

# Considered Judgement Form

*This form is a checklist of issues that may be considered by the Purchasing Guidance Advisory Group when making purchasing recommendations.*

**Meeting date:** 20 February 2008

**Topic:** Evidence based review: Intervertebral Disc Replacements – Lumbar Total Disc Replacement

**Background and purpose:**

In recent years total disc replacement (TDR) has emerged as a viable alternative to spinal fusion for Degenerative disc disease (DDD) in the lumbar spine and DDD/neuropathy in the cervical spine. The benefits over and above the “gold standard” of spinal fusion are potentially to preserve range of motion and prevent the degeneration of the nearby vertebral segments, a sequelae of spinal fusion.

A brief report prepared by ACC in 2002 reviewed the evidence for cervical and lumbar intervertebral disc replacements. Firm conclusions relating to the clinical effectiveness of spinal disc replacement were difficult to make. There was some evidence (from poor quality studies) that lumbar disc replacement may be beneficial in patients with degenerative disc disease aged between 36 and 55 years. No studies were found relating to cervical TDR.

In addition to revisiting this brief, this 2007 report also reviewed the literature with respect to the indications and contraindications for intervertebral TDR and has reported on any new TDR and related technologies.

Currently ACC funds TDR on a case-by-case basis via a formal application process for both cervical and lumbar TDR, under the proviso that patients are part of a formal clinical trial and are informed the treatment is innovative.

This 2007 EBH review has been peer reviewed by two spinal surgeons who currently perform TDR surgery.

***Effectiveness, Volume of Evidence, Applicability /Generalisability and Consistency***

***Safety and Efficacy***

***The MSAC Report***

A pivotal Health Technology Assessment (HTA) by The Medical Services Advisory Committee Australia, (July 2006) was identified that reported on the safety and efficacy of both lumbar and cervical TDR. This report was of high quality, therefore enabling literature after this date only to be reviewed (i.e. January 2006 (literature search completion date) to August 2007).

The MSAC report reviewed 21 clinical trials implanting lumbar TDR. Two large

randomised controlled trials in the lumbar spine were identified. Complete results for the Charité Lumbar TDR Food and Drug Administration (FDA) Investigational Device Exemption (IDE) trial (single-level, L4-S1, TDR=205, fusion= 99) and interim results for the ProDisc Lumbar FDA IDE trial (L3-S1, single- and double-level, results from two sites only of the multi-centre trial; n=73 TDR, 48 fusion) were reported.

The MSAC report concluded that there was sufficient evidence to recommend single-level lumbar TDR in the absence of osteoporosis and prior fusion.

Since the MSAC report, five publications relating to the Charité FDA IDE trial and four relating to the ProDisc FDA IDE trial were identified and reviewed along with 24 additional clinical trials (non-randomised comparative trials and case series). Four of these clinical trials implanted the Maverick Lumbar TDR.

Seventeen of these publications reported on outcomes for the ProDisc. Full and final results were able to be reviewed for the ProDisc FDA trial. Up to four of these publications were case series that may have reported different information on the same trial cohort.

## ***CHARITE TOTAL DISC REPLACEMENT***

### ***Safety***

#### ***Charité FDA IDE trial***

Twenty-four month results indicated 75.6% of TDR group and 77.8% of the fusion group (Bagby and Kuslich (BAK) cages) suffered an adverse event. The fusion group suffered a higher rate of device-related failures (TDR=4.5%, fusion=8.1%), whereas the TDR group had a higher rate of device-related adverse events (TDR=7.3%, fusion=4.0%) and also a higher rate of severe/life-threatening adverse events (TDR=15%, fusion=9%). One death not linked to the procedure occurred in the TDR group within three weeks of surgery. The most common adverse events were persistent back or lower extremity pain (TDR=52.2%, fusion=52.5%; Relative risk=0.99, 95% CI=0.79-1.25). The safety profiles between the groups were not initially analysed and that publications reporting on the Charité trial since the MSAC HTA vary with respect to adverse event rates. The variation in adverse event rates may be due to classification differences only and do not appear to have affected the conclusions regarding Charité TDR with respect to safety.

#### ***Other Trials***

An additional four publications, three of which provide long-term case series data (mean follow-up 10 - 17.4 years), provide additional information regarding adverse events. Long-term follow-up from one case series (mean follow-up 17.4 years) reported 23% (63 TDR) of the operated segments were radiologically fused. A further case series ( follow-up to 10 years) reported an overall adverse event rate of 22%, with minor subsidence in two subjects, two with adjacent level degeneration, and five requiring secondary arthrodesis.

### ***Efficacy***

#### ***Charité FDA IDE trial***

The majority of participants (70%) underwent TDR at L5/S1. “Overall success” at 24 months post-op (as defined by improvement in the Oswestry Disability Index (ODI) scores, no device failures, absence of major complications, and maintenance or improvement in neurological status) was statistically significantly in favour of the TDR group (TDR=62.2%, fusion=52.9%;  $p<0.0001$ ). Secondary outcomes were pain (Visual analog scores /100 – TDR=31.2, fusion= 37.5;  $p=0.107$ ), General Health (Short-Form-36 scores; TDR=72% group; fusion=63%) demonstrated >15% improvement from baseline; patient satisfaction with treatment (TDR=73.7%, fusion=53.1%;  $p=0.0011$ ) and disc height were also significantly better in the TDR group (TDR=12.9mm, fusion=10.7;  $p<0.05$ ). Mean range of motion at 24 months for the TDR group was 7.5°.

Note that the ‘non-inferiority’ statement was upheld using the sponsor’s and the FDA recommended non-inferiority margins (15% sponsor, FDA 10%).

This RCT was assigned an evidence level of “1-“ as per the SIGN criteria as deficiencies were noted with the management of missing data, blinding and concealment allocation.

### ***Other Trials***

An additional three non-randomised comparative studies and four case series reported on Charité TDR. Two case series report follow-up to 8.6 and 11.3 years post-op. Both indicate reasonable long-term clinical outcomes although utilised non-validated outcome tools.

## ***PRODISC TOTAL DISC REPLACEMENT***

### ***Safety***

#### ***ProDisc FDA IDE trial***

The total rate for any adverse event from the ProDisc FDA IDE trial was 84% in the TDR group and 87.5% in the fusion group\*. No statistically significant difference was found between the groups with respect to device-related adverse events between the TDR and the fusion groups\*. There were fewer device-related adverse events in the TDR group (TDR=17.9%, fusion=20%). The most common adverse event was pain and the back and lower extremities (TDR=34%, control =33.8% at 24 months). There were no deaths in either group nor was there major vessel injury, neurologic damage or nerve root injury. None of the four publications that reported on the ProDisc FDA IDE trial compared overall adverse event rates between the fusion and TDR groups, nor were significance levels for other adverse event rates reported.

### ***Other Trials***

Ten further trials were reviewed providing follow-up from 12-47 months. Two further case series did report on long-term follow-up (7-11 years, n=55; 6-11 years, n=42), reporting a 9.1% incidence of long-term radicular pain, with 31% of subjects (n=13) suffering implant subsidence. Additional long-term data indicated 10 cases (/42) of adjacent level degeneration at a mean follow-up of 8.7 years. Only one case series reported an overall adverse event rate of 19.6% (n=92) although over 52% of the cohort was lost to follow-up. One case series reported that adjacent level degeneration was present in 10% of patients (n=64 double and single-level TDR), and this was highly correlated with poor range of motion.

One recent small non-randomised comparative study that compared the ProDisc and Charité TDR outcomes identified a significant difference in range of motion (ROM) at L5/S1 at a mean follow-up of more than 3 years. Unexpectedly high rates of facet degeneration were identified both in the operated levels and the levels adjacent to the TDR with both TDR types.

### ***Efficacy***

#### ***ProDisc FDA IDE Trial***

The majority of participants (66.7%) underwent TDR at L5/S1. “Overall success” was significantly better in the TDR group at 24 months post-op ( $p=0.0438$ , 10% FDA criteria;  $p=0.0053$ , 12.5% sponsor criteria), confirming non-inferiority for both sponsor and FDA criteria. “Overall success” was defined as improvement of  $\geq 15\%$  in the Oswestry Disability Index (ODI), no device failures, any improvement from baseline SF-36 scores, and neurological status improved or maintained. Radiographic success and ROM parameters were also incorporated. Secondary outcomes at 24 months were pain scores (VAS/100) (TDR=37, control =43,  $p=-0.08$ ), neurological success (TDR=91.2%, control= 81.4%,  $p=0.034$ ), patient satisfaction (TDR=77, control =67\*), SF-36 (TDR=79.2%, control=70%,  $p=0.94$ ) and radiographic success (TDR=87.4%, fusion=85.5 %\*). Range of motion at the operated segment was a mean average of  $7.7^\circ$  in the TDR group.

This RCT was assigned an evidence level of “1-“ as per the SIGN criteria as deficiencies were noted with the management of missing data, blinding and concealment allocation.

A recent meta-analysis of the two FDA IDE trials supports non-inferiority for overall success at the 10% FDA recommended margin. Despite the slight variability in inclusion and success criteria across the two studies, this seems reasonable.

#### ***Other Trials***

Six non-randomised comparative trials and 10 additional case series reported follow-up to 38 months. One case series reported outcomes at a mean follow-up of 8.7 years. Sixty percent of the cohort ( $n=55$ , single- and double-level disease) were classified as “excellent”, however the outcomes were using a non-validated outcome measure. One small case series ( $n=22$ ) reported good clinical outcomes in a cohort over the age of 60 years.

Four trials implanting the Maverick TDR (two non-randomised comparative studies and two case series) were reviewed. One small case series implanting the Maverick TDR ( $n=10$ ) reported high serum cobalt and chromium serum levels at a mean follow-up of 14.8 months.

**Note:** The literature is unclear as to the appropriateness of spinal fusion being used as the ‘gold standard’ comparison group when undertaking TDR trials due to the paucity of literature reporting spinal fusion outcomes.

#### ***Summary of Safety and Efficacy for Lumbar TDR***

The literature reviewed after the MSAC report strengthens the earlier conclusions that

were made by the MSAC that support the safety and efficacy of single-level TDR in the lumbar spine.

**Note:** Results for both trials are for medium-term (two-year follow-up) only. There is insufficient evidence to support the claim that TDR preserves motion or prevents ALD, (two of its primary aims) as long-term follow-up data is not available. TDR design is changing quickly and long-term follow-up on earlier TDR types may be of limited relevance.

### ***Indications/Contraindications for Lumbar TDR***

The literature reviewed regarding indications/contraindications presented primarily indirect evidence, coming from enrolment criteria for clinical trials assessing safety and efficacy. Contraindications and indications are inconsistent to a degree across clinical trials; examples being pre-operative radiographic screening and timeframes for failure of conservative treatment before considering TDR. Points of difference between the ACC approval protocol and the current literature relate to TDR purchasing preference, outcome measures and extent of disease (single- versus double-level TDR).

### ***New Technologies***

Numerous other TDR types and other devices and interventions (surgical and non-surgical) were identified as treatments for DDD. A number of the new TDR devices are currently being implanted as part of FDA IDE trials (no results). Many other new technologies are currently in the early research stages as management options for DDD prior to considering TDR.

**Note:** A recent ACC report (2006) has identified that patient data provided to the National Joint Register by surgeons performing TDR is incomplete for both cervical and lumbar cases.

\* = no statistic reported

### ***Cost***

Comment on any economic costs associated with this service, product or procedure

No direct cost effectiveness literature was identified for this review.

ACC currently funds TDR in the lumbar spine for ACC covered conditions on a case-by-case basis provided the patient is part of a formal clinical trial and understands the treatment is innovative. Between 2003 and May 2007 ACC funded 99 lumbar TDR. Total core and non-core cases combined indicate a significant cost and case increase each year. Total core and non-core TDR costs for 2006 were \$1,270,608.20 (excl. GST). Cases have increased from two in 2003 to 41 in 2006.

### ***Clinical impact***

Comment on the clinical impact e.g. size of population, magnitude of effect, relative benefit over other management options, resource implications, balance of risk and benefit.

TDR is purported as better than the current “gold-standard” of spinal fusion for DDD in the lumbar spine and DDD/neuropathy in the cervical spine. The clinical impact of this

technology is unknown as there are no known New Zealand data on the need for such interventions. The population, internationally, however, is ageing, and therefore the need for TDR devices and surgical skills may grow.

### ***Equity, Maori Health, Pacific Health, Acceptability***

Comment on the extent to which the service, product or procedure reduces disparities in health status (equity of access, resources, health outcome), is consistent with the treaty of Waitangi and encourages Maori/ Pacific participation in providing and using service, product and procedures, and is consistent with values and expectations of New Zealanders.

No issues identified.

### ***Possible Purchasing Options***

List the possible purchasing options.

### ***Lumbar TDR***

***1. Purchase on a case-by-case basis with appropriate follow-up and comprehensive outcome reporting to the National Joint Register.***

### ***Evidence Statement***

***Summarise the advisory group's synthesis of evidence relating to this service, product or procedure, taking the above factors into account, and indicate the evidence level that applies.***

- For the surgical treatment of DDD, compared with spinal fusion, the evidence at two years post-operatively from two medium-large sized randomised controlled trials for lumbar TDR:
  - supports the safety of single-level lumbar TDR (L3-S1)
  - indicates the effectiveness of single-level lumbar TDR (L3-S1) with respect to disability (Oswestry Disability Index Scores), patient satisfaction, range of motion and general health (SF-36 scores).
- Based on one low quality non-randomised comparative study and two case series, the evidence that TDR prevents Adjacent level degeneration (ALD) is conflicting
- Based on three low quality case series the evidence is conflicting regarding the safety and efficacy of implanting TDR at lumbar vertebral levels L1-2 and L2-3. No trials compare outcomes between vertebral levels
- With regard to implanting TDR simultaneously at more than one level; there is currently insufficient evidence to assess the safety and efficacy of double- or greater- level lumbar TDR implants of any type. There is a high volume of low quality studies reporting TDR implantation at more than one level (14 publications)
- Safety and efficacy statements can only be made for the Charité and ProDisc TDR. Results may not be generalisable to other TDR types. Two case series and two non-randomised comparative trials only relate to the Maverick TDR. Safety and efficacy conclusions cannot therefore be made with respect to the Maverick lumbar TDR ***specifically***
- There are no high quality studies investigating age parameters for lumbar TDR (18-60 years)

- Low quality data from a small number of case series (up to 17 years follow-up) indicate that fusion and other adverse events such as adjacent level degeneration (ALD) and heterotopic ossification (HO) may be of concern long-term with lumbar TDR
- Low-quality evidence from two case series with long-term follow-up (check time) is inconsistent with respect to outcomes for patients with previous lumbar spine surgery.

Evidence Statement Notes:

- Longer term data reports generally on superseded TDR types (different materials and designs)
- Note that the peer reviewers identified a soon to be published FDA report on the Maverick lumbar FDA IDE trial.

***Purchasing Recommendations***

What recommendation(s) does the advisory group draw from this evidence?

- Purchase lumbar TDR on a case-by-case basis according to the revised (2008) ACC Lumbar TDR Approval protocol with outcome reporting to an appropriate joint register.