INTESTINAL TRANSPLANTATION

DISCUSSION PAPER

HealthPACT
Health Policy Advisory Committee on Technology
Australia and New Zealand
# TABLE OF CONTENTS

**BACKGROUND** ................................................................................................................................. 1  
  Introduction................................................................................................................................. 1  
  Emerging and established technologies – HealthPACT and Nationally Funded Centres........... 1  
  The workshop ................................................................................................................... .......... 1  

**INTESTINAL FAILURE** ................................................................................................................... 2  

**PARENTERAL NUTRITION** ....................................................................................................... 3  

**INTESTINAL TRANSPLANTATION** ........................................................................................... 4  
  Clinical indications for transplantation ....................................................................................... 6  
  International clinical activity ....................................................................................................... 6  
  National clinical activity ............................................................................................................... 7  
  Clinical outcomes ...................................................................................................................... 8  
  Unresolved issues ....................................................................................................................... 8  

**SUMMARY** ......................................................................................................................................... 9
BACKGROUND

Introduction
DLA Piper has been engaged by Queensland Health on behalf of the Health Policy Advisory Committee for Technology (HealthPACT) to facilitate a workshop to be held on 10th November 2011.

The workshop will bring together clinicians, health service managers and policymakers in order to examine the provision of intestinal transplantation services within the Australian health system.

This Discussion Paper has been developed in preparation for the workshop. The Discussion Paper has been informed by a targeted review of the peer-reviewed and ‘grey’ literature and by individual interviews with HealthPACT secretariat-nominated workshop invitees.

Emerging and established technologies – HealthPACT and Nationally Funded Centres
HealthPACT is a sub-committee of the Australian Health Ministers Advisory Council (AHMAC), reporting directly to the Clinical, Technical and Ethical Principal Committee (CTEPC). HealthPACT comprises representatives from all State and Territory health departments, the Australian Department of Health and Ageing, the Medical Services Advisory Committee (MSAC), the New Zealand Ministry of Health and the New Zealand District Health Boards.

HealthPACT provides jurisdictions with evidence-based advice on emerging technologies. This information is used to inform jurisdiction financing decisions and to assist in the managed introduction of new technologies.

The Nationally Funded Centres (NFC) program was established in 1990 by the Australian Health Ministers Conference (AHMC) to implement a national policy for public sector provision of high cost and highly specialised clinical practices and technologies with limited demand, to ensure equitable access to these practices and technologies for all Australians.

For a technology to be considered for provision as a NFC, it must be an established clinical practice requiring a national population base for efficient and effective service provision. A technology may also be considered if it is a clinical practice in the establishment phase and has yet to be incorporated into standard clinical practice, but has the potential for broader diffusion into the Australian health system.

AHMC appointed the Australian Health Minister’s Advisory Council (AHMAC) to oversee all aspects of the NFC program and associated policy. To manage the NFC program, AHMAC established the NFC Reference Group, which comprises of a representative from the Australian Government and each state and territory. The NFC Reference Group is supported by a secretariat to undertake the administration of the program. The NFC Secretariat is currently based in SA Health.

The workshop
The NFC Reference Group received a nomination from Victoria in December 2010 seeking consideration of intestinal transplantation as a potential NFC Program.
Jurisdictions, including relevant clinicians, were consulted on the submission. NFC Reference Group members determined that nationally there had not been enough procedures performed to validate the submission. There was some discussion of NFC funding being used to establish an intestinal transplantation program. However this is not the purpose of NFC funding, a position supported by the CTEPC and AHMAC.

NFC Reference Group members agreed that a level of enhanced leadership was required to work with the Austin Hospital and the Royal Children’s Hospital Melbourne to establish where intestinal transplantation services sit within the Australian health landscape. NFC Reference Group members therefore recommended to CTEPC that HealthPACT work with Austin Hospital to identify options for supporting the development of a service model for provision of access to intestinal transplantation services to Australians in whom the procedure may be indicated.

**INTESTINAL FAILURE**

Intestinal failure is the inability to maintain protein, energy, fluid, electrolyte or micronutrient balance when on a normal diet\(^1\). A variety of endogenous and iatrogenic gastrointestinal diseases lead to intestinal failure. Worldwide, the leading cause of intestinal failure is short gut due to the surgical removal of intestinal length. Underlying pathology leading to intestinal failure is as follows\(^2\):

- in children, intestinal atresia, gastroschisis, Crohn’s disease, microvillus involution disease, nectrotising enterocolitis, midgut volvulus, chronic pseudo-obstruction, tumours and Hirschprung’s disease are leading causes of intestinal failure.
- in adults, Crohn’s disease, superior mesenteric artery or vein thrombosis, trauma, tumours, volvulus, pseudo-obstruction and radiation enteritis are leading causes of intestinal failure.

Untreated, intestinal failure leads to increased malnutrition and may result in premature mortality. The therapeutic options for managing intestinal failure are\(^3\):

- intestinal rehabilitation;
- parenteral nutrition; and
- intestinal transplantation.

Intestinal rehabilitation is the process by which water, macronutrient and micronutrient digestion and absorption are enhanced through bowel adaptation. This is achieved through a

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multidisciplinary approach, and may include enteral feeding, micronutrient supplementation, pharmacotherapy and surgery. As bowel adaptation may take a number of years, patients are generally supported with parenteral nutrition in the short term.

Surgery may be a rehabilitative therapeutic option, particularly for patients with short bowel syndrome. Surgical strategies may be used to restore intestinal continuity, relieve obstruction/dysmotility, lengthen remaining dilated intestine or prolong transit time.

If intestinal rehabilitation fails, therapeutic management of intestinal failure may be long-term parenteral nutrition (PN) or intestinal transplantation. The incidence of irreversible intestinal failure is estimated at 2 to 3 cases per million persons per year. This translates to approximately 40 to 60 Australians each year in whom management of irreversible intestinal failure by either long-term PN or transplantation is required.

PARENTERAL NUTRITION

Home parenteral nutrition (PN) is the standard of care for the majority of patients with intestinal failure. The therapy is used primarily as an outpatient management strategy for intestinal failure but may be administered on an inpatient basis for some patients. The 1-year and 4-year survival rates of patients receiving PN vary according to the underlying condition for which the therapy is provided. Patients with short bowel syndrome achieve estimated 1-year survival of 94% and 4-year survival of 80% whereas those with paediatric motility disorders achieve 70% 4-year survival. For some patient subgroups survival is poorer. For example, those with less than 50 cm of jejunoileum have lower than 60% 5-year survival.

Patients on long-term PN may experience severe and life-threatening complications associated with therapy. Severe complications include recurrent catheter sepsis, thrombosis, hepatic fibrosis.

4 Shatnawei A. Intestinal failure management at the Cleveland Clinic. Archives of Surgery 2010; 145; 521-7.


6 Shatnawei A. Intestinal failure management at the Cleveland Clinic. Archives of Surgery 2010; 145; 521-7.


8 Shatnawei A. Intestinal failure management at the Cleveland Clinic. Archives of Surgery 2010; 145; 521-7.

9 Gupte G. Current issues in the management of intestinal failure. Archives of Disease in Childhood 2006; 91: 259-64.

Severe liver injury has been reported in up to 50% of patients with intestinal failure who receive parenteral nutrition for longer than 5 years. This is typically fatal and is the highest PN-associated mortality complication\textsuperscript{13}. However, approximately 50% of deaths among patients receiving home PN are related to causes other than home PN\textsuperscript{14}.

### Areas for further consideration:

- Management of intestinal failure requires a multidisciplinary team experienced in the assessment and treatment of this group of patients. What are the current service arrangements for management of patients with intestinal failure across jurisdictions?

- Intestinal rehabilitation should be achieved wherever possible as this option presents the best long-term outcome for patients and avoidance of transplantation or PN. Successful intestinal rehabilitation requires coordinated care to be delivered by a multidisciplinary team experienced in the assessment and management of intestinal failure. How is intestinal rehabilitation being delivered across jurisdictions for patients in whom rehabilitation indicated?

- Centres experienced in the management of intestinal failure should select candidates for intestinal transplantation from a pool of patients who have received comprehensive assessment and who have either failed alternative therapies or are unsuitable for alternative therapies. What is the jurisdictional capability for identifying patients in whom transplantation may be indicated?

### INTESTINAL TRANSPLANTATION

Intestinal transplantation is the therapeutic option for managing patients with intestinal failure who develop irreversible complications associated with the chronic use of PN or in whom chronic use of PN is not indicated.


\textsuperscript{13} Chan S. Incidence, prognosis and etiology of end-stage liver disease in patients receiving home total parenteral nutrition. Surgery 1999; 126: 28-34.

Intestinal transplant is an established procedure internationally. The first intestinal transplant in humans was performed in the 1960s. However, morbidity and mortality associated with the procedure were high until the early 1990s, leading to a moratorium being placed on the procedure by the US Medicare agency in 1995.\(^\text{15}\) After 1995 rapid improvements in outcomes were achieved. This was largely attributed to improvements in immunosuppression, particularly the introduction of tacrolimus. Improvements in surgical technique and after-care also contributed to improved morbidity and mortality.\(^\text{16}\)

Since that time surgical activity has increased internationally (Figure 1).

**Figure 1: Intestinal transplants by year, children and adults, 1985 to 2011 (ITR\(^\text{17}\), 2011)**

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\(^\text{17}\) Intestine Transplant Registry Report, 2011
Clinical indications for transplantation

The indications for intestinal transplantation are still debated. However, intestinal transplantation is broadly recommended in patients with:

- failure of parenteral nutrition (impending or overt liver failure, thrombosis of ≥2 central veins, ≥2 episodes per year of systemic sepsis, frequent episodes of severe dehydration);
- high risk of death;
- severe short bowel syndrome (i.e. gastrostomy, duodenostomy, small residual small bowel (<10 cm in infants / < 20 cm in adults);
- intestinal failure with frequent hospitalisations, narcotic dependency or pseudo-obstruction; and
- patient unwillingness to accept long-term parenteral nutrition.

In 63% of children and 65% of adults, short gut is the underlying clinical indication leading to intestinal transplantation. Leading causes of paediatric short gut treated by transplantation include gastroschisis (25%), enterocolitis (15%) and volvulus (13%). In adults, leading causes of short gut resulting in transplantation include ischaemia (24%, Crohns disease (13%) and volvulus (11%). Other leading indications for paediatric intestinal transplantation include motility disorders (29%) and mucosal defects (10%). In adults, motility disorders (15%) and tumours (8%) lead to intestinal transplantation being clinically indicated.

The United Network for Organ Sharing (UNOS) has specified a policy for intestinal organ allocation.

International clinical activity

It is estimated that 2,611 intestinal transplantation procedures have been performed worldwide to date. There are now approximately 35 active intestinal transplant centres worldwide and an additional 44 transplant centres that have performed intestinal transplantation at some time since 1985 but are not currently active.

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20 Intestine Transplant Registry Report, 2011


22 Data in this section derived from The Intestine Transplant Association Intestine Transplant Registry Report (2011) (reported with permission).
There are currently approximately 180 intestinal transplant procedures performed worldwide each year. Numbers are slightly higher for adult compared with paediatric patients (approximately 105 versus 75 procedures a year respectively). The number of transplants that have been performed in total at each centre varies between centres, from fewer than 10 transplants to almost 600 transplants in total.

Intestinal transplants are classified by the Intestine Transplant Association as:

- SBT – intestine, no liver or stomach
- Liver / SBT – intestine, liver, no stomach
- MVT - intestine, stomach, no liver (modified) OR intestine, stomach and liver (full).

UNOS defines a multivisceral transplant as one that includes the intestine and liver and either the pancreas or kidney; however several combinations may be used.

A total of 44% of transplants performed worldwide to date have been SBT, 32% have been liver / SB and 24% have been MVT. Patterns are changing over time. In 2010/2011, almost 60% of transplants were SBT, 25% were MVT (full or modified) and 15% were liver / SB. Up to 15% of all transplantations performed each year are re-transplantation procedures – either second graft (13%) or third graft (2%).

Immediately prior to transplantation, the majority of paediatric (70%) and adult (80%) patients are living at home. However, 5% of paediatric patients and 2% of adult patients are inpatients of ICU and 25% of paediatric patients and 18% of adult patients are hospital inpatients immediately prior to transplantation.

The median length of stay of patients after intestinal transplantation has decreased over time, from over 100 days in the early 1990s to approximately 50 days currently.

**National clinical activity**

National models of care for the management of intestinal failure are not well defined in the peer-reviewed literature. Stakeholders consulted for the purposes of developing this Discussion Paper report that best-practice management of intestinal failure may be under-developed in some jurisdictions and is not provided in a systematic way nationally.

National experience with intestinal transplantation is limited. Australia’s first intestinal transplant was successfully performed in Victoria in 2010\(^2\). Melbourne’s Austin Health and Royal Children’s Hospital Melbourne are currently exploring options and feasibility of offering intestinal transplantation procedures. There are approximately 10 paediatric patients that have been referred from interstate to Victoria for this procedure. There is an inferred expectation by families and clinicians that patient assessment and management will be provided. However this has not occurred to date.

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Patients have been referred overseas to receive intestinal transplantation (3 children and 2 adults since 1997). Costs incurred with international treatment have in some cases been very large, particularly when complications of treatment occurred.

**Clinical outcomes**

The 1-year survival of patients is approximately 80% and the 5-year survival is approximately 50%. Patient survival varies between paediatric and adult patients and has improved over time. Patient survival in paediatric patients is generally better than in adult patients and varies according to graft type (Figure 2).

**Figure 2: Patient survival by surgical ‘era’, children and adults, 1985/89 to 2006/11**

According to the Intestinal Transplant Association a functioning graft is defined by freedom from IV fluids and PN with normal serum albumin (and acceptable growth parameters in children). After transplantation, approximately 50% of children and 45% of adults are free from parenteral nutrition. A further 15% of children and 5% of adults are partially free from parenteral nutrition and receive IV fluids. The remaining 20% of children and adults have no function (functional status of 15% of children and 30% of adults is unknown).

**Unresolved issues**

A range of issues that require further study have been identified in the literature. These include:

- The relative advantages of home PN versus intestinal transplantation in various patient subgroups with intestinal failure;

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24 Data in this section derived from The Intestine Transplant Association Intestine Transplant Registry Report (2011) (reported with permission).

• Long-term graft function and patient outcomes in children, particularly growth and developmental outcomes;

• Quality of life impacts of various treatment options for intestinal failure;

• The post-operative course of patients, including time to recovery after the intestinal transplant, sustainability of the allograft and post-transplant illnesses (including hypertension, diabetes and impaired renal function);

Further, although not extensively studied, available evidence suggests that intestinal transplantation may be less costly than home PN\textsuperscript{26}. Further research is required to assess the cost-effectiveness of various treatment strategies for intestinal failure.

### Areas for further consideration:

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<th>How should Australian patients in whom intestinal transplantation is indicated gain access to the procedure?</th>
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If intestinal transplantation is to be made available in Australia:

• What is the anticipated demand for intestinal transplantation services in Australia?

• Which elements of pre-care should be delivered by the transplantation service? Which elements should be delivered by the jurisdictions?

• Which elements of after-care should be delivered by the transplantation service? Which elements should be delivered by the jurisdictions?

• What are the implications of SBT, liver/SBT, and MVT on access to suitable donor organs, organ retrieval and other transplant services?

• What are the workforce requirements for establishing services – transplant service / jurisdictional / other workforce

### SUMMARY

Best practice management of patients with intestinal failure results in many patients achieving intestinal rehabilitation. Where intestinal rehabilitation fails or is not possible, long-term PN or intestinal transplantation are the available therapeutic options.

Although intestinal transplantation is performed in numerous surgical centres internationally, the procedure is not currently well established in Australia. A small number of patients have received intestinal transplants overseas with varying levels of therapeutic success.

Developing Australia’s capability to perform intestinal transplantation may provide Australians with better access to this service. However, development of a national intestinal transplantation service capability should occur in the context of an integrated, best practice service model for management of intestinal failure.

The forthcoming HealthPACT workshop provides an opportunity for clinicians, health managers and policymakers to discuss the provision of intestinal transplantation services within the Australian health care context, and to consider the capacity of jurisdictional models of care for patients with intestinal failure to support intestinal transplantation service development and delivery.