PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Aquablation vs. Holmium Laser Enucleation of the Prostate in the Treatment of Benign Prostatic Hyperplasia in medium to large size prostates (ATHLETE): Protocol of a prospective randomized trial.
AUTHORS	Müllhaupt, Gautier; Güsewell, Sabine; Schmid, Hans-Peter; Zumstein, Valentin; Betschart, Patrick; Engeler, Daniel; Abt, Dominik

VERSION 1 – REVIEW

REVIEWER	Gild, Philipp University Medical Center Hamburg-Eppendorf
REVIEW RETURNED	15-Jan-2021

GENERAL COMMENTS	I would like to congratulate the authors on their work or rather their proposed trial (randomized (non-blinded)/comparative evidence of HoLEP vs. Aquablation in medium to large-sized glands), which I believe will yield interesting and needed data. Even though the statistics appear to be rather straight forward, I recommend review by a statistician. That asside I recommend publication of this manuscript after a minor revisions. The following concern need to be addressed: Format: -As Aquablation and SecuTrial are registered traidmarks, I recommend labeling them as such troughout the manusctip via ® -Some of the abbreviations are not defined, for example p. 9: CRF; p12: IIEF, MSHQ-EjD p 14. UPN, AE, sE; these need to be defined for readers not familiar with the topic -In the intro: Please change "long" for "flat" learning curve, which is more appropriate and common in the context of the learning curve (doi.org/10.1007/s00345-020-03451-1) Methods: -P. 8, last sentence on page: Please revise, as the statment is incorrect. To the contrary, there is abundant evidence on long-term outcomes of HoLEP. -Randomization: On what grounds where the groups stratified (Age / Prostate size). Was this arbitrarily (if so please mention), or is there a statistical rationale ? -Study Intervention: Surgeon case load is a potential source of bias. Please provide a rationale for the HoLEP learning curve (for example: https://pubmed.ncbi.nlm.nih.gov/27766387/) that supports your criterion (50 casese total/surgeon). How many different surgeons will perform HoLEP. Are these endoscopically trained or novices to transurethral prostate desosntruction ?

	-Simiarly for Aquablation: Is there evidence on the learning curve? Is the cut-off of 20 cases/surgeon chosen arbitrarily or is there evidence to support this decision? -Study outcome measures: Please provide references for the according questionaires used, as well information on language version distributed. Statistical methods: -Please provide the grounds on which the non-inferiority margin was determined

REVIEWER	Elterman, Dean University Health Network
REVIEW RETURNED	27-Jan-2021

GENERAL COMMENTS	Please specify the type of hemostasis method that will be used in the Aquablation arm. The newer technique of focal bladder neck cautery has resulted in lower bleeding and transfusion rates. There may be an undue higher adverse events rate if this newer technique is not utilized.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

Format:
-As Aquablation and SecuTrial are registered traidmarks, I recommend labeling them as such troughout the manusctip via ®

Thank you for pointing this out. We have changed this accordingly in the text with regard to SecuTrial (p. 2, 7 and 12). "Aquablation" describes the procedure and is not a trademark, whereas we have used the ® for the “AquaBeam” system, which corresponds to the trademark.

-Some of the abbreviations are not defined, for example p. 9: CRF; p12: IIEF, MSHQ-EjD p 14. UPN, AE, sE; these need to be defined for readers not familiar with the topic

The abbreviations have been added accordingly (p. 7, 9 and 12).

-In the intro: Please change “long” for “flat” learning curve, which is more appropriate and common in the context of the learning curve (doi.org/10.1007/s00345-020-03451-1)

Long was replaced by flat (p. 5).

Methods:
-P. 8, last sentence on page: Please revise, as the statment is incorrect. To the contrary, there is abundant evidence on long-term outcomes of HoLEP.

We agree, that proper long-term data exist for HoLEP and reworded the sentence to:

“At the same time, lack of detailed knowledge about the long-term outcomes of Aquablation and lack of comparative data of the two procedures regarding their relative merits and side-effects justify the additional investigation of multiple secondary outcomes in a standard superiority setting.” (p. 6 and 7)

-Randomization: On what grounds where the groups stratified (Age / Prostate size). Was this arbitrarily (if so please mention), or is there a statistical rationale ?

It is well-known that older patients have worse outcomes and a higher risk of complications after transurethral resective prostate surgery.
In addition, surgical treatment of larger glands is associated with higher morbidity rates. (Madersbacher et al. Eur Urol 2005 47:499-504; Reich et al. J Urol. 2008 180:246-249)

Prostate size does also influence the operation time of both procedures markedly.

This is the reason why we stratify for both parameters to make sure that patients will be evenly distributed.

In addition, age and prostate size have both been reported to be risk factors for transient urinary stress incontinence following HoLEP. Thus, patients aged <70years have been shown to have a 2.63x odds ratio of suffering from postoperative incontinence (Ibrahim et al. J Urol. 2019 202:795-800).
The cut-off value of 100cc for stratification was chosen, as it represents the median prostate size that matches the study’s inclusion criteria.

-Study Intervention: Surgeon case load is a potential source of bias. Please provide a rationale for the HoLEP learning curve (for example: https://pubmed.ncbi.nlm.nih.gov/27766387/) that supports your criterion (50 casese total/surgeon). How many different surgeons will perform HoLEP. Are these endoscopically trained or novices to transurethral prostate desosntruction ?

Thank you for this comment. As described in the protocol, only experienced endourological surgeons will perform HoLEP. A corresponding literature reference has been added for the learning curve for HoLEP (Enikeev D, Morozov A, Taratkin M, et al. Systematic review of the endoscopic enucleation of the prostate learning curve. World J Urol 2020). (p. 8 and 16)

-Simiarly for Aquablation: Is there evidence on the learning curve? Is the cut-off of 20 cases/surgeon chosen arbitrarily or is there evidence to support this decision?

Thank you for this important input. There is evidence on the short learning curve without however a specific number. With 20 procedures we are rather generous and can guarantee a good quality. A corresponding literature reference has been added. (p. 8 and 17)

-Study outcome measures: Please provide references for the according questionaires used, as well information on language version distributed.

We use only validates versions of well-established questionnaires in German language that are recommended for the assessment of LUTS by the guidelines of the European Association of Urology. Providing the validation reference for each single questionnaire would be beyond the scope of our manuscript.
Nevertheless, we agree that it is an important point that the questionnaires used in the study are validate and generally accepted tools and added an appropriate statement to the text. (p. 9)

For questionnaires that might be less well-known we provide a reference (i.e. SAGA, EQ-5D-5L) (p. 10 and 17)

Statistical methods:
-Please provide the grounds on which the non-inferiority margin was determined

The rational for using an non-inferiority design was already mentioned in "Methods and analysis": “The non-inferiority design was chosen as an efficacy of Aquablation similar of that of HoLEP would justify its use in clinical practice due to the shorter operation time and a faster learning curve.”

The minimal difference in IPSS that is clinically relevant is discussed controversially. Based on a well-known publication by Barry et al. al (J Urol. 1995 154: 1770-4) a threshold of 3 points is used in many studies. (p. 10 and 17)
However, more recent data shows that the relevant difference in IPSS might be higher, i.e. 5.2 points (Blanker et al. BMJ Open 2019;9:e032795. doi:10.1136/bmjopen-2019-032795). (p. 10 and 17)
As a compromise, we defined 4 points as a threshold in our study. We provide a short explanation and the references mentioned above in our manuscript now. (p. 10)

Reviewer #2:

Comments to the Author:

Please specify the type of hemostasis method that will be used in the Aquablation arm. The newer technique of focal bladder neck cautery has resulted in lower bleeding and transfusion rates. There may be an undue higher adverse events rate if this newer technique is not utilized.

Thank you for this important comment. This method represents the standard approach for achieving hemostasis at our department. We absolutely agree that this is an important point, which is why we already mentioned that "Hemostasis is consecutively achieved through bipolar spot-coagulation" in the procedure description.