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Australia and New Zealand Horizon Scanning Network
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AN INITIATIVE OF THE NATIONAL, STATE AND TERRITORY GOVERNMENTS OF AUSTRALIA AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Report

OP-1 Putty® for posterolateral lumbar fusion

March 2006

ASERNIP-S
Australian Safety and Efficacy Register of New Interventional Procedures - Surgical

Royal Australasian College of Surgeons

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This Horizon scanning report was prepared by Irving Lee from the Australian safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

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Executive Summary

OP-1 Putty is a combination of bone morphogenic protein (OP-1) and collagen which was developed for the purpose of inducing arthrodesis in patients requiring posterolateral lumbar fusion. From the studies retrieved, OP-1 Putty appears to be capable of inducing arthrodesis in patients requiring posterolateral lumbar fusion with similar success rates to conventional autografts as no significant differences in radiographic or clinical outcome between patients receiving OP-1 putty and autograph was detected in randomised controlled trials. However, these randomised controlled trials were limited by small sample sizes and may have lacked the power to detect statistically significant differences between the groups (Vaccaro *et al.* 2005a, Johnsson *et al.* 2002). The Vaccaro study was further limited by significant losses to follow-up and missing data (Vaccaro *et al.* 2005a).

In the case series by Vaccaro *et al.* (2005b), OP-1 Putty was used as an adjunct to iliac crest autograft and the results were compared to the autograft alone arm of a separate randomised controlled trial. Unexpectedly no statistically significant improvement in fusion rate was found (Vaccaro *et al.* 2005b). This is surprising as one would expect the osteoconductive nature of OP-1 Putty would enhance the fusion rates when used in combination with conventional autografts. The authors proposed that this was probably due to small patient numbers. However, it would be prudent to conduct further studies as there may be aspects of OP-1 which is not yet known.

The case reports by Govender *et al.* (2002) on high risk patients indicates that OP-1 Putty used in conjunction with conventional autograft is capable of inducing spinal fusion even in patients with medical risk factors (e.g. heavy smoking) that could inhibit osseous fusion. Although limited by the nature of the data (multiple case reports with different follow-up times), most patients exhibited some improvement and patients who had greater than 3 months follow-up all achieved spinal fusion (Govender *et al.* 2002).

The retrieved studies reflect positively on the potential of OP-1 Putty as a substitute to autogenous bone graft. OP-1 is also regarded as generally safe with no systemic or local adverse events directly related to the use of the product reported. Most of the difficulties reported were typical of the complications expected with spinal fusion surgery. In addition to this, the occurrence of adverse events was similar when comparing OP-1 Putty patients to autograft patients (Vaccaro *et al.* 2005). No studies reported systemic toxicity or severe ectopic bone formation, with the exception of 3 patients who experienced minor heterotopic bone formation in the FDA trial, none we considered adverse events (US Food and Drug Administration 2004). However, the high rate of patients with immunogenic response (96% developed antibodies to OP-1) (Stryker Biotech 2004) may be a point of concern despite the lack of elaboration on the significance of this occurrence.

Although studies on OP-1 Putty are supportive of its abilities, the data available so far is limited and often involves a small patient cohort. A large randomised controlled trial with

sufficient follow-up is required to provide better evidence on the efficacy and safety of OP-1 Putty.

Background

Background to the Condition

Spinal fusion is a surgical technique whereby one or more of the spinal vertebrae are united (fused) in order to prevent movement between them. A large range of conditions may warrant the use of spinal fusion, these include: fractured vertebra, spinal deformity, chronic back pain, spinal instability, vertebral displacements (spondylolisthesis) and cervical disc herniations.

The standard surgical approach of achieving spinal fusion involves the placement of an autogenous bone graft (bone harvested from the patient) between decorticated spinal surfaces. When the autogenous bone graft matures, it may fuse the two surfaces together. However, the failure rate for spinal autogenous bone grafts is 5% to 40% (Vaccaro *et al.* 2002) and is sometimes unfeasible in certain patients. Failure of fusion may result in the formation of spinal pseudoarthrosis, and thus may result in continued spinal symptoms in up to 57% of patients (Vaccaro *et al.* 2002). In addition to this, donor site complications (e.g.chronic pain, hypersensitivity, fracture, hernia, cosmetic deformity and surrounding anaesthesia) have been reported in the range of 6% to 25% in autogenous bone graft recipients (Vaccaro *et al.* 2002) with the additional risk of persistent donor site pain up to 2 years post-surgery (Boden 2005). Morbidity from iliac graft harvest, combined with the limited supply of iliac bone has prompted ongoing efforts to overcome the complications related to autograft spinal fusion.

The use of allograft bone (bone harvested from cadavers or deceased individuals who donated their bone for the treatment of patients) has been proposed as an alternative for spinal fusion to avoid the complications related to the use of autogenous bone. The most notable advantage is the elimination of bone harvesting from the patient thus circumventing the complications associated with this procedure. Unfortunately, a number of studies have indicated that the use of allograft bone results in inferior fusion rates and higher rates of bone resorption (Vaccaro *et al.* 2002). These complications were attributed to the fact that allograft bone has little to no demonstrable osteoinductive potential and hence has a significantly lower chance of promoting fusion. In addition to this, the use of allografts increases the risk of host immunologic rejection and infectious agent transmission (Vaccaro *et al.* 2002).

Modern spinal instrumentation devices have also been developed in an attempt to improve the fusion rate. One procedure involves the use of pedicle screws and rods which essentially hold the vertebrae in place while arthrodesis occurs; another instrument which may be used is intervertebral cages which act as a 'spacer' to spread the two

vertebrae apart while fusion occurs. Although these devices when made of titanium or PEEK are magnetic resonance imaging (MRI) compatible, they are not biological materials; and without the addition of bone graft or a suitable bone graft substitute they are unlikely to result in a solid fusion. It is generally accepted that only a biological environment conducive to bone formation and consolidation will enable successful osseous arthrodesis to occur (Govender *et al.* 2002).

As a result of the limitations of autogenous bone graft (donor site complications, supply, unacceptable rates of pseudoarthrosis), research has focused on molecular biology and the development of osteoconductive growth factors. The discovery of osteoconductive protein factors by Marshal Urist in 1965 prompted considerable effort to isolate and characterise bone morphogenic proteins (BMPs). Numerous studies have shown that these proteins have the capacity to stimulate bone formation and thus harness the potential to enhance, augment or even replace autogenous bone grafts when attempting to achieve spinal arthrodesis (Vaccaro *et al.* 2005). BMPs function by inducing the transformation of undifferentiated pluripotent mesenchymal cells into chondroblasts and osteoblasts and eventually resulting in the formation of de novo bone (Govender *et al.* 2002). One protein in particular, osteogenic protein 1 (OP-1), also known as BMP-7, is a member of the TGF-β superfamily and studies thus far has proven its osteogenic characteristics. The commercially available recombinant human OP-1 (rhOP-1) is marketed by Stryker Biotech (Hopkinton, MA) and has undergone several studies to evaluate its effectiveness in inducing spinal arthrodesis. This Horizon Scanning Report focuses on the safety and efficacy of OP-1 Putty® in achieving successful spinal fusion based on the available literature.

Description of the Technology

The actual product (OP-1 Putty) contains 3.5mg of lyophilized rhOP-1, which is combined with a carrier comprising 1g of Type 1 bovine bone collagen, resulting in a final rhOP-1 concentration of 0.875mg/ml. This dry powdered mixture is reconstituted with the use of saline to form a paste just before implantation. The carrier (Type 1 bovine bone collagen) delivers and contains the osteogenic molecules at the site of fusion and acts as a resorbable matrix for bone growth. When 230mg of carboxymethylcellulose (CMC) is added to the OP-1 implant it forms putty. This mixture/putty resembles slurry and was developed to enable accurate delivery of OP-1 to the fusion site (Stryker Biotech 2004).

The Procedure

During the surgical procedure, the patient is placed in a prone position on an appropriate spine table to maintain normal spinal lordosis. A single midline incision is made in both the skin and lumbodorsal fascia. Following this, the paraspinal muscles are stripped subperiostally and laterally retracted. At this stage, any failed instrumentation (from

previous surgery) is removed. Facet joints and transverse processes of all soft and fibrous tissues are denuded and all cortical surfaces are decorticated. The next step is to perform decompression of the stenotic portions of the posterior spine if necessary; this may involve a whole or partial laminectomy and may include one or more levels. Using the preferred surgical method, pedicle screws are inserted and fixation devices (e.g. rods or plates) are added (if necessary). If the fixation interferes with the placement of the OP-1 Putty, its implantation can be delayed until after OP-1 Putty placement.

OP-1 Putty is prepared by mixing OP-1 implant with putty additive and 2.5cc of sterile saline (0.9%) solution. It is important to remember that a second OP-1 Putty mixture must be used for the contralateral side of the spine. Before OP-1 Putty is applied to the spine, adequate irrigation and hemostasis at the site is required to enable the putty to be placed in the site at maximum capacity. The surgeon must ensure that OP-1 Putty is directly in contact with viable tissue. Immediately after OP-1 Putty implantation, the surrounding soft tissues are closed to ensure containment of the putty (Stryker Biotech 2004).

Intended Purpose

OP-1 putty is indicated for use as an alternative to autograft in compromised patients (e.g. osteoporosis, smoking, diabetes) requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and marrow harvest are not feasible or are not expected to promote fusion (Stryker Biotech 2004).

Clinical Need and Burden of Disease

In the United States, more than 250,000 spinal fusions are performed each year. Of these, approximately 40% will fail during the bone healing phase (Boden 2005). In Australia, the clinical need and burden of disease related to spinal fusions is unclear. However, it is known that back and disc problems are a significant cause of ill-health among the Australian community. The Australian Bureau of Statistics stated that 16% of 16-24 year olds and 32% of 55-64 year olds have sought medical attention for back and disc problems between July 2002 and June 2003 (Australian Bureau of Statistics 2001). According to Medicare Australia, the number of claims for procedures relating to spinal fusion (Item numbers: 40321, 48606, 48609, 48612, 48613, 48627, 48640, 48654, 48657, 48660, 48663, 48666, 48669, 48672, 48675) from July 2004 to June 2005 was 2365.

Stage of Development

OP-1 Putty was approved by the FDA under the Humanitarian Devices Exemption (HDE) program on 7 April 2004, thus authorising the use of OP-1 Putty for commercial marketing as a Humanitarian Use Device (HUD). The HDE approval is similar to that of a premarket approval (PMA), except for the fact that the device is exempt from the effectiveness requirements of a PMA approval. According to the FDA, a HUD is a

device intended to benefit patients in the treatment and diagnosis of diseases or conditions that affects or is manifested in fewer than 4000 individuals in the United States per year (Stryker Biotech 2004). At the time of writing, FDA approved clinical trials are currently underway with an expected patient cohort of 312 individuals.

In Australia, OP-1 Putty has not received approval from the TGA and hence is not commercially available. However OP-1 by itself (not the new formulation of OP-1 Putty) is commercially available in Australia. In February 2001, The Australian Drug Evaluation Committee (ADEC) recommended that OP-1 (non-putty) be granted approval for the treatment of long-bone non-unions secondary to trauma for the purpose of initiating new bone formation. TGA approval for OP-1 was granted in April 2001 (Stryker Biotech 2004).

International Utilisation

COUNTRY	LEVEL OF USE		
	Trials underway	**Limited use**	**Widely diffused**
United States		✓	

Treatment Alternatives

Existing Comparators

There are several alternatives to achieve spinal arthrodesis, these include: the current gold-standard of treatment autograft bone harvest and allograft bone. The purported advantages of OP-1 Putty to these alternatives are:

- The potential to completely overcome complications associated with autograft bone harvest (e.g. donor site pain) (Stryker Biotech 2004)
- Virtually no risk of disease transmission compared to the use of allograft bone
- Proven osteogenic properties that may enable faster recovery and better success rates (Stryker Biotech 2004)

However, it is important to note that OP-1 Putty may also be used in conjunction with the above mentioned methods of achieving spinal fusion. Combined usage with OP-1 Putty may result in higher success rates as well as faster recovery. The other BMP that is currently being investigated - rhBMP-2 - has also shown strong osteogenic properties.

Further studies are currently being conducted on rhBMP-2 but this is beyond the scope of the present report.

Clinical Outcomes

A total of 4 studies were identified: Two randomised controlled trials (3 papers), one case series studies (2 papers) and one case report.

Safety

No medical complications or adverse events that were directly related to the use of OP-1 Putty were reported in the RCT by Vaccaro (Vaccaro *et al.* 2005a). However, nearly all patients experienced an adverse event including cardiac and gastrointestinal complications, skin infections, urinary tract infections and respiratory infections. According to the authors these complications are commonplace with lumbar fusion surgery (Vaccaro *et al.* 2005a). The rate of adverse events between the OP-1 Putty (19/24, 79.2% 95%CI: 60.8 to 97.5) and autograft groups (10/12, 83.3%, 95%CI: 58.1 to 100.0) was not significantly different (p=1.00). In the RCT by Johnsson *et al.* (2002), no early, late, local or systemic adverse effects were noted in OP-1 patients, however, four OP-1 patients experienced minor back pains while two other patients had severe back pain requiring regular analgesics. These two patients proceeded to have a re-operation where one patient underwent instrumented fusion and L5 root recompression while the other received instrumented fusion alone. No incidences of systemic toxicity, ectopic bone formation, or recurrence of spinal stenosis were reported in the case series (Vaccaro *et al.* 2005b), although there was one case of symptomatic pseudoarthrosis which eventually required a revision instrumented surgical fusion. However, in the FDA summary of safety and probable benefit (potential patient overlap with Vaccaro *et al.* 2005a), heterotropic bone formation was observed in 3 OP-1 Putty patients at 3 months post-surgery (US Food and Drug Administration 2004). These cases were not classified as clinically adverse events.

With regards to immunogenicity, Stryker Biotech stated that antibodies to OP-1 were detected in 23/24 (96%) patients treated with OP-1 Putty. Neutralising antibodies were detected in 7/24 (29%) patients (Stryker Biotech 2004).

Effectiveness

Oswestry Disability Index

The randomised controlled trial conducted by Vaccaro *et al.* (2005a) compared OP-1 Putty to iliac crest autograft for posterolateral lumbar arthrodesis. No significant difference in clinical success, defined as a greater than 20% improvement in ODI over

the preoperative score, was found between the OP-1 and autograft patients. 17/20 (85%) OP-1 patients and 7/11 (64%) autograft patients were graded as clinically successful at the 24 and 36 month assessment. However, this is not a standard method for reporting ODI results, and no raw ODI scores were reported either pre or postoperatively. The FDA has suggested that a change of at least 15 points in the ODI postoperatively is required to be clinically meaningful (Fairbank & Pynsent 2000). It is not clear whether this was obtained in this study. Furthermore, as there were no actual scores for ODI reported it was not possible to directly compare the means for the two groups. It should also be noted that significant losses to follow-up and missing data were experienced in this study, to the extent that these results consist of 24 month follow-up for the majority of patients but for four patients the follow-up is at 36 months as data for the 24 month follow-up was missing. It is also likely that the small sample size in this study means it lacked adequate power to detect a statistically significant difference between the two groups for this outcome.

In the case series by Vaccaro *et al.* (2005b), patients that were treated with OP-1 putty as an adjunct to iliac crest autograft achieved 89% (8/9 patients) clinical success at 24 months. This study also suffered from losses to follow-up and missing data. If the 3 patients who were lost to follow-up were considered failures, the success rate would be 67% (8/12 patients).

Both studies by Vaccaro and colleagues included only patients who might be considered "good candidates" for spinal fusion surgery (i.e. no previous spinal surgery, non-smokers, non-obese, no comorbidities). Govender *et al.* (2002) reported results for nine high risk patients who might be considered "poor candidates" for spinal fusion surgery (i.e. smokers, obese, comorbidities). Each of the nine patients underwent spinal fusion with the use of OP-1 Putty in conjunction with autograft. Of these, six patients experienced improvement in Oswestry scores; however whether these improvements were clinically significant was not stated (Govender *et al.* 2002). Utilising the FDA minimum requirement for determining clinical significance (defined as a minimum 15 point change after surgery) (Fairbank & Pynsent 2000), we find that 5/9 (56%) patients achieved clinically significant improvement. One patient did not show any improvement while another suffered an increase in Oswestry scores, reflecting increased disability. The increase in Oswestry scores post-surgery for this patient was attributed to the development of myelopathy. However, radiographic analysis revealed evidence of fusion 3 months post-surgery (Govender *et al.* 2002).

Radiographic analysis

Vaccaro *et al.* (2005a) utilised a strict radiographical criteria to determine if a fusion is radiographically successful. A fusion is considered successful if a complete bridging bone exists between the transverse processes with less than 5º angulation and ≤2mm translation at the site of the spondylolisthesis when comparing flexion to extension lateral radiographic views. A total of 11/20 (55%) OP-1 patients and 4/10 (40%) autograft patients were deemed to have achieved radiographic fusio+n at 24 and 36

months based on this criteria (no statistical difference between groups). In addition to this, bridging bone between the transverse processes on the anteroposterior radiograph was evident in 75% of OP-1 patients and 80% of autograft patients.

The other RCT (Johnsson *et al.* 2002) used radiostereometric analysis (RSA) to assess patients randomised to receive OP-1 Putty or iliac crest autograft for the treatment of L5 spondylolisthesis. There was no significant difference in the rate of L5 stabilisation was between the treatment groups. At 12 months post-surgery, the number of patients with L5 stabilisation when standing was similar between the two groups for translations along the sagittal axis ($p = 1.00$) and rotations around the transverse axis ($p = 0.17$). However, more patients in the autograft group achieved stabilisation of the L5 translations along the vertical axis ($p = 0.03$).

At 12 months, 6/10 (60%) OP-1 patients were found to have bilateral bridging bone formation between the transverse processes while partial formation was found in 3/10 (30%) patients (Johnsson *et al.* 2002). Meanwhile, 8/10 patients in the autograft group had complete bridging born formation and 2/10 patients had partial formation. No significant different was detected between the two treatment groups. In these 19 patients who achieved bone fusion, analysis revealed that there was a relation between better bone formation and mean reduction of L5 movements during the follow-up period in all three RSA modes (a) L5 translations along the saggital axis: $p = 0.03$, Mann Whitney U test; 95% CI: 0.2 to 2.9 mm (b) L5 rotations along the transverse axis: $p = 0.06$, Mann Whitney U test; 95% CI:0.3º to 4.5º (c) L5 translations along the vertical axis: $p = 0.02$, Mann Whitney U test; 95% CI: 0.2 to 1.4 mm (Johnsson *et al.* 2002).

Radiologic fusion was achieved in 5/10 (50%) patients treated with OP-1 and iliac crest autograft at 24 months in the case series by Vaccaro *et al.* (2005b), a result which is similar to that of the RCT (Vaccaro *et al.* 2005). However if patients lost to follow-up were considered failures, the success rate decreases to 42% (5/12). Bridging bone between the transverse processes was reported in 7/10 (70% patients).

SF-36 scores

The SF-36 survey measures the self-reported general well-being of a patient. Vaccaro *et al.* 2005a (RCT) reported Physical and Mental Component Summary and compared these with age-based norms for the US population.

Before surgery, both OP-1 (28.8) and autograft (30.1) groups recorded Physical Component Summary scores below the 25th percentile (55 to 64 years old: 38.66; 65 to 74 years old: 35.04) of the age-matched normative data. By the 24 month follow-up, OP-1 patients (46.2) had comparable Physical Component Summary scores to the mean age matched normative values (55 to 64 years old: 45.90 ± 11.25; 65 to 74 years old: 43.33 ± 11.16). On the other hand, autograft patients (29) were lower than the mean normative values (55 to 64 years old: 45.90 ± 11.25; 65 to 74 years old: 43.33 ± 11.16) (Vaccaro *et al.* 2005a).

Mental Component Summary scores were below the 25th percentile (55 to 64 years old: 46.71; 65 to 74 years old: 48.34) of normative values for OP-1 Putty (47.5) and autograft groups (44.4) before surgery. At 24 months post-surgery, the OP-1 group achieved a score of 55.6, which places the group between the 50th (55 to 64 years old: 54.35; 65 to 74 years old: 55.67) and 75th percentiles (55 to 64 years old: 57.9; 65 to 74 years old: 59.13) of the age-matched normative values whereas the autograft group (50.4) were slightly above the 50th percentile (55 to 64 years old: 54.35; 65 to 74 years old: 55.67) of the normative values (Vaccaro *et al.* 2005a).

Hospital stay and operative times

Vaccaro *et al.* (2005a) reported no difference between the OP-1 Putty group and autograft group with regards to hospital stay (3.9 ± 1.7 days versus 4.3 ± 2.0 days respectively) and mean operative time (138 ± 43 minutes versus 155 ± 28 minutes respectively).

Potential Cost Impact

Cost Analysis

The cost/price of OP-1 Putty was not revealed in our searches. However, it is reasonable to expect substantial savings compared to the use of instrumented spinal fusion. If OP-1 Putty is able to reduce patients morbidity and recovery times this may lead to savings in hospital costs and pain medication. However, no data are currently available to indicate the extent to which this might be the case.

According to Bagaria (2005), the cost of BMPs is estimated between USD$3000 to USD$5000. A Stryker Biotech representative stated that the cost of OP-1 Putty in the United Stated is $USD5000 per vial (personal communication 2006).

Ethical Considerations

Informed Consent

Patients undergoing spinal fusion using OP-1 Putty need to be informed of the fact that the product is relatively new and that the evidence available is limited. In addition to this, patients should be aware of the fact that OP-1 Putty contains bovine collagen and thus patient's who are allergic must be advised to undergo an alternate method of fusion.

At the time of writing, a multicentre, prospective, randomised, controlled study on OP-1 Putty is being conducted in the United States. This study implements a similar protocol to the RCT by Vaccaro *et al.* (2005).

Access Issues

No religious or cultural issues were raised from the retrieved material. However, the use of bovine collagen in the OP-1 Putty mixture may be an issue to Hindus.

It is likely that the use of OP-1 Putty would be limited to cities/major medical centres in Australia.

Training and Accreditation

Training

There is no specific statement from the retrieved information that surgeons are required to undergo specific training before using OP-1 Putty. Overall, the procedure appears to be rather similar to that of conventional spinal fusion using autografts except for the fact that there is no harvesting of bone and the OP-1 putty has to be prepared during the procedure. Stryker biotech provides a guide for the use of OP-1 Putty as well as the method of preparing the OP-1 implant from the components provided.

Clinical Guidelines

No clinical practice guidelines which include the use of OP-1 in spinal fusion were located. If OP-1 Putty achieves consistent success upon its application and is approved by the TGA, clinical guidelines will need to be developed.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, a Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

Search Strategy Used for Report

A systematic search of MEDLINE, PubMed, *The Cochrane Library*, the Current Controlled Trials metaRegister, the International Network of Agencies for Health Technology Assessment, relevant online journals and the Internet was conducted up to January 2005. The search terms were: OP-1, OP-1 Putty and BMP-7.

Articles were obtained if the abstract contained safety and efficacy data on OP-1 Putty in the form of randomised controlled trials, other controlled or comparative studies, case series and case reports.

Availability and Level of Evidence

List of studies found:

Total Studies	**4**
Systematic Review	**0**

Four studies were identified from the literature, two randomised controlled trials, one case series and one case report.

Sources of Further Information

FDA Study

A FDA approved multicenter pivotal primary spinal fusion study is currently underway. This trial aims to evaluate the use of OP-1 Putty in patients suffering from symptomatic single level degenerative lumbar spondylolisthesis and spinal stenosis. Patients will be treated with either OP-1 Putty or autograft in a 2:1 ratio. Analyses of results were not available at the time of writing (Stryker 2004).

Impact Summary

In the United States, more than 325,000 spinal fusions (mostly autografts) were performed in 2003 (National Center for Health Statistics 2003). Considering the autograft failure rate of 5% to 40% (Vaccaro *et al.* 2002), approximately 16,250 to 130,000 patients will require some form of additional treatment to overcome their symptoms. A proportion of these patients are likely to require revision spinal surgery.

Statistical data for spinal fusion in Australia was not available at the time of writing; however, according to Walker et al. (2004) 79% of Australian adults suffer from lower back pain at some point of their life.

OP-1 Putty, if proven effective, could result in substantial improvements to the well-being of individuals requiring spinal fusion. Patients would not be subjected to the complications related to iliac crest bone harvest such as persistent donor site pain which occurs in 25% of patients (Boden 2005). In addition to this, OP-1 Putty may have the potential to increase fusion rates and perhaps even more so when used in conjunction with existing techniques.

HealthPACT Advisory

Due to the fact that OP-1 Putty contains a bovine collagen base, it is unlikely to be introduced in Australia given the current stance of the Therapeutic Goods Administration towards bovine derived products. However, OP-1 in the 'non-putty' form has been approved for use in Australia since April 2001. The discovery of OP-1 antibodies and neutralising antibodies in patients treated with OP-1 Putty is a potential point of concern and surgeons currently utilizing the non-putty form of OP-1 should be aware of the potential complications that may arise due to this. More robust evidence stemming from the randomized controlled trial in the United States will be useful in determining any risks that may be associated with the immunogenic response towards OP-1.

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Appendix A: Table of Key Efficacy and Safety Findings

<table>
<tr><th>Study Details</th><th>Key Efficacy Findings</th><th>Key Safety Findings</th><th>Appraisal/Comments</th></tr>
<tr><td colspan="4">Randomised Controlled Trial</td></tr>
<tr>
<td>Vaccaro et al. 2005a

36 patients. (24 OP1, 12 autograft)
Follow-up: 6 wks, 3 months, 6 months, 9 months, 12 months.

Intervention:
Autologous iliac crest bone graft (control) versus OP-1 Putty for one-level non-instrumented posterolateral fusion

Inclusion criteria:
Degenerative lumbar spondylolisthesis (Grade I or II), symptoms of neurogenic claudication, spinal stenosis at the level of spondylolisthesis, minimum Oswestry score of 30, eligible for decompression and single-level fusion with iliac crest autograft, no previous fusion attempts at the level being treated, skeletally mature, failed at least 6 months of nonoperative treatment.</td>
<td>Prior to the 24 month follow-up, 3 OP-1 patients and one autograft patient had discontinued the study.
4 patients who completed the 36 months assessment but whose data for the 24 month assessment were incomplete were included in the analysis. The 36 month data were used in place of the missing 24 month data.

Success rates: Clinical(Oswestry) and Radiographic
<table>
<tr><th></th><th>Success</th><th>%Success</th><th>95% CI</th></tr>
<tr><td>Clinical</td><td></td><td></td><td></td></tr>
<tr><td>OP-1</td><td>17/20</td><td>85</td><td>62.1-96.8</td></tr>
<tr><td>Autograft</td><td>7/11</td><td>64</td><td>30.8-89.1</td></tr>
<tr><td>P=0.21</td><td></td><td></td><td></td></tr>
<tr><td>Radio-graphic</td><td></td><td></td><td></td></tr>
<tr><td>OP-1</td><td>11/20</td><td>55</td><td>31.5-76.9</td></tr>
<tr><td>Autograft</td><td>4/10</td><td>40</td><td>12.2-73.8</td></tr>
<tr><td>P=0.70</td><td></td><td></td><td></td></tr>
</table>
</td>
<td>No medical complications or adverse events were directly attributed to OP-1 Putty with the exception of pseudoarthosis.</td>
<td>Potential for bias:
Method of randomisation and allocation concealment appears adequate. Blinding of patients and surgeons was not possible due due to the nature of the treatment, however, outcomes assessors were blinded to the treatments received.
No power calculation was reported and the study may have lacked the power to detect statistically significant differences in the primary outcomes.
Significant losses to follow-up and missing data, particularly for the 24 month follow-up. It was not possible to recalculate the results using intention to treat analysis.

Outcome measurements and their validity:
The outcome measurements used in this study are validated. However, a non-standard method for reporting the results of the ODI was used.

Other comments:
Same patient cohort as Vaccaro et al. (2004)</td>
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Exclusion criteria:
Signs of active spinal or systemic infections, smokers, morbid obesity, known sensitiviry to collagen, pregnant women or those who plan to become pregnant, patients requiring additional lumbar spine surgery in the following 6 months, patients with >50% anterior translation of the cranial vertebral body or >20º of angular motion on flexion/extension films.

Bridging bone (24 month and 36 month)

Radiographic	Success	95% CI
OP-1	15/20 (75%)	50.9-91.3
Autograft	8/10 (80%)	44.4-97.5
P=1.00		

SF-36 survey
Mean Physical Component Summary scores for both groups were below the 25th percentile of normative data for age-matched US citizens in the general population before treatment. Post-operation at 24 months, OP-1 patients had comparable physical component scores (46.2) to mean age-matched normative values while autograft patients were slightly lower (29.0).

Mean Mental Component Summary score before surgery for both groups were equal to the 25th percentile normative data for age matched US citizens. Post-operation at 24 months, OP-1 patients were between the 50th and 75th percentiles of the normative data while autograft patients were slightly above the 50th percentile of the normative data.

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Randomised Controlled Trial			
Vaccaro *et al.* 2004 36 patients. (24 OP1, 12 autograft) Follow-up: 6 wks, 3 months, 6 months, 9 months, 12 months. *Intervention:* Autologous iliac crest bone graft (control) versus OP-1 Putty for one-level non-instrumented posterolateral fusion *Inclusion criteria:* Degenerative lumbar spondylolisthesis (Grade I or II), symptoms of neurogenic claudication, spinal stenosis at the level of spondylolisthesis, minimum Oswestry score of 30, eligible for decompression and single-level fusion with iliac crest autograft, no previous fusion attempts at the level being treated, skeletally mature, failed at least 6 months of nonoperative treatment. *Exclusion criteria:* Signs of active spinal or systemic	5 OP-1 Putty patients and 2 control patients were lost to follow-up at 12 months. These patients were excluded from the analysis. *Radiographic Assessment* At 12 months, fusion was observed in 14/19 (74%) OP-1 patients and 6/10 (60%) autograft patients (p=0.675). At 12 months, bridging bone between the transverse processes on the anteroposterior radiograph was seen in 17/21 (81%) OP-1 patients and 9/10 (90%) autograft patients (p=0.648). *Oswestry score* At 12 months, 18/21 (86%) OP-1 patients and 8/11 (73%) autograft patients achieved a 20% or greater improvement in their preoperative Oswestry score (clinically successful). There was no significant difference between treatment groups (p=0.39). If missing data point from patients lost to follow up were considered failures: 8/12 (67%) autograft patients and 18/24 (75%) OP-1 patients would be clinically successful. 6/12 (50%) autograft patients and 14/24 (58%)	No complications or adverse events were directly related to the use of OP-1 Putty.	*Potential for bias:* Method of randomisation and allocation concealment appears adequate. Blinding of patients and surgeons was not possible due due to the nature of the treatment, however, outcomes assessors were blinded to the treatments received. No power calculation was reported and the study may have lacked the power to detect statistically significant differences in the primary outcomes. Significant losses to follow-up and missing data, particularly for the 24 month follow-up. It was not possible to recalculate the results using intention to treat analysis *Outcome measurements and their validity:* The outcome measurements in this study are validated. *Other comments:* 2 year patient follow-up data published in Vaccaro *et al.* (2005)

infections, smokers, morbid obesity, known sensitiviry to collagen, pregnant women or those who plan to become pregnant, patients requiring additional lumbar spine surgery in the following 6 months, patients with >50% anterior translation of the cranial vertebral body or >20º of angular motion on flexion/extension films.	OP-1 patients would be considered radiographic success. *SF-36 score* Mean Physical Component Summary scores for both groups were below the 25th percentile of normative data for age-matched US citizens in the general population before treatment. Post-operation at 24 months, OP-1 patients had comparable physical component scores (44.1) to mean age-matched normative values while autograft patients were slightly lower (38.0). Mean Mental Component Summary score before surgery for both groups were equal to the 25th percentile normative data for age matched US citizens. Post-operation at 24 months, OP-1 patients (56.6) were between the 50th and 75th percentiles of the normative data while autograft patients (51.2) were slightly above the 50th percentile of the normative data.	

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Randomised Controlled Trial			
Johnsson et al. (2002) 20 patients (10 OP-1, 10 autograft) Follow-up: 6 months and 12 months *Intervention:* Autologous iliac crest bone graft (control) versus OP-1 Putty for one-level non-instrumented posterolateral fusion *Inclusion criteria* Patients older than 20 year, L5 spondylolysis, maximal vertebral slip of 50%, longstanding (>6 months) intractable lumbosacral pain refractory to nonsurgical measures, no radiating leg pain requiring decompressive surgery.	*Radiostereometric Analysis* L5 stabilisation did not occur any faster in either treatment groups. L5 movements with positional change from supine to standing were similar for both groups at 1 month and 12 months. *Conventional Radiography* At 12 months: OP-1 Putty group - 6/10 (60%) had bilateral bridging bone in the fusion area, 3/10 (30%) had partial bone formation and one patient (10%) had no bone formation. Autograft group – 8/10 (80%) had bilateral bridging bone, 2/10 (20%) had partial bone formation. *Clinical results* At 12 months, 2/10 (20%) OP-1 patients had major back pain requiring analgesics. In the autograph group, 3/10 (30%) experienced major back pain requiring analgesics.	No intraoperative complications were reported. No early, late, local or systemic adverse events related to the OP-1 Putty were observed. 2/10 (20%) OP-1 patients underwent reoperation after the 12 months follow-up. One with instrumented fusion, the other with instrumented fusion and L5 nerve root decompression. 1/10 (10%) autograft patient underwent L5 nerve root decompression.	*Potential for bias:* None noted. Methods of randomisation and allocation concealment not reported. Patients and surgeons were blinded until the time of surgery. It is not clear whether outcomes assessors were blinded. *Outcome measurements and their validity:* The outcome measurements in this study are validated. *Other comments:* Small patient cohort

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Case series			
Vaccaro *et al.* 2005b 12 patients. Follow-up: 6 wks, 3 months, 6 months, 9 months, 12 months and 24 months *Intervention:* Autologous iliac crest bone graft and OP-1 Putty as an adjunct	9/12 patients completed clinical examination at 24 months. 10/12 patients completed 24 month radiograph. Clinical success achieved in 8/9 (89%) patients at 24 months. Radiologic fusion achieved in 5/10 (50%) patients at 25 months. 7/10 (70%) patients had bridging bone between the transverse processes on their anteroposterior radiographs. If patients lost to follow-up were considered failures, clinical success would be 8/12 (67%) and radiographic fusion would be 5/12 (42%).	*Adverse events* One case of symptomatic pseudoarthrosis consisting of worsening back pain. Revision instrumented surgical fusion was required. 25% of patients reported moderate donor site pain. No side effects attributed to OP-1 Putty was detected in all patients. No cases of systemic toxicity, ectopic bone formation or recurrence of spinal stenosis.	*Outcome measures and their validity:* Outcome measures were adequately validated. *Other comments:* Two independent neuroradiologists evaluated the radiographs. Small patient cohort and significant losses to follow-up and missing data Same patient cohort as Vaccaro *et al.* (2003)

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Case series			
Vaccaro *et al.* 2003 12 patients. Follow-up: 6 wks, 3 months, 6 months, 9 months and12 months *Intervention:* Autologous iliac crest bone graft and OP-1 Putty as an adjunct	*Clinical Success* Clinical success was achieved in 9/12 (75%) patients at 12 months. Radiological fusion was achieved in 6/11 (55%) patients at 12 months. 10/11 (91%) patients had bridging bone between the transverse processes on anteroposterior radiographs. No patient had progression of spondylolisthesis.	Two patients underwent revision stabilisation with internal fixation after being diagnosed with pseudarthrosis. No adverse events were attributed to OP-1 Putty.	*Outcome measures and their validity:* Outcome measures were validated *Other comments:* 2 year follow-up data available in Vaccaro *et al.* (2005b)

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Case report			
Govender et al. (2002) 9 high risk patients (individual case reports) Follow-up: no predetermined follow-up schedule identified. Ranges from 2 to 15 months. *Intervention:* Spine fusion using OP-1 Putty and autologous bone graft. Patients are considered high risk due to medical conditions (e.g. mucopolysaccharide syndrome, rheumatoid arthritis, heavy smoling, morbid obesity) that can inhibit osseous fusion.	*Case 1* Patient underwent craniocervical decompression and fixation. ODI decreased postoperatively, SF-36 Role-physical and social functioning scores decreased due to long-term rehabilitation and ongoing medical problems. Radiograph at 5 months post-surgery revealed bone fusion. *Case 2* Patient underwent lumbar decompressive surgery and pedicle screw fixation. Postoperative ODI scores reflected a worsened condition, SF-36 scores were all lower than pre-operative scores. Poor outcomes were attributed to myelopathy. However, lower back symptoms were resolved and fusion was confirmed at 3 months follow-up. *Case 3* Patient underwent suboccipital decompression, duraplasty and occipitocervical fusion. ODI scores decreased to zero postoperatively, physical function, bodility pain and social functioning SF-36 scores decreased. This was attributed to halo vest immobilisation for 3 months. Radiography confirmed fusion.	No adverse events relating to the use of OP-1 was observed.	Authors state fusion was successful in all patients with follow-ups greater than 3 months. Significance of ODI scores post-surgery was not stated. Study provides some evidence of OP-1 Putty efficacy in 'high risk' patients.

Case 4

Patient underwent lumbar decompression, posterior lumbar interbody fusion and pedicle screw fixation. At 2 months ODI scores decreased, indicating improvement. However, general health, vitality, social functioning and mental health SF-36 scores were lower. Lower back and leg pain improved.

Case 5

Patient underwent spinal cord untethering and lumbar pedicle screw fixation. ODI scores improved and no SF-36 scores decreased postoperatively. Evidence of fusion was revealed viz dynamic radiosurgery at 6 months.

Case 6

Patient underwent atlantoaxial stabilisation. At 2 months follow-up, ODI scores decreased. Physical functioning and social functioning scores decreased.

Case 7

Patient underwent cervical laminectomy and occipitocervical fusion. Improvement was observed up to 6 months post-surgery. Condition deteriorated from 15 months onwards due to further spinal cord decompression.

Case 8
Patient underwent suboccipital decompression, duraplasty and occipitocervical fusion. ODI score, physical functioning, bodily pain and mental health scores improved at 2 months follow-up.

Case 9
Patient required a lumbar pedicle subtraction osteotomy and pedicle screw fixation. Role emotional SF-36 score did not improve but the other scores did. At 3 months follow-up ODI scores were similar to preoperative score.