Introduction
This overview has been prepared to assist members of IPAC advise on the safety and efficacy of an interventional procedure previously reviewed by SERNIP. It is based on a rapid survey of published literature, review of the procedure by specialist advisors and review of the content of the SERNIP file. It should not be regarded as a definitive assessment of the procedure.

Procedure name
Deep brain stimulation for Parkinson's disease
Subthalamic nucleus deep brain stimulation

Specialty society
British Society of Neurological Surgeons

Indication(s)
Parkinson’s disease.

Parkinson’s disease is a chronic disease of the brain characterised by gradually worsening tremor, muscle rigidity and difficulties with starting and stopping movements. The condition is usually treated with drugs. Surgery may be considered in people who have responded poorly to drugs, who have severe side-effects from medication, or who have severe fluctuations in response to drugs (on-off syndrome).

Parkinson’s disease is common, affecting about 0.5% of people aged 65 to 74 and 1-2% of people aged 75 and over. Experts believe that 1 to 10% of people with Parkinson’s disease might be suitable for brain surgery.¹

Summary of procedure
Surgery for Parkinson’s disease is carried out on structures within the brain that are responsible for the modification of movements, such as the thalamus, the globus pallidus and the subthalamic nucleus. Each of these structures consists of two parts; one on the left hand side of the brain and one on the right. Surgery may be carried out on one or both sides.

Surgical treatment aims to correct the imbalance created by diminished function of the substantia nigra, the underlying abnormality in Parkinson’s Disease. Surgery alters, through either destruction or electrical stimulation, the function of brain nuclei, such as the thalamus, globus pallidus or subthalamus that interact functionally with the substantia negra (nigra). All these procedures carry the risk of stroke, confusion and speech and visual problems.
Surgery involves inserting very fine needles into the brain through small holes made in the skull to determine the exact position of the nucleus, which may be different in each patient. This part of the procedure is usually carried out under local anaesthetic. A permanent electrode is then placed into this nucleus. Under general anaesthetic this wire is then connected to a pulse generator subcutaneously on the anterior chest wall.

Literature review

Appraisal criteria
We included studies on stimulation of the subthalamic nucleus in Parkinson’s disease.

List of studies found
We found two systematic reviews. The conclusions of the second were based mainly on the findings of the first, so the second is not described further.

We found one randomised controlled trial.

We found six non randomised controlled studies; the table gives details of the three largest.

We found eight case series including 50 or more people.

The table gives details of the largest case series.

References to smaller studies are given in the Annex.
## Summary of key efficacy and safety findings (1)

<table>
<thead>
<tr>
<th>Authors, location, date, patients</th>
<th>Key efficacy findings</th>
<th>Key safety findings</th>
<th>Key reliability and validity issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicholson T1</td>
<td>• identified no controlled studies</td>
<td>Insufficient evidence of safety of subthalamic stimulation</td>
<td>Search date and primary sources described</td>
</tr>
<tr>
<td>Study design: systematic review</td>
<td>• identified four studies comparing function with stimulation on and stimulation off, one case series</td>
<td></td>
<td>Selection criteria for studies described</td>
</tr>
<tr>
<td>Search date: September 1999</td>
<td></td>
<td>Insufficient evidence of efficacy of subthalamic stimulation</td>
<td>Quality of included studies assessed: All papers had methodological limitations including poorly defined patient selection criteria; mixed interventions; short follow up; incomplete follow-up; blinding of assessment unclear and pre-specified outcome measures not always reported</td>
</tr>
<tr>
<td>Burchiel KJ3</td>
<td>Mean improvement in motor score before medication:</td>
<td>Perioperative complications:</td>
<td>Randomisation method not described</td>
</tr>
<tr>
<td>Randomised controlled trial</td>
<td>• STN: 44%</td>
<td>Severe dyskinesia</td>
<td>STN patients older with less disability before surgery than GPS patients</td>
</tr>
<tr>
<td>Portland Oregon, USA</td>
<td>• GPS: 39%</td>
<td>STN: 1 person</td>
<td>Power very low</td>
</tr>
<tr>
<td>1996 to 1997</td>
<td>p=0.71</td>
<td>GPS: none</td>
<td>Patients and physicians blinded to stimulation site</td>
</tr>
<tr>
<td>n=10</td>
<td>Mean improvement in Activities of Daily Living Score before medication:</td>
<td>Haemotoma</td>
<td>Outcomes appropriate</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>• STN: 78%</td>
<td>STN: 1 person</td>
<td>Losses to follow up:</td>
</tr>
<tr>
<td>• prominent rigidity and bradykinesia</td>
<td>• GPS: 63%</td>
<td>GPS: none</td>
<td>• STN: none</td>
</tr>
<tr>
<td>• minor tremor</td>
<td>Reduction in Dyskinesia Rating Scale after medication:</td>
<td>Anxiety attack</td>
<td>• GPS: 1</td>
</tr>
<tr>
<td>• stable dose of medication for at least 1 month</td>
<td>• STN: 67%</td>
<td>STN: 3 people</td>
<td></td>
</tr>
<tr>
<td>• history of fits</td>
<td>• GPS: 47%</td>
<td>GPS: none</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td></td>
<td>Transient confusion</td>
<td></td>
</tr>
<tr>
<td>• major psychiatric illness</td>
<td></td>
<td>STN: 2 people</td>
<td></td>
</tr>
<tr>
<td>• low intelligence</td>
<td></td>
<td>GPS: none</td>
<td></td>
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<tr>
<td>• abnormal radiological findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• previous surgery for Parkinson’s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• other substantial medical problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow up: 12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authors, location, date, patients</td>
<td>Key efficacy findings</td>
<td>Key safety findings</td>
<td>Key reliability and validity issues</td>
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<tr>
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</tr>
<tr>
<td>Obeso JA^4^</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort study</td>
<td></td>
<td>Stroke:</td>
<td>Reasons for allocating people to STN or GPS not described</td>
</tr>
<tr>
<td>Multicentre: Australia, Canada, France, Germany, Italy, Spain, Sweden and USA 1995 to 1999</td>
<td></td>
<td>STN: 3 people</td>
<td>GPS group was younger and included more men</td>
</tr>
<tr>
<td>140 people</td>
<td></td>
<td>GPS: 4 people</td>
<td></td>
</tr>
<tr>
<td>• n=102 subthalamic nucleus stimulation (STN), average age 59</td>
<td></td>
<td>Fits:</td>
<td>Losses to follow up:</td>
</tr>
<tr>
<td>• n=38 stimulation of globus pallidus (GPS), average age 56</td>
<td>Change in motor score before medication:</td>
<td>STN: 3 people</td>
<td>• STN: 5</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td></td>
<td>GPS: 4 people</td>
<td>• GPS: 2</td>
</tr>
<tr>
<td>• good response to levodopa</td>
<td></td>
<td>Infecion:</td>
<td>Funded by manufacturer</td>
</tr>
<tr>
<td>• minimum of 30 points on functional score before medication</td>
<td>Change in motor score after medication:</td>
<td>STN: 4 people</td>
<td></td>
</tr>
<tr>
<td>• symptoms not controlled</td>
<td></td>
<td>GPS: none</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td></td>
<td>Brachial plexus injury:</td>
<td></td>
</tr>
<tr>
<td>• major psychiatric illness</td>
<td></td>
<td>STN: 1 person</td>
<td></td>
</tr>
<tr>
<td>• cognitive impairment</td>
<td></td>
<td>GPS: none</td>
<td></td>
</tr>
<tr>
<td>• other substantial medical problems</td>
<td></td>
<td>Pulmonary embolism:</td>
<td></td>
</tr>
<tr>
<td>• cardiac pacemaker</td>
<td></td>
<td>STN: 1 person</td>
<td></td>
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<tr>
<td>• previous intracranial surgery</td>
<td></td>
<td>GPS: none</td>
<td></td>
</tr>
<tr>
<td>Follow up: 6 months</td>
<td>Change in motor score before medication:</td>
<td>STN: 74% to 15%</td>
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<tr>
<td></td>
<td>• STN: 51%</td>
<td>GPS: 76% to 11%</td>
<td></td>
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<tr>
<td></td>
<td>• GPS: 33%</td>
<td>Patient global assessment of presence of severe disability:</td>
<td></td>
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<td></td>
<td></td>
<td>• STN: 77% to 23%</td>
<td></td>
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<tr>
<td></td>
<td>Change in motor score after medication:</td>
<td>• GPS: 82% to 14%</td>
<td></td>
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<tr>
<td></td>
<td>• STN: 26%</td>
<td>Home diary assessments of increase in time with good mobility during day:</td>
<td></td>
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<tr>
<td></td>
<td>• GPS: 27%</td>
<td>• STN: 27% to 74%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• GPS: 28% to 64%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physician global assessment of presence of severe disability:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• STN: 74% to 15%</td>
<td>• STN: 77% to 23%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• GPS: 76% to 11%</td>
<td>• GPS: 82% to 14%</td>
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</tbody>
</table>

Deep brain stimulation for Parkinson's disease page 4 of 9
<table>
<thead>
<tr>
<th>Authors, location, date, patients</th>
<th>Key efficacy findings</th>
<th>Key safety findings</th>
<th>Key reliability and validity issues</th>
</tr>
</thead>
</table>
| Volkmann J^5^                    | Change in mean motor score before levodopa:  
  • STN: 56/108 to 22/108  
  • GPS: 53/108 to 17/108  
  Change in mean motor score after levodopa:  
  • STN: 15/108 to 16/108  
  • GPS: 30/108 to 17/108  
  Change in mean Activities of Daily Living score before levodopa:  
  • STN: 29/52 to 13/52  
  • GPS: 21/52 to 12/52  
  Change in mean Activities of Daily Living score after levodopa:  
  • STN: 14/52 to 11/52  
  • GPS: 12/52 to 6/52  | Deaths: none  
  Infection:  
  • STN: 1 people  
  • GPS: 2 people  
  Skin erosion:  
  • STN: none  
  • GPS: 2 people  
  Weight gain>10kg:  
  • STN: 6 people  
  • GPS: 3 people  
  Speech difficulties:  
  • STN: 9 people  
  • GPS: none  
  Depression requiring inpatient treatment:  
  • STN: 2 people  
  • GPS: none  
  Sleepiness:  
  • STN: 3 people  
  • GPS: none  | Reasons for allocating people to STN or GPS not described  
  STN group older with longer duration of disease  
  Power limited  
  Non-blinded assessment of outcomes  
  Outcomes appropriate  
  Losses to follow up:  
  • STN: none  
  • GPS: 1 |

n=27  
• 16 subthalamic nucleus stimulation (STN), average age 60  
• 11 stimulation of the globus pallidus (GPS), average age 57  
Inclusion/exclusion criteria not described  
Follow up: 12 months
### Summary of key efficacy and safety findings (4)

<table>
<thead>
<tr>
<th>Authors, location, date, patients</th>
<th>Key efficacy findings</th>
<th>Key safety findings</th>
<th>Key reliability and validity issues</th>
</tr>
</thead>
</table>
| **Krause M**<sup>6</sup>  
Non randomised controlled study  
Heidelberg, Germany  
1995 onwards (published 2001)  
n=18  
• 12 subthalamic nucleus stimulation (STN), average age 59 (range 45-69)  
• 6 stimulation of globus pallidus internus (GPS), average age 57 (range 46-65)  
Inclusion criteria  
• advanced Parkinson’s (defined)  
Follow up: 12 months | Change in mean Activities of Daily Living Score:  
• STN: 24/52 to 17/52  
• GPS: 17/52 to 17/52 | Deaths: none  
Stroke:  
• STN: 1 person  
• GPS: none  
Strong increase in libido:  
• STN: 1 person  
• GPS: 2 people  
Speech difficulties:  
• STN: 2 people  
• GPS: 2 people  
Hyperkinesias:  
• STN: 2 people  
• GPS: none | Reasons for allocating people to STN or GPS not described  
Groups of similar age and duration of disease  
Power limited  
Assessor of outcomes blinded to procedure  
Outcomes appropriate |
| **Vesper J**<sup>7</sup>  
Case series  
Multicentre: 18 centres in Australia and Canada and 16 in Europe  
1998 to 1999  
n=111 people, average age 59  
Inclusion criteria:  
• severe disease with motor fluctuations or dyskinesia or tremor  
• medical therapy ineffective  
Exclusion criteria:  
• dementia or other psychiatric conditions  
• pregnancy  
Follow up: 6 months | • mean operation time 5 hours (range 3 hours to 8 hours)  
• activity of daily living score ‘significantly improved’ (p<0.0001)  
• motor scores ‘significantly improved’ (p<0.0001)  
• duration and severity of levodopa-induced dyskinesia ‘significantly reduced’ (p<0.0001)  
(Data presented graphically – no absolute figures provided) | Complications:  
• death: 1 person  
• subcutaneous haematoma: 6 people  
• stroke: 3 people  
• dislodged lead: 2 people  
• fit: 1 person  
• infection: 9 people  
• seromas: 2 people  
• pain at neurostimulator site: 1 person  
• gait disorders: 10 people  
• psychiatric disturbances: 10 people  
• speech difficulty: 3 people  
• difficulty swallowing: 3 people  
• pins and needles: 3 people  
• difficulty with shutting eye: 3 people | Uncontrolled case series  
Data available for 44/111 patients at 6 months  
Short follow up |
Validity and generalisability of the studies
All the studies were carried out in settings applicable to the UK.

We found one very small randomised controlled trial which lacked power to
demonstrate statistically significant differences in efficacy and safety outcomes
between subthalamic and globus pallidus stimulation.3

We found three non-randomised studies comparing subthalamic and globus pallidus
stimulation.4-6 These studies are susceptible to confounding. One was fairly large so
provides useful information on risk of complications.4

We found no studies comparing subthalamic stimulation with non-surgical treatment.

Bazian comments
None.

Specialist advisor’s opinion / advisors’ opinions
Specialist advice was sought from the British Society of Neurological Surgeons

• Now established practice
• Randomised controlled trial currently in progress comparing subthalamic
  stimulation versus medical treatment
• Long term efficacy unknown
• Specialised training essential

Issues for consideration by IPAC
None other than those discussed above.
References


### Annex: References to studies not described in the table

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparison studies</strong></td>
<td></td>
</tr>
</tbody>
</table>