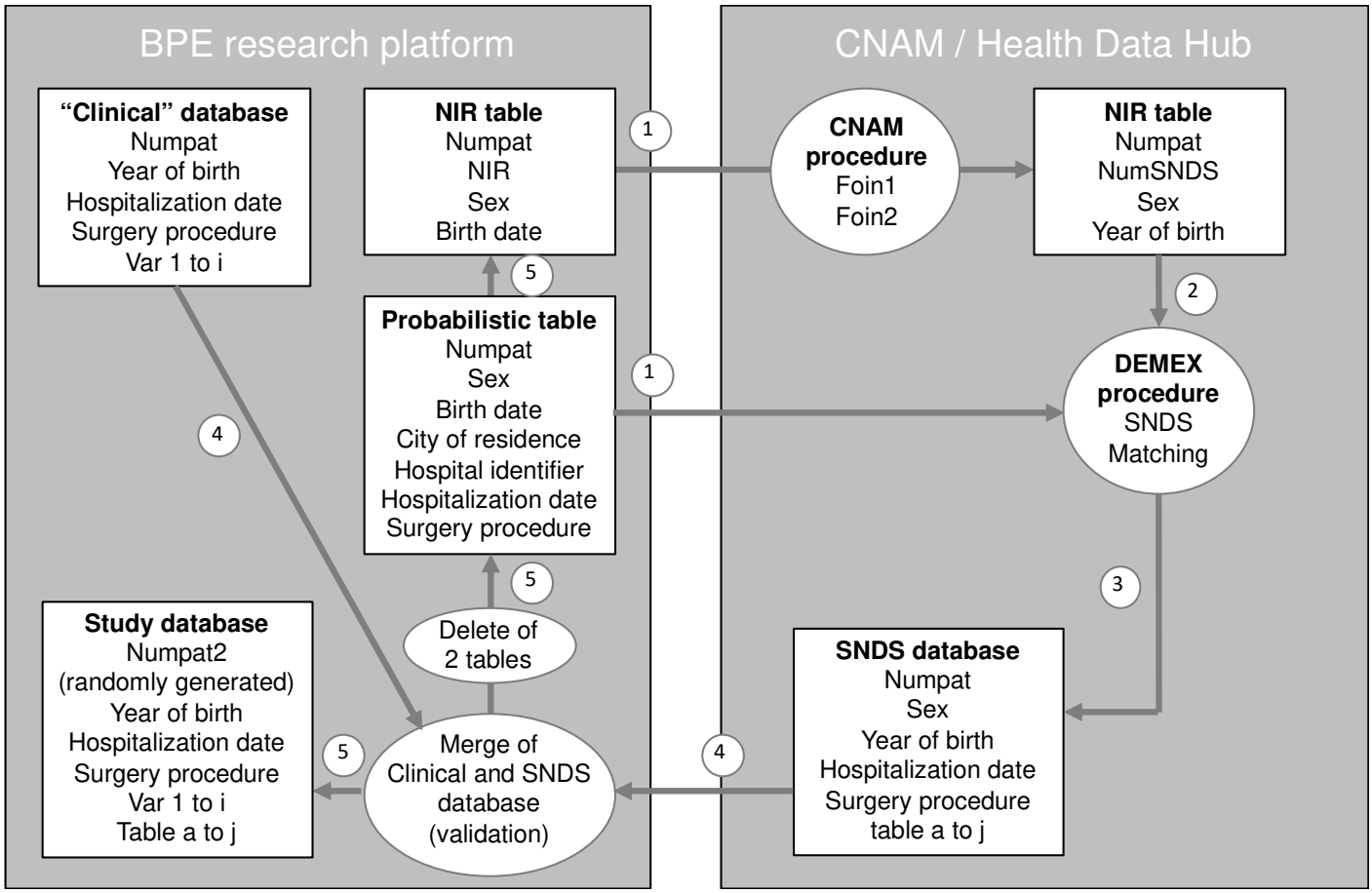

Figure to illustrate the process of linkage between patient data and SNDS data

In both cases, the CNAM will extract the required data (sociodemographic characteristics, date of death, LTD registration, outpatient reimbursed healthcare expenditures, hospital-discharge summaries and the corresponding costs).
The SNDS database extraction criteria will be described in a Data Extraction Plan (DEP) approved prior to initiating extraction. After data extraction, the CNAM will provide the requested SNDS data and the confidential patient identification number to the BPE research platform through dedicated networks ensuring a private and secured data transfer. The dataset [Prostatic_Surgery] and SNDS data will be merged by the BPE team using the confidential patient identification number. After data integration and validation, the table used for data linkage will be deleted and a new identification number will be created randomly for each patient of the study.

Data transformation, including decision rules, disease definition, exposure definition, outcomes, risk factors, healthcare resources and calculated variables will be detailed in a data management plan (DMP). Raw data and transformed data will be stored on a network meeting security standards as required by the French law:

- order of 22 March 2017 relating to the security reference system applicable to the National Health Data System (SNDS, 2017)
- SNDS security standards (available on: https://www.snds.gouv.fr/SNDS/Protection-de-la -donnée)

Data management programs will be developed with SAS® software (SAS Institute, latest current version, North Carolina, USA). After verification and resolution of incoherencies, the database will be locked for extraction and statistical analysis.

14.4. AUDIT AND INSPECTION

An audit may be conducted at any time by persons appointed by the sponsor and independent of the persons conducting the research. Its purpose is to verify the participants' safety and respect for their rights, compliance with applicable regulations and the reliability of data.
An inspection can also be carried out by a competent authority (ANSM for France or EMA in the context of a European study, for example).
The audit, as well as the inspection, can be applied at all stages of the research, from the development of the protocol to the publication of the results and the classification of the data used or produced as part of the research.

Investigators agree to comply with the sponsor's requirements as regards an audit and the competent authority for a research inspection.

15. ETHICAL AND REGULATORY CONSIDERATIONS

DATA PROTECTION

Once all data are collected on eCRF, and data extracted from the SNDS database are received by the BPE research platform, data management and statistical analysis will be carried out by the BPE research platform in accordance with the requirements of the French legal and regulatory framework governing, particularly for the access to the data of the SNDS: the order of March 22nd, 2017 on security standard applicable to the national health data system and the order of July 17th, 2017 on the reference terms determining confidentiality, expertise and independence criteria for research laboratories and research firms.

To store individual data extractions from the SNDS, the BPE research platform has added in its IT system an internal secured network (cut off from the outside), called “Bulle BPE” which was initially homologated on November 23rd, 2018, and on March 22nd, 2019. All study data will be hosted in the "Bulle BPE" with a limited and restricted access to authorized persons involved in the study project. Access to users’ sessions needs strong 2-level authentication, and all the user’s activities in the “Bulle BPE” are registered. The physical access to the office hosting the treatment is controlled by input-output badge, digital code, intrusion alarm connected to a security PC and a video surveillance system. To guarantee data confidentiality, only the full date of care will be kept on the 5 so-called sensitive variables and the other so-called sensitive variables will be truncated (year of birth, month and year of death, department of residence and department of death).

REGULATORY ASPECTS

The sponsor and the investigator(s) undertake to ensure that this research is carried out in accordance with law no. 2012-300 of 5 March 2012 on research involving the human person, as well as in agreement with Good Clinical Practices (ICH version 4 of 9 November 2016 and the decision of 24 November 2006) and the Declaration of Helsinki (which can be found in full at https://www.wma.net).

The research is conducted in accordance with this protocol. Except in emergency situations that require the implementation of specific therapeutic acts, the investigator(s) undertake(s) to respect the protocol in all points especially with regard to the collection of subject informed consent, and notification and follow-up of serious adverse events.

This research has received a favourable opinion from the Committee for the Protection of Persons (CPP) by CPP Sud Est I.

The CHU de Bordeaux, sponsor of this study, has taken out a civil liability insurance contract with HDI GLOBAL SE in accordance with the provisions of the Public Health Code.

The data recorded during this research will be subject to computerised processing, i.e. the BPE research platform, in accordance with:

- EU regulation 2016/679 of the European Parliament and European Council, dated 27th April, 2016, pertaining to the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation); and

- law 78-17, known as "Informatique et Liberté", dated 6th January, 1978 and relating to the processing of data files and freedoms; law 2018-493, dated June 20th, 2018 and relating to the protection of personal data, modifying Law No. 78-17; and Law No. 2004-801, dated 6th August, 2004, on the protection of individuals with regard to the processing of personal data.

The BPE research platform has declared the research to the French National Commission for Informatics and Liberties (CNIL). The SNDS study is a database analysis with individual anonymous information for which subject informed consent is not required. Data extraction from the SNDS is regulated from National Institute of Health Data (*Institut National des Données de Santé* - INDS). According to the advice of CPP, a submission to the committee in health data research (*Comité d'Expertise pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé* - CEREES) may be required. Data extraction from the SNDS needs the authorization from the French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL).

This research has been registered on the site http://clinicaltrials.gov/, and on the site ENCePP http://www.encepp.eu (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance).

CHANGES TO THE PROTOCOL

Any substantial change, i.e. any change that is likely to have a significant impact on the protection of persons, on the conditions of validity and on the results of the research, on the quality and safety of the products tested, on the interpretation of scientific documents that support the conduct of the research or the way in which the research is conducted, is subject to a written amendment submitted to the sponsor. The latter must obtain, prior to its implementation, a favourable opinion from the CPP.

Non-substantial changes, i.e, those that do not have a significant impact on any aspect of the research, are communicated to the CPP for information.

All changes are validated by the sponsor, and by all research stakeholders involved in the change, before submission to the CPP.

All changes to the protocol must be made known to investigators, who are participating in the research. The investigators undertake to respect the content.

Any modification that modifies participant care or the benefits, risks and constraints of the research is the subject of a new information note and a new consent form whose collection follows the same procedure above.

16. DATA HANDLING AND RECORD KEEPING

The following documents related to this research are archived by the investigator in accordance with Good Clinical Practices guidelines:

- ***for a period of 15 years following the end of the research***

  • The protocol and any modifications to the protocol
  • Case report forms (copies) and specific auto-questionnaires
  • Source records of participants who have signed a consent form
  • All other documents and correspondence related to research

- ***for a period of 15 years following the end of the research***

  • Original copies of the informed consent forms signed by the participants

All of the above-listed documents are the responsibility of the investigator during the regulatory archiving period.
No documents may be destroyed or removed without the agreement of the sponsor. At the end of the archiving period, the sponsor will be consulted regarding the destruction of certain documents. All data, documents and reports may be subject to audit or inspection.

17. STUDY REPORTS

Within four year after the end of the research (i.e. 3-year follow-up post LPLV) or its interruption, a final report including full SNDS data analysis will be prepared and signed by the sponsor and the investigator. This report will be kept at the disposal of the competent authority.

18. RULES FOR PUBLICATION

18.1. SCIENTIFIC COMMUNICATIONS

The data analysis provided by the investigating centers is carried out by the BPE research platform of University of Bordeaux. This analysis gives rise to a written report which is submitted to the sponsor, who will forward it to the Committee for the Protection of Persons and to the competent authority.
Any written or oral communication of the results of the research must have the prior consent of the coordinating investigator and, where appropriate, of all committees that were established for the research.
The coordinating/ principal investigator undertakes to make available to the public both negative and inconclusive and positive research results.
The publication of the main results must mention the name of the sponsor, all the persons who helped in the inclusion or follow-up of participants in the research, methodologists, biostatisticians and data managers who participated in the research, health vigilance personnel who participated in the safety analysis of the participants, members of the committee(s) constituted for the research and the involvement of the laboratory NEOTRAC INC source of funding.
International rules of writing and publication will be taken into account (*The Uniform Requirements for Manuscripts* of the ICMJE, April 2010).

18.2. COMMUNICATION OF RESULTS TO PARTICIPANTS

In accordance with law no. 2002-303 of 4 March 2002, the participants are informed, at their request, of the overall results of the research.

18.3. TRANSFER OF DATA

Data management is provided by the BPE research platform. The conditions for the transfer of all or part of the research database are decided by the research sponsor are the subject of a written contract.

19. BIBLIOGRAPHIC REFERENCES

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5. Gratzke C, Barber N, Speakman MJ, Berges R, Wetterauer U, Greene D, et al. Prostatic urethral lift vs transurethral resection of the prostate: 2-year results of the BPH6 prospective, multicentre, randomized study. BJU Int. 2017;119(5):767-75.

20. APPENDICES

Appendix 1 : Haute Autorité de Santé (French National Health Authority) statement on Urolift

HAS
HAUTE AUTORITÉ DE SANTÉ

COMMISSION NATIONALE D'EVALUATION
DES DISPOSITIFS MEDICAUX ET DES TECHNOLOGIES DE SANTE

AVIS DE LA CNEDiMTS
30 mai 2017

Faisant suite à l'examen du 16/05/2017, la CNEDiMTS a adopté le projet d'avis le 30/05/2017

CONCLUSIONS

UROLIFT, implant intra-prostatique

Demandeur : NEOTRACT Inc (Etats-Unis)

Fabricant : NEOTRACT Inc (Etats-Unis)

Les modèles et références retenus sont ceux proposés par le demandeur : *UL-400-4*

Indications retenues :	Traitement des symptômes du bas appareil urinaire (SBAU) liés à une hypertrophie bénigne de la prostate chez les patients intolérants à un traitement médical optimal ou en cas de contre-indication aux autres traitements chirurgicaux endoscopiques.
Service Attendu / Rendu (SA) :	**Suffisant**, en raison de : - son intérêt pour traiter les symptômes du bas appareil urinaire - l'intérêt de santé publique compte tenu de la dégradation de la qualité de vie engendrée par cette pathologie.
Comparateur(s) retenu(s) :	Traitement chirurgical endoscopique de résection transurétrale de la prostate
Amélioration du SA :	ASA de niveau IV (mineure)
Type d'inscription :	Nom de marque
Durée d'inscription :	5 ans

Appendix 2 : French International Prostatic Symptom Score (IPSS)

Nom : ..... Prénom : ..... Date : .....

IPSS : International Prostate Score Symptom							
	Jamais	Environ 1 fois sur 5	Environ 1 fois sur 3	Environ 1 fois sur 2	Environ 2 fois sur 3	Presque toujours	
Au cours du dernier mois, avec quelle fréquence avez vous eu la sensation que votre vessie n'était pas complètement vidée après avoir uriné ?	0	1	2	3	4	5	☐
Au cours du dernier mois, avec quelle fréquence avez vous eu besoin d'uriner moins de 2 heures après avoir fini d'uriner ?	0	1	2	3	4	5	☐
Au cours du dernier mois, avec quelle fréquence avez vous eu une interruption du jet d'urine c'est à dire démarrage de la miction puis arrêt puis redémarrage ?	0	1	2	3	4	5	☐
Au cours du dernier mois, après avoir ressenti le besoin d'uriner, avec quelle fréquence avez vous eu des difficultés à vous retenir d'uriner ?	0	1	2	3	4	5	☐
Au cours du dernier mois, avec quelle fréquence avez vous eu une diminution de la taille ou de la force du jet d'urine ?	0	1	2	3	4	5	☐
Au cours du dernier mois, avec quelle fréquence avez vous dû forcer ou pousser pour commencer à uriner ?	0	1	2	3	4	5	☐
	Jamais	1 fois	2 fois	3 fois	4 fois	5 fois	
Au cours du dernier mois écoulé, combien de fois par nuit, en moyenne, vous êtes-vous levé pour uriner (entre le moment de votre coucher le soir et celui de votre lever définitif le matin ?	0	1	2	3	4	5	☐

- 0 – 7 = léger
- 8 – 19 = modéré
- 20 – 35 = sévère

Total = IPSS : ☐

Évaluation de la qualité de vie liée aux symptômes urinaires							
	Très satisfait	Satisfait	Plutôt satisfait	Partagé (ni satisfait, ni ennuyé)	Plutôt ennuyé	Ennuyé	Très ennuyé
Si vous deviez vivre le restant de votre vie avec cette manière d'uriner, diriez-vous que vous en seriez :	0	1	2	3	4	5	6

Barry MJ, Fowler FJ, O'leary MP et al. The American Urological Association Symptom Index for benign prostatic hyperplasia. Journal of Urology 1992;148:1549-1557

Appendix 3 : French Incontinence Severity Index (ISI)

Nom : _____ Prénom : _____ Date :_____

Incontinence Severity Index (ISI)

Merci de répondre aux questions suivantes et d'entourer le chiffre correspondant.

1. A quel fréquence avez vous des fuites urinaires?

   1 Moins d'une fois par mois
   2 Plusieurs fois par mois
   3 Plusieurs fois par semaine
   4 Tout les jours ou nuits

2. Quelle quantité d'urine perdez vous à chaque fois?
   1 Gouttes
   2 Quantité faible
   3 Quantité plus importante

La valeur du score correspond au produit des deux chiffres correspondants aux deux réponses.

Score ISI : ____

- 1-2 : Incontinence minime
- 3-6 : Incontinence modérée
- 8-9 : Incontinence sévère
- 12 : Incontinence très sévère

Sandvik, H., Seim, A., Vanvik, A., and Hunskaar, S. ***A severity index for epidemiological surveys of female urinary incontinence: comparison with 48-hour pad-weighing tests.*** *Neurourol Urodyn. 2000; 19: 137–145*

Appendix 4 : French International Index of Erectile Function (IIEF-15)

SCORE IIEF5

Ce questionnaire permet d'évaluer votre fonction sexuelle au court des 6 derniers mois :

Au cours des six derniers mois :

I. A quel point étiez-vous sûr de pouvoir avoir une érection et de la maintenir ?

1. Pas sûr du tout
2. Pas très sûr
3. Moyennement sûr
4. Sûr
5. Très sûr

II. Lorsque vous avez eu des érections à la suite de stimulations sexuelles, avec quelle fréquence votre pénis a-t-il été suffisamment rigide (dur) pour permettre la pénétration ?

0. Je n'ai pas été stimulé sexuellement
1. Presque jamais ou jamais
2. Rarement (beaucoup moins que la moitié du temps)
3. Quelquefois (environ la moitié du temps)
4. La plupart du temps (beaucoup plus que la moitié du temps)
5. Presque tout le temps ou tout le temps

III. Lorsque vous avez essayé d'avoir des rapports sexuels, avec quelle fréquence avez-vous pu rester en érection après avoir pénétré votre partenaire ?

0. Je n'ai pas essayé d'avoir de rapports sexuels
1. Presque jamais ou jamais
2. Rarement (beaucoup moins que la moitié du temps)
3. Quelquefois (environ la moitié du temps)
4. La plupart du temps (beaucoup plus que la moitié du temps)
5. Presque tout le temps ou tout le temps

IV. Pendant vos rapports sexuels, à quel point vous a-t-il été difficile de rester en érection jusqu'à la fin de ces rapports ?

0. Je n'ai pas essayé d'avoir de rapports sexuels
1. Extrêmement difficile
2. Très difficile
3. Difficile
4. Un peu difficile
5. Pas difficile

V. Lorsque vous avez essayé d'avoir des rapports sexuels, avec quelle fréquence en avez-vous été satisfait ?

0. Je n'ai pas essayé d'avoir de rapports sexuels
1. Presque jamais ou jamais
2. Rarement (beaucoup moins que la moitié du temps)
3. Quelquefois (environ la moitié du temps)
4. La plupart du temps (beaucoup plus que la moitié du temps)
5. Presque tout le temps ou tout le temps

Interprétation : :
Trouble de l'érection sévère (score de 5 à 10), modéré (11 à 15), léger (16 à 20), fonction érectile normale (21 à 25) et non interprétable (1 à 4).

Rosen, R., Cappelleri, J., Smith, M. et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-15) as a diagnostic tool for erectile dysfunction. Int J Impot Res ***11,*** *319–326 (1999) doi:10.1038/sj.ijir.3900472*

Appendix 5 : French Male Sexual Health Questionnaire – Ejaculatory Dysfunction (MSHQ-EjD)

Nom : ..... Prénom : ..... Date : .....

Male Sexual Health Questionnaire for Ejaculatory Dysfonction (MSHQ-EjD)

Ces questions sont en rapport avec vos éjaculations au cours du dernier mois

Avec quelle fréquence avez-vous été capable d'éjaculer au cours de vos rapports sexuels ?	Tout le temps (5)	Le plus souvent (4)	Une fois sur deux (3)	Moins d'une fois sur deux (2)	Jamais / Absence d'éjaculation (1)	
Comment considérez-vous la force de votre éjaculation ?	Toujours aussi forte (5)	Un peu moins forte qu'avant (4)	Plutôt moins forte qu'avant (3)	Moins forte qu'avant (2)	Beaucoup moins forte qu'avant (1)	Ne peut pas éjaculer (0)
Comment évaluez-vous la quantité de sperme lorsque vous éjaculez	Toujours autant (5)	Un peu moins qu'avant (4)	Plutôt moins qu'avant (3)	Moins qu'avant (2)	Beaucoup moins qu'avant (1)	Ne peut pas éjaculer (0)
Si vous avez eu des difficultés ou n'avez pas réussi à éjaculer, en avez-vous été gêné ?	Pas de problème avec mes éjaculations (0)	Pas du tout gêné (1)	Un peu gêné (2)	Modérément gêné (3)	Très gêné (4)	Extrêmement gêné (5)

Total : .....

Rosen RC, Catania JA, Althof SE, Pollack LM, O'Leary M, Seftel AD, Coon DW. Development and validation of four-item version of Male Sexual Health Questionnaire to assess ejaculatory dysfunction. Urology. 2007 May;69(5):805-9

Appendix 6 : French Quality of Recovery – Visual Analog Scale (QoR-VAS)

Nom : ..... Prénom : ..... Date : .....

Qualité de récupération : Échelle visuelle analogique

Instructions : pour évaluer la qualité de votre récupération après la chirurgie, veuillez placer une croix sur la ligne.

Par exemple, si vous avez très bien récupéré, placez votre croix comme ceci :

Si votre récupération est mauvaise, placer la croix comme ceci :

Veuillez placer votre croix :

Mauvaise récupération — Récupération excellente

Par ex. : douleurs importantes, mobilisation impossible

Par ex. : aucune douleur, reprise d'une activité normale

Myles, P., Hunt, J., Nightingale, C. et al. ***Development and psychometric testing of a quality of recovery score after general anesthesia and surgery in adults.*** *Anesth Analg. 1999; 88: 83–90*

Appendix 7 : French EQ-5D-5L (EuroQol Group) questionnaire

Pour chaque rubrique, veuillez cocher UNE case, celle qui décrit le mieux votre santé AUJOURD'HUI.

MOBILITÉ

- Je n'ai aucun problème pour me déplacer à pied ☐
- J'ai des problèmes légers pour me déplacer à pied ☐
- J'ai des problèmes modérés pour me déplacer à pied ☐
- J'ai des problèmes sévères pour me déplacer à pied ☐
- Je suis incapable de me déplacer à pied ☐

AUTONOMIE DE LA PERSONNE

- Je n'ai aucun problème pour me laver ou m'habiller tout(e) seul(e) ☐
- J'ai des problèmes légers pour me laver ou m'habiller tout(e) seul(e) ☐
- J'ai des problèmes modérés pour me laver ou m'habiller tout(e) seul(e) ☐
- J'ai des problèmes sévères pour me laver ou m'habiller tout(e) seul(e) ☐
- Je suis incapable de me laver ou de m'habiller tout(e) seul(e) ☐

ACTIVITÉS COURANTES *(p. ex., travail, études, travaux domestiques, activités familiales ou loisirs)*

- Je n'ai aucun problème pour accomplir mes activités courantes ☐
- J'ai des problèmes légers pour accomplir mes activités courantes ☐
- J'ai des problèmes modérés pour accomplir mes activités courantes ☐
- J'ai des problèmes sévères pour accomplir mes activités courantes ☐
- Je suis incapable d'accomplir mes activités courantes ☐

DOULEURS / GÊNE

- Je n'ai ni douleur ni gêne ☐
- J'ai des douleurs ou une gêne légère(s) ☐
- J'ai des douleurs ou une gêne modérée(s) ☐
- J'ai des douleurs ou une gêne sévère(s) ☐
- J'ai des douleurs ou une gêne extrême(s) ☐

ANXIÉTÉ / DÉPRESSION

- Je ne suis ni anxieux(se) ni déprimé(e) ☐
- Je suis légèrement anxieux(se) ou déprimé(e) ☐
- Je suis modérément anxieux(se) ou déprimé(e) ☐
- Je suis sévèrement anxieux(se) ou déprimé(e) ☐
- Je suis extrêmement anxieux(se) ou déprimé(e) ☐

Appendix 8 : French traduction of Jenkins Sleep Evaluation Questionnaire

Nom : ..... Prénom : ..... Date : .....

Jenkins Sleep Evaluation Questionnaire

Parmi les 30 derniers jours, vous est-il arrivé :	Jamais	1 à 3 jours	4 à 7 jours	8 à 14 jours	15 à 21 jours	22 à 30 jours
D'avoir du mal à vous endormir	0	1	2	3	4	5
De vous réveiller quelques fois dans la nuit sans avoir de problème à vous rendormir	0	1	2	3	4	5
De vous réveiller une ou plusieurs fois dans la nuit (y compris vous réveiller trop tôt), et avoir du mal à vous rendormir	0	1	2	3	4	5
De vous réveiller après votre durée de sommeil habituelle en étant fatigué ou épuisé	0	1	2	3	4	5

Jenkins DC, Stanton B, Niemcryk SJ et al. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol 1988;41(4):313-321

Appendix 9 : French version of International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF)

ICIQ-UI Short Form (French)

Numéro | Initiales du participant | J J M M M A A **Date**

Beaucoup de personnes ont des pertes d'urine de temps en temps. Nous essayons de savoir combien les personnes ont des pertes d'urine et à quel point ça les gêne. Veuillez répondre aux questions suivantes, en pensant à votre cas, en moyenne, au cours des QUATRE DERNIERES SEMAINES.

1 Votre date de naissance: JOUR MOIS ANNÉE

2 Sexe *(cochez la réponse)*: Femme ☐ Homme ☐

3 A quelle fréquence avez-vous des pertes d'urine? *(ne cochez qu'une seule réponse)*

jamais	☐	0
environ une fois par semaine	☐	1
deux à trois fois par semaine	☐	2
environ une fois par jour	☐	3
plusieurs fois par jour	☐	4
tout le temps	☐	5

4 Nous aimerions savoir quelle est la quantité de vos pertes d'urine, selon votre estimation.
Quelle est la quantité habituelle de vos pertes d'urine (avec ou sans protection)?
(Ne cochez qu'une seule réponse)

nulle	☐	0
une petite quantité	☐	2
a moderate amount	☐	4
a large amount	☐	6

5 De manière générale, à quel point vos pertes d'urine vous dérangent-elles dans votre vie de tous les jours? *Entourez un chiffre entre 0 (pas du tout) et 10 (vraiment beaucoup)*

0 1 2 3 4 5 6 7 8 9 **10**
pas du tout — vraiment beaucoup

Score de l'ICIQ : ajoutez les scores 3+4+5 ☐☐

6 Quand avez-vous des pertes d'urine? *(cochez toutes les réponses qui s'appliquent à votre cas)*

vous ne perdez jamais d'urine	☐
vous avez des pertes d'urine avant de pouvoir arriver au toilettes	☐
vous avez des pertes d'urine quand vous toussez ou éternuez	☐
vous avez des pertes d'urine quand vous dormez	☐
vous avez des pertes d'urine quand vous avez une activité physique ou quand vous faites de l'exercice	☐
vous avez des fuites d'urine quand vous avez fini d'uriner et que vous êtes rhabillé	☐
vous avez des pertes d'urine sans cause apparente	☐
vous avez des pertes d'urine tout le temps	☐

Merci d'avoir pris le temps de répondre à ces questions.