



Australian Government

Department of Health

Application Form

(New and Amended Requests for Public Funding)

(Version 2.5)

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires in order to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

The application form will be disseminated to professional bodies / organisations and consumer organisations that have will be identified in Part 5, and any additional groups that the Department deem should be consulted with. The application form, with relevant material can be redacted if requested by the Applicant.

Should you require any further assistance, departmental staff are available through the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): Not applicable

Corporation name: REDACTED

ABN: REDACTED

Business trading name: REDACTED

Primary contact name: REDACTED

Alternative contact name: REDACTED

2. (a) Are you a consultant acting on behalf of an Applicant?

- Yes
 No

(b) If yes, what is the Applicant(s) name that you are acting on behalf of?

Not applicable

3. (a) Are you a lobbyist acting on behalf of an Applicant?

- Yes
 No

(b) If yes, are you listed on the Register of Lobbyists?

- Yes
 No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

Vagus Nerve Stimulation (VNS) for the treatment of treatment resistant depression (TRD)

5. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Major depressive disorder (MDD) is a common psychiatric disorder, characterised by depressed mood, loss of interest and enjoyment and other psychological and somatic symptoms. MDD causes substantial psychosocial dysfunction and high individual mental strain, as well as excess morbidity and mortality – the risk of suicide is considerable.

Initial treatment involves antidepressant medication. Around 30% of patients do not respond to multiple treatment steps and are considered as treatment resistant. Even if they achieve a response, these patients have a higher likelihood to relapse. Tolerability issues also negatively impact treatment outcomes.

Treatment resistant depression (TRD) is defined as having failed to achieve adequate response after at least two appropriate antidepressant trials from two different pharmacological classes (Berlim and Turecki 2007). VNS is proposed for funding for patients who have failed at least 4 lines of therapy – difficult-to-control subpopulation with significant unmet clinical need due to the lack of viable treatment alternatives.

6. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

VNS device consists of an implanted pacemaker-like pulse generator and a nerve stimulation electrode, which deliver intermittent stimulation to the left vagus nerve; the same technology has been accepted by MSAC for refractory epilepsy. The proposed services cover implantation, programming, explantation / repositioning and battery replacement.

Implantation requires two small incisions to (i) place the pulse generator under the skin below the collar bone and (ii) wrap the electrode around the left vagus nerve in the neck. The procedure takes 1-2 hours under general anaesthesia in an inpatient setting, usually by a neurosurgeon.

Post-implantation, the patient must visit their specialist psychiatrist for dose (pulse) titration to clinical efficacy. Once a therapeutic dose is established, 1-2 visits per year are recommended thereafter for monitoring purposes. The therapy is continuous and long-term with a typical battery life of up to 10 years (replaceable for continuing treatment).

7. (a) Is this a request for MBS funding?

- Yes
 No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

- Amendment to existing MBS item(s)
 New MBS item(s)

The Applicant is also happy to amend the refractory epilepsy listings (expected to be on the schedule in early-mid 2017) to add a new indication of TRD if this is preferred by PASC and / or MSAC.

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

Not applicable

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

Not applicable (see above)

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

- i. New item which also seeks to allow access to the MBS for a specific health practitioner group
- ii. New item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
- iii. New item for a specific single consultation item
- iv. New item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

- Yes
- No

(g) If yes, please advise:

8. What is the type of service:

- Therapeutic medical service
- Investigative medical service Single
- consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology
- Hybrid health technology

9. For investigative services, advise the specific purpose of performing the service (which could be one or more of the following):

Not applicable

10. Does your service rely on another medical product to achieve or to enhance its intended effect?

- Pharmaceutical / Biological
- Prosthesis or device
- No

11. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

- Yes
- No

(b) If yes, please list the relevant PBS item code(s):

Not applicable

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

- Yes (please provide PBAC submission item number below)
- No

Not applicable

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Not applicable

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

- Yes
 No

(b) If yes, please provide the following information (where relevant):

Not applicable

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

- Yes
 No.

Note: LivaNova Australia Pty Ltd intends to submit an application to the PLAC in time for Prosthesis Listing in February 2018.

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

- Yes
 No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

Not applicable

13. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables:

- VNS Therapy Accessory pack (includes a single-pin generator test resistor assembly, a dual-pin generator test resistor assembly, four lead tie-downs, and a hexscrewdriver)
- Tunneler
- Clamp
- Stitching thread
- Transparent dressing
- Alcohol wipes
- Gauze pads
- Surgical drape
- Gloves
- Others as required by a surgery of this type (i.e., minimally invasive, 1-2 hours under general anaesthesia).

Multi-use consumables:

- No specific items but as required by a surgery of this type (i.e., minimally invasive, 1-2 hours under general anaesthesia).

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: Medical Device
 Manufacturer's name: LivaNova Australia Pty Ltd
 Sponsor's name: LivaNova Australia Pty Ltd

- (b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

- Class III
 AIMD
 N/A

15. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

- Yes (If yes, please provide supporting documentation as an attachment to this application form)
 No

- (b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

- Yes (if yes, please provide details below)
 No

| Registered item | ARTG listing, registration or inclusion number: | TGA approved indication(s), if applicable: | TGA approved purpose(s), if applicable: |
|---|---|--|---|
| Implantable portion of VNS Therapy System | | | |
| VNS Therapy DemiPulse Generator Model 103 - Stimulator | 168817 | Indicated for the treatment of chronic or recurrent depression in patients that are in a treatment-resistant or treatment-intolerant major depressive episode and for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures or generalized seizures that are refractory to antiepileptic medications. | The Pulse Generator is an implantable, multiprogrammable pulse generator that delivers electrical signals to the vagus nerve. The Pulse Generator is housed in a hermetically sealed titanium case and is powered by a single battery. Electrical signals are transmitted from the Pulse Generator to the vagus nerve by the Lead. The Lead and the Pulse Generator make up the implantable portion of the VNS Therapy System. |
| VNS Therapy Model 303 Lead (303.2 and 303.3) | 192080 | Not applicable | Silicone insulated implantable patient lead, delivering the electrical signal from the Pulse™ (Model 102) or DemiPulse™ (Model 103) Generators to the vagus nerve. |
| VNS Therapy PerenniaFLEX Model 304 Lead (304.2 and 304.3) - | 192081 | Not applicable | Silicone insulated implantable patient lead, delivering the electrical signal from the Pulse™ (Model 102) or DemiPulse™ (Model 103) Generators to the vagus nerve Available in two sizes (2.0 and 3.0 mm electrode diameter) to ensure optimal electrode fit on the nerve. The Lead has 2 helical electrodes and an anchor tether, which coil around the left vagus nerve. The connector end is tunnelled subcutaneously to the Generator pocket |

| Non-implantable portions of the VNS Therapy System | | | |
|--|--------|----------------|--|
| VNS Therapy® Model 250 Programming Software | 277451 | Not applicable | A small hand-held tablet computer enabling the interrogation and programming of the Cyberonics' VNS Therapy® Implantable Pulse Generator range using the Programming Wand. Enables the treating physician to program and interrogate the VNS Therapy® Implantable Pulse Generator (IPG) range. |

16. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

- Yes (please provide details below)
 No

Not applicable.

17. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

- Yes (please provide details below)
 No

Not applicable

PART 4 – SUMMARY OF EVIDENCE

18. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). Please do not attach full text articles, this is just intended to be a summary.

| ID | Type of study design* | Title of journal article or research project (including any trial identifier or study lead if relevant) | Short description of research (max 50 words)** | Website link to journal article or research (if available) | Date of publication** * |
|---|-------------------------------------|---|--|---|----------------------------|
| Systematic reviews and meta-analyses | | | | | |
| 1 | Meta-analysis | A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression. Berry et al., 2013 | A meta-analysis of patient-level data from 6 company studies using Bayesian hierarchical models to compared response and remission rates in patients with TRD treated with VNS+TAU or TU alone. MADRS response and remission rates were consistently superior and more likely to persist with VNS+TAU compared to TAU alone. | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3590011 | March 2013 |
| 2 | Systematic review | Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. Daban et al., 2008 | A SR to evaluate the safety and efficacy of VNS. SR identified 98 references of which 18 met required quality criteria, including one RCT. VNS associated with significant reduction in depressive symptoms. VNS was reported to be safe and feasible procedure. | http://www.jad-journal.com/article/S0165-0327(08)00095-5/pdf | September 2008 |
| 3 | Systematic review and meta-analysis | Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: variable results based on study designs Martin et al., 2012 | SR and MA of 14 analytical VNS studies reporting depressive symptoms. Efficacy evaluated according to severity of illness and % responders Outcomes assessed in short (≤ 12 week), medium (>12 to < 48 week) and long term (>48 week). | http://www.europsy-journal.com/article/S0924-9338(11)00125-8/pdf | April 2012 |
| Randomised controlled trials | | | | | |
| 4 | RCT - VNS vs sham | Vagus nerve stimulation for treatment resistant depression: A randomized, controlled acute phase trial Rush et al., 2005 Trial: D-02 | MC, MN, masked RCT comparison of adjunctive VNS vs sham; 10-weeks duration Outpatients with nonpsychotic MDD (n=210) or nonpsychotic, depressed phase, bipolar disorder (n=25), not responding to 2-6 medications. Mean number of prior drug treatment classes: 7.3 ± 2.1 . Primary outcome was HRSD24 response (week-10): rates were 15.2% vs 10% (VNS vs sham respectively; evaluable patients [N=222]). | http://www.biologicalpsychiatryjournal.com/article/S0006-3223(05)00620-7/pdf | September 2005 |

| ID | Type of study design* | Title of journal article or research project (including any trial identifier or study lead if relevant) | Short description of research (max 50 words)** | Website link to journal article or research (if available) | Date of publication** * |
|--|--|--|--|---|----------------------------|
| 5 | RCT - VNS dosing | Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: Acute and chronic effects. Aaronson ST et al., 2013 Trial: D-21 | MC, DB, RCT comparison of low, mid or high VNS doses; acute phase: 22 -weeks; Long-term phase: 50-weeks 331 patients with MDD or BP (21%) and MDE, not responding to ≥ 4 medications (97% had failed ≥ 6 previous treatments; mean number of failed drug classes: 6.4 ± 2.0). All groups showed significant improvements in the primary outcome (IDS-C score) with no differences observed between groups. VNS was well tolerated. | http://www.brainstimjrn.com/article/S1935-861X(12)00188-X/pdf | July 2013 |
| Comparative non-randomised trials | | | | | |
| 6 | Prospective Non-randomised Comparative Trial | Clinical benefits and cost effectiveness of vagus nerve stimulation in a long-term treatment of patients with major depression Sperling W et al., 2009 Trial: Erlangen Study 1 | Comparative prospective study in 9 VNS-implanted patients vs 9 matched patients with TRD. Significant improvements in symptoms were observed in HAMD scores after 12 months for VNS vs baseline. No changes were observed in the non-treated group. Duration of hospitalisation, treatment frequency, and drug treatment were decreased in the VNS group. | https://www.thieme-connect.com/DOI/DOI?10.1055/s-0028-1103294 | May 2009 |
| 7 | Retrospective Comparative Trial | A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. George MS et al., 2005 Trial: D-02/D-04 | Comparison of those receiving VNS+TAU (N=205) with TAU alone (N=124). Number of prior treatment classes: 6.0 ± 2.1 and 7.3 ± 2.1 for TAU and VNS+TAU, respectively. Greater improvements were observed in IDS-SR30 scores in VNS+TAU vsTAU at 12 months. Response rates per the HRSD24 at 12 months were 27% for VNS+TAU and 13% for TAU ($p < .011$). | http://www.biologicalpsychiatryjournal.com/article/S0006-3223(05)00917-0/pdf | September 2005 |
| 8 | Retrospective Comparative Trial | The effects of stimulation parameters on clinical outcomes in patients with vagus nerve stimulation implants with major depression Muller et al., 2013 Trial: Erlangen study 2 | Retrospective examination of 2 parallel groups of 10 patients each comparing high strength/low frequency and low strength/high frequency stimulations parameters. Significant decreases in HRSD scores were observed in the latter groups. No changes were observed in patients with high strength low frequency stimulation. | https://www.ncbi.nlm.nih.gov/pubmed/23728236 | September 2013 |

| ID | Type of study design* | Title of journal article or research project (including any trial identifier or study lead if relevant) | Short description of research (max 50 words)** | Website link to journal article or research (if available) | Date of publication** * |
|---------------------------------------|------------------------------------|---|---|---|----------------------------|
| Single arm observational study | | | | | |
| 9 | Prospective observational study | Vagus Nerve Stimulation (VNS™) for Treatment-Resistant Depression: Efficacy, Side Effects, and Predictors of Outcome Sackeim et al., 2001 Trial: D-01 | An open pilot study in 60 patients with TRD for 10 weeks. The mean number of prior treatment classes: 10.4 ± 2.3. Response rates were 30.5% and 34.0% for MADRAS and CGI-I scores respectively. No patients who had previously received more than 7 courses of antidepressants responded to therapy compared to 39.1% in the remaining patient population. | http://www.nature.com/npp/journal/v25/n5/full/1395714a.html | April 2001 |
| 10 | Prospective observational study | Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Rush et al., 2000 Trial: D-01 | Thirty adult patients with non-psychotic TRD received an NCP System implantation for VNS and followed for 12 weeks. The mean number of prior treatment classes was 10.4 ± 2.3. Baseline HAMD scores averaged 38.0. Response rates (>50% reduction in BL scores) were 40% for HDRS28 and CGI, and 50% for MADRS. | http://www.biologicalpsychiatryjournal.com/article/S0006-3223(99)00304-2/pdf | Feb 2000 |
| 11 | VNS Single arm observational study | Two-year outcome of Vagus nerve Stimulation (VNS) for treatment of major depressive episodes Nahas et al. 2013 Trial: D-01 | Fifty-nine adult patients with chronic or recurrent MDD or bipolar disorder treated with VNS and followed for 2 years. The mean number of prior treatment classes was 10.4 ± 2.3. HAM-D28 response rates were 31%, 44% and 42% after 3 months, 1 year and 2 years with remission rates of 15%, 27% and 22% for the same time points. | http://www.psychiatrist.com/jcp/article/Pages/2005/v66n09/v66n0902.aspx | September 2013 |
| 12 | VNS Single arm observational study | Two-year outcome of vagus nerve stimulation in treatment resistant depression Bajbouj et al 2010 Trial: D-03 | Naturalistic study of VNS in 74 European patients with TRD. Mean number of prior treatment classes was 6.5 ± 1.8. The response and remission rate were 53.1% and 38.9%, respectively, after 2 years. Mixed model repeated measures ANOVA revealed significant reductions in the HRSD28 score. | https://www.ncbi.nlm.nih.gov/pubmed/20473062 | June 2010 |
| 13 | VNS Single arm observational study | Vagus nerve stimulation for depression: efficacy and safety in a European study Schlaepfer et al., 2008 Trial: D-03 | An open label study of VNS in 74 patients with TRD. Mean number of prior treatment classes was 6.5 ± 1.8. Baseline HAMD-28 scores averaged 34. Response and remission rates reached 37% and 17% after 3 months and 53% and 33% after 1 year. Sustained response was met by 44% of patients in the 1 st year. VNS efficacy increased over time. | https://www.cambridge.org/core/journals/psychological-medicine/article/vagus-nerve-stimulation-for-depression-efficacy-and-safety-in-a-european-study/AF511029F46B81E993A6C3909F43C3AE | May 2008 |

| ID | Type of study design* | Title of journal article or research project (including any trial identifier or study lead if relevant) | Short description of research (max 50 words)** | Website link to journal article or research (if available) | Date of publication** * |
|----|------------------------------------|--|---|---|----------------------------|
| 14 | VNS Single arm observational study | Vagus nerve stimulation for chronic major depressive disorder: 12-month outcomes in highly treatment-refractory patients Christmas et al., 2013 | Response rates determined for 28 patients with chronic (≥2 years) major depression who had failed to respond to ≥4 adequate treatment trial and 13 patients within the neurosurgery treatment programme in Dundee, who underwent VNS. Response rates were 35.7% and 30.8%, respectively. | http://www.iad-journal.com/article/S0165-0327(13)00459-X/pdf | September 2013 |
| 15 | VNS Single arm observational study | Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDA approval: outcomes at 1 year Cristancho et al., 2011 | 15 outpatients with TRD, including 10 with major depressive disorder and 5 with bipolar disorder were treated with VNS. BDI scores decreased significantly from baseline to 6 and 12 months. Improvements were also observed in the DRS24 scale with a 43% response and 14.3% remission rate. | http://www.psychiatrist.com/jcp/article/Pages/2011/v72n10/v72n1012.aspx | October 2011 |
| 16 | VNS Single arm observational study | Vagus nerve stimulation for the treatment of depression: acute and follow-up results of an Italian case series Dell'Osso et al., 2013 | Evaluation of efficacy and tolerability of VNS in 6 patients with TRD. Significant improvements from baseline were observed in HDRS21 and MADRS scores after 3 months. Significant improvements at 12 months were also observed in HDRS21, MADRS and clinical global impression scores. Patients showed an overall favourable tolerability. | https://www.ncbi.nlm.nih.gov/pubmed/23303420 | March 2013 |
| 17 | VNS Single arm observational study | Hamilton rating scale for depression-21 modifications in patients with vagal nerve stimulation for treatment-resistant depression: series report Franzini 2008 | Observational study of 9 patients with severe TRD. Outcomes were evaluated using the HRSD21 instrument. Five patients with >1 year follow-up were found to respond to treatment with four patients achieving remission. A further two patients with follow-up periods of three month showed decreasing HRSD21 scores. | http://onlinelibrary.wiley.com/doi/10.1111/j.1525-1403.2008.00174.x/abstract;jsessionid=93875B184CA2679DA0A834AD316DA932.f03t01 | October 2008 |
| 18 | VNS Single arm observational study | Vagus nerve stimulation therapy in treatment-resistant depression: a series report. Tisi et al., 2014 | A prospective observational study of 27 patients with unipolar TRD treated with VNS. Efficacy of VNS in reducing depressive symptoms was evaluated at baseline and at 1,3 and 5 years post VNS surgery using the HAM-D21 scale. VNS was shown to be successful in 20% of TRD patients. | http://onlinelibrary.wiley.com/doi/10.1111/pcn.12166/epdf | March 2014 |
| 19 | TAU single arm observational study | Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. Dunner et al., 2006 | 2-year prospective, multicenter, observational study (patients enrolled from January 2001 through July 2004) tracked the outcomes of 124 patients with non-psychotic TRD (N = 109) or bipolar depressed phase disorder (N = 15) who received treatment as usual (TAU) | http://www.psychiatrist.com/jcp/article/pages/2006/v67n05/v67n0501.aspx | May 2006 |

Abbreviations: ANOVA, Analysis of variance; BDI, Beck Depression Inventory; BL, baseline; BP, bipolar; CGI-I, Clinical Global Impressions Scale – improvement; DB, double-blind; ECT, electroconvulsive therapy; FDA, federal drug administration; HAM-D, Hamilton Rating Scale for Depression; HDRS28, Hamilton 28 item Depression Rating Scale; HRSD24, Hamilton 24 item Depression Rating Scale for Depression; IDS-C,

Inventory of Depressive Symptomatology - clinician rated; IDS-SR30, Inventory of Depressive Symptomatology – self-rated 30 items; MADRS, Montgomery-Åsberg Depression Rating Scale; MA, meta-analysis; MC, multi-centre; MDD, major depressive disorder; MDE, major depressive episode; MN, multi-national; N, Number; NCP, NeuroCybernetic prosthesis; RCT, randomised controlled trials; SR, systematic review; TAU, treatment as usual; TRD, treatment resistant depression; VNS, vagus nerve stimulation.

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

**** If the publication is a follow-up to an initial publication, please advise.*

19. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). Please do not attach full text articles, this is just intended to be a summary.

| ID | Type of study design* | Title of research (including any trial identifier if relevant) | Short description of research (max 50 words)** | Website link to research (if available) | Date*** |
|---|--|--|---|--|--|
| Non-randomised Comparative Trial | | | | | |
| 1. | Prospective Non-Randomised Comparative Trial | <p>A five-year observational study of patients with treatment-resistant depression treated with VNS Therapy or treatment as usual: Comparative response, remission and suicidality.</p> <p>Aaronson ST et al., Submitted to American Journal of Psychiatry 2016</p> <p>Trial: D-23</p> | <p>A multi-centre open label prospective TRD registry study to follow clinical outcomes for TRD patients receiving either VNS+TAU or TAU over five years. Significant improvements in MADRS in VNS compared to TAU were observed with higher remission rates, longer duration of remission and decreased mortality and suicide over five-year period.</p> | <p>Abstract 893 available at: https://books.google.com.au/books/about/SOBP_2015_Abstracts.html?id=AO58CAAQBAJ&redir_esc=y</p> | <p>In-press Publication accepted January 24th 2017</p> |

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; TAU, treatment as usual; TRD, treatment-resistant depression; VNS, vagus nerve stimulation.

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

***Date of when results will be made available (to the best of your knowledge).

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

20. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

- Royal Australian and New Zealand College of Psychiatrists (RANZCP) - Professor David Castle currently elected director on RANZCP and he sits on LivaNova advisory board
- Prince of Wales Hospital – Professor Perminder Sachdev
- Eurora Centre- Black Dog Institute – Professor Gordon Parker
- St Vincents Hospital – Professor David Castle
- Under consideration - Royal Melbourne Hospital – Professor Richard Bittar (neurosurgeon)
- Under consideration - Monash University Central Clinical School and The Alfred Hospital - Professor Paul Fitzgerald

Psychiatrist refers patient to neurosurgeon for implants of VNS. Neurologist or psychiatrist trained in programming and dosing VNS will follow up patient with programming as required. Hence, a team of specialists (i.e., psychiatrist, neurosurgeon and neurologist; all with appropriate VNS training) working at a same centre will manage a patient.

21. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

- Royal Australian and New Zealand College of Psychiatrists (RANZCP) - Professor David Castle currently elected director on RANZCP and he sits on LivaNova advisory board

The target patient group and the provision of SoC for these patients are currently performed by psychiatrist.

22. List the relevant consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

- Black Dog Institute – Professor Gordon Parker

23. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

Not applicable

24. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

Justification of expertise: Professor Paul Fitzgerald is Deputy Director of MAPrc, Professor of Psychiatry, and Consultant Psychiatrist at Alfred Psychiatry. He also runs an academic program at The Victoria Clinic, a private psychiatric hospital in Prahran. He is a qualified psychiatrist, has a Masters of Psychological Medicine and research PhD. He runs a substantive research program utilising brain stimulation and neuroimaging techniques including transcranial magnetic stimulation, functional and structural MRI, EEG and near infrared spectroscopy. He hence has relevant expertise and experience for VNS under the proposed indication.

Justification of expertise: Dr. Aaronson currently serves as a Clinical Assistant Professor of Psychiatry at the University of Maryland School of Medicine and Distinguished Fellow of the American Psychiatric Association. He is also the Associate Medical Director and Director of Clinical Research at The Retreat at Sheppard Pratt, a premiere, self-funded psychiatric setting. He specialises in treatment-resistant affective disorders. He is a thought leader in the areas of biological psychiatry, diagnosis and the integration of somatic and psychological therapies. He is the principal investigator for multiple studies on the development of novel therapies for mood, anxiety and psychotic disorders, including VNS.

PART 6 – POPULATION (AND PRIOR TESTS), INDICATION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

25. Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease in terms of both morbidity and mortality:

Major depressive disorder (MDD) is a common and debilitating psychiatric disorder associated with low mood, loss of interest and enjoyment, and a number of other psychological and somatic symptoms including reduced energy, concentration/attention, and self-esteem; ideas of guilt/unworthiness; bleak or pessimistic views of the future; ideas or acts of self-harm/suicide; and disturbed sleep and appetite. The lowered mood varies little on a day to day basis, and is often unresponsive to circumstances. (Therapeutic Guidelines, Psychotropic). At least 70% of depressed patients experience somatic symptoms such as pain, shortness of breath, or fatigue (Kroenke and Price 1993, Corruble and Guelfi 2000). MDD is not a benign disorder, being associated with substantial psychosocial dysfunction and high individual mental strain, as well as excess morbidity and mortality—the risk of suicide is considerable.

According to the World Health Organisation (WHO Global Burden of Disease 2004), unipolar major depression is the fourth leading cause of global disease burden. It is the single largest contributor to the burden of disease in high income countries and the leading cause of disease and injury burden among young adult women across the globe. It is predicted, by 2030, unipolar major depression will be the single largest contributor to the burden of disease around the world. The lifetime and 12-month prevalence of DSM-IV MDD in higher income countries has been estimated at 14.6% and 5.5%, respectively (Kessler and Bromet, 2013). Women are more likely than men to develop MDD (e.g., odds ratio 0.6, reported in Akhtar-Danesh and Landeen 2007). The 12-month prevalence of MDD in the Australian community has been reported to be ~4% (see Question 47 below).

Initial treatment typically involves antidepressant medication, typically involving an SSRI or SNRI. The treatment intent is achievement of full remission or recovery and prevention of relapse and recurrence (Thase 2006). Around 30% or more of patients fail to achieve adequate response to first line monotherapy (Thase et al 1995, Rush et al 2006), with many patients switching to an alternative class of antidepressant medication or using combination and augmentation strategies to improve health outcomes. More than one third of patients go on to develop treatment resistance (Fava and Davidson 1996). Many patients who respond to treatment experience residual depressive symptoms (McClintock et al 2011). Tolerability issues associated with antidepressants also negatively impact treatment outcomes. Depression is recurrent in 75% to 80% of patients, and is chronic (duration of 2 or more years) in 15% to 20% of patients (Angst 1992, Montgomery 2006). The risk of relapse/ recurrence, chronicity, and treatment resistance increases with each new depressive episode (Rush et al 2006).

TRD refers to a subset of MDD which persists even after adequate antidepressant therapy. The complexity of MDD and the multitude of pharmacological treatments available means numerous treatment definitions and staging models exist for TRD, based on the number of past treatment failures, chronicity of illness, modalities of treatment, dosage and duration of treatment (Fava 2003). Based on European Medicine Agency (EMA) guidelines, TRD is considered when treatment with at least two different antidepressant agents (of the same or a different class) prescribed in adequate dosages for adequate duration and adequate affirmation of treatment adherence showed lack of clinically meaningful improvement in the regulatory setting (EMA, 2013). *See Question 26 below for further disease definition in the context of the proposed listing.*

Here, it is important to note that, while the practical definition necessarily relies measurable treatment outcomes or patient characteristics (i.e., number of previously failed treatments in this case), “treatment resistance” in reality has a multitude of implications and does not just mean the lack of treatment response:

- Patients experience limited efficacy of current treatments
- They represent a difficult-to-control patient group facing a high risk of relapse
- They are chronically ill and the current episode extends over many years (i.e., chronicity is independent of the number of treatments)
- They tend to have poor treatment adherence and compliance
- They experience multiple side-effects

The heterogeneity in the clinical presentation and treatment history means that there is no one size fits all approach to TRD treatment and management. Five main treatment strategies exist for TRD; including optimisation of current treatment (maximisation of dose and duration), switch to another antidepressant of same or different class, combining antidepressant medications, augmentation with a second agent (not antidepressant) or the use of somatic, non-pharmacological therapies such as electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS). However, as noted above, remission and response rates have been shown to decrease with increasing number of therapies required, while chances of relapse increase and tolerability issues pose further problems (Rush et al., 2006).

A lack of consensus regarding the criteria means there is variation in the literature regarding the prevalence rates of TRD. For example, Souery et al (1999) reported 10%–20% of MDD patients as TRD, Corey-Lisle et al (2002) determined TRD-likely to be 12%, while Gibson et al (2010) reported this prevalence to be 29%. Based on TRD defined as an MDD episode which contained at least 2 distinct failed regimens, based on treatment discontinuation or switch, Kubitz et al (2013) estimated an approximate TRD prevalence within MDD as 13.6%. It should be noted however that many patients with depression have been reported as not receiving any treatment at all in Australia (Tiller 2012; Andrews et al 2000; see Question 47).

The impact of depression on patient quality of life (QoL) is substantial and debilitating. Indeed, it is estimated that unipolar major depressive disorders alone account for 11% of global year lived with disabilities (YLD) and ranks 4th among all diseases when disability adjusted life years were compared despite having a relatively low mortality rate (Murray and Lopez, 1996). A 2014 literature review assessed the impact of TRD on HRQOL (Mrazek et al 2014). The available evidence suggested that by measuring HRQOL on a continuous scale (1 indicating perfect health and 0 death) patients with MDD had a baseline score of 0.552±0.120 compared to 0.417±0.126 for patients who had not responded to treatment (TRD) (Mravek et al 2014). Health states in-between these were 0.826±0.065 for patients in remission and 0.673± 0.031 for patients who had responded to therapy but without achieving remission.

Mortality rates are significantly higher among patients with MDD compared to the general population with reported estimates of 7-27 years of potential life lost due to premature death (Colton and Manderscheid, 2006; Chang et al., 2011). Patients with TRD have higher rates of suicide than patients with MDD. A 2014 literature review of patients with TRD found that 15% of TRD patients reported suicidal ideation compared with only 6% of the treatment sensitive patients (Mravek et al 2014). Similarly, 31% of patients classified as TRD had attempted suicide compared with only 15.4% of patients who were considered responsive to treatment (Amital et al 2008).

Compared to depressive disorders responsive to therapy, the clinical burden seen in MDD is amplified in TRD (Mrazek et al 2014). TRD has shown greater prevalence of symptoms such as malaise, fatigue, anxiety and personality disorder with higher proportion of patients reporting suicide ideation. The adverse events from antidepressant use further contribute to the loss in QoL if patients who repeatedly fail treatment (Mrazek et al 2014). Reflecting this, 50% of the annual cost for the treatment of depression is due to TRD despite only 15-30% of patients having TRD (Russell et al 2004). While patients of all ages are diagnosed with MDD, patients with TRD tend to have their first onset of disease at a younger age (24.3 compared to 30-39 for patients with MDD only) (Conway et al 2015). For many it is a lifelong disease, starting in early adulthood that has a significant impact on their education, employment and development and maintenance of relationships at this key age.

The proposed listing of VNS targets those patients with at least 4 lines of therapy previously trialled; meaning these patients have significant unmet clinical need due to the limited availability of viable

medication-based treatment alternatives. Importantly, VNS offers a chronic, continuous treatment for these patients, improving treatment adherence which can be a frequent problem for these patients. The proposed listing should hence address this unmet clinical need and will represent a significant addition to the treatment algorithm relevant to this difficult-to-control patient subpopulation.

A summary of the proposed patient population, intervention, comparator and outcomes (PICO criteria) to define the research questions for the evaluation of VNS for the treatment of TRD are presented in Attachment 1 below (see Table 8).

26. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

Patients proposed as being eligible to receive the proposed medical service are adults, under the care of a psychiatrist, who have TRD. The definition of TRD slightly vary in literature, including treatment guidelines across different countries. For example, the 2013 EMA guidelines define TRD as “a lack of clinically meaningful improvement despite the use of adequate doses of at least two antidepressant agents, derived from the group(s) of commonly used first line treatment, prescribed for adequate duration with adequate affirmation of treatment adherence. At least one treatment failure should be shown prospectively” (pg 12) while the Royal Australian and New Zealand College of Psychiatrists Clinical practice guidelines defines TRD as “a lack of improvement following adequate trials of two or more antidepressants” (RANZCP guidelines, 2015).

Reflecting the armamentarium currently available for TRD, including pharmacologic treatment options (also combination / augmentation therapies), non-pharmacologic therapies such as ECT and psychobehavioural therapy in Australia (see Attachment 1), the proposed listing of VNS will aim to target highly-resistant and difficult-to-control patients who have tried many, if not all, of the available treatment options (i.e., those reached a later stage in the TRD treatment algorithm). Of note, the available trial data for VNS is primarily applicable to this subpopulation, providing further justification for the proposed positioning.

A systematic review of staging methods developed for TRD in the literature has been performed by Ruhé et al (2012). Five staging methods were identified including the Antidepressant Treatment History Form, Thase and Rush Model, European Staging Model, Massachusetts General Hospital Staging model and the Maudsley Staging Model (MSM). As an example, Thase and Rush Staging Model (TRSM) is presented in **Table 1** below. By and large, other staging methods suggest similar treatment work-ups for the staging purpose.

A detailed assessment of these staging methods and their relevance / utility in patient selection for VNS are discussed in the forthcoming submission.

Table 1 Thase and Rush Staging Model for treatment resistant depression

| | |
|-----------|---|
| Stage I | Failure of at least 1 adequate trial of 1 major class of antidepressants |
| Stage II | Failure of at least 2 adequate trials of at least 2 distinctly different classes of antidepressants |
| Stage III | Stage II resistance plus failure of an adequate trial of a TCA |
| Stage IV | Stage III resistance plus failure of an adequate trial of an MAOI |
| Stage V | Stage IV resistance plus a course of bilateral ECT |

Source: Ruhé et al (2012)

Abbreviations: TCA, Tricyclic antidepressant; MAOI, Monoamine oxidase inhibitor; ECT, Electroconvulsive therapy.

For the proposed eligibility criteria for VNS, patients are under the care of a specialist psychiatrist and are required to have failed at least 4 adequate courses of anti-depressive medications from different pharmacological classes.

According to the TRSM criteria above, the proposed positioning is hence after Stage IV or V depending on the previous use of ECT. It should be noted that VNS is to be provide adjunctively with other TRD care provided as SoC today (see Question 25 above).

The Applicant acknowledges that “appropriate response” and “adequate course of medication” are open to interpretation; a similar observation was noted in the Public Summary Document(PSD) for rTMS (November 2014 PSD for rTMS, Application 1196). As set out above, definitions employed to describe TRD vary in the literature and treatment guidelines. The Applicant will continue to work with local KOLs and propose a set of eligibility criteria that are locally relevant and acceptable in the forthcoming submission. In general, however, the following definitions appear to be operational in practice and the Applicant is happy to explicitly include them in the item descriptor if considered as necessary by MSAC:

- According to the Royal Australian and New Zealand College of Psychiatrists Clinical (RANZCP) practice guidelines for mood disorders (Malhi et al 2015), an adequate course of treatment is defined as a minimum of three weeks at the recommended therapeutic dose. An appropriate clinical response is defined as a significant reduction in signs/symptoms, and this is quantified as a 50% reduction in the total score on a standardised rating scale, such as the Hamilton Depression Rating Scale (HAM-D).

Of relevance, the patient population proposed for rTMS in its recent MSAC application (MSAC application no. 1196) consisted of patients with at least two lines of previous therapy (i.e., all TRD population, as previously described). The patient population targeted by the proposed VNS listing hence consists of patients with more previous treatment trials – at least 4 lines of therapy. Of note, the available trial data for VNS (see Part 4 above) are adequately applicable to this patient subpopulation.

Under the proposed listing, eligibility for VNS therapy can only be determined by a psychiatrist. It is expected that most patients considered candidates for VNS will have been in secondary or tertiary care (i.e., in specialist centres) for the treatment for resistant depression for many years.

Once VNS therapy is prescribed, the patient will be referred to a qualified neurosurgeon working as part of the treatment team for an assessment of their suitability for and the undertaking of VNS implantation. Post-implantation follow-up consultations would be provided by a neurologist or psychiatrist who titrate and monitor therapeutic dose of VNS.

27. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

The point of entry for care for MDD patients is typically a GP who will then determines the severity and complexity of symptoms to make an accurate diagnosis and decide whether a referral to a psychologist or psychiatrist is required (RANZCP guidelines, 2015). Referrals to see a psychiatrist are typically suggested if the depressive episode is severe; presenting with a high risk of self-harm or suicide; if the episode is long lasting or recurrent and if there is a persistent failure to respond to treatment.

The clinical management pathway presented here and illustrated in Attachment 1 below (Figure 1) has been adapted from the Royal Australian and New Zealand College of Psychiatrists Clinical practice guidelines for mood disorders (2015):

Initial treatment strategies for MDD (to confirmation of TRD)

- 1) Following a diagnosis of MDD, patients are typically placed onto antidepressant therapy with a major class of antidepressant therapy (AD) such as a SSRI or serotonin and norepinephrine reuptake inhibitor (SNRI). Following therapy, patients will either:
 - a. Not respond (typically defined as a $\geq 50\%$ reduction in depressive symptoms)
 - b. Achieve a partial response
 - c. Achieve remission (and may remain on maintenance therapy).
- 2) The first step in the assessment of a treatment non-response following initial treatment is to review the diagnosis and treatment adherence. After ensuring that the patient has been taking their medication as prescribed, several strategies can be used:
 - a. Improve a partial response: either through optimisation of the current medication, augmentation with a second agent or combination therapy with a second AD
 - b. Switching to a different anti-depressant typically of a different class.

- 3) If at any point during treatment, the patient does not show to be responding, the diagnosis must be re-evaluated to determine if any new symptoms have developed or if an alternative diagnosis may be more appropriate.
- 4) When switching a patient to a new antidepressant, a different class of drug to the original antidepressant is typically considered. If only a partial response to therapy is observed (plateau of symptoms) the dose of the new antidepressant can be optimised (to receive the maximum dose) and augmentation/combination of treatment can be considered.
- 5) If after further evaluation, the patient is not showing to have an adequate response to treatment, the patient is considered to have TRD.

Treatment strategies for TRD

- 6) Treatment of TRD typically involves persisting with the pharmacological strategies as described above, but ECT, rTMS and/or psychotherapeutic approaches may also be considered in this difficult to treat population.

It should be noted that in Australia, ECT is mainly reserved for the treatment of acute depression and/or psychotic cases (for which VNS therapy is not intended). This was also previously recognised by MSAC; “it is often used for serious acute and psychotic episodes requiring a rapid response” (pg 2; November 2014 PSD for rTMS, Application 1196). It is also noted that rTMS therapy is only provided at few facilities in Australia and its MBS funding has been rejected by MSAC due to “uncertain effectiveness and cost-effectiveness due to insufficient comparative data” (pg 1; November 2014 PSD for rTMS, Application 1196).

As noted above in Question 26, the proposed patient population for VNS are patients who have failed at least 4 adequate courses of antidepressant medications. The aforementioned absence of viable non-pharmaceutical (i.e., ECT or rTMS) and non-acute (i.e., rTMS) alternatives available for these highly resistant, heavily treated patients highlight a strong clinical need for the proposed listing of VNS. Of note, the proposed positioning places VNS after what was proposed for rTMS in Application no. 1196 (subsequently rejected by MSAC), i.e., after 4 lines of anti-depressant medications instead of only 2.

PART 6b – INFORMATION ABOUT THE INTERVENTION

28. Describe the key components and clinical steps involved in delivering the proposed medical service:

The proposed medical services refers to all necessary services that are directly related to the management of patients receiving VNS therapy; i.e., initial implantation / positioning of the pulse generator and lead, repositioning / removal, analysis and programming of VNS and battery replacement. The MSAC application for the use of VNS in refractory epilepsy (MSAC application no. 1358.1) recently received a positive recommendation at the October 2016 meeting and its use for refractory epilepsy has been well established in Australia. The implantation / explantation / battery replacement procedures are currently performed by neurosurgeon or other suitably qualified surgeon and the same physicians would be performing these procedures for TRD. The programming (i.e., dosing) will be however performed by psychiatrist for the TRD indication. All relevant surgical procedures would be performed within approved hospitals.

The procedure is routinely undertaken in an inpatient setting. The implant is inserted under general anaesthetic by a neurosurgeon (or suitably qualified ear nose and throat (ENT) surgeon who has undertaken VNS training by LivaNova) and takes 1-2 hours to complete.

A primary vertical incision is made in the left side of the neck and a secondary incision is made on the left side of the chest below the collarbone, to accommodate the pulse generator (a disc about 2 in [5 cm] in diameter) under the skin. Once the vagus nerve in the neck has been identified, it is circumferentially freed from fascial attachments along a distance sufficient to accommodate the length of the electrode which is then gently wrapped around the vagus nerve. The attached anchor tether of the lead is then threaded from the neck to the chest incisions using a tunnelling tool supplied by the sponsor.

Approximately 3cm of lead is kept parallel to the nerve to provide strain relief and is attached to the deep fascia using lead tie-downs provided in the accessory pack. The lead is attached to the generator in the chest and locked into place with a small screwdriver before inserting the device into a subcutaneous pocket and fixed to the chest wall with a suture placed through a suture hole in the generator. A system diagnostics test is then performed to confirm that the lead impedance is correct and that the generator

functions normally. The two incisions are then closed. The generator is kept at 0mA output until the first post-operative visit.

The stimulation parameters are adjustable and the patient may require several visits to their psychiatrist to find the right settings. Settings are adjusted with a magnetic wand which delivers commands to the stimulator's computer chip.

Thereby, for optimal and holistic service delivery, the medical services being proposed comprise the insertion / positioning / replacement of the VNS device by a neurosurgeon and follow-up with the psychiatrist to achieve the correct programming and includes the required consumable procedure pack.

The VNS generator is powered by a battery which is estimated to last an average of seven years though battery life may vary depending on the dose and frequency of the stimulation. It is replaced during an inpatient procedure under general anaesthesia. Of note, a separate item is proposed for listing specifically for battery replacement. This was requested by MSAC for the refractory epilepsy indication (MSAC application no. 1358.1).

29. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

No. However, the LivaNova VNS Therapy System is currently the only device approved for VNS therapy for the treatment of TRD in Australia.

30. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

VNS therapy offers a new approach to managing TRD where there has been a failure to respond to pharmacological therapy.

31. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

Accessibility

The main limitation at present is accessibility. There are very few centres which can currently offer VNS Therapy for the treatment of TRD.

Durability and longevity

As with any active implantable medical device, the device or parts thereof may require replacement.

All VNS Therapy pulse generators eventually require surgical replacement as a result of battery depletion.

The longevity of the pulse generator battery varies, depending on the choice of programmed settings. Higher output currents, frequencies, pulse widths, and duty cycles generally deplete the battery over a shorter period of time than lower settings. Based on current experience, for the 103 model, median survival is approximately 10 years.

Pulse generator replacement or removal requires dissection to the pulse generator's pocket, with care being taken not to damage or cut the lead. The entire surgical procedure generally requires about 1 hour. The pulse generator replacement does not, of itself, require lead replacement unless a lead discontinuity is suspected signalled by an increase in clinical signs and symptoms. Events that can shorten the life expectancy of the lead are as follows:

- Blunt trauma to the neck and/or any area of the body beneath which the lead is implanted
- Twisting or picking (Twiddler's Syndrome) at either the implanted lead or the pulse generator
- Improper surgical implantation of the VNS Therapy System, including (but not limited to) providing an inadequate strain-relief loop, placing sutures directly on the lead body rather than using the tie-downs, and suturing the lead body to muscle

Lead replacement requires dissection to both the pulse generator pocket and to the VNS electrode scar.

32. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

Any ongoing treatment for TRD, including pharmacotherapy and/or behavioural therapy and/or ECT as required (i.e., SoC).

33. If applicable, advise which health professionals will primarily deliver the proposed service:

A trained neurosurgeon is required to deliver the proposed service in terms of the implantation / explantation / battery replacement of the device.

Programming of the device settings (i.e., dosing) would be managed by a psychiatrist (working with a neurosurgeon / neurologist).

34. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

The implantation procedure may be delegated to suitable qualified ear, nose and throat surgeons who has undergone specialised training in VNS by LivaNova. Only centres of excellence and accredited centres in Australia should implant VNS for TRD.

Psychiatrists, neurologists or psychiatric nurses with adequate training, working as part of the multidisciplinary team, can perform the programming.

35. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

The device should be prescribed and monitored only by physicians who have specific training and expertise in the management of TRD and the use of this device. It should be implanted only by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device.

36. If applicable, advise what type of training or qualifications would be required to perform the proposed service as well as any accreditation requirements to support service delivery:

LivaNova provide a comprehensive proctorship and training program for neurosurgeons wanting to implant VNS in Australia. Only centres of excellence and accredited centres in Australia should implant VNS-TRD. Surgeons will spend time with an experienced neurosurgeon to learn implant technique. Psychiatrists and neurologists along with treating team including nurses will participate in programming training to understand titration and dosing to provide optimal therapy.

37. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):

- Inpatient private hospital
- Inpatient public hospital
- Outpatient clinic (NOTE: for programming only)
- Emergency Department
- Consulting rooms (NOTE: for programming only)
- Day surgery centre
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

The implantation of the VNS device would take place in a hospital inpatient setting. Activation, programming and monitoring of the device would take place in the outpatient clinic or consulting rooms.

38. Is the proposed medical service intended to be entirely rendered in Australia?

- Yes
- No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

- 39. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):**

Standard of care (SoC, or treatment as usual) is proposed as the main comparator for VNS (see Figure 2 in Attachment 1). This is consistent with the proposed positioning of VNS, reflected in treatment eligibility defined in the proposed item descriptors. Of relevance, the proposed positioning is akin to what was proposed in the refractory epilepsy submission (MSAC application no. 1358.1) and SoC was accepted as the appropriate comparator by MSAC.

As previously described (see Question 27), treatment of TRD is complex and individualised. There are several strategies depending on the number of treatments attempted, adverse reactions experienced, the nature and severity of underlying clinical presentation and the number of treatment options remaining. These typically comprise alternative pharmacological strategies (switching, augmentation or combination), psychotherapeutic strategies or brain stimulation therapies such as ECT. For patients who have undergone at least four lines of therapy in Australia, new medication-based treatment alternatives are relatively limited; the anti-depressants currently listed on the PBS primarily consist of selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitor (NRI), reversible Inhibitor of monoamine oxidase (RIMA), tetracyclic antidepressants (TeCAs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and lithium.

The available comparative evidence for VNS is also versus SoC or treatment as usual and VNS was added onto the underlying care. *The submission will exhaustively examine the applicability of the available comparator data, including an important applicability question “what represents SoC for these patients in Australia?”*

ECT and rTMS are not considered as a relevant comparator. ECT is not included on the basis that it targets a different population than that proposed for VNS. MSAC has previously considered ECT is often used for serious acute and psychotic episodes requiring a rapid response (see Public Summary Document – Application 1196: for rTMS - Nov 2014). In contrast VNS offers a chronic, continuous treatment. Also, VNS would be considered for non-psychotic patients and the potential for replacement of ECT by VNS is small.

rTMS is not included as a comparator because it is not currently reimbursed on the MBS and availability to patients is limited to a small number of hospitals in Australia. Furthermore, MSAC considered clinical evidence to be insufficient to support funding and, based on this, its cost-effectiveness is uncertain and unlikely to be favourable (see Public Summary Document – Application 1196: for rTMS - Nov 2014). Also, the positioning of rTMS in the treatment algorithm appears to be before the proposed positioning for VNS (MSAC Application 1196).

- 40. Does the medical service that has been nominated as the comparator have an existing MBS item number(s)?**

Yes (please provide all relevant MBS item numbers below)
 No

- 41. Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources):**

Generally speaking, as previously described, patients with TRD may elect to continue with their current pharmacological therapy or to implement an alternative strategy by switching to a different anti-depressant, combining anti-depressant medications or through augmentation using a second agent such as lithium or thyroid medications. Patients may also consider brain stimulation methods such as ECT or rTMS. However, in Australia, ECT is reserved mainly for acute depression and psychotic cases and rTMS is not widely available (see discussion in Question 27). Psychobehavioural strategies may also be used in combination with any of the strategies described. Following any of the above treatments, patients may

either achieve remission and go on to receive maintenance therapy or fail to respond adequately to treatment and subsequently elect another therapeutic option (see Attachment 1).

More specifically for patients for which the listing of VNS is proposed, their treatment options are further limited because they have exhausted many, if not all, classes of anti-depressants; thus, SoC for these patients would consist of repeated use of previously tried medication class(es) or combination / augmentation therapies. Of relevance, patient populations represented in the available VNS trials are also those who have gone through numerous medication changes; i.e., approximately 6-10 lines of therapy on average and generally considerably higher than the respective minimal inclusion criteria of each trial (see Question 18). *It is considered that the comparator data from the trials are generalizable to the Australian SoC; this applicability issue will be discussed and addressed in the submission.*

42. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

- In addition to
 Instead of

VNS will be used adjunctive to any ongoing therapy. Patients are not expected to substitute any ongoing therapy as a result of receiving VNS.

(b) If yes, please outline the extent of which the current service/comparator is expected to be substituted:

The proposed listing is not expected to create any specific substitution effects. It is nonetheless expected that as a result of treatment effects patients on average may require less medications and other care (especially those related to acute episodes / relapse). These represent treatment outcome of VNS, rather than “substituted” services or comparator. The economic model will capture possible cost savings associated with this treatment outcome.

43. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):

VNS is to be used adjunctive to treatment as usual with their ongoing therapy. Accordingly, once the VNS device has been implanted, the clinical management remains the same as before. Patients may require additional consultations with the treating physician to monitor and if necessary change the frequency and dose of the stimulations. VNS will not necessarily enable patients to cease any of their ongoing therapy. As noted above, VNS is expected to produce a reduction in the intensity / extent of some of the cares provided as SoC reflecting improved treatment outcome; e.g., gaining / maintaining remission would lead to a reduction in the extent / intensity of care provided to a patient.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Relative to the main comparator, VNS is expected to provide superior health outcomes for patients with TRD, with greater remission and response rates equating to significant improvements in patient quality of life.

45. Please advise if the overall clinical claim is for:

- Superiority
 Non-inferiority

46. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

Complications (related to device or surgery)

Adverse events

Withdrawals due to adverse events

Clinical Effectiveness Outcomes:

Response/remission rates and time to response (based on key measures of depression, e.g., HAMD, MADRS, IDS, CGI-I measures of depression)

Duration of response/remission

QoL

Adaptive functioning

Cognitive functioning

Suicide ideation

Mortality (all cause)

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

47. Estimate the prevalence and/or incidence of the proposed population:

While depressive disorder is relatively common in the Australian population, the proposed listing of VNS restricts the MBS-subsidised use to a small subset of the patient population, i.e., TRD with at least 4 lines of anti-depressant medications tried previously. Importantly, the implantation and programming of VNS device need to be performed by a trained specialist (e.g., neurosurgeon for implantation and psychiatrist for programming and follow-up) and therefore the subsidised usage will be further restricted by available caseload capacity to perform VNS within Australia (see Question 50 below).

Internationally, the lifetime and 12-month prevalence of DSM-IV MDD in higher income countries has been reported to be 14.6% and 5.5%, respectively in high income countries (Kessler and Bromet, 2013). A similar estimate has been also reported for Australia. According to the 2007 National Survey of Mental Health and Wellbeing (SMHWB), funded by the Australian Government Department of Health and Ageing (DoHA), the 12-month prevalence of depressive episode (all severity) was estimated to be 4.1% (ABS 2007). This survey was conducted in a representative sample of people aged 16–85 years who lived in private dwellings across Australia. This Australian prevalence rate means that there are 799,466 adults experiencing depression in any 12-month period.

Many patients suffering from mental disorders like MDD does not seek treatment; two thirds of patients were reported to be left untreated (Whiteford et al 2014). According to the 1997 Australian National Survey of Mental Health and Wellbeing, 65% of patients with depression sought a mental health consultation in the previous 12 months (Andrews et al 2000).

While a lack of consensus regarding the criteria for TRD means there is variation in the reported prevalence, 10-30% of all patients are considered as suffering from TRD. For example, Souery et al (1999) reported 10%–20% of MDD patients as TRD. Corey-Lisle et al (2002) determined TRD-likely to be 12% while Gibson et al (2010) reported this prevalence to be 29%. Based on TRD defined as an MDD episode with at least 2 distinct failed regimens, based on treatment discontinuation or switch, Kubitz et al (2013) estimated an approximate TRD prevalence within MDD as 13.6%. It should be noted, however, none of these estimates are Australia specific.

The proposed positioning of VNS is associated with a more restrictive definition of TRD in terms of previous medication use, i.e., more than 4 lines of therapy. This suggests a lower end estimate of the reported range (10%) would be more applicable in estimating the number of patients who would be potentially eligible for VNS under the proposed indication. Based on this assumption, the number of potentially eligible patients can be estimated to be 51,965. While the available epidemiological evidence suggests a sizable TRD population, not all patients would be receiving on-going active care at any given time thus unlikely to become eligible for VNS. *The Applicant will seek local KOL inputs to pride a more accurate patient number estimate in the submission.*

It is important to note that many patients in practice “exit” the treatment algorithm before reaching the 4th line treatment, and many of them are likely to receive no on-going active treatment. For example, a study of adult outpatient sample with nonpsychotic MDD suggested only 123 patients out of the 3,671 patients who entered the treatment algorithm (by receiving a first-line anti-depressant medication) reached the 4th-line treatment (Rush et al 2006). While many patients achieved remission and thus did not require a next line of therapy (the authors reported a theoretical cumulative remission rate to be 70% after 4 lines of therapy by ignoring patient dropouts), 1358 patients in fact dropped out of the study before the 4th-line of treatment. Indeed, only 4 patients entered the 5th line of treatment (Rush et al 2006). The presence of these “untreated” or “inadequately treated” patients, very likely in the actual clinical practice, would further reduce the size of patient population who would meet the proposed eligibility for VNS.

Table 2 Estimated prevalence of treatment resistant depression (TRD) in 2017

| Variable | Estimate | Source / notes |
|--|------------|---|
| Australian population, aged above 18 | 19,499,177 | Australian Bureau of Statistics, 3222.0 Population Projections, Australia (Series B) |
| Prevalence of depression | | |
| - Prevalence rate | 4.10% | 2007 National Survey of Mental Health and Wellbeing Including all severities. |
| - Estimated prevalence each year | 799,466 | Calculated |
| Prevalence of depression receiving any treatment | | |
| - % seeking treatment | 65% | 1997 National Survey of Mental Health and Wellbeing % seeking treatment in the previous 12 months; assumed to represent the % receiving current / ongoing care (likely overestimate). |
| - Estimated number of treated cases | 519,653 | Calculated |
| Treatment resistant cases | | |
| - % | 10% | Assumption, based on published range of 10-30%. |
| - Estimated prevalence each year | 51,965 | Calculated, likely overestimate because the rate of treatment is likely to be considerably lower than the overall rate reported for depression of 65%. |

The PBS statistics for monoamine oxidase inhibitors (MAOIs; phenelzine, tranylcypromine) and reversible MAOI (RIMA; moclobemide) suggest relatively small usage for these treatments, as shown in **Table 3** below, providing further evidence that the number of patients who would meet the proposed eligibility for VNS would be far smaller than what is suggested by the “top-line” epidemiological data. Of note, the Thase and Rush Staging Model place monoamine oxidase inhibitors as the last line pharmacotherapy (Stage IV; see **Table 1** above). In total, the combined usage is less than 130,000 packs and by assuming each pack lasts for one months of therapy, the total estimated patient year of therapy met by these treatments is less than 11,000 in 2015. When only MAOIs are considered, this number would be far smaller (approximately 2000 patient years). The proposed positioning of VNS (i.e., after failing these treatments) hence suggests the number of patients who would become eligible for VNS would be even smaller.

Table 3 Extent of use for phenelzine, tranylcypromine and maclobemide on the PBS in 2015

| Drug | Dispensed packs in 2015 |
|---------------------------|-------------------------|
| RIMA, total (moclobemide) | 104,420 ^a |
| MAOIs, total | 24,406 |
| Phenelzine | 3,901 |
| Tranylcypromine | 10,460 |

Source: Medicare PBS statistics.

^a Moclobemide prices on the PBS are below the general patient co-payment; thus no complete usage data are available. The presented estimate was derived from the reported concessional usage data adjusted by assuming 60% of the total usage would be due to concessional patients (based on the MAOI data).

As also discussed in the refractory epilepsy submission (MSAC application no. 1358.1), an epidemiology-based approach for the purpose of generating usage estimation would be, while may be informative in setting the upper limit, difficult because the actual usage would be limited by the available caseload capacity of VNS in Australia. This is discussed in Question 50 below.

Of relevance, the rTMS submission (MSAC application no. 1196) estimated 2000-3000 procedures per annum in total (November 2014 PSD). Furthermore, the current ECT usage on MBS was estimated to be less than 3000 patients annually in recent years (MSAC application no. 1196). While these technologies are not appropriate comparators, the evidence suggests the likely use of VNS on MBS would be relatively small (likely smaller due to the restrictive, tightly targeted eligibility being proposed for VNS).

48. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

The insertion of the pulse generator and lead would be delivered only once to a patient with TRD (plus follow-up consultations to analyse and program the therapeutic pulse). The patient may require further intervention to replace the battery of the pulse generator estimated to be approximately every seven years depending on the dosing frequency. In some cases (see Question 31), the lead may require repositioning but this is expected to be very rare.

49. How many years would the proposed medical service(s) be required for the patient?

TRD is a chronic long term disease. It is anticipated that the patient will require VNS Therapy device indefinitely or until the patient requests the device to be removed. Noting that a patient can request that the device be simply turned off if required without the need for any further surgical intervention.

50. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

The actual “uptake” of VNS would be relatively low given its “invasive” nature and, more importantly, the actual usage will be limited by caseload capacity available to perform the insertion / programing procedures each year.

As also noted in the refractory epilepsy submission, only a small number of centres of excellence are providing VNS therapy in Australia. For the treatment of refractory epilepsy, a total of 16 centres are currently providing the treatment.

For the TRD indication, only those psychiatric centres that can provide a multidisciplinary management approach involving psychiatrist, neurosurgeon, neurologist (and other specialists with adequate training) would be able to provide the service. Hence, the number of centres where VNS therapy could be potentially provided, is small in Australia, as enlisted below. Also, there are currently few specialist psychiatrists who can deliver VNS therapy (i.e., dose titration and adjustment, patient follow up) in Australia; of note, the initial referral for VNS device implantation will have to be made by a psychiatrist under the proposed listing.

LivaNova plan to implement a specialist training program targeting psychiatrists in Australia. The forthcoming MSAC submission will provide details of this program.

Table 4 Australian hospitals where the VNS device implantation procedure could be potentially provided for the TRD indication

| State / institution |
|--|
| Victoria |
| Alfred Hospital |
| Monash Medical Centre |
| Royal Melbourne Hospital (Melbourne Private) |
| St Vincent’s Hospital Public and Private |
| NSW |
| Eurora Centre (Black Dog Institute) |
| Prince of Wales Hospital |

51. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of ‘leakage’ to populations not targeted by the service:

The proposed listing effectively positions VNS after the availability of viable medication-based treatment alternatives for many patients. “Leakage” in this sense hence means the use of VNS in patients who have alternative medication-based treatment options still available. While it is minimally invasive and does not have undesirable side effects often associated with anti-depressants, VNS requires a permanent device implantation involving surgery. To this end, the risk for such leakage would be reasonably small. This is especially likely given that VNS under the proposed indication is administered and managed by a specialist psychiatrist with sufficient training and knowledge of the therapy. LivaNova are also in communication with local KOLs and will continue to provide adequate education and information to minimise inappropriate use of VNS on the MBS. Again, LivaNova plan to implement a specialist training program targeting psychiatrists in Australia. The forthcoming MSAC submission will provide details of this program.

PART 8 – COST INFORMATION

52. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

Estimated per-procedural cost of VNS surgical implantation procedure, explantation procedure and battery replacement are presented. These three procedures should cover the entirety of VNS therapy as provided on the MBS. The same cost estimates were presented in the recent MSAC application for the epilepsy indication (MSAC application no. 1358.1), and no specific issues were raised during the evaluation process or by MSAC.

As noted above, patients may require routine check-ups each year; however, many of them would not be specific to VNS, but represent routine patient follow-ups (thus not attracting the requested item “electrical analysis and programming of electrical pulse generator”). Importantly, these costs would also exist under SoC, thus creating no additional cost implications to the healthcare system.

Surgical implantation of VNS device (generator and lead), plus follow-up visits

Table 5 Cost for initial implantation and follow-up care

| Resource item | Unit cost | Source / notes |
|---|------------|--|
| <i>Pre-operative</i> | | |
| Pre-op neurosurgeon review | \$129.60 | MBS item 6007; Professional attendance at consulting rooms or hospital by a specialist practising in the specialty of neurosurgery |
| <i>VNS device (generator + lead)</i> | | |
| VNS therapy device | | |
| <i>Surgical implantation</i> | | |
| Surgical placement of lead | \$674.15 | Proposed fee |
| Placement of electrical pulse generator | \$170.30 | Proposed fee for placement of electrical pulse generator (\$340.60), adjusted for Multiple Service Rule (50%) |
| Assistance | \$168.89 | MBS item 51303; 20% x (\$674.15 + \$170.30) |
| Subtotal (implant procedure) | \$1,013.34 | Calculated |
| <i>Anaesthetics</i> | | |
| Pre-operative review | \$43.00 | MBS item 17610; Anaesthetist, pre-anaesthesia consultation |
| Initiation of management | \$99.00 | MBS item 20420; Initiation of management of anaesthesia. |
| Anaesthesia time units | \$158.40 | MBS item 23083; Anaesthesia time units, up to 2 hours |
| Subtotal (anaesthetics) | \$300.40 | Calculated |
| <i>Post-operative</i> | | |
| Post-operative reviews for programming | \$569.10 | Proposed fee (\$189.70) x 3 |
| Total per procedure, implantation | | |

Note: All fees at full benefit amount. Existing MBS items and their fees are as of 20/1/2017.

Explantation

Non-responding patients may have the VNS device removed after 10 years or before if necessary. Total explantation costs are estimated at \$985, consisting of the procedure and anaesthetics. The costs of this explantation procedure are presented in Table 6 below.

Table 6 Explantation Costs due to surgical site infection

| Resource item | Unit cost | Source / notes |
|--|-----------|---|
| <i>Explantation procedure</i> | | |
| Surgical removal of lead | \$605.35 | Proposed fee |
| Removal of electrical pulse generator | \$79.90 | Proposed fee for placement of electrical pulse generator (\$159.40), adjusted for Multiple Service Rule (50%) |
| Subtotal (explant procedure) | \$685.05 | Calculated |
| <i>Anaesthetics</i> | | |
| Pre-operative review | \$43.00 | MBS item 17610; Anaesthetist, pre-anaesthesia consultation |
| Initiation of management | \$99.00 | MBS item 20420; Initiation of management of anaesthesia. |
| Anaesthesia time units | \$158.40 | MBS item 23083; Anaesthesia time units, up to 2 hours |
| Subtotal (anaesthetics) | \$300.40 | Calculated |
| Total per procedure, explantation | | |

Note: All fees at full benefit amount. Existing MBS items and their fees are as of 20/1/2017.

Battery replacement, plus follow-up visits

Table 7 Costs of Battery Replacement

| Resource item | Unit cost | Source / notes |
|---|-----------|---|
| Battery Replacement | | |
| VNS battery | | |
| Battery replacement procedure | | |
| Battery replacement | \$340.60 | Proposed fee |
| Anaesthetics | | |
| Pre-operative review | \$43.00 | MBS item 17610; Anaesthetist, pre-anaesthesia consultation |
| Initiation of management | \$99.00 | MBS item 20420; Initiation of management of anaesthesia. |
| Anaesthesia time units | \$158.40 | MBS item 23083; Anaesthesia time units, up to 2 hours |
| Subtotal (anaesthetics) | \$300.40 | Calculated |
| Post-operative | | |
| Post-operative reviews for programming | \$37.94 | Proposed fee (\$189.70) x 20%; assuming the original settings are programmed at time of generator replacement and only 20% of patients have additional programming visit as outpatient (as per MSAC application no. 1358.1) |
| Total per procedure, battery replacement | | |

Note: All fees at full benefit amount. Existing MBS items and their fees are as of 20/1/2017.

53. Specify how long the proposed medical service typically takes to perform:

Each procedure of implantation, explantation and battery replacement typically takes 1-2 hours.

54. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

The item descriptors proposed in this application are based on those accepted for the refractory epilepsy indication. The proposed fees are also based on corresponding items for refractory epilepsy. Importantly, MSAC advised that the item descriptor should specify stimulation via the left vagal nerve and that there should be a separate item for battery replacement (PSD; Application No. 1358.1); these are captured in the proposed item descriptors (see below).

Please note LivaNova is currently working with local KOLs to formulate eligibility descriptor that is acceptable and implementable.

Proposed MBS item descriptors specifically for use with VNS Therapy

Category 3 - THERAPEUTIC PROCEDURES

| |
|--|
| <p>XXXX1</p> <p>VNS Therapy ELECTRICAL PULSE GENERATOR, subcutaneous placement of electrical pulse generator for the management of treatment resistant depression that has not had an adequate response to four or more adequate antidepressant treatments in a patient 18 years of age or older, through stimulation of the left vagus nerve</p> <p>Multiple Services Rule (Anaes.) (Assist.) Fee: \$340.60 Benefit: 75% = \$255.45</p> |
| <p>Category 3 - THERAPEUTIC PROCEDURES</p> |
| <p>XXXX2</p> <p>VNS Therapy ELECTRICAL PULSE GENERATOR, that was inserted for the management of treatment resistant depression that has not had an adequate response to four or more adequate antidepressant treatments in a patient 18 years of age or older, surgical repositioning or removal of</p> <p>Multiple Services Rule (Anaes.) Fee: \$159.40 Benefit: 75% = \$119.55</p> |
| <p>Category 3 - THERAPEUTIC PROCEDURES</p> |
| <p>XXXX3</p> <p>VNS Therapy LEAD, surgical placement of lead including connection to the left vagus nerve, including intraoperative test stimulation, for the management treatment resistant depression that has not had an adequate response to four or more adequate antidepressant treatments in a patient 18 years of age or older, through stimulation of the left vagus nerve</p> <p>Multiple Services Rule (Anaes.) (Assist.) Fee: \$674.15 Benefit: 75% = \$505.65</p> |
| <p>Category 3 - THERAPEUTIC PROCEDURES</p> |
| <p>XXXX4</p> <p>VNS Therapy LEAD, that was inserted and attached to the left vagal nerve for the management of treatment resistant depression that has not had an adequate response to four or more adequate antidepressant treatments in a patient 18 years of age or older, surgical repositioning or removal of</p> <p>Multiple Services Rule (Anaes.) Fee: \$605.35 Benefit: 75% = \$454.05</p> |
| <p>Category 3 - THERAPEUTIC PROCEDURES</p> |
| <p>XXXX5</p> <p>VNS Therapy ELECTRICAL PULSE GENERATOR, electrical analysis and programming of VNS Therapy device using an external wand, for the management of treatment resistant depression that has not had an adequate response to four or more adequate antidepressant treatments in a patient 18 years of age or older.</p> <p>Fee: \$189.70 Benefit: 75% = \$142.58</p> |
| <p>Category 3 - THERAPEUTIC PROCEDURES</p> |
| <p>XXXX1</p> <p>VNS Therapy ELECTRICAL PULSE GENERATOR, subcutaneous replacement of battery for the management of treatment resistant depression that has not had an adequate response to four or more adequate antidepressant treatments in a patient 18 years of age or older</p> <p>Multiple Services Rule (Anaes.) (Assist.) Fee: \$340.60 Benefit: 75% = \$255.45</p> |

PART 9 – FEEDBACK

The Department is interested in your feedback.

55. How long did it take to complete the Application Form?

Three weeks.

56. (a) Was the Application Form clear and easy to complete?

- Yes
 No

(b) If no, provide areas of concern:

Many questions are ambiguous.

Questions on clinical management are repetitive and lengthy.

57. (a) Are the associated Guidelines to the Application Form useful?

- Yes
 No

(b) If no, what areas did you find not to be useful?

58. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

- Yes
 No

(b) If yes, please advise:

References

All references are available on request.

Aaronson ST, Carpenter LL, Conway CR, Reimherr FW, Lisanby SH, Schwartz TL, Moreno FA, Dunner DL, Lesem MD, Thompson PM, Husain M, Vine CJ, Banov MD, Bernstein LP, Lehman RB, Brannon GE, Keepers GA, O'Reardon JP, Rudolph RL, Bunker M. Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. *Brain Stimul.* 2013 Jul;6(4):631-40.

Andrews G, Sanderson K, Slade T, Issakidis C. Why does the burden of disease persist? Relating the burden of anxiety and depression to effectiveness of treatment. *Bull World Health Organ.* 2000;78(4):446-54.

Akhtar-Danesh N and Landeen J. Relation between depression and sociodemographic factors. *International Journal of Mental Health Systems.* 2007;1:4.

Amital D, Fostick L, Silberman A, Beckman M, Spivak B. Serious life events among resistant and non-resistant MDD patients. *Journal of Affective Disorders.* 2008;110 260–264.

Angst J. How recurrent and predictable is depressive disorder? In: Montgomery S, Rouillon F, editors. *Long-Term Treatment of Depression; Perspectives in Psychiatry.* Chichester, UK: John Wiley & Sons Ltd.; 1992:Vol. 3, p. 1-13.

Australian Bureau of Statistics. *National Survey of Mental Health and Wellbeing: summary of results, 2007.* Canberra: ABS, 2007. (ABS Cat. No. 4326.0.)
[http://www.ausstats.abs.gov.au/Ausstats/subscriber.nsf/0/6AE6DA447F985FC2CA2574EA00122BD6/\\$File/43260_2007.pdf](http://www.ausstats.abs.gov.au/Ausstats/subscriber.nsf/0/6AE6DA447F985FC2CA2574EA00122BD6/$File/43260_2007.pdf) (accessed Feb 2017).

Bajbouj M, Merkl A, Schlaepfer TE, Frick C, Zobel A, Maier W, O'Keane V, Corcoran C, Adolfsson R, Trimble M, Rau H, Hoff HJ, Padberg F, Müller-Siecheneder F, Audenaert K, van den Abbeele D, Matthews K, Christmas D, Eljamel S, Heuser I. Two-year outcome of vagus nerve stimulation in treatment-resistant depression. *J Clin Psychopharmacol.* 2010;30(3):273-81.

Berry SM, Broglio K, Bunker M, Jayewardene A, Olin B, Rush AJ. A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression. *Medical Devices: Evidence and Research.* 2013;6:17–35.

Chang C-K, Hayes RD, Perera G, Broadbent MTM, Fernandes AC, et al. (2011) Life Expectancy at Birth for People with Serious Mental Illness and Other Major Disorders from a Secondary Mental Health Care Case Register in London. *PLoS ONE* 6(5): e19590

Christmas D, Steele JD, Tolomeo S, Eljamel MS, Matthews K. Vagus nerve stimulation for chronic major depressive disorder: 12-month outcomes in highly treatment-refractory patients. *J Affect Disord.* 2013 Sep 25;150(3):1221-5.

Colton CW, Manderscheid RW (2006) Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis.* Available: http://www.cdc.gov/pcd/issues/2006/apr/05_0180.htm

Corey-Lisle PK, Birnbaum HG, Greenberg PE, Marynchenko MB, Claxton AJ (2002) Identification of a claims data “signature” and economic consequences for treatment-resistant depression. *J Clin Psychiatry* 63: 717–726.

Corruble E, Guelfi JD. Pain complaints in depressed inpatients. *Psychopathology* 2000; 33(6):307-9.

Cristancho P, Cristancho MA, Baltuch GH, Thase ME, O'Reardon JP. Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDA approval: outcomes at 1 year. *J Clin Psychiatry.* 2011 Oct;72(10):1376-82.

Daban C, Martinez-Aran A, Cruz N, Vieta E. Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. *Journal of Affective Disorders.* 2008. 110(1-2):1-15.

Dell'Osso B, Oldani L, Palazzo MC, Balossi I, Ciabatti M, Altamura AC. Vagus nerve stimulation in treatment-resistant depression: acute and follow-up results of an Italian case series. *J ECT.* 2013 Mar;29(1):41-4.

Dunner DL, Rush AJ, Russell JM, Burke M, Woodard S, Wingard P, Allen J. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. *J Clin Psychiatry*. 2006

European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of depression. 2013 (available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143770.pdf)

Fava M, Davidson KG. Definition and epidemiology of treatment resistant depression. *Psychiatr Clin North Am* 1996; 19: 179-200.

Franzini A, Messina G, Marras C, Savino M, Miniati M, Bugiani O, Broggi G. Hamilton rating scale for depression-21 modifications in patients with vagal nerve stimulation for treatment of treatment-resistant depression: series report. *Neuromodulation*. 2008 Oct;11(4):267-71.

George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, Howland R, Kling MA, Moreno F, Rittberg B, Dunner D, Schwartz T, Carpenter L, Burke M, Ninan P, Goodnick P. A one year comparison of vagus nerve stimulation with treatment as usual for treatment resistant depression. *Biol Psychiatry*. 2005;58(5):364-73.

Gibson TB, Jing Y, Smith Carls G, Kim E, Bagalman JE, et al. (2010) Cost burden of treatment resistance in patients with depression. *Am J Manag Care* 16: 370–377.

Kessler RC and Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Public Health*. 2013;34:119-38.

Kroenke K, Price RK. Symptoms in the community. Prevalence, classification, and psychiatric comorbidity. *Arch Intern Med* 1993; 153 (21):2474-80.

Kubitz N, Mehra M, Potluri RC, Garg N, Cossrow N (2013) Characterization of Treatment Resistant Depression Episodes in a Cohort of Patients from a US Commercial Claims Database. *PLoS ONE* 8(10): e76882.

Martin JLR, Martín-Sánchez E. Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: Variable results based on study designs. *European Psychiatry*. 2012;27(3) 147-155.

Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, Hopwood M, Lyndon B, Mulder R, Murray G, Porter R, Singh AB. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry*. 2015 Dec;49(12):1087-206.

Mathers, C., Fat, D. M., Boerma, J. T., & World Health Organization. (2008). *The global burden of disease: 2004 update*. Geneva, Switzerland: World Health Organization.

May;67(5):688-95. Berlim MT and Turecki G. What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials. *Eur Neuropsychopharmacol*. 2007;17(11):696–707.

McClintock, SM et al., Residual Symptoms in Depressed Outpatients Who Respond by 50% But Do Not Remit to Antidepressant Medication, *J Clin Psychopharmacology* 2011; 31(2): 180-186.

Montgomery SA. Why do we need new and better antidepressants? *Int. Clin. Psychopharmacol*. 2006; 21 (Suppl 1):S1-S10.

Mrazek DA, Hornberger JC, Altar CA, Degtjar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996–2013. *Psychiatric Services*. 2014;65:977–987.

Müller HH, Kornhuber J, Maler JM, Sperling W. The effects of stimulation parameters on clinical outcomes in patients with vagus nerve stimulation implants with major depression. *J ECT*. 2013 Sep;29(3):e40-2.

Murray and Lopez. *Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020, vol 1*. WHO. Cambridge, Mass: Harvard University Press: 1996.

Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, Martinez JM, George MS. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *J Clin Psychiatry*. 2005 Sep;66(9):1097-104.

- Parikh SV, Segal ZV, Grigoriadis S, et al. (2009) Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. II. Psychotherapy alone or in combination with antidepressant medication. *Journal of Affective Disorders* 117: S15–S25.
- Ruhé HG, van Rooijen G, Spijker J, Peeters FP, Schene AH. Staging methods for treatment resistant depression. A systematic review. *J Affect Disord*. 2012 Mar;137(1-3):35-45.
- Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, Nahas Z, Haines S, Simpson RK Jr, Goodman R. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry*. 2000 Feb 15;47(4):276-86.
- Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, Kling MA, Rittberg BR, Burke WJ, Rapaport MH, Zajecka J, Nierenberg AA, Husain MM, Ginsberg D, Cooke RG. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry*. 2005a;58:347-354.
- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163:1905-1917.
- Russell JM, Hawkins K, Ozminkowski RJ, Orsini L, Crown WH, Kennedy S, Finkelstein S, Berndt E, Rush AJ. The cost consequences of treatment-resistant depression. *J Clin Psychiatry*. 2004;65(3):341-347.
- Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, Johnson CR, Seidman S, Giller C, Haines S, Simpson RK, Goodman RR. Vagus nerve stimulation (VNS™) for treatment-resistant depression: efficacy, side effects, and predictors for outcome. *Neuropsychopharmacology*. 2001b;25:713-728.
- Schlaepfer TE, Frick C, Zobel A, Maier W, Heuser I, Bajbouj M, O'Keane V, Corcoran C, Adolfsson R, Trimble M, Rau H, Hoff HJ, Padberg F, Müller-Siecheneder F, Audenaert K, Van den Abbeele D, Stanga Z, Hasdemir M. Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med*. 2008 May;38(5):651-61.
- Souery D, Amsterdam J, de Montigny C, Lecrubier Y, Montgomery S, et al. (1999) Treatment resistant depression: methodological overview and operational criteria. *Eur Neuropsychopharmacol* 9: 83–91.
- Sperling W, Reulbach U, Kornhuber J. Clinical benefits and cost effectiveness of vagus nerve stimulation in a long-term treatment of patients with major depression. *Pharmacopsychiatry*. 2009;42(03): 85-88.
- Thase ME et al., Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The fourth Generation of Progress*. New York, NY: Raven Press, Ltd; 1995.
- Thase ME. Preventing relapse and recurrence of depression: a brief review of therapeutic options. *CNS Spectr* 2006; 11(12 Suppl 15):12-21.
- Tiller, John W. G. (2012): 'Depression and Anxiety', *The Medical Journal of Australia*, 1:4, 28-31.
- Tisi G, Franzini A, Messina G, Savino M, Gambini O. Vagus nerve stimulation therapy in treatment-resistant depression: a series report. *Psychiatry Clin Neurosci*. 2014 Aug;68(8):606-11.
- Whiteford HA, Buckingham WJ, Harris MG, Burgess PM, Pirkis JE, Barendregt JJ, Hall WD. Estimating treatment rates for mental disorders in Australia. *Aust Health Rev*. 2014 Feb;38(1):80-5.

Attachment 1

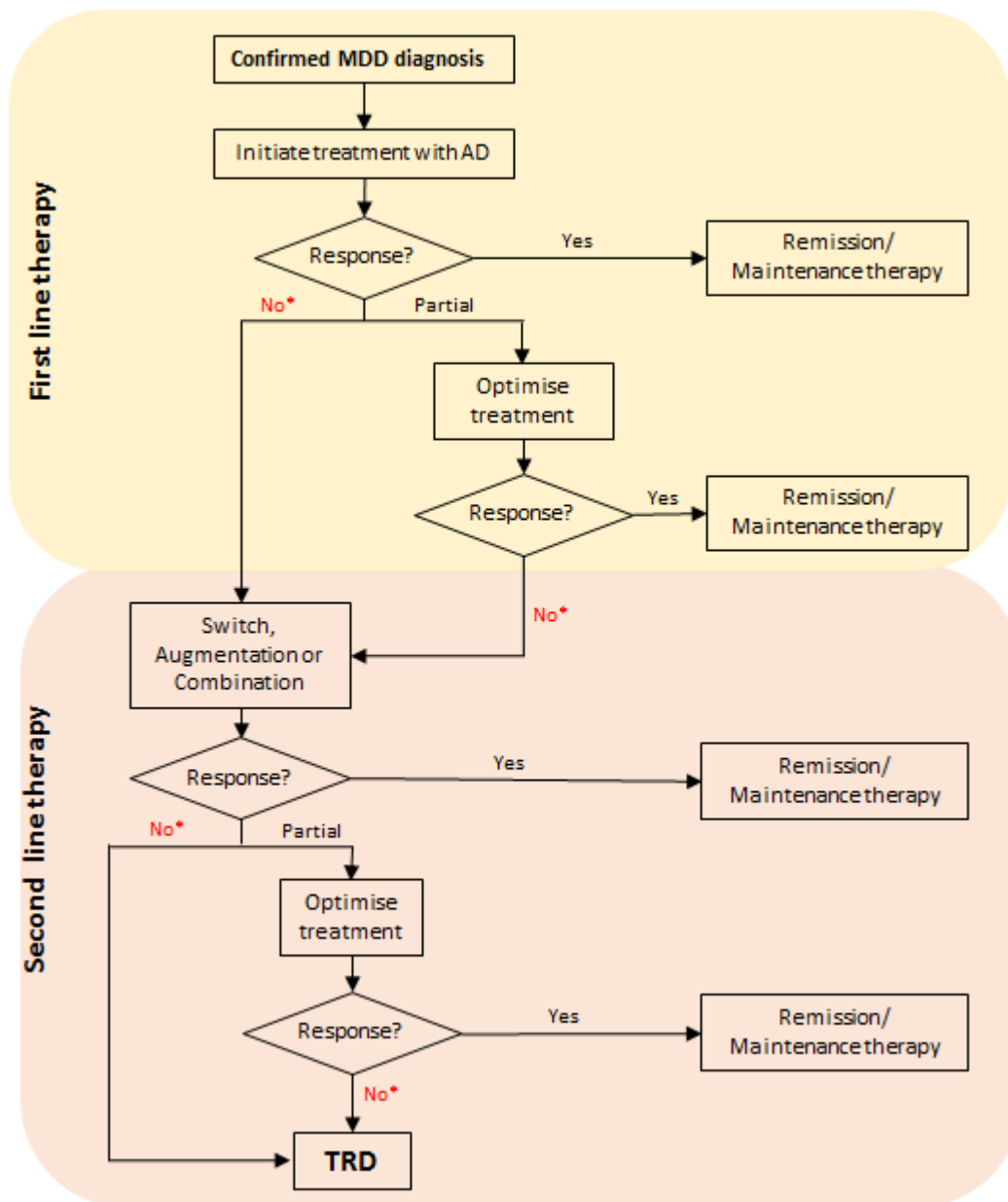


Figure 1 Treatment algorithm before a patient is considered as treatment resistant

Abbreviations: AD, anti-depressant; MDD, major depressive disorder; TRD, treatment resistant depression.

Relevance to the proposed VNS positioning: The proposed positioning for VNS is after 4 trials with anti-depressant medications. That is, a patient is required to undergo two more lines of therapy after he / she is considered as suffering from TRD in the algorithm above.

Notes: Formal MDD diagnosis is typically made by a GP, psychologist or psychiatrist who may prescribe both initial and subsequent therapies. In severe cases and/or where there is risk of self harm, the patient will typically be under the care of a psychiatrist. Psychobehavioural therapy can be considered/implemented at any stage on its own or adjunctive to AD therapy. However, as it does not form part of the diagnostic criteria for TRD, it has been omitted from this clinical management scheme for the purpose of simplicity.

* Patients who do not show to respond adequately to treatment require their diagnosis to be reviewed. This may comprise a review of adherence and dose; a re-assessment of co-morbidities or seeking a second opinion.

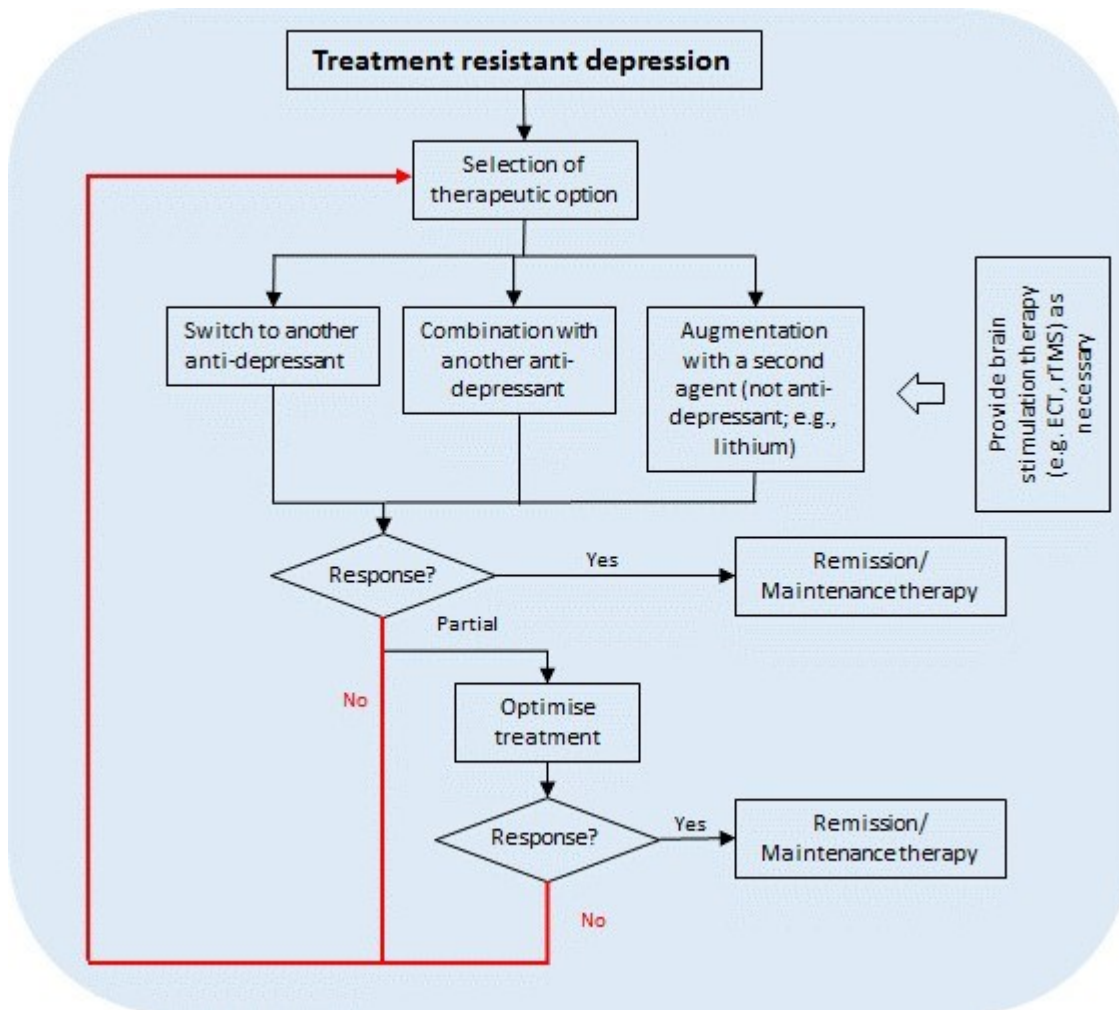


Figure 2 Standard treatment algorithm for treatment resistant depression in the current clinical practice – see *Question 26* for a detailed description / discussion of TRD definition relevant for the proposed VNS eligibility on the MBS

Relevance to the proposed VNS positioning: The proposed positioning for VNS is after 4 trials with different anti-depressant medications. The patient would be also receiving specialist psychiatric care.

Note: Psychobehavioural therapy can be considered/implemented at any stage.

Table 8 Summary of PICO criteria to define research questions that assessment will investigate

| Patients | Intervention | Comparator | Outcomes |
|---|--|---|---|
| <p>Patients with treatment-resistant depression (TRD) who have failed to achieve an adequate response after at least four appropriate antidepressant trials</p> | <p>Vagus nerve stimulation (VNS) VNS therapy involves an implanted pacemaker-like pulse generator and a nerve stimulation electrode to deliver intermittent stimulation to the left vagus nerve.</p> | <p>Standard of care (SoC) or treatment as usual SoC for these patients consist of alternative pharmacological strategies (switching, augmentation or combination), psychotherapeutic strategies or brain stimulation therapies such as ECT. Of note, VNS is to be added onto SoC; VNS provides a chronic, continuous therapy alongside the SoC provided to the patient as required.</p> | <p><u>Effectiveness measures:</u> Response/remission rates and time to response (based on key measures of depression, e.g., HAMD, MADRS, IDS, CGI-I measures of depression) Duration of response/remission QoL / utility values Adaptive functioning Cognitive functioning Suicide ideation Mortality (all cause) <u>Safety measures:</u> Complications (related to device or surgery) Adverse events Withdrawals due to adverse events <u>Resource use:</u> Reduced hospitalisation and other acute care (to be considered in the economic model).</p> |