NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT413 Rezum

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
X.	*XX/XX/XXXX*	*Who was contacted? (if an expert, include clinical area of expertise)* *Why were they contacted? (keep this brief)*	*Insert question here. If multiple questions, please break these down and enter them as new rows*	*Only include significant correspondence and attach additional documents/graphics/tables in Appendix 1, citing question number*
1.	30/08/2019	Richard Hindley, expert adviser (Consultant urologist, Hampshire Hospitals)	Dear Richard My name is Iain Willits and I am part of the Newcastle External Assessment Centre (EAC) assessing the clinical effectiveness and cost saving potential for Rezum for the treatment of men with benign prostatic hyperplasia (MT413). I am aware that you are already signed up by NICE as an expert	Hi Iain Yes very happy to help. We have presented abstracts on Rezum at the EAU (European Urology), the AUA (American) as well as BAUS (British) annual meetings. We also have 2 abstracts to present at the World Congress of Urology in October this year. I will forward all of these over the weekend when I am sitting with my laptop.

			adviser and have read your input from the questionnaire, so thank you for that. The reason I am contacting you is that you have been identified by some of your peers as being a particular expert in this technology, and NICE are interested to know if you have any UK-based research you could share to aid the assessment? Such research could be conference abstracts or posters, or slides of any talks you or your group may have given, or any on-going research manuscripts prior to publication you could share. All data can be redacted as academic in confidence as necessary. Alternatively, if you could let us know of the anticipated date of publication for any research that could also be helpful to MTAC (the committee can consider evidence right up to the meeting date, I believe this one will be held on the 15th November all things going to plan), so if you could let us know of any research to be published before this date that would be useful. Many thanks and kind regards Iain	We are also looking at hospital stay for Rezum and are comparing with TURP and Greenlight at our institution. This is work in progress but am happy to share. We looked at HES data over a 6 month period, however, when we interrogated the data we were disappointed at how inaccurate it was largely due to coding issues. We have cleaned this data and now have comparative lengths of stay for the 3 procedures. We are adding data to our database as the patients come through and clearly are keen to write up the data for publication ASAP - this we had agreed to do jointly with Imperial (as was the case with our first Rezum abstract). However, this has slowed the process slightly but this is also work in progress. I am also happy to forward presentations. We do need data. I am not so sure regarding the randomised trial proposed but we will have to wait and see. I have been very impressed with this technology and did do some research on interstitial treatments over 20 years ago. The clear difference now is the discovery of the unique properties of convective heating rather than conductive. It could sit very well in the NHS as it is more durable than Urolift and avoids any implants. Hope this is ok. Happy to help. Richard

2.	03/09/2019	Initial teleconference with the company, raising EAC queries on company submission of clinical evidence		EAC notes from call: Appendix 1
3.	12/09/2019	EAC query to Company re bugs found in economic model.	Good afternoon Jean and Michelle Many thanks for sending over the economic submission ahead of schedule yesterday, it is very much appreciated. Kim has a couple of queries on the model she would appreciate your help with at this stage please: 1. HoLEP worksheet. Stated in narrative report and in excel model that 0% of HoLEP will have repeat TURP surgery. And that the risks of incontinence associated with repeat surgery are assumed to be the same as the initial surgery. However Cells N11 and K11, are different to H5 and E5. Can you explain why these cells are different please? 2. UroLift worksheet. 100% of repeat surgeries are TURP, and therefore the risks of developing incontinence associated with repeat surgery should equal that of TURP. 50% use monoTURP (3.0% risk of incontinence), and 50% use biTURP (1.8% risk of incontinence) which would give an overall risk of 2.4%	Dear Emma, There was an error in the formula which was copied across the Calculation sheets for each technology. The error was that we were incorrectly applying the *% retreatment with index surgery* input for Rezum to the respective inputs for UroLift, Greenlight, and HoLEP (it didn't apply to Mono-TURP and Bi-TURP because we assumed they were always retreated by the index surgery) in the transition matrices to determine patients who experience incontinence and/or erectile dysfunction (ED) after re-treatment surgery. In the base-case this only affected that UroLift results because in the base case GreenLight has the same proportion of patients retreated with index surgery as Rezum and for HoLEP there is no re-treatment at all, so the error didn't make any difference to the GreenLight and HoLEP results. The UroLift in the base case and the main scenario analysis are shown below for the erroneous and corrected model. The impact is a minimal increase in costs for UroLift which is what we'd expect because in the corrected version, UroLift re-treatment is now carried out with exclusively with TURP and so carries a greater risk of incontinence and/or ED.

<table>
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<td>(calculated via 50% of 3% added to 50% of 1.8%). However the actual values in the model (Cells N11, K11) are the same as Rezum (which assumes 50% index surgery repeated and 50% TURP=1.2%). Can you explain the calculation behind N11 and K11 of the UroLift worksheet please?

Just a reminder, as discussed on the call on 03/09/2019, EAC queries and your responses will be recorded in the external communications log (public domain), so please can you highlight anything in your response that is commercial in confidence or academic in confidence, and we will make sure it is redacted before it goes in the log.

Thanks again for your help
Best wishes
Emma</td>
<td>
<table>
<tr><td></td><td colspan="2">Base case</td><td colspan="2">Erectile dysfunction included</td></tr>
<tr><td></td><td>Urolift Total costs (£)</td><td>Cost Difference to Rezum (£)</td><td>Urolift Total costs (£)</td><td>Cost Difference to Rezum (£)</td></tr>
<tr><td>Erroneous Model</td><td>2,908.79</td><td>-531.84</td><td>2,910.36</td><td>-532.79</td></tr>
<tr><td>Corrected Model</td><td>2,913.21</td><td>-536.26</td><td>2,916.33</td><td>-538.77</td></tr>
</table>

The model has now been updated to reflect these changes, please see attached.

A question for the EAC team, would you like all the results to be re-run including scenario and sensitivity analyses and compiled in a revised version of the written submission so that it aligns with the revised model?

Kind regards,
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<td>4.</td>
<td>12/09/2019</td>
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<td>Good evening Jean,

Thank you for this clarification this is really helpful. As you say the effect is minimal, however I just need to ensure that we understand the underlying mechanics of the model.

However I think the error should be corrected in row 12 of the model also in the two worksheets.</td>
<td>Hi Kim,

Thanks for bringing this to our attention. Please find attached v3 of the economic model updated with errors corrected.

The error affected cells L12 and M12 in the following sheets: Greenlight, UroLift, and HoLEP. The highlighted cells in the following formulas were all erroneously pointing to Clinical!M13 , which is the input for Rezum. Cell M12 in the Greenlight, UroLift, and HoLEP sheets was affected similarly.</td>
</tr>
</table>

			1) On the Urolift worksheet N11 and K11 now reflect the risks of TURP (correctly). However shouldn't M12 and L12 reflect the same proportions (when the ED switch is off)? 1. You will notice the problem is exaggerated if you then switch on ED in the Setting worksheet (when you switch on ED the proportions don't add up – e.g. M11+N11 does not equal M12, K11+L11 does not equal L12). 2) Similar issue for HoLEP worksheet (same cells) I don't think you need to revise the written submission to reflect these changes as this will be documented in the external communication log. However I will ask Yingying to clarify (in case my understanding is incorrect). [As instructed by Emma I also need to formally remind you that EAC queries and your responses will be recorded in the external communications log (public domain), so please can you highlight anything in your response that is commercial in confidence or academic in confidence, and we will make sure it is redacted before it goes in the log.] Many thanks Kim	**Urolift L12 Formula =** ((Settings!$M$9*(1-INDEX(Clinical!$M$41:$W$41, MATCH("Mono-TURP",Clinical!$M$39:$W$39,0)))+(1-Settings!$M$9)*(1-INDEX(Clinical!$M$41:$W$41, MATCH("Bi-TURP",Clinical!$M$39:$W$39,0))))*Clinical!S13)+((1-Clinical!S13)*(1-INDEX(Clinical!$M$41:$W$41, MATCH($D$1,Clinical!$M$39:$W$39,0)))) **GreenLight L12 Formula =** ((Settings!$M$9*(1-INDEX(Clinical!$M$41:$W$41, MATCH("Mono-TURP",Clinical!$M$39:$W$39,0)))+(1-Settings!$M$9)*(1-INDEX(Clinical!$M$41:$W$41, MATCH("Bi-TURP",Clinical!$M$39:$W$39,0))))*Clinical!U13)+((1-Clinical!U13)*(1-INDEX(Clinical!$M$41:$W$41, MATCH($D$1,Clinical!$M$39:$W$39,0)))) **HoLEP L12 Formula =** ((Settings!$M$9*(1-INDEX(Clinical!$M$41:$W$41, MATCH("Mono-TURP",Clinical!$M$39:$W$39,0)))+(1-Settings!$M$9)*(1-INDEX(Clinical!$M$41:$W$41, MATCH("Bi-TURP",Clinical!$M$39:$W$39,0))))*Clinical!W13)+((1-Clinical!W13)*(1-INDEX(Clinical!$M$41:$W$41, MATCH($D$1,Clinical!$M$39:$W$39,0)))) Please let me know if you need anything further. Kind regards,

5.	23/09/2019	EAC query to company re Dr Raj Persad's contribution to economic model.	Good morning Jean NICE have passed on the details of your expert correspondence to us. Can I please check and confirm whether Prof. Raj Persad actually participated as a "KOL" or otherwise directly informed your economic modelling work? I can see your invitation email to him in March 2019, but no response? Many thanks and all the best. Helen	Dear Helen, We engaged Dr Persad as a KOL to understand the disease management/treatment options available to patients based on the size of their prostate glands. Please see attached the response that we obtained from Dr Raj Persad, apologies if this was not included in the zip folder. Please let me know if you need anything further. Kind regards, Jean  {External} Re Rezum MTEP expert advisor.

Appendix 1

MT413 Rezum
NICE-EAC Call with Company
Tuesday 03 September 2019 @ 13:00
NOTES

In Attendance:
NICE: Ying-Ying Wang (YYW), Bernice Dillon (BD)
Newcastle EAC: Helen Cole (HC), Kim Fairbairn (KF), Iain Willits (IW), Emma Belilios (EB)
Company: Jean Binns (JB), Michelle Sullivan (MS), Glyn Burtt (GB), Deirdre Blisset (DB)

Apologies: Iain Willits (IW), Newcastle EAC

1) **Welcome and Introductions**

Newcastle EAC
Helen Cole – Head of Service, Project Lead
Iain Willits – Lead author for clinical evidence appraisal, will also be assisting KF with appraisal and write up of economics
Kim Fairbairn - leading critique of economics model (with Andrew Sims, EAC Director)
Emma Belilios – Administrator

Boston Scientific
Jean Binns – Senior Analyst, Health Economics and Market Access
Michelle Sullivan – Senior Manager, Health Economics & Market Access
Glyn Burtt – Director of Medical Affairs and Medical Education – Urology and Pelvic Health
Deirdre Blisset – Independent health economist.

Notes will be circulated following the call. The company will have the chance to correct any inaccuracies/omissions and redact any confidential information. The final notes will form the formal record of the call and will be added to the external communications log (public domain). Going forward, the EAC will contact the company directly with ad hoc queries. MS asked colleagues to respond promptly. All additional queries and responses will be recorded in the communications log. HC asked the company to highlight any commercial in confidence or academic confidence content in their responses so that this can be redacted before publication.

2) **Company clinical evidence submission (Part 1): EAC questions (sent 30/08/2019)**

<u>General</u>

1. **In a number of places in the submission, you refer to using "UK Expert Opinion" to inform claimed benefits and other content.**

a. **How was this Expert Opinion sought and assimilated?**

Expert opinion was sought primarily to support the economic (Part 2) submission (due 12/09/2019), which will include a more detailed description of how expert opinion was gathered and assimilated. For the clinical evidence submission, expert opinion was sought mostly by email correspondence as validation of the published evidence.

b. Please can you provide us with copies of any questionnaires / correspondence with Experts, so that we may independently substantiate their contributions?

JB is happy to share email exchanges with experts with the EAC. It was agreed that copies of correspondence will be sent with the economic submission.

ACTION: JB to send copies of correspondence with experts with economic (Part 2) submission.

Sustainability

2. Page 13 of the submission asks the company to briefly describe the environmental impact of the technology. Your response only details broader sustainability considerations from Boston Scientific. Do you have an environmental impact statement relating specifically to the Rezum technology please?

The company now have some additional device-specific statements they can share with the EAC. The original submission was very general as Boston Scientific was going through the acquisition process at the time and it has taken some time to get the device-specific information. MS will send the information to YYW after the call (the original submission cannot be altered).

ACTION: MS to send device-specific environmental impact information to YYW.

POST MEETING - Received 03/09/2019 from JB:

- The packaging is recyclable
- The device and generator comply with Restriction of Hazardous Substances (ROHS) and Registration Evaluation Authorisation and Restriction of Chemicals (REACH) directives https://www.rohsguide.com/rohs-reach.htm
- There are no unique disposable requirements.
- The system does not produce any by-products as part of normal use.
- The environmental and sustainable impact of using Rezum vs TURP or other longer or more invasive procedures with a longer length of stay and Rezum's favourable retreatment rate at 4 years results in:

  Reduction in inpatient resource use, such as theatre operating time
  Reduction in use of facilities, power, food, bed linen, etc
  Reduction in use of anaesthetics
  Reduction in use of disposable and packaging elements vs some procedures

(McVary et al, J Urol. 2016;195(5):1529-38, Woo HH, Gonzalez RR Medical Devices: Evidence and Research 2017;10:71-80).

Intervention

3. **In Section 2 of the submission there are two versions of the device listed (C1 and C2), concerning differences in the power source for the needle generator. Can you please provide us with the technical specifications for each version? Do you have any data to demonstrate that these device versions are equivalent in terms of clinical efficacy and safety? Could you advise which version of the device was used in which study (in particular, the Rezum II trial)?**

GB confirmed that there have been changes made to the delivery device (from manual to automatic needle deployment) and the generator for ease of use and manufacturing efficiency. The mode of action and steam generation (and therefore efficacy and safety) have remained constant. All published studies used the latest version available at the time. The first in human studies used the manual version and the pivotal Rezum II trial used the automatic version.

YYW asked if the different versions had different training requirements. GB confirmed that the automatic and manual versions of the device would have had different training requirements. Only the automatic version is available now and the training currently offered reflects this.

Clinical pathway

4. **The illustration in Section 3 of the submission (page 16) positions "Rezum as an alternative to drug therapy or before surgical invasive treatments" in the clinical pathway. Also in section 8, the quasi-comparative study by Gupta et al. (2017) (Rezum vs. drug treatment) is cited [1]. However, drug therapy was not a comparator in scope of this evaluation and the company has not proposed to vary and add drug therapy as a comparator for evaluation (page 3 of the submission).**

Can you clarify whether Rezum is only indicated for patients who have already trialled drug therapy and are now considering Rezum as a minimally invasive alternative to surgery, or do you consider Rezum a direct comparator instead of initiating drug therapy?

The company expects that clinicians will follow the latest guidance, currently conservative management, then drug therapy, then surgical options (including minimally invasive alternatives, which would include Rezum). Future guidance may recommend scenarios where men can opt to avoid the drug therapy stage to avoid the potential side effects but this is not what the current guidance recommends.

Literature search

5. **During our preliminary searches we have identified 56 conference abstracts on Rezum. In the submission, you state 7 abstracts were identified (Section 4) but it is not clear how many of these are duplicates of the same data (there seems to be some contradictions):**

a. Can you please provide a long list of all conference abstracts known to the company? Could you also please provide us with a rationale for the inclusion of the 7 identified abstracts and why other abstracts were not included?

JB clarified that abstracts were excluded initially as lower quality evidence (not peer reviewed). However, there were 7 abstracts identified that could not be matched to published papers and which had relevant information that helped to validate the procedure time given by experts in a UK setting (particularly applicable to the economics submission).

Rationale for inclusion of the abstracts is in section 5a of the clinical submission.

b. Concerning the potential to "double count" patients - are you aware of any of these conference abstracts being later published as full studies?

JB will provide the company's long list of abstracts (22), some were matched with published outputs (and therefore excluded to avoid double counting).

ACTION: JB to provide company's long list of abstracts.

POST MEETING - Received 03/09/2019 from JB:

Abstracts and Presentations, we have on file for Rezum that were not included in Part 1

- Dixon C, Huidobro C, Rijo Cedano E, Hoey M, Larson T. Acute Effects in the Human Prostate Following Treatment with High-Calorie Water Vapor (Rezūm). Abstract #0838. World Congress of Endourology 2012, Istanbul, Turkey.
- Dixon C, Pacik D, Huidobro C, Rijo Cedano E, Mynderse L, Hanson D, Hoey M, Larson T. Preliminary Data Following Treatment with Vapor for BPH: The Rezūm System. Abstract #1476. World Congress of Endourology 2012, Istanbul, Turkey.
- Dixon C, Rijo Cedano E, Pacik D, Vit V, Varga G, Mynderse L, Hanson D, Larson T. Transurethral Water Vapor Therapy for BPH; Initial Clinical Results of the First-In-Man and Rezūm I Pilot Study. Abstract #631. European Association of Urology 2013, Milan, Italy.
- Dixon C, Rijo Cedano E, Pacik D, Vit V, Varga G, Mynderse L, Hanson D, Larson T. Transurethral High Energy Water Vapor Therapy for BPH; Initial Clinical Results of the First-In-Man and Rezūm™ 1 Clinical Trials Using the Rezūm™ System. Journal of Endourology 2013, 27 (s1): A340. Abstract nr MP23-13.
- Dixon C, Rijo Cedano E, Pacik D, Vit V, Varga G, Mynderse L, Hanson D, Larson T. Serial MRI and 3D Rendering Following Treatment of BPH Using High Energy Water Vapor Therapy and the Rezūm™ System; Initial Results from the First-In-Man and Rezūm™ 1 Clinical Trials. Journal of Endourology 2013, 27 (s1): A69. Abstract nr MP03-08.
- Mynderse L, Hanson D, Robb R, Rijo Cedano E, Pacik D, Vit V, Varga G, Larson T, Dixon, C. Characterizing Rezūm® System Water Vapor Treatments for Benign Prostatic Hyperplasia with Serial Magnetic Resonance Imaging and 3D Rendering. Abstract #230. European Association of Urology 2014, Stockholm, Sweden.
- Wagrell L, Tornblom, M. Transurethral Water Vapor Therapy for BPH; A Single Center's Experience Using the Rezūm® System. Abstract #234. European Association of Urology 2014, Stockholm, Sweden.
- Dixon C, Rijo Cedano E, Pacik D, Vit V, Varga G, Mynderse L, Larson, T. Transurethral Water Vapor Therapy for BPH; 1-year Clinical Results of the First-In-Man and Rezūm® I Clinical Trials

Using the Rezūm® System. Abstract #1816. American Urological Association Annual Meeting 2014, Orlando, Florida.

- Wagrell L, Tornblom, M. Transurethral Water Vapor Therapy for BPH; A Single Center's Experience Using the Rezūm® System in an Office-based Setting. Abstract #1817. American Urological Association Annual Meeting 2014, Orlando, Florida.
- Mynderse L, Hanson D, Robb R, Rijo Cedano E, Pacik D, Vit V, Varga G, Larson T, Dixon C. Rezūm® System Water Vapor Treatment for Benign Prostatic Hyperplasia: Characterization with Magnetic Resonance Imaging and 3D Rendering. Abstract #1890. American Urological Association Annual Meeting 2014, Orlando, Florida.
- McVary K, Roehrborn C, et al. Using the Thermal Energy of Convectively Delivered Water Vapor for the Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia: The Rezūm II Study. Abstract #15-8068. Plenary II Late-Breaking Abstract Session. American Urological Association Annual Meeting 2015, New Orleans, Louisiana.
- Dixon C, Rijo Cedano E, Pacik D, Vit V, Varga G, Mynderse L, Larson, T. Convective Water Vapor Energy (WAVE) Ablation: Two-Year Results Following Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. Abstract ID 16-5612. American Urological Association Annual Meeting 2016, San Diego, California.
- McVary K, Gange, S, et al. Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia with Convective Water Vapor Energy Ablation: Preserved Erectile and Ejaculatory Function. Abstract ID 16-1219. American Urological Association Annual Meeting 2016, San Diego, California.
- Gupta N, Kohler TS, McVary KT et al. Convective radiofrequency water vapor energy ablation (Rezūm®) effectively treats lower urinary tract symptoms due to benign prostatic enlargement regardless of obesity while preserving erectile and ejaculatory function. Abstract ID Pl-01: Best Abstract. American Urological Association Annual Meeting 2017, Boston, Massachusetts.
- Roehrborn CG, Gange SN, Gittelman MC et al. Convective radiofrequency thermal therapy: durable two-year outcomes of a randomized controlled and prospective crossover study to relieve lower urinary tract symptoms due to benign prostatic hyperplasia. Abstract ID 17-2138. American Urological Association Annual Meeting 2017, Boston, Massachusetts.
- Gupta N, Holland B, Dynda D et al. Comparison of convective radiofrequency water vapor energy ablation of prostate (Rezūm®) to MTOPS trial cohort. Abstract ID 17-7218. American Urological Association Annual Meeting 2017, Boston, Massachusetts.
- Gupta N, Holland B, Delfino, K, et al. Convective radiofrequency water vapor energy prostate ablation (Rezūm®) effectively treats urinary retention. Abstract ID 17-7241. American Urological Association Annual Meeting 2017, Boston, Massachusetts.
- McVary KT, Gupta N, Rogers T, Holland B, Helo S, Dynda D. Risk of clinical progression and changes in sexual function in men with lower urinary tract symptoms due to benign prostatic hyperplasia (BPH) treated with water vapor thermal therapy or with long-term use of doxazosin, finasteride or both drugs: 3-year outcomes. European Association of Urology 2018, Copenhagen, Denmark.
- Johnston M, Emara A, Gehring T, Nedas T, Ahmed H , Hindley R Rezūm water vapour thermal therapy for benign prostatic hyperplasia: Early results from the United Kingdom. Abstract AM18-3603. European Association of Urology 2018, Copenhagen, Denmark.

- Ulchaker JC, Martinson M. Analyzing the Cost-Effectiveness of Six Therapies for Treating Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. American Urological Association Annual Meeting 2018, San Francisco, California.
- McVary KT. Water Vapor Thermal Therapy with Rezūm System: 3-Year Results of Prospective Crossover Trial Replicate Durable Outcomes of Phase III Randomized Controlled Study (RCT) for Treatment of Lower Urinary Tract Symptoms (LUTS)/Benign Prostatic Hyperplasia (BPH). Late Breaking Session. American Urological Association Annual Meeting 2018, San Francisco, California.
- Helo S, Tadros N, Gupta N, Holland B, Dynda D, McVary KT. Comparison of Convective Radiofrequency Thermal Therapy of Prostate (Rezűm®) to MTOPS Study Cohort Sexual Function Response at 3 Years. American Urological Association Annual Meeting 2018, San Francisco, California.

In the PRISMA diagram of the submission (Appendix A), you state there were 5 studies excluded following assessment for eligibility (full text), with reasons given. However, no studies are listed in the excluded studies table. Could you tell us what these studies were and why they were excluded please?

JB agreed this was an oversight. In the new submission template, the excluded studies table comes before the PRISMA diagram which led to its inadvertent omission. She suggested NICE consider revising the template. BD thanked her for this feedback.

JB will provide the details of the 5 excluded studies and the reasons for their exclusion in an email.

ACTION: JB to provide details of the excluded studies.

POST MEETING - Received 03/09/2019 from JB (next page):

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Mynderse et al (2015) Urology 86: 122-127, 2015	A prospective, nonrandomised pilot study. As per the original pilot study design, 45 of these patients were subjected to 4, modified, multiparametric gadoliniumenhanced MRI sequences of the prostate and pelvis at 1 week,1, 3, and 6 months after convective water vapor energy Treatment with Rezum	The aim of this study was to evaluate by magnetic resonance imaging the physical effects of convective thermal energy transfer with water vapor as a means of treating lower urinary tract symptoms due to benign prostatic hyperplasia. This paper did not look at clinical and safety outcomes included in the scope of this review.	None
Woo HH, Gonzalez RR Medical Devices: Evidence and Research 2017;10:71-80.	Review paper	Paper was excluded as it was only a clinical review paper, that did not conduct a systematic literature review and meta-analysis.	None
Gupta et al (2018) Urology DOI: 10.1016/j.juro.2018.02.3088	Multicentre randomised controlled trial (RCT). Propensity matched analysis of active arms form two separate studies (MTOPs and Rezum Pivotal study) without direct trial comparison	The comparator arm of this study was medical therapy of prostatic symptoms (MTOPs). Medication management is outside the scope of this review.	None
Helo et al (2017) Curr Urol Rep2017 Oct;18(10):78. doi: 10.1007/s11934-017-0728-1	Review paper	Paper was excluded as it was only a clinical review paper, that did not conduct a systematic literature review and meta-analysis.	None
Magistro et al (2017) Eur Urol. 2017 Dec;72(6):986-997. doi: 10.1016/j.eururo.2017.07.005	Review paper	Paper was excluded as it was only a clinical review paper, that did not conduct a systematic literature review and meta-analysis.	None

Rezum trial

6. **Can you clarify whether this RCT [2] was the pivotal (phase III) trial used to gain FDA approval for this technology? If so, are there any additional data submitted to the FDA that you may be able to share (sensitive data can be redacted).**

   GB, yes, all data are in the public domain, and can be accessed via: https://www.clinicaltrials.gov/ct2/results?term=NCT01912339. The company do not hold any additional trial data.

   Safety / adverse events

   We have observed one Injury report in the FDA MAUDE database (April 2017) for which the following response (abridged) was given in the Manufacturer Narrative: *"….NXTHERA CONDUCTED AN INTERNAL CLINICAL REVIEW OF THE REPORTED ADVERSE EVENT NOTING THE PATIENTS BASELINE PROSTATE SIZE WAS 184 GRAMS WHICH IS OUTSIDE OF THE APPROVED INDICATION FOR USE WHICH LIMITS THE PROSTATE SIZE TO 30-80 GRAMS…….. NXTHERA OUTLINES THE APPROVED INDICATION FOR USE AS WELL AS THE ANTICIPATED ADVERSE EVENTS WITHIN THE INSTRUCTIONS FOR USE MANUAL WHICH IS AVAILABLE ON LINE AT HTTP://MAX1.REZUM.COM/WP-CONTENT/ UPLOADS/2016/07/3032-001_B_REZUM_IFU.PDF. ALL PHYSICIANS TRAINED ON THE REZUM PROCEDURE RECEIVE A COPY OF THE IFU AND THIS DOCUMENT IS ALSO AVAILABLE TO THE GENERAL PUBLIC."*
   This Manufacturer response refers to the US version of the IFU, with latest copy downloaded from: http://www.nxthera.com/pdf/3032-001-Rev-H_Rezum_IFU.pdf.

   We observe that there is an upper limit of 80cm^3 prostate volume in the US IFU. This is not the case in the EU/UK IFU, downloaded from: http://www.nxthera.com/pdf/3032-004-Rev-H_Rezum_IFU.pdf, for which there is no upper limit on prostate volume for Rezum treatment. Age is also a limiting factor in the USA, with Rezum treatment only indicated in men over 50 years old.

   This is not due to lack of evidence on the benefits of Rezum in larger prostates or younger men. Nx Thera submitted Rezum to the FDA for pre-market approval via the 510(k) substantial equivalance route, claiming the Medtronic Prostiva as the predicate device. The Medtronic Prostiva clinical indications for use had an upper limit of 80cm^3, therefore Nx Thera used matched exclusion criteria in its Rezum II trial, to demonstrate equivalence to the FDA. These restrictions do not apply to the CE mark application – this application asks for a larger indication to match the clinical evidence available for Rezum. GB can provide more information on this if needed.

   Regarding the specific incident from the FDA MAUDE database, it looks likethe patient had a complication that is a well known risk in transurethral procedures, and that the prostate size was irrelevant. Any transurethral procedure carries a small risk.

7. **Can the company please comment on the restriction to smaller prostate volumes and US patients over 50 years old, compared with no such restrictions for UK patients? Are there any known safety / adverse event implications for larger prostates and younger men?**

   GB clarified that smaller prostate size is probably more relevant. If the prostate is small (e.g. 20 mls), there is potentially a risk of penetration of the Rezum steam ablation needle out of the prostate volume and into the rectal wall, causing damage to surrounding tissue. In clinical practice, there is a theoretical upper limit on prostate volume (around 150 mls) for successful treatment with Rezum. However, the overall shape (width and length) of the prostate is the consideration, rather than total volume. Boston Scientific holds data on Rezum patients with prostate volumes ranging from 12.9 to 183 mls.

   Economics

8. **Can you please offer any insight into the company's plans for the economic model? For example:**

a. **Model structure (decision tree or Markov)**

Relatively simple Markov structure with 4 health states and 2 long term consequences (risks of incontinence and erectile dysfunction) considered. Markov cycles are 3 monthly.

b. **Time perspective -** 4 years – selected because there are 4 year data for Rezum (longer than other technologies assessed by NICE MTEP, e.g. Urolift and surgical comparators), including re-treatment rates.

c. **Software package used**

Microsoft Excel

d. **Comparators**

Comparators were aligned with the scope, i.e. surgical options including monopolar or bipolar transurethral resection of the prostate (TURP) and Urolift. Open prostatectomy was not included as a comparator (more invasive procedure, very selected patient group).

e. **Clinical outcomes intended as model inputs**

It was agreed that JB would provide this in an email after the call.

POST MEETING - Received 03/09/2019 from JB:

As a follow up to our call this afternoon, please see below a summary of our economic modelling approach that was discussed on our call:

Clinical outcomes intended as model inputs
Part 1 of this submission demonstrates that Rezum is associated with similar clinical outcomes with respect to alleviating symptoms of LUTS as all surgical and minimally invasive comparators listed above. This is a cost consequence model which assumes equal efficacy between all comparators and aims to capture all short- and medium-term differentiators between Rezum and comparators that are expected to have resource use implications for the NHS.

The resource use implications considered in the model include:

- Procedure costs: Differences in equipment costs, operating costs and hospital stay
- Short-term complications: Differences in short-term adverse events associated with BPH surgery, including non-acute and acute urinary retention (AUR), urinary tract infection (UTI), bleeding or blood transfusion, bladder neck contracture or stricture and transurethral resection syndrome (TUR)
- Long-term complications: Differences in the risk of developing a long-term complication, including incontinence or ED
- Retreatment: Differences in retreatment rates, defined as a patient requiring a repeat surgery with either TURP or the index surgery to treat symptoms for LUTS that have returned

f. **Sensitivity analysis (deterministic or probabilistic)**

It was agreed that JB would provide this in an email after the call.

POST MEETING - Received 03/09/2019 from JB:

Three types of sensitivity analyses were undertaken, a deterministic sensitivity analysis (DSA), a probabilistic sensitivity analysis (PSA) and multiple scenario analyses.

Approach to conducting DSA

Separate DSAs were conducted for each comparator. All primary inputs were varied in the DSA within a 20% range of the base-case value. Variables excluded from the sensitivity analysis included micro-costing inputs used to estimate the bundled equipment costs, the bundled adverse event costs and pre-and post-operative costs. The results of the DSA are presented on a tornado plot for each comparator, ranking the inputs in order of impact on net difference in cost per patient treated at 4 years compared to Rezum.

Approach to conducting PSA

The PSA varied the same model inputs using plausible ranges to define probability distributions from which random number draws were used to sample parameters.

All probabilities were modelled using a beta distribution. Where the n values from the source data were known these were used to compute alpha and beta. Where the model input was derived by applying a rate ratio to the input for Mono-TURP, as in the case for the rate of adverse events for Bi-TURP and HoLEP, the confidence interval around the rate ratio was used to generate a log normal distribution was sampled from and these numbers transformed back to the format of the parameter in the model.

As there was little data informing the uncertainty of the length of stay and operation times, an assumption was made that the 95% confidence interval was bounded by plus or minus 50% of the mean, and a lognormal distribution was used to sample these parameters.

Distributions were applied to cost data using a gamma distribution.

- Where the data was sourced from NHS reference costs, the gamma distribution was defined by making an assumption that the standard error was 10% of the mean; alpha and beta were calculated using a method of moments approach. This assumption was necessary because the latest schedule of NHS reference costs no longer contains the upper and lower quartile ranges of the data from which an estimation of the standard error could be made.
- The same approach was used to estimate the standard error of the comparator technologies.

Scenario analysis

Several scenario analyses were undertaken to vary inputs identified as key model drivers or areas of greater uncertainty within extreme ranges, keeping all other base-case model inputs constant. The variables were varied to show best- and worst-case scenarios favouring Rezum or a comparator respectively.

Confidential information declaration (Appendix C)

9. **Please can you confirm that there is no confidential information contained in the Part 1 submission? The "No" box on page 91 has not been checked, although signed declaration is given.**

The company confirmed that no confidential information is included in the Part 1 submission. MS will send an email confirming this to YYW, who will then share the email and company contact details with HC for future correspondence. JB is the main company contact, MS is happy to be copied into correspondence.

POST MEETING - Received 03/09/2019 from JB:

Confidential Data

None provided

ACTION: YYW to forward email to HC with contact details for JB and MS for future correspondence.

References

1. Gupta N, Holland B, Dynda D, Kohler T, McVary K. Comparison of convective radiofrequency water vapor energy ablation of prostate (rezum®) to MTOPS trial cohort. J Urol. 2017;197(4):e511-.

2. McVary KT, Gange SN, Gittelman MC, Goldberg KA, Patel K, Shore ND, et al. Minimally Invasive Prostate Convective Water Vapor Energy Ablation: a Multicenter, Randomized, Controlled Study for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. J Urol. 2016;195(5):1529-38.

3) Economic submission

Economic submission is due for submission on 12/09/2019, but may be ready earlier. The EAC confirmed that early submission would be extremely helpful if possible.

The company have experience some difficulties sending larger files to NICE. NICE are looking at options, but currently advise companies to send docs separately if possible.

NICE are happy to receive any feedback on the new submission template.