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**Department of Health and Ageing**



Australia and New Zealand Horizon Scanning Network

**ANZHSN**

AN INITIATIVE OF THE NATIONAL, STATE AND TERRITORY GOVERNMENTS OF AUSTRALIA AND THE GOVERNMENT OF NEW ZEALAND

## Horizon Scanning Technology Prioritising Summary

# Dermal regeneration template (Integra®) for deep hand burns

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**ASERNIP(S)**

**Australian  
Safety  
and Efficacy  
Register  
of New  
Interventional  
Procedures -  
Surgical**



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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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

**NAME OF TECHNOLOGY:**

Dermal regeneration template (Integra®) for deep hand burns.

**PURPOSE & TARGET GROUP:**

The Integra® template supports the regeneration of dermal tissue and may become an alternative treatment for patients with third-degree hand burns and in those who require reconstructive procedures to restore hand function subsequent to deep burn injuries. This template may benefit patients who lack suitable graft material due to severe burns. Use of a full-thickness graft to cover the new dermis is not necessary, thus minimizing wound sites and encouraging healing.

**STAGE OF DEVELOPMENT (IN AUSTRALIA):**

- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use

The Integra® artificial skin is registered in the Australian Register of Therapeutic Goods (ARTG number 74131).

**INTERNATIONAL UTILISATION:**

COUNTRY	LEVEL OF USE		
	Trials underway	Limited use	Widely Diffused
*France		✓	

\* For treatment of deep hand burns

**IMPACT SUMMARY****Background:**

Integra® is a bilayer matrix composed of a thick underlay of collagen (bovine) and glycosaminoglycan (shark cartilage) and a removable thin outer layer of silicone. After removal of the damaged skin, Integra® is shaped to the exact size of the skin to be replaced, secured over the area with surgical sutures or staples and then covered by protective dressings. After approximately 14 to 21 days, the silicone layer (which aids wound closure and prevents fluid loss) is removed and an ultra-thin graft of the patient's epidermis is applied to the wound area. The shark cartilage and collagen mimic the substructure of the dermis providing a support framework for the blood vessels and other cells to regrow a new layer of dermis.<sup>1</sup>

The purported advantage of Integra®, is that only a very thin graft of the patients own epidermis is required (0.13 mm), compared to traditional grafts (0.25 mm - 0.35 mm), in

addition, removal of large areas of skin is unnecessary, minimising donor-site morbidity and therefore reducing healing time.

### **Clinical need and burden of disease:**

Burns to the hands and upper limbs are common, whether in isolation or in combination with other parts of the body.<sup>2</sup> Ineffective treatment of severe hand burns can result in joint stiffness, scar contracture and ultimately severe disability.<sup>3</sup> In Australia data from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database<sup>4</sup> indicates that 7,107 patients were admitted to public and private hospitals for burns between 2001-2002 (31% were under the age of 10 years). Of these 1,384 patients were hospitalised for burns to the wrist and hand, with 407 of these patients being hospitalised for full thickness burn of the wrist and hand (23% were under the age of 10 years).

### **Estimated speed, geographic and practitioner use patterns of diffusion in the health system:**

Since its introduction in 1981, approximately 10 000 patients have been treated with Integra<sup>®</sup>. It is the only approved product for permanent dermal regeneration of severe burns in both the United States and Europe. This product is also approved for use in Canada and Australia for plastic and reconstructive surgery and the treatment of excisional wounds.<sup>5</sup> In Australia, Integra<sup>®</sup> is marketed by Johnson & Johnson Medical Pty Ltd and is available in three sizes, Australian Register of Therapeutic Association (ATGN) number 74131, product numbers: 140755 (10 cm x 25 cm), 140756 (10 cm x 12.5 cm), 140757 (20 cm x 25 cm).<sup>6</sup>

### **Existing comparators:**

- skin flaps - healthy tissue (including epidermis, fat, blood vessels and sometimes fat) is taken from the patient and applied to the wound
- full- or split-thickness grafts - epidermis, dermis and fat\* are taken from an unaffected portion of the patient's body and grafted to the wound
- skin expansion - saline filled implants are used to stretch areas of skin so that it can be closed as a primary or Z-plasty closure, in some cases it may be used as a flap
- synthetic skin substitutes
- biological skin substitutes (xenograft, human cadaveric and living allografts).<sup>1,5</sup>

\* only used in full-thickness grafts

### **Estimated cost impact:**

The cost of Integra<sup>®</sup> is related to the size used. In Australia, a small template costs \$1 556, medium \$2 652 and large \$5 304 (see above for details of product dimensions).<sup>7</sup> The cost of surgery for grafting of burn injuries in Australia is not available, the Medicare Benefits Schedule fee (procedure only) ranges from A\$370 to \$1 125.<sup>8</sup>

### **Efficacy and safety issues:**

Short-term safety and efficacy data exist from one case series.<sup>3</sup>

Between February 1997 and July 2002, Integra® dermal regeneration template was used to treat 22 patients who presented with either acute third-degree burns of the hand requiring immediate surgical excision and grafting, or hypertrophic scars, contractures or adherent grafts on the hand necessitating reconstructive procedures with full- or split-thickness grafts. Patients were excluded if they were unfit for early excision and grafting or if the wound site was infected. All procedures were performed on an inpatient basis under general anaesthesia. Autografts were harvested at 0.13 mm from either the inner thigh or arm.

#### **ACUTE GRAFTING**

In total, 15 hands in 11 patients (eight males, three females) were treated for acute burn injuries, 14 grafts were to the dorsum and one to the palmar region. Median length of follow-up was 12 months (range 1-12 months).

#### **Safety:**

- the template vascularised with no infection reported
- localised infection of the epidermis was resolved with use of antibiotics in 1/15 (7%) hands\*
- no infections occurred at any of the donor sites.

#### **Efficacy:**

- average time for the Integra® graft to take was 17 days (range 14-23 days) and was 100% (15/15) on all hands
- no loss of template was reported
- silicone layer detached prematurely in 2/15 (13%) hands with no negative consequence
- median epidermal autograft take was 100% (range 60-100%), sites healed on average 12 days after autograft surgery
- donor sites healed within 8-10 days
- no appreciable scarring occurred at any of the donor sites
- 2/15 (13%) hands required Z-plasties for interdigital contractures
- minor epidermal graft problems were encountered in several patients, but only one patient required a supplementary epidermal graft on both hands (2/15; 13%)
- restoration of normal function occurred between one and three months after the injury was sustained and was dependent on the length of intensive care and commencement of rehabilitation
- grafted skin was flexible and supple with free articular and functional movement
- hypertrophic scar formation was not observed on areas grafted with Integra®, but did occur in some instances on neighbouring injured sites

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\* In the text, it was reported that no infections were associated with the use of Integra®. However in Table 1, patient 4 was reported to have had a localised infection. There are no details of when this infection occurred (i.e. before, during or after Integra® grafting), thus these results appear to contradict each other.

- after amputation of finger extremities, Integra<sup>®</sup> was successfully grafted over the exposed bones of the dorsal area of the fingers with optimal cosmetic and functional results.

Patient characteristics can be found in Table 1 at the end of the summary.

### **RECONSTRUCTIVE SURGERY**

In total, reconstructive surgery was performed on 14 hands in 11 patients (five males, six females); ten were treated for thermal burns and one for an electrical burn. Median time after burn was 18 months (range 3-132 months). Median length follow-up was 12 months (range 3-36 months).

#### **Safety:**

- no infections were reported with Integra<sup>®</sup>
- no infections occurred at any of the donor sites.

#### **Efficacy:**

- Integra<sup>®</sup> was successfully grafted on all patients
- 2/15 (13%) hands required Z-plasties for interdigital contractures
- significant improvements in suppleness based on Vancouver Scar Scale (validated scale) (p=0.0002) were reported, with the median decreasing from 10 to 2
- significant improvements in function status were achieved:
  - thumb opposition score (p=0.0005), median increased from 3.5 to 9.5
  - fingertip-to-palm distance (p=0.0039), median decreased from 6.5 to 2.0
  - prehensile score (p=0.0039), median increased from 13 to 61
- donor sites healed within 8-10 days
- no appreciable scarring occurred at any of the donor sites.

Patient characteristics and cosmetic and functional outcomes can be found in Table 2 and 3, respectively, at the end of the summary.

In this small study, the results indicate that from both a cosmetic and functional outcome, grafting with Integra<sup>®</sup> may become a promising treatment for deep hand burns either for acute grafting or reconstructive surgery.

#### **Ethical issues:**

- the use of animal tissue may raise issues for vegans/vegetarians and animal rights activists.

#### **Cultural or religious considerations:**

- the collagen portion of the graft is composed of bovine material which is eventually absorbed by the body; this may raise issues for the Hindu and Buddhist community

#### **Other issues:**

- this procedure is technically demanding and requires meticulous surgical technique

- patients with an allergy to bovine collagen, chondroitin or silicone materials should not be treated by this graft
- Integra<sup>®</sup> should not be used in the presence of infection
- there are no clinical studies evaluating the use of Integra<sup>®</sup> in pregnant women
- regulatory approval has been granted in 24 countries, with approval in additional countries pending
- multicentre trials evaluating the safety and efficacy of Integra<sup>®</sup> for burn injuries have been conducted with encouraging results<sup>1,5</sup>
- Integra<sup>®</sup> is the only treatment proven to regenerate functional dermal tissue
- advantages of using Integra<sup>®</sup> in reconstructive surgery are immediate availability of large quantities, simplicity of the technique, use of only thin grafts of the patient's own epidermis, pliability and cosmetic appearance of the resulting skin
- disadvantages of using Integra<sup>®</sup> are the necessity of a two-stage operation, risk of infection under the silicone layer and detachment of silicone layer.<sup>9</sup>

### **Conclusion:**

Limited evidence exists on the safety and efficacy of this procedure for treatment of deep hand burns. Long-term safety and efficacy data would be required before this procedure could be routinely used. With reports of patient satisfaction and few negative outcomes for treatment of deep hand burn injuries, this study demonstrates the feasibility of grafting with Integra<sup>®</sup>.

### **HealthPACT decision:**

Due to the sizeable amount of information on the safety and efficacy of Integra<sup>®</sup> as a skin substitute in patients with third-degree burns (not detailed in this summary), it is recommended that this procedure should be included in an Accelerated Systematic Review on various types of artificial skin to be assessed by ASERNIP-S in the future.

### **REFERENCES:**

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#### **SOURCES OF FURTHER INFORMATION:**

Dantzer E, Queruel P, Salinier L *et al.* The use of Integra<sup>®</sup> Artificial Skin in the treatment of deep burns of the hands in the acute phase and in reconstructive surgery. *Brûlures* 2000;**1**:89-97.

Jones I, Currie L, Martin R. A guide to biological skin substitutes: review. *British Journal of Plastic Surgery* 2002;**55**:185-93.

Jones I, James E, Rubin, P, Martin R. Upward migration of cultured autologous keratinocytes in Intergra<sup>™</sup> artificial skin: a preliminary report. *Wound Repair and Regeneration* 2003;**11**(2):132-8.

#### **SEARCH CRITERIA:**

A search of MEDLINE, PubMed and Cochrane Library, Current Controlled Trials metaRegister, UK National Research Register, International Network for Agencies for Health Technology Assessments, relevant online journals and the Internet was conducted in January 2004.

Search terms used were: Integra dermal regeneration template, Integra hand, Integra hand burn, burn injur\* Australia, hand burn, reconstruct\* Integra.

**TABLE 1: Characteristics of acute surgery patients with 3<sup>rd</sup>-degree burns to the dorsum of the hand (Dantzer *et al.* 2003)<sup>3</sup>**

Patient	Sex	Age (y)	Initial % TBSA burned	Days to graft	Hands grafted	Vancouver Scar Scale	Follow-up (mo)	Comment
1	M	18	45	5	1	4	12	Spontaneous healing after mechanical dislodgement of epidermal autograft on left hand; Z-plasties required for interdigital contractures on 2 <sup>nd</sup> , 3 <sup>rd</sup> and 4 <sup>th</sup> web spaces of both hands
2	F	41	40	3	1	3	12	
3	F	62	28	3	1	0	12	Localised infection of the epidermis resolved with use of topical antibiotics Silicone layer on left hand detached prematurely
4	M	45	6	3	1	2	12	
5	M	52	50	2	2	4	1	Silicone layer on left hand detached prematurely
6	F	73	30	2	1	4	1	
7 <sup>a</sup>	M	29	1	3	1	5	12	Silicone layer on left hand detached prematurely
8	M	54	7	3	2	1	8	
9	M	51	51	3	2	4	12	Spontaneous healing after mechanical dislodgement of epidermal autograft on right hand; Z-plasties performed to treat interdigital web contractures on 1 <sup>st</sup> and 4 <sup>th</sup> web spaces of left hand and 1 <sup>st</sup> , 2 <sup>nd</sup> and 3 <sup>rd</sup> of right hand
10	M	56	54	2	2	4	12	
11	M	58	60	3	1	-	9	Integra grafted directly over exposed bones obviated amputation

TBSA – total body surface area. Size of Integra graft 250 cm<sup>2</sup> in all cases except patients 4 and 7, who received 125 cm<sup>2</sup> grafts.

<sup>a</sup>Thermal injury to the palm.

**TABLE 2: Characteristics of reconstructive surgery patients (Dantzer *et al.* 2003)<sup>3</sup>**

Patient	Sex	Age (y)	Initial % TBSA burned	Months from burn	Hands grafted	Follow-up (mo)	Comment
1	F	30	57	11	2	36	Contractures, hypertrophy on dorsum of both hands
2	F	43	47	11	1	24	Contracture of left thumb
3	M	45	6	3	1	12	Palmar, wrist scarring with neurovascular compression of median and ulnar nerves
4	M	53	7	12	1	18	Palmar scarring resulting in thumb adduction and extended fingers; normal palmar arch restored
5	F	58	30	18	2	12-20	Adherent grafts on forearm and dorsal hand
6	F	19	55	24	1	3	Adherent grafts of right hand and forearm, finger and wrist flexion impossible
7	M	39	16	24	2	14	Bilateral hypertrophic scars of dorsum, thumb column and forearms
8	F	32	38	132	1	9	Resurfacing of dorsum of left hand
9	M	25	35	18	1	9	Hypertrophic scarring of dorsum of left hand
10	M	60	75	24	1	5	Adherent grafts on dorsum of left hand
11	F	8	7	8	1	5	Hypertrophic scarring of dorsum of right hand

TBSA – total body surface area. Average surface area of graft was 182 cm<sup>2</sup> (80-250).

**TABLE 3: Cosmetic and functional outcomes in hands after reconstructive procedures (Dantzer *et al.* 2003)<sup>3</sup>**

Outcome	Pretreatment		Posttreatment		Pre- vs. posttreatment		n	p
	Median	Range	Median	Range	Median	95% CI		
Cosmetic status								
Vancouver Scar Scale score	10	4-14	2	1-3	7.0	5.0-8.0	13 <sup>a</sup>	0.0002
Functional status								
Thumb opposition score	3.5	0-7	9.5	6-10	5.2	4.0-7.0	12 <sup>b</sup>	0.0005
Fingertip-to palm distance (cm)	6.5	4.0-8.5	2.0	0.0-5.5	4.2	3.6-5.2	9 <sup>c</sup>	0.0039
Prehensile score	13	0-46	61	36-72	33.0	24.5-43.5	9 <sup>d</sup>	0.0039

CI – confidence interval, <sup>a</sup> 13 hands in 11 patients, <sup>b</sup> 12 hands in 9 patients, <sup>c</sup> 9 hands in 7 patients; analysis was performed using pooled median values for the separate measurements of distance from palm to each of four fingertips on each hand, <sup>d</sup> 9 hands in 7 patients.