Review of Paediatric Liver Transplantation

Nationally Funded Centres Program

Report - 5/5/2014

DLA Piper
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EXECUTIVE SUMMARY

This is the report of a comprehensive review of the Australian Nationally Funded Centres ("NFC") Program for paediatric liver transplantation. The three NFC sites are the Sydney Children's Hospital Network (Westmead), the Royal Children's Hospital (Brisbane) and the Royal Children's Hospital (Melbourne).

The review team considers that paediatric liver transplantation fulfils the requirements for continuation in the NFC Program because the surgical procedure is an established clinical practice, the current national annual caseload is low and the procedure is high cost, with an estimated total cost of $270,681 for each transplant. Current caseloads are sufficient to support a maximum of three NFC sites nationally.

Liver transplantation is the definitive treatment for end-stage liver disease in children, metabolic conditions in a small subgroup of patients without end-stage liver disease and patients with hepatoblastoma or other liver tumours. Advances over the last two decades have resulted in improved patient and graft survival, attributed to improved surgical techniques, surgical experience, immunosuppressive regimens, intraoperative anaesthetic management and pre and post-operative care. Patient and graft survival at one and five years is over 90% in Australia and internationally.

The number of paediatric patients receiving liver transplantation has increased over time and is currently between approximately 30 and 40 per year.

Surgical techniques for paediatric liver transplantation include whole liver transplantation, reduced-size liver transplantation, split liver transplantation and living donor liver transplantation. Split liver grafts are the most common type of graft transplanted in paediatric patients in Australia. Patient survival after transplantation is equivalent for different graft types.

Listing for transplantation occurs after comprehensive clinical assessment of the patient. The Transplantation Society of Australia and New Zealand defines donor liver allocation criteria based on category of urgency. Patients have potentially prolonged preoperative waiting periods for donor organs to become available. Care needs during this period are highly specialised. Peri-operative management depends on the type of graft the recipient receives and their underlying clinical condition. The immediate post-operative phase includes an intensive care unit admission of approximately 10 days and a ward stay of approximately twenty-five days.

Health-related quality of life after paediatric liver transplantation is good and improves over time. In the long-term the majority of patients are satisfied with their quality of life and health status. However, delayed educational attainment and higher unemployment are more common than in the general population. Rejection is the most common complication after liver transplantation and occurs in approximately one third of patients over time. Between 10% and 30% of paediatric patients will require re-transplantation at some stage over the course of their life. The most common indication for re-transplantation is vascular complications.

Within Australia, access to paediatric liver transplantation is equitable across jurisdictions. Approximately 70% of patients referred are accepted for transplantation and, of these, 90% receive a liver transplant. The Sydney Children’s Hospital Network (Westmead) performs the largest number of paediatric liver transplants of the three NFC sites (46%). Patient and graft survival are comparable between NFC sites and current procedure volumes are sufficient to achieve high quality outcomes across the three sites.

Current NFC arrangements for paediatric liver transplantation maximise the support that is delivered locally in the pre- and post-operative phases of the patient’s care. Referring clinicians are well
supported by transplant centres to have ongoing involvement in the patient's care and have close communication with the paediatric transplant team when appropriate.

The review team identified opportunities for improvements in succession planning, referral practices, clinical decision protocols and guidelines, data collection, reimbursement and the management of patients with biliary atresia over the course of the review.

Succession planning has been recognised in previous reviews as an important issue affecting the program's sustainability and was found in this review to continue to be an issue for the program. All three services draw on a similar mix of clinical staff. Whilst succession planning for paediatric liver transplant surgeons has improved, further succession planning for paediatric hepatologists and specialist liver transplant nurses is required.

The early referral of patients with end-stage liver disease assists NFC liver transplant sites to maximise the patient’s pre-transplant health, schedule liver transplantation at the best time for the patient and maximise opportunities for recovering hepatic function in patients whose illness is reversible. The review team identified that referring sites do not necessarily refer patients with end-stage liver disease in a timely manner, with negative morbidity and mortality consequences for patients. In view of this, promulgation of guidance is warranted for paediatric intensive care units and general paediatric units on the assessment and early management of liver failure to ensure patients are referred early and in a stable condition to the NFC transplant units.

Although outcomes across the three sites appear broadly consistent and comparable to the best paediatric liver transplant centres internationally, direct comparison between sites was problematic for the review team due to multiple variations in data collection practices. Standardised data definitions and reporting methods are required to improve the quality of reporting from the three NFC sites. It is the review team’s opinion that the Australian and New Zealand Liver Transplant Registry provides an appropriate data collection system to aggregate data that is collected and to streamline reporting processes for the Program.

Living donor liver transplants require procurement of a liver graft from an adult donor. This is a subject of ethical debate due to the impacts on the live donor of partial hepatectomy, including the morbidity and risk of mortality that is associated with the procedure. Liver transplantation in paediatric patients of grafts of marginal quality is also a subject of ethical debate as morbidity and mortality after such procedures are higher. The review team was made aware of variations in clinical decision-making across the three sites in relation to when living donor transplants were performed and in the use of marginal donors. The review team considers that the NFC paediatric liver transplant program requires clinical guidelines and protocols for clinical decision-making that are harmonised across the three sites to ensure a consistent approach to living donor transplantation and the use of marginal donors.

Reimbursement for NFC sites does not remunerate sites for delivering all elements of the paediatric liver transplant service model. Costs associated with procuring the donor graft from the adult are not currently reimbursed by the NFC Program. The hospital performing the adult donor procedure is significantly financially disadvantaged because usual funding streams do not cover the costs associated with providing this service for the paediatric liver transplantation NFC site. The review team considers that in order to ensure this cost does not impact on the best management of the child it is appropriate that the NFC Program reimburses this cost. Similarly, costs of organ retrieval represent a significant impost in terms of workforce availability and costs. These costs are also not reimbursed by the NFC Program. The NFC Reference Group should consider whether these costs should be incorporated into the NFC funding stream.

Finally, biliary atresia is the most common cause of liver failure in paediatric patients awaiting liver transplantation. When diagnosed at birth the treatment of choice is Kasai portoenterostomy. When
performed promptly and effectively, this procedure delays primary liver transplantation. There is an established volume-quality relationship for the Kasai procedure. High volume centres generally achieve better outcomes than lower volume centres, particularly when the high volume centre also performs liver transplantation. It was outside the scope of this review to determine current clinical practice for Kasai portoenterostomy in Australia. However, because this is a significant upstream issue that affects demand for, and outcomes associated with, paediatric liver transplantation, the review team considers that exploration of current surgical practice for Kasai portoenterostomy in Australia is warranted.
RECOMMENDATIONS

Recommendation 1

That based on caseload, current equitable geographic access and efficient provision of services, paediatric liver transplantation continues to be funded as a Nationally Funded Centres Program, with three sites continuing to provide transplants.

Recommendation 2

That to address succession planning, each Nationally Funded Centres site and host jurisdiction develops, implements and maintains a comprehensive workforce management and training plan.

Recommendation 3

That the Nationally Funded Centres sites develop and promulgate nationally agreed guidance for general paediatric units on the assessment and early management of liver failure to ensure that where possible patients are referred early and in a stable condition to the Nationally Funded Centres sites.

Recommendation 4

That the Nationally Funded Centres sites continue to provide annual reports about quality of care to the Nationally Funded Centres Secretariat, but that reporting requirements are extended to include annual and aggregate complication rates across the full cohort of transplant patients by all three sites in accordance with standardised data definitions and reporting methods.

Recommendation 5

That the Nationally Funded Centres sites continue to progress implementing recommendations 1 and 3 of the 2007 review, with a view to standardising clinical care and data collection by:

- working towards consistent clinical practice guidelines and protocols across all three sites, particularly in relation to living donor liver transplantation and the use of marginal donors, but not where it is likely to impede the development of new, effective techniques;
- developing a post-transplant care pathway which facilitates the involvement of the patient’s usual paediatrician; and
- developing a systematic process of data collection that is based on the Australian and New Zealand Liver Transplant Registry data collection system and that meets the needs of the Nationally Funded Centres Secretariat for regular reporting by sites.

Recommendation 6

That paediatric liver transplants provided through the Nationally Funded Centres Program are funded at a rate of $270,681 for each transplant.

Recommendation 7

That the Nationally Funded Centres Reference Group considers mechanisms to fund the assessment, work-up, surgery and outpatient care for living related donor surgery undertaken by adult liver transplant hospitals to provide donor organs for the Nationally Funded Centres paediatric liver transplantation sites.
Recommendation 8

That the Nationally Funded Centres Reference Group considers undertaking further work in collaboration with the Australian Organ and Tissue Authority regarding opportunities for funding organ retrieval that is being undertaken to provide organs for the Nationally Funded Centres sites.

Recommendation 9

That the Nationally Funded Centres Reference Group explores service concentration for Kasai portoenterostomy in Australia.
## TERMS AND ABBREVIATIONS USED IN THIS REPORT

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABO</td>
<td>The ABO blood group system</td>
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<td>ABS</td>
<td>Australian Bureau of Statistics</td>
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<td>ACR</td>
<td>Acute cellular rejection</td>
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<td>AHMAC</td>
<td>Australian Health Ministers’ Advisory Council</td>
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<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
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<tr>
<td>ANLTU</td>
<td>Australian National Liver Transplant Unit</td>
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<tr>
<td>ANZLTR</td>
<td>Australian and New Zealand Liver Transplant Registry</td>
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<tr>
<td>BA</td>
<td>Biliary atresia</td>
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<tr>
<td>CAH: AI</td>
<td>Chronic active hepatitis: Autoimmune</td>
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<tr>
<td>CC</td>
<td>Cryptogenic cirrhosis</td>
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<tr>
<td>CMP</td>
<td>Comprehensive metabolic panel</td>
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<tr>
<td>CNC</td>
<td>Clinical nurse consultant</td>
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<tr>
<td>CT</td>
<td>Computerised tomography</td>
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<tr>
<td>DCD</td>
<td>Donation after cardiac death</td>
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<tr>
<td>ECG</td>
<td>Electrocardiograph</td>
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<tr>
<td>FBC</td>
<td>Full blood count</td>
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<tr>
<td>FBE</td>
<td>Full blood examination</td>
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<tr>
<td>FCH</td>
<td>Free-standing children's hospital</td>
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<td>FHF</td>
<td>Fulminant hepatic failure</td>
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<td>HCC</td>
<td>Hepatocellular carcinoma</td>
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<td>HPC</td>
<td>Hospitals Principal Committee</td>
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<td>ICU</td>
<td>Intensive care unit</td>
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<td>IGF</td>
<td>Insulin-like growth factor</td>
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<td>INR</td>
<td>International Normalised Ratio</td>
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<td>LDLT</td>
<td>Living donor liver transplantation</td>
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<td>LFT</td>
<td>Liver function test</td>
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<td>MAL</td>
<td>Malignancy</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<tr>
<td>MELD</td>
<td>Model for end-stage liver disease</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>MSAC</td>
<td>Medical Services Advisory Committee</td>
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<td>NFC</td>
<td>Nationally Funded Centres</td>
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<td>OLT</td>
<td>Orthotopic liver transplantation</td>
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<td>OPTN</td>
<td>Organ Procurement and Transplant Network</td>
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<tr>
<td>PAH</td>
<td>Princess Alexandra Hospital</td>
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<td>PELD</td>
<td>Paediatric end-stage liver disease</td>
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<td>PICU</td>
<td>Paediatric intensive care unit</td>
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<tr>
<td>PSC</td>
<td>Primary sclerosing cholangitis</td>
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<tr>
<td>PTLD</td>
<td>Post-transplant lymphoproliferative disease</td>
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<tr>
<td>RCHB</td>
<td>Royal Children's Hospital Brisbane</td>
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<td>RCHM</td>
<td>Royal Children's Hospital Melbourne</td>
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<tr>
<td>RPAH</td>
<td>Royal Prince Alfred Hospital</td>
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<tr>
<td>RSLT</td>
<td>Reduced-size liver transplantation</td>
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<tr>
<td>SCHN(W)</td>
<td>Sydney Children’s Hospital Network (Westmead)</td>
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<tr>
<td>SLT</td>
<td>Split liver transplantation</td>
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<tr>
<td>SPLIT</td>
<td>Studies of Paediatric Liver Transplantation registry</td>
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<tr>
<td>Split-LRD</td>
<td>Split living related donor</td>
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<td>TSANZ</td>
<td>Transplant Society of Australia and New Zealand</td>
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<tr>
<td>UCSF</td>
<td>University of California, San Francisco</td>
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<tr>
<td>UEC</td>
<td>Urea, electrolytes and creatinine</td>
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<tr>
<td>UNOS</td>
<td>United Network of Organ Sharing</td>
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<tr>
<td>VLTU</td>
<td>Victorian Liver Transplant Unit</td>
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THE NATIONALLY FUNDED CENTRES PROGRAM

At the June 1990 Australian Health Ministers’ Conference (now called the Standing Council on Health), Ministers endorsed a national policy for public sector provision of high cost, highly specialised clinical practices and technologies with limited demand – the NFC Program.

NFCs are established to provide Australians with access to certain high cost, low demand, new and emerging technologies in a manner which optimises equitable access. They are approved by the Australian Health Ministers’ Advisory Council ("AHMAC") and funded by the State and Territory Governments. The NFC Reference Group, which includes representatives from the Australian Government and each State and Territory Government, is responsible for planning and managing the NFC Program including the assessment of new submissions and the commissioning of reviews of existing programs. The NFC Reference Group reports to AHMAC through the Hospitals Principal Committee ("HPC").

The objectives of the NFC Program are to ensure that:

- there is optimal access to certain high cost, low demand, new and emerging technologies regardless of geographic location, in the context of workforce and resource availability;
- these technologies are provided efficiently and effectively;
- requirements for high quality and safe introduction and ongoing provision of these technologies have been defined and implemented; and
- health and cost outcomes of these technologies are monitored and evaluated.

For a technology to be considered for inclusion in the NFC Program, it must be an established clinical practice requiring a national population base for efficient and effective service provision. Technologies eligible for consideration for provision through the NFC Program include devices, prostheses, techniques, skills or expertise (or personnel with skills or expertise) and/or procedures, or combinations of these.

NFCs for a particular technology may be established in one or more sites and there is an expectation that the technology will only be provided at those sites. States and Territories are expected to discourage the proliferation of NFC technologies in other health services within their jurisdictions. States and Territories are still required to contribute their share of funding to the NFC Program even if they elect to provide the procedure at a site other than an approved NFC site.

Funding for NFCs is provided by the States and Territories according to a weighted population-based formula. There is an agreed level of funding for each procedure. Because each State and Territory contributes financially, it is the expectation that the populations of each jurisdiction will receive equitable access to the services which are funded through the NFC.

Review of an existing NFC is commissioned when required by the NFC Reference Group. The basis of the assessment of proposals is set out in Nationally Funded Centres Guidance for Governance, Management, Funding, Establishment, Review ("NFC Guidance document"), the latest version of which was endorsed by AHMAC in September 2011.
Appendix 9 of the NFC Guidance document sets out the review criteria by which NFC Programs are to be assessed, which include:

- access to the NFC;
- health outcomes;
- model of care and service delivery;
- non-inpatient services;
- quality and safety;
- teaching, training and research;
- changes to clinical practice;
- service demand;
- cost; and
- risk management.

The assessment results in a report to the NFC Reference Group which in turn provides a report to AHMAC through the HPC. The possible recommendations from an assessment include:

- continue the existing activities of the NFC for a further defined period, with a further review to be conducted at the end of that period;
- withdraw NFC status effective by 30 June in the next calendar year from the date of the decision; or
- increase or decrease the number of sites for the delivery of the NFC.

Previous assessments

Reviews of liver transplantation were conducted in 1991 and 1993. The 1991 review recommended that NFC units for liver transplantation should be established. The 1993 review found that adult liver transplantation no longer met the criteria applying to NFCs, but recommended that liver transplantation should continue to be funded by this program for children less than three years of age to ensure high quality of care for these patients.

The 1993 NFC assessment resulted in three sites being approved for NFC status for the provision of paediatric liver transplantation ("PLT"):

- the Royal Children's Hospital, Brisbane ("RCHB")
- the Royal Children's Hospital, Melbourne ("RCHM"), and
- the New Children's Hospital, Westmead, Sydney, now known as the Sydney Children’s Hospitals Network (Westmead) ("SCHN(W)").
AHMAC requested a review of these sites in 1997. The results of that review were published in 2002. The review concluded that the sites continued to meet the criteria for NFC funding. Other significant recommendations were:

- that the age for PLT be raised to include all children up to and including 14 years of age, with children at the age of 14 to be assessed on an individual basis;

- that all sites develop the capacity to perform split liver transplantation ("SLT"); and

- that a prescribed format for data collection, including costs, be established to ensure uniformity in reporting.

In 2006, sites providing the PLT service were again scheduled for review to determine the need for continued NFC status. The review was conducted in accordance with AHMAC guidelines and considered access; health outcomes; service delivery; quality and safety; teaching, training and research; the need for continued service concentration; cost; and cost estimates. The criteria for the review of established NFCs were defined in the NFC Guidance document (April 2006) and the review was undertaken by the Medical Services Advisory Committee ("MSAC").

MSAC recommended that the procedure should continue to be funded under NFC arrangements with a further review in three years and based on estimated national demand of around 20 patients per year, the Committee considered that one NFC unit would be sufficient, but that two units would be appropriate having regard to access issues.

The review determined that the outcomes of all three sites compared well with international data in relation to one-year survival. It found that combined adult-paediatric units appeared to function at least as well, if not better, than stand-alone paediatric surgical units. It was therefore MSAC's view that combined adult-paediatric transplant units and a protocol driven approach to service delivery were likely to be a more viable approach in the future.

Specifically the review recommended:

- the development of paediatric liver transplant treatment and management guidelines to achieve reduction of morbidity and complications, especially those associated with split liver transplantation;

- that living-donor liver transplantation be performed in accordance with agreed selection and treatment guidelines;

- improved and consistent data collection, with a stronger emphasis on health outcomes, including quality of life; and

- that surgical workforce succession planning be addressed in a coordinated plan for training and workforce management.

This assessment

This report is the outcome of a comprehensive assessment of the NFC Program for paediatric liver transplantation. Once established as a NFC, the clinical practice/technology is reviewed between every three and five years.
The assessment was undertaken by DLA Piper (formerly DLA Phillips Fox) (Consultants: Dr Heather Wellington, Dr Paul Woodhouse, Dr Kelly Shaw) who were appointed following a competitive tender process. Expert clinical advice was provided by:

- Professor Stephen Munn, Clinical Director of the Intra-abdominal Organ Transplant Services Auckland City Hospital and Starship Children's Hospital New Zealand;
- Professor Hock Lim Tan, former Professor of Paediatric Surgery the University of Adelaide; and
- Dr Barry Duffy, former Director of Intensive Care Sydney Children's Hospital.

Copies of Professor Munn's and Professor Tan's comments on this report are included at Schedule 1. Dr Duffy also endorsed the report.

The assessment was conducted in accordance with the criteria set out in the NFC Guidance document. A Project Management Group was established by the NFC Reference Group to oversee and guide the assessment.

The three current NFC sites are the SChN(W), the RCHB and the RCHM.

The process for the assessment incorporated:

- a literature review;
- a site visit to the SChN(W) on 28 May 2012 with jurisdictional representatives and key staff from SChN(W) in attendance;
- a site visit to RCHM on 21 June 2012 with jurisdictional representatives and key staff from the RCHM in attendance;
- a site visit to RCHB on 16 July 2012 with jurisdictional representatives and key staff from the RCHB in attendance;
- telephone interviews and email surveys with clinicians from referring units in all jurisdictions;
- face-to-face and telephone interviews with patients and carers identified by SChN(W), RCHB and RCHM;
- review of information provided by SChN(W), RCHB and RCHM including:
  - each NFC site's annual Appendix 3 activity report to the NFC for the years 2008/09, 2009/10 and 2010/11;
  - a report based upon Appendix 9 in the NFC Guidance document;
  - costing data;
  - the presentations provided to the review team at the SChN(W), RCHB and RCHM site visits;
• analysis of Australian and New Zealand Liver Transplant Registry ("ANZLTR"), Australian Bureau of Statistics ("ABS") and Australian Institute of Health and Welfare ("AIHW") data; and

• further data requests to SHN(W), RCHB, and Austin Health, Melbourne, and analysis.

A summary of feedback provided by referring centres and by families accessing NFC sites is included at Schedule 2.

This report addresses the elements noted in Appendix 9 of the NFC Guidance document.
PAEDIATRIC LIVER TRANSPLANTATION

A detailed review of the peer-reviewed and "grey" literature is provided at Schedule 3. This section provides a summary of the key findings from the literature.

Liver transplantation is the definitive treatment for end-stage liver disease in children and adults. Advances over the last two decades have resulted in improved patient and graft survival. These advances are attributed to improvements in a range of factors, including surgical techniques, surgical experience, immunosuppressive regimens, intraoperative anaesthetic management and pre and post-operative care.\(^1\)\(^2\)

Patient and graft survival for orthotopic liver transplant ("OLT") (meaning the new liver is placed in the same location as the diseased liver) have continued to improve over time and patient survival at one year is now in excess of 90\%.\(^3\)

Children account for 10% to 18% of all liver transplants performed nationally and internationally.\(^4\)\(^5\) The majority receive their transplant before the age of five years. The paediatric patient group is distinct from adults receiving liver transplants in their aetiology of underlying disease, peri-operative transplant management, anaesthetic and surgical approach and post-operative care.\(^6\)

A major obstacle to paediatric OLT has been a lack of availability of a size-matched small liver allograft. Over time, innovative surgical techniques have been introduced to address this problem. Reduced-size liver transplantation ("RSLT"), split liver transplantation ("SLT") and living donor liver transplantation ("LDLT") have increased the allograft pool in paediatric patients. The first successful LDLT was performed in Brisbane, Australia, by Dr Russell Strong.\(^7\)

Clinical indications for transplantation

Liver transplantation is indicated most commonly when end-stage liver disease progresses to: \(^8\)

- hepatic encephalopathy;
- complications of portal hypertension (eg variceal bleeding or ascites that is medically difficult to manage);
- hepatic synthetic failure (eg prolonged prothrombin time or decreased serum albumin); and/or
- growth failure (as a consequence of progressive hepatic metabolic failure and anorexia).

\(^5\) ANZLTR. 23rd Australian and New Zealand Liver Transplant Registry Report, 2011.
Specific underlying causes of end-stage liver disease in children differ from those in the adult population. However, the main categories of underlying disease are the same and include:

- chronic liver diseases;
- metabolic diseases;
- acute liver failure;
- malignancy; and
- other reasons.

A subgroup of paediatric patients receives liver transplantation in the absence of end-stage liver disease. In these patients, who have metabolic conditions such as Crigler-Najjar syndrome and hyperoxaluria, the transplanted liver improves the patient’s overall metabolic function rather than treating end-stage liver disease per se.

The most common primary disease affecting children requiring liver transplantation in Australia and New Zealand is biliary atresia, which accounts for 57% of all paediatric liver transplants (Figure 1)\(^9\)\(^{10}\).

**Figure 1: Primary diseases of paediatric patients receiving liver transplantation, Australasia\(^{11}\)**

CAH:AI=chronic active hepatitis (autoimmune); BA=biliary atresia; OTH=other; FHF=fulminant hepatic failure; MAL=malignancy; PSC=primary sclerosing cholangitis; CC=cryptogenic cirrhosis; MET=metabolic diseases

**Activity and demand in Australia and New Zealand**

The ANZLTR defines children as persons aged <16 years. Between 1985 and 2011, there were 3,735 Australasian patients who received a liver transplant – 3,065 adults and 670 children\(^{12}\). The

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\(^9\) ANZLTR. 23rd Australian and New Zealand Liver Transplant Registry Report, 2011.


\(^{11}\) ANZLTR. 23rd Australian and New Zealand Liver Transplant Registry Report, 2011.

\(^{12}\) Ibid.
ages of paediatric liver transplant recipients ranged from 24 days to 15.9 years and 46% were male (Table 1).

Table 1: Age and gender of paediatric liver transplant recipients, 1985 to 2011

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<tr>
<td>Number of patients</td>
<td>670</td>
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<tr>
<td>Mean (SD) age</td>
<td>4.5 (4.5) years</td>
</tr>
<tr>
<td>Median age</td>
<td>2.4 years</td>
</tr>
<tr>
<td>Age range</td>
<td>24 days to 15.9 years</td>
</tr>
<tr>
<td>Male</td>
<td>310 (46%)</td>
</tr>
<tr>
<td>Surviving</td>
<td>536 (80%)</td>
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The number of paediatric patients receiving liver transplantation has increased over time, but has not increased at the same rate as transplants performed in adults (Figure 2).

Figure 2: Number of new patients transplanted each year, Australasia, 1985 to 2011

The average age at which paediatric recipients receive their primary liver transplant has not changed significantly across different surgical eras of transplantation (Figure 3).

13 Ibid.
14 ANZLTR. 23rd Australian and New Zealand Liver Transplant Registry Report, 2011.
Split grafts make a significant contribution to the total number of paediatric transplants performed across Australia and New Zealand. Split grafts provided 14 of 35 grafts in 2011 (40%) and 176 of 766 (23%) grafts overall between 1985 and 2011 (Figure 4).

New Zealand performs more split - living related donor (split-LRD) transplants per capita than Australia. Over the past five years 58% of all split-LRD transplants in paediatric patients were performed in New Zealand\textsuperscript{16}.

**Figure 4: Type of graft in Australian and New Zealand paediatric patients by year, 1985 to 2011\textsuperscript{17}**

Table 2 presents the number and the percentage breakdown of graft type over the last five years across all NFC paediatric liver transplantation sites and New Zealand.

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\textsuperscript{15} Ibid.

\textsuperscript{16} S. Munn. Personal communication.

\textsuperscript{17} ANZLTR. 23rd Australian and New Zealand Liver Transplant Registry Report, 2011.
Table 2: Type of paediatric liver transplant graft, 2007-2011

<table>
<thead>
<tr>
<th>Type of graft</th>
<th>2011</th>
<th>2010</th>
<th>2009</th>
<th>2008</th>
<th>2007</th>
<th>Total over five year period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Split</td>
<td>14 (40%)</td>
<td>18 (39%)</td>
<td>14 (36%)</td>
<td>17 (45%)</td>
<td>17 (52%)</td>
<td>80 (42%)</td>
</tr>
<tr>
<td>Split LRD</td>
<td>7 (20%)</td>
<td>10 (22%)</td>
<td>8 (21%)</td>
<td>7 (18%)</td>
<td>7 (21%)</td>
<td>39 (20%)</td>
</tr>
<tr>
<td>Reduced</td>
<td>7 (20%)</td>
<td>7 (15%)</td>
<td>7 (18%)</td>
<td>7 (18%)</td>
<td>6 (18%)</td>
<td>34 (18%)</td>
</tr>
<tr>
<td>Whole</td>
<td>7 (20%)</td>
<td>11 (24%)</td>
<td>10 (26%)</td>
<td>7 (18%)</td>
<td>3 (9%)</td>
<td>38 (20%)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (100%)</td>
<td>46 (100%)</td>
<td>39 (100%)</td>
<td>38 (100%)</td>
<td>33 (100%)</td>
<td>191 (100%)</td>
</tr>
</tbody>
</table>

International comparison of activity and demand

There is no international paediatric liver transplant registry and international comparison data are not widely available. Paediatric liver transplantation clinical activity data from the United States of America (US) and the United Kingdom (UK) are provided in this section in lieu of international data.

In the US, there are 127 liver transplant centres, 58 of which perform paediatric liver transplants. In the UK there are seven liver transplant units, three of which perform paediatric liver transplants. The US Organ Procurement and Transplantation Network ("OPTN") and the Scientific Registry of Transplant Recipients ("SRTR") record patterns of paediatric transplantation activity. Between 2007 and 2009 1,790 paediatric liver transplants were performed in the US. In 2012 there were 106 transplants in the UK, up from 99 the previous year. Consistent with Australasian patterns, the majority were performed in children aged five years or less (Table 3). Approximately 50% of paediatric liver transplant recipients were male.

Table 3: Paediatric liver transplant recipients, US, 2007-2009

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>542</td>
<td>30.3%</td>
</tr>
<tr>
<td>1-5 years</td>
<td>692</td>
<td>38.7%</td>
</tr>
<tr>
<td>6-10 years</td>
<td>232</td>
<td>13.0%</td>
</tr>
<tr>
<td>11-17 years</td>
<td>324</td>
<td>18.1%</td>
</tr>
</tbody>
</table>

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18 ANZLTR. 23rd Australian and New Zealand Liver Transplant Registry Report, 2011.
However, rates of paediatric transplantation vary between countries. In the US, the rate of paediatric liver transplantation is 1.8 per million population, similar to the rate in New Zealand (1.9 per million population) and the UK (1.7 per million population) but higher than the Australian rate (1.3 per million population). The reason for the lower rate of paediatric liver transplantation in Australia compared with the US and New Zealand is unknown.

Consistent with Australasian clinical practice, cholestatic disease is the primary disease leading to paediatric transplantation in the US (Table 4).

### Table 4: Primary disease leading to paediatric liver transplantation, US, 2007-2009

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestatic disease</td>
<td>809</td>
<td>45.2%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>282</td>
<td>15.8%</td>
</tr>
<tr>
<td>Acute hepatic necrosis</td>
<td>186</td>
<td>10.4%</td>
</tr>
<tr>
<td>Metabolic liver disease</td>
<td>184</td>
<td>10.3%</td>
</tr>
</tbody>
</table>

Whole paediatric liver transplantation rates are reported to be higher in the US than in Australia. Approximately 64% of paediatric patients received a whole liver transplant, 20% received a partial liver transplant and 16% received a SLT in the US between 2007 and 2009 compared with 18% of Australasian paediatric patients who received a whole liver transplant, 40% who received a partial liver transplant and 43% who received a SLT. However, data are not directly comparable as US data include paediatric patients over the age of 16 years whereas Australasian data do not.

At the time of paediatric liver transplantation in the US, 25.5% of patients are hospitalised in the intensive care unit ("ICU"), 18% are hospitalised but not in ICU and 56.5% are not hospitalised.

The number of deceased donor liver transplants actually performed in the US has remained steady over time, and the number of LDLTs has decreased over time, from 120 in 2000 to 51 in 2009 (Figure 5). The median number of months waiting for a liver transplant was 2.6 months in 2009. Figure 4 (above) describes comparative data for Australia and New Zealand.

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22 Ibid.
Figure 5: Deceased and living donor transplants, US, 1998 to 2009\textsuperscript{24}

Ibid.
PAEDIATRIC LIVER TRANSPLANTATION CLINICAL PATHWAY

Preoperative assessment

Preoperative assessment comprises confirmation of the diagnosis and assessment of the severity of liver disease. Specific assessment includes for:

- the presence of advanced portal hypertension (eg variceal haemorrhage, intractable ascites, spontaneous bacterial peritonitis, encephalopathy);
- worsening metabolic and synthetic function (including failure to thrive); and
- development of extrahepatic complications (eg hepatorenal syndrome, hepatocellular carcinoma, osteoarthropathy).

Transplantation is not indicated if an acceptable alternative treatment is available or if contraindications such as a terminal condition or poor expected outcome exist.

The assessment is conducted by a multidisciplinary team comprised of the transplant surgeon, paediatric specialists in hepatology, cardiology, infectious diseases, psychiatry, anaesthesia, radiology, intensive care, transplant nurse coordinators, social work and nutrition.

Imaging conducted preoperatively may include doppler ultrasound, MRI and / or CT.

Listing for transplantation

Patients who qualify for liver transplantation are assigned a score based on a ranking system. This system is called the Model for End-Stage Liver Disease ("MELD") for adults and children aged 12 years or older, and the Paediatric End-Stage Liver Disease ("PELD") for children younger than 12 years.

MELD uses a mathematical formula based on a patient's creatinine level, International Normalised Ratio ("INR") for prothrombin time, and bilirubin. The MELD score quantifies the risk of death within three months (the higher the score, the higher the mortality).

The PELD score also includes albumin level, growth failure and the patient's age when first placed on the waiting list in the calculation but does not include the creatinine level. The PELD system ranks children based on the severity of illness by increments in predicted three month survival outcomes.

According to the Transplantation Society of Australia and New Zealand ("TSANZ"), inclusion criteria for liver transplantation are for chronic liver disease with life-threatening complications:

- the principal indication in patients with end-stage liver disease is a MELD score of >15 in an adult or a PELD score of >17;

25 The Organ Procurement and Transplantation Network. National Data Reports. OPTN.
patients may also be suitable candidates if they have small hepatocellular carcinomata ("HCCs") that fulfil the University of California San Francisco ("UCSF") criteria;

additional indications include:

- liver disease that would result in a two year mortality rate of >50% without liver transplantation;
- diuretic-resistant ascites;
- recurrent hepatic encephalopathy;
- recurrent spontaneous bacterial peritonitis;
- recurrent or persistent gastrointestinal haemorrhage;
- intractable cholangitis (in patients with primary or secondary sclerosing cholangitis);
- hepatopulmonary syndrome;
- portopulmonary hypertension;
- metabolic syndromes (with severe or life-threatening symptoms) that are curable with liver transplantation (eg familial amyloidosi, urea cycle disorders, oxalosis etc.);
- polycystic liver disease with severe or life-threatening symptoms; and
- acute liver disease unlikely to result in spontaneous recovery as determined by the King's College criteria.

Contraindications to listing for transplantation

Absolute contraindications to paediatric OLT include:

- metastatic cancer to the liver;
- extrahepatic malignancy (except in some children with hepatoblastoma with metastases and neuroendocrine tumours where OLT is indicated);
- multi-organ failure that cannot be cured by OLT eg generalised mitochondrial disorder; and
- active, untreated bacterial, fungal or viral infection at the time of transplantation including uncontrolled systemic sepsis.

Relative contraindications are more variable and tend to be centre-specific. They may include:

- irreversible and devastating neurological injury;

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• severe cardiopulmonary disease (except if the patient is a suitable candidate for heart-liver and/or heart-liver-lung transplant); and/or

• psychosocial problems that may interfere with adherence to post-operative management.

TSANZ exclusions (medical or psychosocial) to listing for liver transplantation include those conditions or circumstances that would make a post-transplant survival rate of >50% at five years unlikely.

**Timing of transplantation**

TSANZ outlines the following donor liver allocation criteria based on category of urgency. Any liver becoming available from a deceased donor within Australia or New Zealand is first to be allocated to patients listed as urgent. There are three separate categories for urgent liver transplantation:

• **Status 1** Patients suitable for transplantation with acute liver failure who are ventilated in an ICU and at risk of imminent death. When such patients are listed, allocation to them is mandatory.

• **Status 2a** Patients suitable for transplantation with acute liver failure from whatever cause who are not yet ventilated but who meet the King's College criteria. This includes patients who have acute liver failure because of vascular thrombosis in a liver allograft.

  In addition, this category includes paediatric candidates with severe acute or chronic liver disease who have deteriorated and are in a paediatric ICU. When such patients are listed, allocation to them is usual but not mandatory. It is subject to discussion between the directors (or delegates) of donor and recipient state (or NZ) liver transplant centres.

• **Status 2b** Paediatric patients suitable for transplantation who suffer from severe metabolic disorders or hepatoblastoma (after initial treatment) for whom a limited time period exists during which liver transplant is possible.

If no patient is listed in the urgent category then the local liver unit will allocate livers according to principles described in the TSANZ Consensus Statement on Organ Transplantation from Deceased Donors – Eligibility Criteria and Allocation Protocols (version 1.2, 16 May 2012).

**Preoperative care**

Pre-transplantation care needs to take into consideration the potentially prolonged waiting periods for donor organs to become available and to manage the specific care needs of children with end-stage liver disease. Specialised preoperative care needs relate to growth and development, cirrhotic complications and psychosocial problems. Nutritional failure is also an important clinical challenge with end-stage liver disease.

Infections that occur preoperatively may be life-threatening, particularly spontaneous bacterial peritonitis, bacterial or fungal sepsis, and cholangitis. Invasive investigations may be required,

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eg diagnostic paracentesis. Some surgical centres provide prolonged antibiotic prophylaxis, particularly for cholangitis.

Pre-transplantation management also includes updating immunisations including providing vaccination for hepatitis A and B and meningococcal and pneumococcal disease.

The paediatric patient is evaluated immediately prior to surgery in order to determine whether to proceed with a deceased-donor liver transplant. The recipient should not have any infection, including upper respiratory tract infection, fever or elevated white cell count. Each of these may lead to postponement of surgery. Children with continuous episodes of cholangitis present a particular challenge to appropriate timing of transplant. Some surgical centres prefer LDLT in this patient group as surgery may be scheduled between episodes of infection.

**Peri-operative management**

The transplant procedure in a child commences with a bilateral subcostal incision, careful mobilisation of the anatomic structures around the liver and excision of the diseased liver with or without the retro-hepatic vena cava.

Recipient hepatectomy can be complicated, especially in patients with previous hepatic surgical procedures who may have extensive adhesions and scar tissue that result in higher complication rates and higher blood loss at operation. Patients may also have congenital anatomic malformations that increase the surgical complexity of the procedure.

The new liver is placed in the same location as the diseased liver. The implantation technique depends on the type of graft used.

Options for implantation include:

- **Reduced size liver transplantation** - This technique involves the procurement of an adult donor liver as a whole organ, which is then reduced with an appropriate segmental dissection based on the recipient's body size. The reduction procedure is performed in the recipient hospital;

- **Split liver transplantation** - This technique procures the deceased donor liver as a whole liver and separates the liver to create two liver allografts. Classically, the left lateral segment (segments two and three) is used for a paediatric recipient and the larger right lobe or extended right lobe graft (segments four or five to eight) is used for a larger recipient; or

- **Living donor liver transplantation** - This technique involves transplanting a segment or lobe of the liver from a living adult donor into a child. Donors are usually healthy individuals aged between 18 and 55 years who are related to the recipient and have normal liver function and ABO-compatible blood type.

32 Ibid.
34 Ibid.
The surgical techniques associated with each graft type are described at Schedule 3.

Anaesthetic management of paediatric patients receiving transplantation is a specialised area of practice. Advances in understanding of the physiological and metabolic changes that occur with end-stage liver disease and their anaesthetic implications have improved the ability of the anaesthetic team to anticipate and manage the derangements that occur pre-, intra- and post-operatively in a timely fashion.\textsuperscript{38}

**Early post-operative care**

Patients are transferred to ICU intubated and sedated for ongoing management by a paediatric intensivist. The initial focus includes resuscitation with fluids and blood products, as well as correction of metabolic abnormalities.\textsuperscript{39}

Patients frequently remain on a ventilator for the first 24 to 48 hours. Patients leave intensive care in a few days, depending on their recovery. The post-operative course is dependent on the medical condition of the patient prior to transplantation, the intraoperative course and the graft function.\textsuperscript{40}

Prior to discharge, the transplant team provides follow-up care and medication instructions. The patient's and caregivers' questions are answered, and signs of rejection are discussed with the patient in an age-appropriate manner and with the family. The patient and family receive instructions regarding rehabilitation that includes exercise, proper nutrition and the continuation of immunosuppression and other medications.\textsuperscript{41}

**Post-discharge care**

Follow-up visits commence soon after the patient returns home. Initially, outpatient visits may occur weekly or more often. Over time the frequency of follow-up visits usually decreases.

Ongoing post-discharge care is complex and lifelong. Patients require routine follow-up investigations with monitoring and ongoing management overseen by a specialist multidisciplinary team working in partnership with the child's usual paediatrician and general practitioner.\textsuperscript{42} It is therefore desirable that these clinicians are fully informed and aware of the treatment strategy for their patients. The development of a post-transplant care pathway will ensure that the shared care process is explicit and agreed.

Following liver transplantation, patients require at-home rehabilitation. Recommendations for rehabilitation vary depending on the age of the patient.

Immunosuppressive treatment is lifelong and involves ensuring immunological efficacy of immunosuppressant medications whilst limiting the number and severity of side effects. This requires using a combination of medications. Treatment regimens used for immunosuppression vary between paediatric transplant centres.\textsuperscript{43}

\textsuperscript{38} Yudkowitz F. Anaesthetic issues in paediatric liver transplantation. Paediatric Transplantation 2005; 9: 666-72.
\textsuperscript{40} Yudkowitz F. Anaesthetic issues in paediatric liver transplantation. Paediatric Transplantation 2005; 9: 666-72.
The majority of patients receive tacrolimus as part of their initial maintenance immunosuppression after transplant. Approximately 84% receive steroids at the time of transplant. However, nearly 50% of these patients are no longer on steroids at one year after transplant\textsuperscript{44}. By five years, 25% or fewer are still on steroids\textsuperscript{45}.

\begin{flushleft}
\textsuperscript{44} The US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Annual Data Report, 2010.

\textsuperscript{45} Ng V. Outcomes of 5-year survivors of paediatric liver transplantation. Paediatrics 2008; 122: e1128-35.
\end{flushleft}
COMPLICATIONS AFTER TRANSPLANTATION

Complications of liver transplantation include:\[46\]:

- rejection;
- hepatic artery thrombosis;
- other thromboses (portal vein, hepatic vein) and stenoses;
- liver fibrosis;
- lymphoproliferative disorders and other malignancies (especially skin cancers);
- biliary complications;
- infection;
- nephrotoxicity;
- central nervous system toxicity;
- cardiovascular disease;
- osteoporosis; and
- psychosocial stress.

These are discussed in detail at Schedule 3.

Rejection is the most common complication after OLT. It occurs in approximately one third of patients over time. Acute rejection is most likely to occur in the first few months following transplant and decreases in frequency over time. Approximately 80% of acute rejection occurs by six months post-transplant.\[47\] Chronic rejection is the most common cause of graft loss after the first year post-transplant.\[48\] Chronic rejection is manifest by distinct histological presentations – ductopaenia / progressive loss of bile ducts without hepatocellular injury, degeneration of medium sized arteries and / or worsening ischemic hepatocellular damage and fibrosis. The latter histological markers are associated with greater deterioration in hepatic function.\[49\] \[50\]

By one year, 47% of patients who receive a whole organ and 41% of those who receive living donor transplants will have experienced at least one rejection episode.\[51\] The probability of an episode of

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\[48\] Soltys K. Late graft loss or death in paediatric liver transplantation. Liver Transplantation 2005; 11: C-21.


acute cellular rejection occurring within five years is approximately 60% and chronic rejection occurs in approximately five per cent of patients\textsuperscript{52}.

Hepatic artery thrombosis is an important complication after OLT. The incidence is between 5% and 30%. It most commonly occurs within 30 days of transplant\textsuperscript{53}. Treatment is by revascularisation including interventional radiologic approaches using thrombolysis, transluminal angioplasty, balloon dilation or intraluminal stents. Between 67% and 100% of patients can be treated successfully without the need for re-transplantation\textsuperscript{54, 55}.

Long-term, patients frequently develop liver fibrosis after transplantation, leading to progressive loss of hepatic function. Clinical studies where children with normal liver function tests ("LFTs") are followed over time with serial biopsies demonstrate increasing prevalence of fibrosis within the liver graft, from 31% at one year after transplant to 70% at 10 years\textsuperscript{56, 57}.

Post-transplant malignancy is a significant long-term complication after liver transplantation and is estimated to lead to 10% of deaths in children within 10 years of transplantation\textsuperscript{58}. The true incidence of malignancy in long-term survivors after paediatric transplantation is unknown. In adults the relative risk of cancer in recipients is more than twice that of an age-matched population\textsuperscript{59}.

Some complications are specific to the use of immunosuppression medications. Concerns regarding the effects of steroids on post-transplant catch-up linear growth may influence clinical management towards low-dose or no steroids as part of the immunosuppressive regime. Cyclosporine and tacrolimus cause significant nephrotoxicity and their use is associated with a five-year cumulative incidence of significant renal disease of 18% and three-year and ten-year incidence of renal insufficiency of 33% and 77% respectively\textsuperscript{60}.

Post-transplantation chronic renal failure is closely related to the use of calcineurin inhibitors. The treatment for chronic renal dysfunction related to calcineurin inhibitors is not well established. In patients with mild renal dysfunction, reduction of the medication dose may be sufficient. In other patients modification of immunosuppressive regime is required. Renal transplantation for management is uncommon\textsuperscript{61}.

Between 10% and 30% of paediatric patients will require re-transplantation at some stage over the course of their life\textsuperscript{62, 63}. The most common indications for re-transplantation include vascular complications (42%), rejection (29%), biliary complications (seven per cent), poor graft function

\textsuperscript{52} Ng V. Outcomes of 5-year survivors of paediatric liver transplantation. Paediatrics 2008; 122: e1128-35.


\textsuperscript{55} Singhal A. Endovascular treatment of hepatic artery thrombosis following liver transplantation. Transplant International 2010; 23: 245-56.


\textsuperscript{57} Ng V. Outcomes of 5-year survivors of paediatric liver transplantation. Paediatrics 2008; 122: e1128-35.


\textsuperscript{60} Ibid.


\textsuperscript{63} Urahashi T. Paediatric liver retransplantation from living donors can be considered as a therapeutic option for patients with irreversible living donor graft failure. Paediatric Transplantation 2011; 15: 798-803.
(six per cent), recurrent primary biliary cirrhosis / primary sclerosing cholangitis/chronic active hepatitis: autoimmune (two per cent) and other causes combined (14%)64.

Relative to primary transplantation, re-transplantation is associated with an increased rate of death. Younger children undergoing re-transplantation appear to have higher mortality rates than older children65. There are also greater technical difficulties in total hepatectomy of the failed liver graft and the implantation of the new liver graft in paediatric recipients, which contribute to higher morbidity and mortality66.

**Mortality**

Patient survival after paediatric liver transplantation in Australasia is approximately 96% at one year, 92% at five years and 84% at 10 years67. This compares favourably with patient survival in US cohorts of approximately 93% at one year, 87% at five years and 81% at 10 years68 69 and UK cohorts where patient survival at one year is 94% and at three years is 92%.

Patient survival after paediatric liver transplantation has increased over time, from 61% five-year survival between 1985 and 1989 to 92% five-year survival in the most recent surgical era (2005 to 2009)70.

Patients whose primary disease is malignancy have poorer long-term survival compared with other indications for liver transplantation (Figure 6).

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64 ANZLTR. 22nd Australian and New Zealand Liver Transplant Registry Report, 2010.
66 Urahashi T. Paediatric liver retransplantation from living donors can be considered as a therapeutic option for patients with irreversible living donor graft failure. Paediatric Transplantation 2011; 15: 798-803.
68 ANZLTR. 23rd Australian and New Zealand Liver Transplant Registry Report, 2011.
The type of primary deceased donor graft (whole, reduced or split liver) does not affect patient survival in children and all types of graft are associated with similar patient survival rates. Graft survival following re-transplantation is not as favourable as after a first liver transplant.

**Quality of life**

Health-related quality of life after paediatric liver transplantation is good but differs from that of the general population. Children may have poorer physical function and their families may experience higher levels of emotional distress and disrupted family activities compared with the general population.

Health-related quality of life generally improves over time. Interviews with 116 patients at 14 years after transplant showed that 75% of patients are satisfied with their quality of life and 81% are satisfied with their health status.

However, delayed educational attainment and higher unemployment are observed long-term in patient cohorts. In one study, at between 10 and 15 years post-transplant, one third of recipients had

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71 ANZLTR. 23rd Australian and New Zealand Liver Transplant Registry Report, 2011.
72 Ibid.
75 Dommergues J. Medical follow-up, personal experiences and everyday life of young adults after liver transplantation during childhood. Bulletin of the Academy of Medicine 2008; 192: 1641-54.
received age-appropriate schooling and 31%, 23% and 13% were one, two and three years behind in their schooling respectively.\textsuperscript{76}
VOLUME-QUALITY RELATIONSHIPS

In the US, there are 127 liver transplant centres, 58 of which perform paediatric liver transplants. The minimum surgical centre volume (adult and paediatric liver transplants) in 2010 was one, the maximum was 192 and the median was 40. Thirteen centres performed fewer than 10 transplants a year (Figure 7).

Figure 7: Distribution of US centre volume of liver transplants (paediatric and adult), 2009

Published volume-quality data for paediatric liver transplant outcomes are limited. Available information comparing high (≥16 procedures), middle (eight-fifteen procedures) and low (less than seven procedures) annual surgical volume centres suggests that:

- high volume paediatric liver transplant centres achieved significantly lower aggregate one year patient death ratios than low-volume centres (odds ratio=0.77; p=0.03);
- when freestanding children's hospitals (FCH – 23% of facilities), children's hospitals within adult hospitals (CAH – 32%) and other centres (OC – 46%) are considered separately, a significant volume-outcomes association persists among OC centres but not among FCH or CAH centres; and
- low volume ‘other’ centres, which represent 41.6% of all paediatric liver transplant centres and perform 10% of all paediatric liver transplantation, had the least favourable aggregate one-year patient death rates of all groups (odds ratio = 1.2; p=.03).


Ibid.
PAEDIATRIC LIVER TRANSPLANTATION IN AUSTRALIA

The Nationally Funded Centres

Paediatric liver transplantation is performed at three hospitals all located on the east coast of Australia:

- in Sydney it is carried out by the Australian National Liver Transplant Unit ("ANLTU"), which is a collaborative program between the SCHN(W) and the Royal Prince Alfred Hospital ("RPAH");
- in Brisbane the paediatric liver transplant service is based at RCHB, with transplant surgeons from Princess Alexandra Hospital ("PAH") performing the surgery; and
- in Melbourne, the paediatric liver transplantation service is based at RCHM, with the surgery undertaken at RCHM by the Austin Health-based Victorian Liver Transplantation Unit ("VLTU").

In each of the above centres the paediatric liver transplant surgery is performed at the paediatric hospital, whilst assessment of living donors is undertaken at the collaborating adult hospital.

Patients aged less than 16 years are usually considered for paediatric liver transplantations, although RCHB makes a judgement as to whether the paediatric or adult service is most appropriate for children aged more than 14 years.

Once transplanted, paediatric patients remain with the paediatric service until they transition to the adult service at age 18 or after their final year of schooling. The close collaboration between paediatric and adult liver transplant services is helpful during the often difficult transition to adulthood by paediatric transplant patients.

National access

Referral patterns are generally stable, although clinicians may refer individual families to a different centre if there is better family support in that city. In the last five years patients from:

- New South Wales, Australian Capital Territory and Western Australia have been referred to SCHN(W);
- Queensland, Northern New South Wales and the Northern Territory have been referred to RCHB; and
- Victoria, South Australia and Tasmania have been referred to RCHM.

Table 5 sets out the rates of transplantation by place of residence and NFC site for the five-year period 2006 to 2011. Western Australia currently has the highest per population rate of transplantation – about 15% higher than NSW, Queensland and Victoria, all of which have rates above the Australian average. The ACT is somewhat below the national average, whilst South Australia's transplant rate is about half the national average and Tasmania's is about 40% below the national average. There were no transplants for residents of the Northern Territory during that period, although patients had been referred to RCHB.
Table 5: Paediatric liver transplants by Nationally Funded Centres site and place of residence 2006-2011\textsuperscript{80}

<table>
<thead>
<tr>
<th>NFC Site</th>
<th>NSW</th>
<th>VIC</th>
<th>QLD</th>
<th>SA</th>
<th>WA</th>
<th>TAS</th>
<th>NT</th>
<th>ACT</th>
<th>Aust</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCHN(W)</td>
<td>45</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>64</td>
</tr>
<tr>
<td>RCHB</td>
<td>1</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>32</td>
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<tr>
<td>RCHM</td>
<td>0</td>
<td>36</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>43</td>
</tr>
<tr>
<td>All sites</td>
<td>46</td>
<td>36</td>
<td>30</td>
<td>5</td>
<td>18</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>139</td>
</tr>
</tbody>
</table>

| Five-year rate per 100,000 population aged <16 years | 3.19 | 3.36 | 3.18 | 1.61 | 3.80 | 1.94 | 0.00 | 2.86 | 3.11 |
| Average annual rate per 100,000 population aged <16 years | 0.64 | 0.67 | 0.64 | 0.32 | 0.76 | 0.39 | 0.00 | 0.57 | 0.62 |

Analysis of referral and acceptance data shows that all jurisdictions have made referrals in the current five-year period under review (Table 6). Importantly the rate of referral for the three jurisdictions with the lowest transplantation rates, South Australia, Tasmania and the Northern Territory was at or above the national average, which provides support for the premise that this NFC Program is fulfilling its remit to provide equitable access to residents of all States and Territories. The apparently anomaly of the transplantation rate for Western Australia being higher than the acceptance rate appears to be due to referrals and transplants not being exactly aligned in the same time periods.

Referring clinicians from all States and Territories expressed high levels of satisfaction with the referral process and confirmed that there are well-established processes for referral to the NFC sites, assessment for suitability for transplantation and provision of care once the patient is accepted on to the waiting list. Clinicians also advised that the transplant teams at each site are very supportive and respond promptly to email, telephone or written requests for patient assessment. Protocols for work-up prior to referral are clear. However harmonisation of protocols by the NFC sites would be beneficial. Referring clinicians report that nursing and allied health support and communication from the NFC sites is also of very high quality.

\textsuperscript{80} NFC Secretariat, annual reports from NFC Sites.
Table 6: Rate (average of 5 years) of referral, acceptance and transplantation, by place of residence, 2006/07 – 2010/11

<table>
<thead>
<tr>
<th></th>
<th>NSW</th>
<th>VIC</th>
<th>QLD</th>
<th>SA</th>
<th>WA</th>
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<th>Aust</th>
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<tbody>
<tr>
<td>Average annual rate of referral per population aged &lt; 16 years</td>
<td>0.78</td>
<td>1.29</td>
<td>1.15</td>
<td>0.97</td>
<td>0.76</td>
<td>1.55</td>
<td>1.07</td>
<td>0.57</td>
<td>1.01</td>
</tr>
<tr>
<td>Average rate of acceptance per population aged &lt; 16 years</td>
<td>0.68</td>
<td>0.69</td>
<td>0.89</td>
<td>0.32</td>
<td>0.63</td>
<td>0.97</td>
<td>0.0</td>
<td>0.57</td>
<td>0.69</td>
</tr>
<tr>
<td>Average rate of transplantation per population aged &lt; 16 years</td>
<td>0.64</td>
<td>0.67</td>
<td>0.64</td>
<td>0.32</td>
<td>0.76</td>
<td>0.39</td>
<td>0.0</td>
<td>0.57</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Activity and outcomes

Overall there were 225 assessments, with 70% of patients accepted and 90% of accepted patients transplanted. The final transplantation rate will be higher because some accepted patients were still waiting at the time the NFC sites made their annual report to the NFC Secretariat.

The actual number of transplants performed at each site for the period 2006-07 to 2010-11 is set out in Table 7, with 46% undertaken at SCHN(W), 31% at RCHM and 23% at RCHB.

Table 7: Paediatric liver transplants by site, 2006/07 - 2010/11

<table>
<thead>
<tr>
<th></th>
<th>2006/07</th>
<th>2007/08</th>
<th>2008/09</th>
<th>2009/10</th>
<th>2010/11</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCHN(W)</td>
<td>16</td>
<td>9</td>
<td>15</td>
<td>11</td>
<td>13</td>
<td>64</td>
</tr>
<tr>
<td>RCHB</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>9</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>RCHM</td>
<td>5</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>25</td>
<td>30</td>
<td>30</td>
<td>29</td>
<td>139</td>
</tr>
</tbody>
</table>

Each NFC site reports to the NFC Secretariat annually on patient outcomes including graft and patient survival. The most recent report from the NFC Secretariat provided data on one-year and five-year survival for the current cohort of patients. The results are set out in Table 8. There were no statistically significant differences in patient and graft survival between sites.
Table 8: Patient and graft survival, by site, patient cohort 2005-2010

<table>
<thead>
<tr>
<th>Treatment period 2005-2010</th>
<th>Survival period</th>
<th>Patient survival</th>
<th>Graft survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCHK(W)</td>
<td>1 year survival</td>
<td>93.3%</td>
<td>93.3%</td>
</tr>
<tr>
<td></td>
<td>5 year survival</td>
<td>93%</td>
<td>90%</td>
</tr>
<tr>
<td>RCMH</td>
<td>1 year survival</td>
<td>100%</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>5 year survival</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>RCHB</td>
<td>1 year survival</td>
<td>97%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>5 year survival</td>
<td>90%</td>
<td>80%</td>
</tr>
</tbody>
</table>

RCHM in its documentation for this review provided additional information about its transplant outcomes. Survival of all patients, by graft type for the period 1995-2012 is presented in Table 9 and ranges from 87% for split liver grafts to 90% for whole liver transplants.

Table 9: Type of graft and patient survival (1995-2012), Royal Children’s Hospital Melbourne

<table>
<thead>
<tr>
<th>Type of graft</th>
<th>Number</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole</td>
<td>31</td>
<td>90% (28/31)</td>
</tr>
<tr>
<td>Cut-down</td>
<td>38</td>
<td>89% (34/38)</td>
</tr>
<tr>
<td>Split (includes one LDLT)</td>
<td>32</td>
<td>87% (28/32)</td>
</tr>
</tbody>
</table>

Referring clinicians recognised that a critical volume of procedures is required to maintain world-class outcomes. Respondents expressed the view that case volumes in Australia are insufficient to sustain additional paediatric liver transplantation sites. Although the majority of stakeholders were supportive of three NFC sites, some stakeholders expressed a view that two NFC sites would be more appropriate given current case volumes.

Having regard to the current and future likely caseload, the equitable geographic access to transplantation which has now been established and the complexity and length of time needed to develop high quality paediatric liver transplant units, continuation of transplantation at three sites appears the optimal arrangement. Caseload does not warrant the establishment of a fourth unit, which would in any case suggest the procedure is widely dispersed in Australia and therefore would fall outside the definitional scope of the NFC Program.

Age of patients managed according to a paediatric care pathway

Patients aged less than 16 years are usually considered for paediatric liver transplantations, although RCHB makes a judgement as to whether the paediatric or adult service is most appropriate for children aged more than 14 years.

Older children from South Australia and Western Australia could theoretically receive their liver transplant in the adult liver transplant facility in their home State, resulting in numerous benefits to
the patient and their family. This approach would provide care closer to the patient’s and family’s home, minimising the dislocation of families and reducing the need for prolonged periods of accommodation and support in a jurisdiction away from the family’s usual social networks. Feedback obtained from families shows that transport and accommodation, loss of social supports, and difficulties maintaining employment and schooling for other members of the family are often problematic when patients and families travel interstate to access care.

However, there are a number of disadvantages associated with the provision of transplant services to children in adult liver transplant facilities. Firstly, staff working in adult transplant centres are less familiar with managing the complex psychological, social and medical needs of paediatric patients. In the existing paediatric liver NFC sites this is addressed through close partnerships between paediatric and adult hospitals or by locating the service in a paediatric facility. Although these staff could acquire the necessary skills or form partnerships with paediatric providers who could support delivery of paediatric services in an adult liver transplant setting, the number of children that would be expected to access such a service would be small, limiting the extent to which this service model could be embedded within practice. Secondly, the number of paediatric liver transplants performed across Australian sites is only sufficient to maintain high quality outcomes in a limited number of surgical centres. If older children from South Australia and / or Western Australia received their transplants in their home state, this would further deplete the national pool of patients receiving transplants at the NFC sites. This may affect the capacity of the NFC Paediatric Liver Program as a whole to maintain the high quality outcomes that are currently being achieved. Further, older children may require reduced sized liver allografts. The expertise in performing these procedures is currently predominantly within the existing NFC paediatric liver sites. Adult liver transplant facilities would require support to access this expertise or to develop it in-house.

Therefore, weighing the pros and cons of making liver transplantation available to older paediatric patients in centres other than the NFC sites, it would seem preferable to continue to refer these patients to existing NFC sites.

Each NFC site coordinates transition of patients from paediatric to adult services over the duration of the patient’s after-care. Although the NFC does not fund sites for after-care long-term, the majority of patients maintain a therapeutic relationship with their treating site for a prolonged period. Each site actively commences transitioning paediatric patients from paediatric providers to adult providers at the appropriate time.

Conformance with criteria for continuation in the NFC Program

Paediatric liver transplantation fulfils the requirements for continuation in the NFC Program because:

- the surgical management of end-stage paediatric liver disease by liver transplantation is an established clinical practice which is available world-wide. It requires a national population base and service concentration given small numbers of donor organs available to patients requiring transplantation and the influence of institutional surgical caseload on surgical outcomes;

- the current annual caseload in Australia is up to 30 procedures per year; and

- paediatric liver transplantation is a high cost procedure, with an estimated total cost of $270,681 for each transplant, although this amount does not include the cost of retrieval or the costs associated with living donor related liver transplantation.
The review team considers that the Paediatric Liver Transplant Program continues to meet the criteria for designation as a NFC Program. Ongoing designation of paediatric liver transplantation as a NFC Program will ensure that the objective of equity of access for Australian residents will continue to be met. In particular we note that good geographic access is provided by the referral pathways as they are currently organised to each of the three sites and that high quality outcomes are being achieved across the three sites, which supports the continuation of three sites.

**Recommendation 1**

That based on caseload, current equitable geographic access and efficient provision of services paediatric liver transplantation continues to be funded as a Nationally Funded Centres Program, with three sites continuing to provide transplants.
MODEL OF CARE FOR PAEDIATRIC LIVER TRANSPLANTATION ACROSS NFC SITES

The three NFC sites provided information about the model of care they have developed to ensure that paediatric liver transplantations are provided in the most effective, efficient and safe way possible. Models of care across sites are similar. However, the review team identified variation in:

- the structure of the unit's workforce;
- the type of graft used; and
- the expected length of stay.

There was also the commentary at the SCHN(W) site visit that their patients appeared to be more unwell as measured by PELD scores at the time of transplantation than patients in other states, which was felt to reflect problems in accessing donor organs. No data were available to the review team to assess this.

All three sites apply the TSANZ Consensus Statement on Organ Transplantation from Deceased Donors – Eligibility Criteria and Allocation Protocols (version 1.2, 16 May 2012), which stipulate that within Australia assessment, listing and transplantation can only occur after careful evaluation by a recognised multidisciplinary Australian Liver Transplant Unit. The criteria also form the basis for assessment processes at the three NFC sites.

Primary workforce

All three services draw on a similar mix of clinical staff, however with respect to the staff primarily employed within the service, the staff complements are set out in Table 10. SCHN(W) has onsite surgeons who also undertake renal transplant work and other paediatric surgery, whereas at RCHB and RCHM transplant surgery is performed by hepatobiliary surgeons from collaborating adult hospitals. The gastroenterology care is provided by hepatologists at SCHN(W) and RCHM and by specialist gastroenterologists at RCHB. All three services are supported by an on-call roster from the paediatric hospital's department of gastroenterology. However, the medical specialists are not solely available to the paediatric liver transplant program.

The level of staffing by liver transplant clinical nurse consultants ("CNC") / coordinators across sites varies from one and a half EFT to two EFT for relatively similar caseloads.
Table 10: Liver transplant staff complement, by site

<table>
<thead>
<tr>
<th></th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant surgeons</td>
<td>3 on-site</td>
<td>3 from PAH</td>
<td>&gt;3 from Austin Health</td>
</tr>
<tr>
<td>Hepatologists / gastroenterologists</td>
<td>2</td>
<td>3.7 EFT gastroenterologists, though not solely dedicated to the transplant program</td>
<td>1 EFT (2 head count)</td>
</tr>
<tr>
<td>On-call gastroenterologists</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Clinical nurse consultants / LT coordinators</td>
<td>1.8 EFT (2 head count)</td>
<td>1.5 EFT (2 head count)</td>
<td>2.0 EFT (2 head count)</td>
</tr>
<tr>
<td>Fellows</td>
<td>1 transplant fellow</td>
<td>1 gastroenterology fellow (is not a dedicated transplant unit resource)</td>
<td>1 hepatobiliary fellow at Austin Health</td>
</tr>
<tr>
<td>Allied health</td>
<td>0.6 EFT social worker</td>
<td>Sourced from department / hospital pool</td>
<td>Sourced from department / hospital pool</td>
</tr>
<tr>
<td></td>
<td>0.6 EFT occupational therapist</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6 EFT dietician</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SCHN(W) reports that it currently has good succession planning in place for paediatric transplant surgeons. It acknowledges that it will be important to maintain a surgical transplant fellow position to provide incentives and opportunities for future generations in an area of surgical endeavour which is relatively unattractive compared to other surgical opportunities. The combination of paediatric and transplantation surgery is demanding with long and unpredictable hours, relatively poor remuneration and onerous patient expectations, making this an area which requires careful planning to ensure the long-term viability of the Paediatric Liver Transplant Program.

Similarly, there needs to be more attention given to succession planning in paediatric hepatology physician positions - the traditional lack of a career path with limited staff specialist positions in Australian teaching hospitals threatens the long-term viability of this service.

The RCHB surgical team has an established national and overseas surgical exchange training program with one local fellow and one each from the US and Europe.

Austin Health has appointed an additional surgeon who in the last 12 months has been able to undertake paediatric liver transplants as a lead surgeon. Additional surgical staff members are still required, and this could be coordinated with a possible expansion of the surgical service related to intestinal transplantation. The surgeons required for these procedures have similar skills and therefore are able to be involved in adult and paediatric liver and intestinal transplantation as well as donor retrieval and splitting of suitable livers.

To assist with succession planning and service sustainability RCHM identified the following additional staff members that are required but not yet appointed: a paediatric transplant consultant, a
transplant fellow and a liver transplant CNC / coordinator. One of the major constraints in respect to continuing education of non-medical staff, particularly the liver transplant CNC / coordinators, is the availability of funds to support further education and research opportunities.

The liver transplant CNC / coordinators play a fundamental role in the timely and effective functioning of transplant units. Whilst the role may vary from site to site, typically they:

- are involved in the initial consultation after referral;
- consult and meet with the family on an ongoing basis, providing education to the family about the "clinical pathway", multidisciplinary team roles;
- coordinate and support the family during the four to five day work-up, which includes an introduction to other transplant families, a hospital tour, extensive education and question and answer discussions and coordination of ongoing monitoring and care for the patient;
- calculate the PELD score for the unit’s patients on a weekly to monthly basis;
- are responsible for development, management and dissemination of individual patient protocols for transplant, activation of patient on transplant waiting list, and entry of data into the transplant database;
- notify the family that they are on the waiting list and need to be contactable at all times should a donor organ become available;
- have regular contact with the family and patient during the pre-transplantation monitoring phase;
- coordinate the entire transplant procedure, including notifying the patient, arranging transport, admission, preoperative investigations and preparation; notification of medical, surgical, anaesthetic, theatre and ICU staff, assembly of donor retrieval and recipient surgical teams, transport of team members to donor retrieval and recipient hospitals, transport of donor organ to recipient hospital, support of family throughout surgery, including regular updates on progress, and management of adverse events;
- support and educate the family during the ICU and ward admissions;
- provide the family with the NFC survey at discharge; and
- participate in outpatient visits until the patient is discharged from the NFC Program.

The complexity of the work and the specific knowledge required makes recruitment and induction of new staff difficult unless there are sufficient resources to allow this to occur.

The workload at each site is sufficient to warrant the appointment of two EFT liver transplant CNC / coordinators to allow for leave and overtime cover. As they are funded through the NFC Program, their responsibilities should be directly referable to the management of paediatric liver transplant patients. Funding at this level would provide some flexibility to allow an increase in the head count and provide better opportunities for relief and cover.

It would also be timely to assess the scope of practice and skills required of the liver transplant CNC / coordinators, so that a standard approach to workload and requisite funding can be determined.
Recommendation 2
That to address succession planning, each Nationally Funded Centres site and host jurisdiction develops, implements and maintains a comprehensive workforce management and training plan.

Care pathway

Provision of transplantation services requires a number of discrete stages of referral, assessment, maintenance, management and ongoing follow-up. The stages in the model of care are outlined in Figure 8 and described below and are consistent with the NFC clinical practice and funding model. At each of the three services there is a continuum of care from referral to transplantation through to long-term follow-up which continues for years after discharge from the NFC Program. Patients and their families receive ongoing case management and support from the liver transplant CNC / coordinator and communication is maintained with referring practitioners.

Figure 8: Nationally Funded Centres model of care

Referral and screening consultation

A comprehensive patient assessment is performed at an initial consultation to establish the suitability of the patient for transplantation.

Patients are referred to the service via a number of pathways including through their general practitioner, by another health service or internally from another department of the paediatric hospital. Critically unwell patients may be transferred directly to the hospital from another health service for assessment.

Families advised the review team that they became aware of transplantation as a treatment option through their usual treating paediatric health care provider when their child first became unwell.

The paediatric hospital manages the referral process and usually undertakes the initial assessment, with patients assessed by a gastroenterology consultant and liver transplant CNC / coordinator. The consultation includes a medical history, examination, additional tests and a determination as to whether the patient is an appropriate candidate for transplantation according to TSANZ protocols.
The liver transplant CNC / coordinator meets with the family on an ongoing basis, providing education and support to the family about the "clinical pathway" and multidisciplinary team roles.

Referring clinicians reported that they have well-established relationships with medical, nursing and allied health staff at their interstate NFC centres. Processes for communication with the transplant team at referral and after assessment of the patient were reported to be of high quality. Clinicians also advised that the transplant teams at each site are very supportive and respond promptly to email, telephone or written requests for patient assessment. Protocols for work-up prior to referral are clear. Nursing and allied health support and communication from the NFC sites is also of very high quality.

Referring clinicians from all States and Territories reported high levels of satisfaction with processes for referring patients for assessment for liver transplantation. There are well-established processes for referral to the NFCs, both for assessment for suitability for transplant and for care once the patient is accepted on the waiting list. Families also reported a high level of satisfaction with the information they received at referral regarding transplantation and its advantages and disadvantages.

However, referring clinicians did report that there is a lack of clarity regarding the type of liver transplant that will be provided to their patients. Some clinicians expressed a view the NFC sites adopt different practices regarding the type of liver transplant performed, that criteria describing the type of liver transplant performed at each of the three NFCs are not standardised and that, as a result, there can be inconsistency between the sites regarding whether the patient will receive a split liver, living donor, reduced, cadaveric or whole transplant. Notwithstanding these concerns, transplant sites cannot predict or guarantee what type of graft each patient will receive from a deceased donor until the organ becomes available. The best approach would be to provide data on the proportion of each graft type at each site.

Some stakeholders consulted for this report advised that clinicians from outside the field of gastroenterology generally have poor levels of knowledge and awareness regarding the causes of hepatic failure in neonates and young people and tend to refer patients late in the course of their illness. Although data were not available for this review to enable comparison of timing of referral between sites, the impacts of referrals that are either too early or too late are acknowledged. Early referral may contribute to a high number of assessments that do not proceed to transplantation. Late referral of patients with liver failure reduces the likelihood of recovery of hepatic function in some patient groups and may increase the likelihood that liver transplantation will be required. Further, late referral may increase the morbidity and / or mortality associated with the transplantation.

**Recommendation 3**

That the Nationally Funded Centres sites develop and promulgate nationally agreed guidance for general paediatric units on the assessment and early management of liver failure to ensure that where possible patients are referred early and in a stable condition to the Nationally Funded Centres sites.

**Full assessment and work-up**

Once the diagnosis is confirmed and the decision is made to proceed with ongoing assessment for liver transplantation, the work-up phase commences. The work-up can take four to five days and is coordinated by the liver transplant CNC / coordinator. On average, it appears that about 20 referrals and screening assessments yield about 12 full assessments, although this information does not form part of the data communicated annually to the NFC Secretariat by the NFC sites.

Donor organs are allocated on a national basis. The information provided by the NFC sites includes the number of assessments and the number of decisions to accept for a transplant or not accept for a transplant, and where the decision is still pending (Table 11). Overall where a final decision has
been made, listing rates are on average 76% for the three years, but fall within the range of 58% at RCHM, 81% at RCHB and 88% at SCHN(W).

Table 11: Referrals and assessments, by site

<table>
<thead>
<tr>
<th>NFC site</th>
<th>2010/11</th>
<th>2009/10</th>
<th>2008/09</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCHN(W)</td>
<td>9 assessments; 8 accepted; one not accepted; 16 assessments; 13 accepted; three not accepted</td>
<td>18 assessments; 17 accepted; one not accepted; one decision pending at time of report</td>
<td>11 assessments; 7 accepted; two not accepted; two decisions pending at time of report</td>
</tr>
<tr>
<td>RCHB</td>
<td>11 assessments; 9 accepted; one not accepted; one decision pending at time of report</td>
<td>15 assessments; 10 accepted; three not accepted; two decisions pending at time of report</td>
<td>11 assessments; 7 accepted; two not accepted; two decisions pending at time of report</td>
</tr>
<tr>
<td>RCHM</td>
<td>24 assessments; 8 accepted; four not accepted; 12 decisions pending at time of report</td>
<td>22 assessments; 10 accepted; 7 not accepted; five decisions pending at time of report</td>
<td>11 assessments; five accepted; six not accepted</td>
</tr>
<tr>
<td>All</td>
<td>44 assessments; 25 accepted; six not accepted; 14 decisions pending</td>
<td>53 assessments; 33 accepted; 13 not accepted; 7 decisions pending</td>
<td>40 assessments; 29 accepted; 9 not accepted; 9 pending</td>
</tr>
</tbody>
</table>

The work-up includes multiple medical consultations with the gastroenterology consultant and other specialists to determine the patient’s suitability for a transplant, and prepare them for the procedure and post-transplant care and follow-up. There are also multiple consultations with allied health specialists.

The assessments are very detailed – for example the social work assessment includes discussion about support networks, accommodation and travel requirements (provided for interstate and rural families; pre-transplant, transplant and outpatient/post-transplant care); work and financial implications; sibling needs; and ongoing emotional support.

Pathology and imaging protocols include extensive testing covering: blood grouping; clotting; infectious serologies; renal, lung and cardiac function; imaging of the portal vein, hepatic artery and liver; brain and bone scans and where indicated metabolic liver disease testing.

The patient is immunised and each member of their immediate family is tested for their immunity to chickenpox, measles, mumps and rubella and is vaccinated against influenza virus and viruses that could compromise the patient's immunity. The patient may require certain interventional radiology procedures prior to the transplant such as drainage of bile lakes and insertion of central venous lines for emergency vascular access.

The liver transplant CNC / coordinator supports the patient and family during the work-up including making introductions to other transplant families, providing a hospital tour, extensive education and question and answer discussions with the family and coordinating ongoing monitoring and care for patients.
As described above, prioritising paediatric patients for a liver transplant is informed by the MELD / PELD score (depending on the patient's age) and other factors including patient size and blood group. The patient is given a numerical score based on the results of a number of tests. This score is calculated on a weekly to monthly basis by the liver transplant CNC / coordinator whilst the patient is on the waiting list, to assist in prioritising candidates. Prioritising and updating of children waiting for a liver transplant occurs every week in a liver transplant meeting and priorities are discussed and decided by the physicians and liver transplant surgeon.

**Living donor transplants**

At the SChN(W) when a paediatric candidate and their family commence assessment for liver transplant they are provided with written information about LDLT. Management of this process is invested in the hands of the transplant unit at the adult hospital and is protocol driven. By way of example the ANLtu protocol sets out the process, which is described below.

The RPAH surgeon discusses transplant surgical issues in general including LDLT as an option of last resort. If there is a positive inquiry, then SChN(W) performs preliminary ABO blood grouping on the most suitable one or two potential donors. If a compatible grouping emerges, the candidate is referred to the surgical director at ANLtu for further discussion about possible surgery. At this point much of the logistics and risk and expected outcome of live donation will be discussed.

The surgical director makes an assessment based on history and examination as to whether the potential donor is likely to be suitable for donation. The discussion will also include the possibility of undergoing early workup so that if the child's condition deteriorates, there is the possibility of live donation at relatively short notice.

Testing follows the ANLtu protocol and includes:

- routine bloods;
- thrombotic screen;
- viral serology;
- relevant screening for inheritable disorders;
- triple phase abdominal CT scan plus CT angiogram;
- upper abdominal ultrasound, chest X-ray; and
- pulmonary function tests, electrocardiograph (ECG), fundoscopic examination and echocardiogram;

and if indicated:

- exercise ECG (>50 years of age);
- 24 hour blood pressure monitoring;
- carotid duplex;
- lower limb doppler;
- upper/lower gastrointestinal endoscopy (colonoscopy >50 years); and
• blood donation for autologous transfusion once a date has been set for surgery.

Additional clinical assessments are also undertaken by a liaison psychiatrist, anaesthetist and social worker.

There is a multidisciplinary team meeting to discuss suitability of the donor for the donor procedure, with complete presentation of data. A recommendation to proceed with donation from a living donor only takes place following unanimous agreement between donor and family, the transplant team (surgical, medical and paediatric) and the independent medical/psychiatric "donor team".

Once a decision is made to proceed with LDLT a "cooling off" period is usually required, although exceptions may be necessary in very urgent cases.

Within ten days, and no more than four days prior to surgery, the live donor coordinator will collate all of the information including the consent form. They will ensure that all relevant parties are informed of the plan to proceed.

**Acceptance on list and to NFC Program**

Once a patient has been accepted onto the list and consent for surgery is obtained, they become activated on the state and national waiting list according to clinical urgency. The liver transplant CNC / coordinator is responsible for development, management and dissemination of individual patient protocols for transplant, activation of patients on the transplant waiting list, and entry of data into the transplant database. The liver transplant CNC / coordinator notifies the family that they are on the waiting list and need to be contactable at all times should a donor organ become available.

A joint expert multidisciplinary review is held on a weekly basis to discuss each patient’s continued suitability and prioritisation for transplantation.

**Pre-transplant monitoring**

Every month blood tests are required for antibody testing which is available to be checked with the donor organ at the time of transplant. The patient receives regular medical monitoring by relevant staff including the gastroenterology consultant, dietician and pharmacist and has regular contact with the liver transplant CNC / coordinator. The patient also sees the clinical nutrition team if he or she is receiving total parental nutrition. The allied health team, including physiotherapy, dentistry, social work, occupational therapy, dietetics, play therapy and education institute professionals, also regularly monitors and reviews the patient. General pathology and diagnostic tests to monitor the patient’s condition and continued suitability are undertaken. Unwell patients may need to be admitted for management of liver failure symptoms.

During this phase the patient and family usually meet with the surgical team on a six monthly basis for the consent process to be repeated. Depending on the waiting time for a suitable organ, the work-up (or elements of it) may need to be repeated.

Families who were consulted for this review and who relocated to the transplant centre whilst awaiting transplant were satisfied with the level of support they received whilst awaiting the transplant. There were no reported difficulties about accessing transport and accommodation although there are difficulties associated with relocation including:

• being away from family, friends and community;
• extended time off work for working parents;
- often long commutes between home and the hospital for family members; and
- finding schooling and child care for other children in the family.

Having a designated transplant coordinator and social worker was viewed as essential to assist families to navigate access to available supports. Families also reported that the support of other families who had greater experience accessing services was vital, helping them receive accurate information regarding the supports available.

**Preoperative preparation**

The liver transplant CNC / coordinator is usually responsible for coordinating the entire transplant procedure. When a liver becomes available the patient is notified by the on-call liver transplant CNC / coordinator who also arranges transport to hospital for the patient if necessary. Patients are typically admitted to a general ward for preoperative preparation, which is coordinated by relevant clinical staff and the liver transplant CNC / coordinator.

Preoperative arrangements include the application of the individual protocol for patient preparation, medications and investigations, which include routine imaging and biochemistry, blood cross-match, coagulation screen, and repeat serology.

**Transplant surgery, paediatric intensive care unit admission and ward stay**

The liver transplant takes on average one theatre bed-day, with actual operating time being 10 to twelve hours. The staff required for the operation are listed in Table 10. In addition, anatomical pathology tests may be performed on the livers and a pathologist may be called in to examine a donor liver if there is a concern about its suitability.

Table 12 sets out the type of grafts that were implanted in 2010/11, with a clear shift to split liver transplants, both from living and deceased donors. The overall proportion of split liver transplants was 72% (21/29), ranging from 56% at RCHM, through 77% at SCHN(W) to 86% at RCHB.

**Table 12: Type of liver transplant graft, by site, percentage of total, 2010/11**

<table>
<thead>
<tr>
<th></th>
<th>SCHR(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Split (including Living Related Donor)</td>
<td>77% *</td>
<td>86% #</td>
<td>56%</td>
</tr>
<tr>
<td>Reduced</td>
<td>15%</td>
<td>0%</td>
<td>22%</td>
</tr>
<tr>
<td>Whole</td>
<td>8%</td>
<td>14%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Note * In 2009/10 at SCHR(W), nine donors worked up; up to 25% of transplants are LDLT.

Note # In 2009/10 at RCHB, six donors worked up.

Where feasible, the use of split rather than whole donor grafts is potentially advantageous to improve access to grafts for patients on the waiting list. The available pool of donor livers is increased when a graft is split because two grafts are created from one donor liver which allows two patients on the waiting list to receive a transplant. Splitting is not feasible with all donor livers, however, due to the poorer underlying quality of the donor graft in some cases. Further, the right lobe portion of a split liver is of lesser quality compared with a whole liver. In some patients, particularly those with a higher PELD score, this has the potential to adversely affect surgical
outcomes and graft survival rates. Therefore, although the use of split rather than whole grafts should be maximised, this is not possible for all donor grafts or all recipients.

Through the consultation some referring clinicians questioned why poor availability of donor organs was not being addressed through increasing access to LDLT or to cadaveric transplantation. Some stakeholders expressed a view that LDLT was under-utilised as a transplant option and that numbers of LDLTs should be increased to facilitate earlier transplantation, particularly as some patient cohorts appear to have very high PELD scores at transplantation.

**Paediatric intensive care unit**

Post-transplant the patient is admitted directly to the paediatric intensive care unit ("PICU"). During this time the patient is cared for, monitored and reviewed by surgical, medical, nursing and allied health staff. The child usually returns to the PICU with a naso-tracheal tube, indwelling urinary catheter, naso-gastric tube, triple-lumen central venous catheter, at least one arterial line, two to four peripheral intravenous lines and a variable number of abdominal drains. Some patients have a temporary closure (a "gusseted" abdomen using silastic patch and betadine packs), with definitive closure performed three to four days later.

The patient is subject to very close monitoring and testing during the PICU stay including post-operative doppler ultrasound daily for up to five days post-operatively. Blood tests, the nature of which are targeted to the particular patient circumstances, are done post-operatively. These commonly include urea, electrolytes and creatinine ("UEC"), LFTs and coagulation profile.

Other monitoring includes a daily chest x-ray whilst the endotracheal tube is in place. Cultures are performed daily until there are three negative results and a Diisopropyl Iminodiacetic Acid scan is done on days one and five.

The expected PICU length of stay is ten days at RCHM and 15 days at SCHN(W). The average length of stay for the last four years at RCHB was 12 days.

**Ward admission**

Patients are nursed in protected isolation. Intensive clinical therapy is commenced, in particular with the physiotherapist, occupational therapist and play therapist. Successful liver transplantation requires aggressive nutritional rehabilitation both pre- and post-transplant, so the dietician is closely involved in the nutritional care of these children.

Family and psychological support is provided by the liver transplant CNC / coordinator, social worker, psychologist and psychiatrist. At a weekly meeting with the ward staff and all team members, all the issues facing patients and their families are reviewed.

Blood tests are performed frequently for the first three to four weeks post-transplant and then as clinically indicated. The usual tests are LFTs, tacrolimus level, full blood count ("FBC"), UEC and CMP.

Prior to discharge, the liver transplant CNC / coordinator, ward nurses and pharmacist provide support and education to family members to enable them to competently and safely care for the child at home.

Patients return to theatre on average twice post-transplant. This can occur during the admission or as an outpatient prior to discharge from the NFC Program, although with access to percutaneous procedures these rates are reducing.
The expected ward length of stay is 25 days at RCHM and 37 days at SCHN(W). At RCHB the average length of ward stay for the last four years was 27 days.

**Post-transplant monitoring and follow-up**

Planning for discharge includes ensuring parents are appropriately educated in giving medications and attending to appliance requirements.

After discharge patients are seen for follow-up in the liver transplant clinic. Initially this occurs weekly but usually by around three months after transplant the frequency of visits is reduced depending on the clinical situation and stability of the patient. Ongoing management is tailored to the needs of the patient and family and becomes less intrusive over time, with outpatient visits organised around school holidays so as to minimise disruption to schooling. Pathology is reviewed quarterly. Standard clinic review includes history-taking, physical examination, height and weight measurements, blood pressure measurement; routine blood tests, trough tacrolimus level, fasting cholesterol and triglyceride levels, review of Epstein Barr virus and cytomegalovirus status and assessment as required by the dietician, social worker, occupational therapist, psychologist, and psychiatrist.

Jurisdictions advised that current NFC arrangements maximise the amount of support that can be delivered locally. Referring clinicians report that they are well supported by transplant centres to have ongoing involvement in the patient's care and have close communication with the paediatric transplant teams when appropriate.

Referring clinicians utilising the NSW centre report that the transplant team provides post-transplant review protocols which are clear and well communicated to clinicians. This is viewed favourably by referring clinicians as it facilitates consistency and transparency in shared management of patients. Communication regarding management that can be provided locally is reported to be prompt and clear.

Referring clinicians using the Victorian centre report high levels of support, particularly from the paediatric hepatologist, and that the service makes every effort to manage patients as close to home as possible. All clinicians in the transplant team are reported to be available should referring clinicians require support.

The RCHB organises patients who live outside Brisbane to have shared care arrangements with local paediatricians and general practitioners. Queensland health services have access to high quality telehealth facilities which also reduces the need for face-to-face consultations in Brisbane.

Clinicians consulted also advised that transplant teams maintain close contact with patients. Transplant teams at all three centres are reported to be always willing to provide telephone advice and to accept transfer where appropriate for patients, even at times of bed shortages in their institution. Families valued the transplant teams' support of local nursing, primary care and allied health providers to enable multidisciplinary supports to be more available locally.

At SCHN(W) the unit also undertakes a significant Anniversary Transplant (‘Birthday’) Review, although as this is longer than three months post-discharge it falls outside the funding envelope of the NFC Program. This information is included so as to give a sense of the ongoing costs incurred in managing post-transplant patients.

The anniversary review includes testing for autoantibodies and immunoglobulins, EBV viral load, CMV quantitative PCR and viral serology. Abdominal doppler ultrasound is performed to screen for possible PTLD. There is assessment of hearing, renal function, bone density, and dentition.
There may be occupational therapist and psychological reviews. Protocol-based liver biopsies are performed, at two and five years post-transplant.
QUALITY OF CARE OUTCOMES, MORBIDITY AND MORTALITY

Each NFC site must report each year to the NFC Reference Group on the following measures of patient outcome:

- Did any catastrophic events occur during the year?
- Were there unplanned readmissions to ICU?
- Were there any admissions post-discharge?
- Quality of life measures.

In 2009/10 the data collection was being redeveloped, so the sites were not required to provide the full suite of data for that year.

Quality of care outcomes are summarised for SCHN(W) at Table 13 and demonstrate generally low rates of complications and readmissions.

Table 13: Quality of care outcomes, Children’s Hospital Westmead Sydney, 2006-2011

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of transplants</td>
<td>64</td>
</tr>
<tr>
<td>Number of transplants reported on</td>
<td>53. No outcomes data reported on the 11 transplants in 2009/10 due to a technical issue.</td>
</tr>
<tr>
<td>Did any catastrophic events occur during this period?</td>
<td>Yes. Four deaths post-transplant, 10 rejections, three sepsis, three biliary stricture, six vascular, small number of other events</td>
</tr>
<tr>
<td>Where there any unplanned readmissions to ICU?</td>
<td>Yes. Post-surgical intervention for hepatic artery thrombosis and post-operative bleeding, neurological deterioration, laparotomy for artery thrombosis.</td>
</tr>
<tr>
<td>Were there any readmissions post discharge.</td>
<td>Yes. Hepatic vein stricture, acute cellular rejection, enterocutaneous fistula, chronic rejection, ACR, cholangitis, fever, fractures, biliary strictures requiring interventional radiology.</td>
</tr>
<tr>
<td>Quality of life measures</td>
<td>Reported on school/preschool attendance, developmental delay and/or age appropriate schooling.</td>
</tr>
</tbody>
</table>

RCHM advised a re-transplantation rate of 6 % (6/101). The principle reason for re-transplantation was chronic rejection (2/101), with other complications measured included hepatic artery thrombosis (1/101), portal vein thrombosis (0/101), ischaemic duct disease (1/101) and primary non-function (1/101).

The rate of PTLD resulting in death at RCHM was 2% for the transplant cohort from 1995-2012. Long-term outcomes for patient and graft survival at the RCHM site compare favourably with those reported by paediatric transplant programs overseas (Table 14).
Table 14: Long-term patient and graft survival, Royal Children’s Hospital Melbourne, patient cohort 1995-2012

<table>
<thead>
<tr>
<th>Years since transplant</th>
<th>Patient survival</th>
<th>Graft survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>92%</td>
<td>87%</td>
</tr>
<tr>
<td>5 years</td>
<td>86%</td>
<td>78%</td>
</tr>
<tr>
<td>10 years</td>
<td>80%</td>
<td>70%</td>
</tr>
</tbody>
</table>

The quality of care outcomes reported annually to the NFC Secretariat by RCHM are set out in Table 15.

Table 15: Quality of care outcomes, Royal Children’s Hospital Melbourne, 2006-2011

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of transplants</td>
<td>43</td>
</tr>
<tr>
<td>Number of transplants reported on</td>
<td>33. No outcomes data reported on the 10 transplants in 2009/10 due to a technical issue.</td>
</tr>
<tr>
<td>Did any catastrophic events occur during this period?</td>
<td>Yes. Patient bowel obstruction and perforation, pulmonary vein stenosis, bile leak; hepatic vein outflow tract stenosis; bile duct obstruction and rejection, passenger lymphocyte disorder, vascular stenosis, vascular thrombosis, small pericardial effusion, intraoperative sepsis and shock, haematomesis/melaena -1; gastric ulcers, pleural effusion, EBV, surgical removal of broken T tube, death post-transplant.</td>
</tr>
<tr>
<td>Where there any unplanned readmissions to ICU?</td>
<td>Yes. Patient bowel obstruction and perforation, hypotension, intussusception, EBV infection, PTLD, necrosis in CBD and biliary leak, biliary venous fistula, insertion of hepatic vein stent &amp; ASD closure, Hypernatraemic dehydration secondary to acute gastro.</td>
</tr>
<tr>
<td>Were there any readmissions post discharge.</td>
<td>Yes. Diarrhoeal disease, rejection, EBV, abnormal LFTs, intussusception, PTLD; Budd Chiari, pulmonary vein obstruction, bile leak, Haematemesis / melaena, bowel obstruction, Hypernatraemic dehydration, , fever sepsis, bone marrow suppression, biliary sepsis secondary to biliary obstruction, abnormal LFTs – biopsy.</td>
</tr>
<tr>
<td>Quality of life measures</td>
<td>Two PhDs – Quality of life and family functioning following paediatric liver transplant at (RCHM); Family functioning, parent stress, and child outcomes in serious paediatric liver disease (RCHM and SCHN(W)).</td>
</tr>
</tbody>
</table>

RCHB also makes annual reports, a summary of which is presented in Table 16. Outcomes are generally similar to the other two NFC sites.
### Table 16: Quality of care outcomes, Royal Children’s Hospital Brisbane, 2006-2011

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of transplants</td>
<td>32</td>
</tr>
<tr>
<td>Number of transplants reported on</td>
<td>23. No outcomes data reported on the 9 transplants in 2009/10 due to a technical issue.</td>
</tr>
<tr>
<td>Did any catastrophic events occur during this period?</td>
<td>Yes. Biliary leak, biliary stricture, CMV infection, CMV seroconversion, temporary right phrenic nerve palsy, allergy management, atraumatic fractures, portal vein thrombosis, hepatic artery thrombosis, bowel obstruction, primary non-function of a graft, severe neurological dysfunction (decided not to proceed to re-transplantation).</td>
</tr>
<tr>
<td>Where there any unplanned readmissions to ICU?</td>
<td>Yes. Biliary complications, sepsis; haemolytic uraemic syndrome, GI haemorrhage, biliary stent dislodged, portal vein thrombosis, respiratory failure and viral illness.</td>
</tr>
<tr>
<td>Were there any readmissions post discharge.</td>
<td>Yes. Liver Bx, PTC – D procedure, cholangitis, biliary reconstruction, sub-diaphragmatic collection, chest infection, endoscopy, pleural effusion, laparotomy, biliary stricture, PTLD, metastatic disease, influenza.</td>
</tr>
<tr>
<td>Quality of life measures</td>
<td>Preliminary results of a study of patients surviving five years after PLT who are school age (6-17 years) with school aged siblings indicates no significant difference in cognitive or academic functioning.</td>
</tr>
<tr>
<td></td>
<td>Results of a study assessing hearing, cognitive function and academic potential of school aged long-term transplant patients when compared with sibling control group. Their underlying genetic and familial factors are more likely to predict school performance.</td>
</tr>
<tr>
<td></td>
<td>Part of international multicentre trial.</td>
</tr>
<tr>
<td></td>
<td>Ongoing participation in international multicentre research to develop universal QoL questionnaire.</td>
</tr>
</tbody>
</table>

Consistently across all sites, and not unexpectedly given the severity of illness and the complexity of the interventions, there are catastrophic complications, unplanned readmissions to PICU and readmissions after discharge each year. The reports on quality of life measures provide important information about non-surgical aspects of care, which are important in the continued evolution of the NFC Program.

Although outcomes across the three sites appear broadly consistent, direct comparisons between sites are not possible due to variations in data collection practices. Further, information presented in Tables 12 to 16 demonstrates that quality of life data are limited and not comparable across the three sites.
Recommendation 4

That the Nationally Funded Centres sites continue to provide annual reports about quality of care to the Nationally Funded Centres Secretariat, but that reporting requirements are extended to include annual and aggregate complication rates across the full cohort of transplant patients by all three sites in accordance with standardised data definitions and reporting methods.

PROGRESS IN RESPONDING TO 2007 REVIEW RECOMMENDATIONS

On an annual basis each NFC site has reported to the NFC Reference Group on progress in responding to the recommendations of the 2007 review of Paediatric Liver Transplant Programs. The most recent responses of the sites are set out in Table 17, along with some additional information provided in previous years. Broadly, each site describes:

- protocol driven clinical practice;
- increased efforts to assess health and quality of life outcomes and patient and family satisfaction, while also highlighting the need for support to research neurocognitive, developmental and behavioural issues in children who receive a liver transplant; and
- progress in establishing a sustainable workforce.

Key features of the progress reported by the three sites are outlined in Table 17.

Table 17: Nationally Funded Centres site progress on meeting 2007 review recommendations

<table>
<thead>
<tr>
<th>Recommendation 1</th>
<th>Development of paediatric liver transplant treatment and management guidelines to achieve reduction of morbidity and complications, especially those associated with split liver transplantation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCHN(W)</td>
<td>The Liver Transplant Unit Protocol has been updated to reflect experience with management of split grafts, which has been recently published. The updated protocol includes: routine microvascular techniques for hepatic artery anastomosis; daily doppler ultrasound monitoring for early post-operative hepatic artery problems; laboratory monitoring for post-operative hypercoagulable states; and changes to ICU fluid management post-operatively to avoid intravascular fluid depletion.</td>
</tr>
<tr>
<td>RCHB</td>
<td>No complications of split liver transplants in the past 12 months.</td>
</tr>
<tr>
<td>RCHM</td>
<td>The internal liver transplant protocol was updated in 2010 and has been further updated this year including antibiotic guidelines and immunisation recommendations being developed in conjunction with our infectious diseases department and immunisation service. Surgical staff are active in ongoing professional development including attendance at meetings related to surgical techniques related to split liver transplantation.</td>
</tr>
<tr>
<td>Recommendation 2</td>
<td>That living donor liver transplantation is performed in accordance with agreed selection and treatment guidelines.</td>
</tr>
<tr>
<td>SCHN(W)</td>
<td>Live donor liver transplantation is undertaken in collaboration with colleagues from the ANLTU (Royal Prince Alfred Hospital) using a</td>
</tr>
<tr>
<td>Institution</td>
<td>Action/Comment</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------</td>
</tr>
<tr>
<td>RCHB</td>
<td>RCHB constructed guidelines so as to be congruent with those in use in NSW. The LDLT Program has reopened with two donor-recipient pairs proceeding to transplant thus far with three more partially completed workups in progress.</td>
</tr>
<tr>
<td>RCHM</td>
<td>Follow the guidelines of the Transplant Society of Australia &amp; New Zealand Liver transplant standing committee.</td>
</tr>
<tr>
<td>Recommendation 3</td>
<td>Improved and consistent data collection, with a stronger emphasis on health outcomes, including quality of life.</td>
</tr>
<tr>
<td>SCHN(W)</td>
<td>The Data Manager at SChN(W) has established a dedicated paediatric LTU database, which complements the existing ANLTU data collected since 1986. Patients are now entered prospectively and work is underway to enter the retrospective data. QoL data collection is difficult to accurately collect. SChN(W) is involved in a nearly completed international multi-centre study based in Canada to establish an accurate, reproducible QoL tool which can be applied to children after liver transplant. This tool will be in use in the next financial year for new patients. Other long-term outcomes which are an increasing issue for children after liver transplant are cognitive, behavioural and learning problems. Assessing factors which impact on such outcomes will be an important area of future research which will require attention and funding.</td>
</tr>
<tr>
<td>RCHB</td>
<td>Have completed validity phase, as part of an international multicentre project to develop a disease specific quality of life questionnaire for children following liver transplantation.</td>
</tr>
<tr>
<td>RCHM</td>
<td>Data collection will be streamlined and simplified with the use of the existing ANZ Liver Transplant Registry with the addition of fields as suggested at the last NFC meeting. We await rollout of the approved version of the patient satisfaction survey so we can incorporate this into our data collection. In addition, we have a doctoral student working on a project related to quality of life in paediatric liver transplant patients. The data from this study should be available in the next 12 months.</td>
</tr>
<tr>
<td>Recommendation 4</td>
<td>That surgical workforce succession planning is addressed in a coordinated plan for training and workforce management.</td>
</tr>
<tr>
<td>SChN(W)</td>
<td>CHW has three transplant surgeons to enable appropriate succession planning. These surgeons are paediatric transplant surgeons who undertake both liver and renal transplantation, as well as general paediatric surgery. They also undertake duties on the Organ Procurement Service roster. A Surgical Transplant Fellow position also provides suitable training for candidates interested in either transplantation or hepatobiliary sub-speciality work.</td>
</tr>
</tbody>
</table>
A new liver transplant surgeon, Peter Hodgkinson, has been appointed. He has gained experience in paediatric liver transplantation in Miami and at the Cleveland Clinic in the US. He has also developed expertise in small bowel transplantation and will be able to provide remote support, such as patient assessments, to the Victorian unit who have just commenced a program in this area.

Surgical workforce issues are variable across jurisdictions and therefore need to be addressed by each jurisdiction. We are developing a plan for workforce management in our jurisdiction.

All sites have further developed their paediatric liver transplant treatment and management guidelines. However, stakeholders reported that much of the guideline / protocol development work completed by each site has occurred independently of the other two sites. As a result, some stakeholders reported to the review team that diagnostic and management practices between NFC sites vary. The effect of this on patient outcomes is unable to be determined.

In particular, the reviewers note variations in clinical decision-making across the three sites in relation to when LDLT is performed and in transplantation of grafts acquired from marginal donors, including donation after cardiac death and ABO incompatible grafts. Presentations by the three NFC sites revealed different approaches to the use of marginal donors within each site's paediatric transplant unit. DCD or ABO incompatible grafts may provide a marginal donor treatment option to patients with acute liver transplantation or reduce the time on the waiting list, although the use of marginal donors is uncommon across the three sites. However, marginal donor grafts are more susceptible to initial dysfunction and the risk of re-transplantation is higher\textsuperscript{81, 82}. The appropriateness of their use, particularly in paediatric patients, is debated because of the higher associated morbidity and mortality\textsuperscript{83}.

The review team acknowledges that LDLT is a subject of ethical debate due to the impacts on the live donor of partial hepatectomy, including the morbidity and risk of mortality that is associated with the donation\textsuperscript{84}. The review team also acknowledges that LDLT incurs additional costs to the jurisdictions in which it is performed, as there is no specific funding available for the donor procedure. However, equitable access to technologies and reductions in unwanted variations in clinical practice are expected of Programs funded under the NFC model. The overarching objectives of NFCs include the provision of technologies (in this case liver transplantation) effectively; and that requirements for high quality and safe introduction and ongoing provision of these technologies have been defined and implemented.

It is therefore an expectation of the review team that clinical guidelines and protocols for clinical decision-making are harmonised across the three sites to ensure a consistent approach to LDLT and the use of marginal donors across sites.

Data collection has improved across the three sites since 2007. However, the review team found significant variations in data collection between the three sites. This made the task of analysing outcomes and site costs for various types of transplantations particularly problematic. Stakeholders reported that the NFC reporting requirements were not aligned with the usual reporting requirements.

\textsuperscript{84} Ventura K. Ethical considerations in live liver donation to children. Progress in Transplantation 2010; 20: 186-90.
for participation in the ANZLTR and therefore resulted in additional reporting burden. Pleasingly there has been recent progress in improving the data collection arrangements, so that ideally the ANZLTR would become the single reporting requirement for NFC sites with the data collected by the registry also addressing the needs of the NFC Secretariat.

**Recommendation 5**

That the Nationally Funded Centres sites continue to progress implementing recommendations 1 and 3 of the 2007 review with a view to standardising clinical care and data collection by:

- working towards consistent clinical practice guidelines and protocols across all three sites particularly in relation to living donor liver transplantation and the use of marginal donors but not where it is likely to impede the development of new, effective techniques;

- developing a post-transplant care pathway which facilitates the involvement of the patient’s usual paediatrician; and

- developing a systematic process of data collection that is based on the Australian and New Zealand Liver Transplant Registry data collection system and that meets the needs of the Nationally Funded Centres Secretariat for regular reporting by sites.
COSTS AND FINANCIAL MODELLING

The NFC Guidance document requires that there is a clear definition of the start and end for the episode of care for each procedure. It determines that in general the jurisdiction will pay for the patient until their acceptance onto the NFC Program and the NFC Program is responsible for the costs of care for up to three months post-discharge, after which the jurisdiction will again be responsible for the costs of patient care.

It has also been determined that the costs of those patients who are accepted onto the Program, receive an assessment and work-up but do not proceed to the procedure stage, need to be considered in calculating the cost per procedure.

The suggested phases of care in the NFC Program are:

- acceptance for NFC treatment;
- pre-treatment outpatient monitoring;
- pre-treatment inpatient care;
- theatre / surgery and other procedures integral and required as part of care;
- high dependency / intensive care;
- general ward admission;
- outpatient care prior to discharge from the NFC site; and
- other direct patient costs including transport and accommodation.

As noted above, although the NFC Guidance document stipulates that the episode of care starts when the patient is accepted onto the Program, in practice this can occur only for paediatric liver transplant candidates after the work-up. On strict reading of the guidelines the initial screening assessment in response to the referral falls outside the scope of the NFC Program. Whilst a distinction is made between the work-up and acceptance on to the Program in the care pathway, the steps are not necessarily separable, so the costs of the work-up need to be included.

NFC Program management costs and health service and overhead costs are indirect patient costs that can be funded.

Financial analysis

The three NFC sites provided care pathway cost data of varying levels of detail. The most comprehensive information was provided by RCHM and was consistent with the cost pro forma in Appendix 2 of the NFC Guidance document. SCHN(W) and RCHB also supplied information in the form set out in Appendix 2, although it was not possible to draw such detailed conclusions from it. RCHB supplemented this information with all costs from two recent admissions and length of stay data on all patients treated since 2002/03. It was not possible to substantially reconcile the data presented by RCHB in the costing pro forma and the actual costs incurred in the two recent admissions. This will be discussed in more detail in the following sections.

The total estimated costs for each stage of the treatment process for the three NFC sites are set out in Table 18. The cost range is from a low of $311,867 at RCHB to a high of $339,306 at SCHN(W).
Table 18: Estimated total cost of paediatric liver transplantation, submitted by Nationally Funded Centres

<table>
<thead>
<tr>
<th>Care pathway step</th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referral</td>
<td>$31,790</td>
<td>$589</td>
<td>$2,574</td>
</tr>
<tr>
<td>Work-up</td>
<td>$4,159</td>
<td>$2,114</td>
<td>$6,234</td>
</tr>
<tr>
<td>Acceptance</td>
<td>$1,000</td>
<td>$4,433</td>
<td>$735</td>
</tr>
<tr>
<td>NFC Pre-transplant monitoring</td>
<td>$11,246</td>
<td>$18,154</td>
<td>$13,323</td>
</tr>
<tr>
<td>Transplant – theatre cost</td>
<td>$22,444</td>
<td>$67,240</td>
<td>$52,655</td>
</tr>
<tr>
<td>Other procedures</td>
<td>$1,080</td>
<td>Not specified</td>
<td>$1,700</td>
</tr>
<tr>
<td>PICU admission</td>
<td>$110,077</td>
<td>$51,519</td>
<td>$51,342</td>
</tr>
<tr>
<td>Ward admission</td>
<td>$99,848</td>
<td>$102,933</td>
<td>$76,075</td>
</tr>
<tr>
<td>Post-discharge monitoring</td>
<td>$20,282</td>
<td>Not specified</td>
<td>$7,888</td>
</tr>
<tr>
<td>Other</td>
<td>$240</td>
<td>$22,564</td>
<td>$2,213</td>
</tr>
<tr>
<td>Accommodation and transport</td>
<td>$5,721</td>
<td>$13,970</td>
<td>$13,983</td>
</tr>
<tr>
<td>Total direct costs</td>
<td>$307,887</td>
<td>$283,516</td>
<td>$228,724</td>
</tr>
<tr>
<td>Indirect costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overhead</td>
<td>$21,157</td>
<td>$2,651</td>
<td>$44,742</td>
</tr>
<tr>
<td>Program management</td>
<td>$10,262</td>
<td>$25,700</td>
<td>$24,679</td>
</tr>
<tr>
<td>On-costs</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$12,574</td>
</tr>
<tr>
<td>Education</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$851</td>
</tr>
<tr>
<td>Neuro-developmental review</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$5,000</td>
</tr>
<tr>
<td>Total indirect costs</td>
<td>$31,419</td>
<td>$28,695</td>
<td>$87,846</td>
</tr>
<tr>
<td>Total costs</td>
<td>$339,306</td>
<td>$311,867</td>
<td>$316,570</td>
</tr>
</tbody>
</table>

The 2007 MSAC review of the NFC Paediatric Liver Transplant Program reported that the estimated cost of each whole liver transplant ranged from a low of $170,590 at RCHB, through $195,812 at SCHN(W) to $201,490 at RCHM. Each transplant is currently funded by the NFC Program at about $205,000.
Table 19 summarises key cost drivers for paediatric liver transplantation. With respect to the 2012 data, the information for RCHM was explicitly stated in the information provided, however it had to be derived for the other two sites. In the case of length of stay at RCHB, these figures represent the average of the 30 transplants in the period 2009/10 – 2012/13. The estimated costs at RCHB are from the actual unit costs incurred for the two recent admissions. The costs at RCHB for a PICU and ward bed day are significantly higher than the estimated costs at both SCHN(W) and RCHM. In turn, the estimated length of stay at SCHN(W) is about 50% longer than RCHM for both ward and PICU stays. The 2007 data are as reported in the MSAC review.

**Table 19: Key cost drivers in paediatric liver transplantation, 2007 and 2012**

<table>
<thead>
<tr>
<th></th>
<th>PICU length of stay</th>
<th>PICU per day cost</th>
<th>Ward/Unit length of stay</th>
<th>Ward per day cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCHN(W) 2007</td>
<td>5.5 days (132 hours)</td>
<td>$630</td>
<td>22.0 days (529 hours)</td>
<td>$1,500</td>
</tr>
<tr>
<td>SCHN(W) 2012</td>
<td>15.3 days (367 hours)</td>
<td>$4,300</td>
<td>37.0 days (888 hours)</td>
<td>$1,295</td>
</tr>
<tr>
<td>RCHB 2007</td>
<td>7.0 days</td>
<td>$2,956</td>
<td>30.0 days</td>
<td>$512</td>
</tr>
<tr>
<td>RCHB 2012</td>
<td>10 days</td>
<td>$6,333</td>
<td>28.5 days</td>
<td>$1,483</td>
</tr>
<tr>
<td>RCHM 2007</td>
<td>10.0 days</td>
<td>$2,379</td>
<td>35.0 days</td>
<td>$543</td>
</tr>
<tr>
<td>RCHM 2012</td>
<td>10.0 days</td>
<td>$3,500</td>
<td>25.0 days</td>
<td>$950</td>
</tr>
</tbody>
</table>

The total average inpatient length of stay in 2012 therefore is estimated to be 52.3 days at SCHN(W), 38.5 days at RCHB and 35.0 days at RCHM, compared with 2007 length of stays of 27.5 days, 37.0 days and 45.0 days at each of the three hospitals respectively.

An analysis of the 2007 estimated costs and those submitted by the NFC sites for this review has been undertaken, with key issues discussed in Table 20.

**Table 20: Key issues in 2007 and 2012 cost submissions**

<table>
<thead>
<tr>
<th>Care pathway stage</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral</td>
<td>All three sites indicate an increase in referral costs compared with 2007, most notably at SCHN(W) which has determined that the cost of a preceding inpatient episode represents the cost of referral. In 2007 it identified no referral costs which MSAC attributed to all transplant patients being inpatients at the time of referral. Consequently SCHN(W) underestimated referral costs in 2007 and has overestimated them in 2012. The increase in costs at RCHB and RCHM appear to be justifiable on the information presented.</td>
</tr>
<tr>
<td>Work-up and acceptance</td>
<td>In 2007 the costs at RCHM were significantly higher than the other sites. Since then RCHM has determined that its costs have increased by a modest 14%, with the other sites identifying much more substantial increases, which brings them closer to but not exceeding the RCHM figure.</td>
</tr>
<tr>
<td>Care pathway stage</td>
<td>Comment</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>NFC Pre-transplant monitoring</td>
<td>On average the costs have increased from $10,383 to $14,241, however the detailed costing from the 2012 RCHM submission satisfactorily justifies the increase on the basis of an expected 8 detailed reviews, including for interstate candidates, whilst on the waiting list.</td>
</tr>
<tr>
<td>Transplant – theatre cost</td>
<td>In 2007 the SChN(W) theatre costs were estimated as an unaccountably low $8,553, with RCHM at $17,300 and RCHB at $28,995. In the 2012 submission SChN(W) increased to $28,995, RCHM to $55,655 and RCHB to $68,995. The RCHB costs are driven by very high surgical and anaesthetist cost, which outstrip the other sites by a wide margin. The 2012 RCHM estimate includes about $15,000 for replacement lists, which as discussed below has been discounted. Higher fee-for-service payments to the surgeons and anaesthetists at RCHM represent an additional $13,000, but in the context of the complexity of the surgery and time commitment do not appear excessive.</td>
</tr>
<tr>
<td>Other procedures</td>
<td>No costs were attributed to this item in 2007, so the costs in 2012 are new.</td>
</tr>
<tr>
<td>PICU admission</td>
<td>In 2007 SChN(W) estimated the base PICU bed day cost at just $630, which led to a low estimate of only $14,885 for a five and a half day length of stay. In comparison its 2012 submission projects a 15.3 day length of stay at about $4,300 per day, which leads to a total cost estimate of more than $110,000. This is more than twice as much as RCHB and RCHM, which both estimate about $51,000, which represents a reasonable 20% increment on their 2007 figure.</td>
</tr>
<tr>
<td>Ward admission</td>
<td>All three sites foreshadow significant increase in ward costs, which in the case of SChN(W) represents a substantial increase of length of stay in the context of a surprising reduction in the estimated bed day cost. RCHB and RCHM have increased cost estimates due to significant increases in bed day costs, probably from an artificially low base, with a reduction in length of stay. Overall the RCHM bed day cost of $950, the lowest of the three, is in line with the cost provided for the surgical management of hypoplastic left heart syndrome NFC review. However whilst the expected ward length of stay is longer than some international benchmarks, it is less than length of stay at SChN(W) and RCHB.</td>
</tr>
<tr>
<td>Post-discharge monitoring and other related expense</td>
<td>In 2007, SChN(W) identified $92,725 in post-discharge monitoring, which extended for a full 12 months after discharge, whilst the other two sites identified no costs for this care. In 2012, these are newly attributed costs for RCHB and RCHM. The SChN(W) costs are significantly reduced to $20,282, which are more in line with its peer hospitals.</td>
</tr>
<tr>
<td>Accommodation and transport</td>
<td>The cost estimate for RCHM has increased from a low $3,800 in 2007 to $13,983 in 2012, a level consistent with the estimate from RCHB, which does not provide a detailed basis for its estimate. SChN(W) estimates a much lower figure.</td>
</tr>
<tr>
<td>Overhead</td>
<td>Administrative overhead potentially represents a significant proportion of total costs, but in 2012 the submitted amounts range from 1% to 20%.</td>
</tr>
<tr>
<td>Care pathway stage</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>whereas in 2007 the range was 0% to 22%, with one site going from 14% to 1% and another from 0% to 7%. In the Pancreas Transplant NFC review overheads were estimated at 10%, with a figure of 15% in the surgical management of hypoplastic left heart syndrome syndrome review.</td>
</tr>
<tr>
<td>Program management</td>
<td>Two sites project costs in the order of $25,000. The third attributes secretarial and database expenses of about $10,000, but with no head of unit expense. With an annual caseload of 10 transplants, the head of unit expense would be $150,000 which represents a 0.3 EFT commitment for the head of unit. This is consistent with NFC Paediatric Lung review, which established a 0.2 EFT appointment for that smaller Program.</td>
</tr>
<tr>
<td>On-call</td>
<td>The costs for the Austin Hospital are presented separately from RCHM, with a line item for on-call for the transplant team. The amount has reduced from $36,754 to $12,574 in the 2012 submission which presumably represents the shift to higher fee-for-service payments for the surgeons and anaesthetists. It is assumed that the other sites have rolled on-call payments into the overall salary expense. The residual amount of $12,574 largely represents the on-call costs of staff who make up the usual staffing complement of a teaching hospital and is therefore already funded from other sources.</td>
</tr>
<tr>
<td>Neuro-developmental review</td>
<td>This is a new amount of $5,000 identified by RCHM, which also featured in the costing for the NFC Surgical Management of Hypoplastic Left Heart Syndrome Program.</td>
</tr>
<tr>
<td>Summary comment</td>
<td>The aspects of the care pathway which are most pertinent in the comparison between 2007 and 2012 are for: SCHK(W) – referral, PICU and ward; RCHB – theatre and ward; and RCHM – theatre, ward and overhead.</td>
</tr>
</tbody>
</table>

The following section provides a detailed analysis of the costs submitted for this review, whilst taking account of data provided for the 2007 review and international experience as to expected PICU and ward length of stays.

**Referral to the service**

Referral may occur months to years before the patient is listed for transplantation. For cost estimation purposes, the RCHM cost estimate is based upon the historical experience that for every 20 patients referred for initial screening assessment twelve will proceed to a full work-up and 10 will proceed to transplantation. The additional costs of assessment and work-up where patients do not subsequently proceed to transplantation have been factored into the analysis (Table 21).
Table 21: Estimated costs of the referral to the service

<table>
<thead>
<tr>
<th>Referral to service</th>
<th>Estimated cost</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCHM</td>
<td>$2,574</td>
<td>This represents the cost of a four and a half hour review by senior medical specialist and a five hour review by a senior social worker. The hourly rates used include an increment of 25% for overheads. The hourly rates equate to the highest specialist medical grade and a level 4 allied health grade, notwithstanding the actual seniority of the staff is lower. The cost of one assessment is $1,287, but as noted above in general two are undertaken for each patient.</td>
</tr>
<tr>
<td>SCHN(W)</td>
<td>$31,790</td>
<td>This figure appears to represent the cost of the admission which resulted in the patient being accepted for transplant. A more detailed analysis is provided below.</td>
</tr>
<tr>
<td>RCHB</td>
<td>$589</td>
<td>There were insufficient data to analyse this cost.</td>
</tr>
</tbody>
</table>

As noted above patients have not been accepted into the Transplant Program until after the work-up therefore the cost of referral and screening assessment falls outside the NFC Program.

Pre-transplant admissions

In the data provided by RCHB it was possible to identify a number of related admissions for both patients prior to the admission for the transplant. The first patient had 18 inpatient admissions in the six months before definitive transplant surgery, whilst the second patient had five admissions in the two and a half months before transplant. The RCHB costing systems identified costs of $64,526 and $85,699 for these waiting list patients (Table 22). These costs do not form part of the RCHB NFC cost estimate, but rather are included as they highlight the costs incurred outside NFC funding streams.

Table 22: Pre-transplant admissions at Royal Children’s Hospital Brisbane and Children’s Hospital Westmead Sydney

<table>
<thead>
<tr>
<th>Service parameter</th>
<th>RCHB patient one</th>
<th>RCHB patient two</th>
<th>SCHN(W) patient one</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>18 inpatient episodes, 34 inpatient days in prior six months</td>
<td>5 inpatient episodes, 13 inpatient days in prior 2.5 months</td>
<td>1 inpatient episode, 8 inpatient days</td>
</tr>
<tr>
<td>Emergency department</td>
<td>$4,757</td>
<td>$1,288</td>
<td>$187</td>
</tr>
<tr>
<td>Imaging</td>
<td>$1,905</td>
<td>$2,429</td>
<td>$3,458</td>
</tr>
<tr>
<td>Pathology</td>
<td>$1,180</td>
<td>$2,885</td>
<td>$3,253</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$6,111</td>
<td>$10,690</td>
<td>$736</td>
</tr>
<tr>
<td>Theatre</td>
<td>$7,236</td>
<td>$11,245</td>
<td>$2,818</td>
</tr>
<tr>
<td>Service parameter</td>
<td>RCHB patient one</td>
<td>RCHB patient two</td>
<td>SCHN(W) patient one</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------</td>
<td>------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Ward</td>
<td>$40,828</td>
<td>$54,952</td>
<td>$20,738</td>
</tr>
<tr>
<td>Outpatients</td>
<td>$2,509</td>
<td>$0</td>
<td>$240</td>
</tr>
<tr>
<td>Other investigations</td>
<td>$0</td>
<td>$0</td>
<td>$360</td>
</tr>
<tr>
<td>Total</td>
<td>$64,526</td>
<td>$85,699</td>
<td>$31,790</td>
</tr>
</tbody>
</table>

SCHN(W) highlighted that the current national organ donation rate limits organs suitable for paediatric recipients and children on the waiting list are sicker and require frequent and/or continual hospitalisation prior to transplant. SCHN(W) is of the view that these costs should be met by the NFC Program. Sicker malnourished children in the pre-transplant period also experience increased post-transplant complications resulting in poorer outcomes, increased length of hospital stay and increased costs. Consequently, SCHN(W) used the first inpatient episode to represent the cost of referral (Table 22). This method has not been used in other NFC Programs, but does reflect the concern of NFC sites about the cost of management of patients awaiting transplant. The national introduction of activity based funding should to a significant extent meet the cost of these pre-transplant admissions, so whilst there are large costs involved, the new arrangements should alleviate a significant proportion of the impost on hospitals. In addition as the NFC transplant hospitals will care for a high proportion of all patients with the relevant DRGs their actual costs will over time drive the level of reimbursement for these patients.

**Work-up and acceptance onto NFC Program**

As noted above, RCHM provided the most detailed breakdown of costs, whilst RCHB only provided a rolled-up sum from which it was not possible to determine the specific costs for aspects of the work-up.

The work-up usually takes about four days, however all or a substantial proportion of the investigations are performed as an outpatient service, so if patients have come from interstate with their parents accommodation costs will be incurred. Based on availability of accommodation at local serviced apartments, it is estimated that the average cost is $180 per night compared with the RCHM estimate of $250.

The Victorian Department of Health also advises that RCHM has access to its own Fibroscan, which was funded by the Department and purchased by the hospital. Therefore, the $1,400 for a scan would appear to exceed the actual recurrent cost incurred by the hospital in undertaking the investigation, which is likely to be negligible and so has been excluded.

With respect to the RCHM costs, the staff costs reflect 14 hours of allied health assessments by eight different clinicians and a one hour consultation with a psychiatrist and a clinical nutritionist. There are the expected other pathology and imaging costs. There is also about two hours of Austin Health transplant coordinator time included in the cost, which would appear reasonable given the need to ensure good continuity of care between the two hospitals.

The level of detail provided by SCHN(W) and RCHB is set out in full in Table 23. It is not possible to draw conclusions from their estimated costs for the work-up. The most significant aspect of the RCHB costs is the $4,433 for a multidisciplinary team meeting, which exceeds the estimates for the other two sites by about a factor of four. However, if the meeting lasts for one hour and surgeons, specialist gastroenterologists, anaesthetists and the full complement of allied health clinicians attend, it is possible that the cost would be in the order of $4,000.
### Table 23: Estimated costs for work-up and acceptance onto Nationally Funded Centres Program

<table>
<thead>
<tr>
<th>Service</th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist medical consults</td>
<td>$1,040</td>
<td>$1,084</td>
<td>$1,147</td>
</tr>
<tr>
<td>Allied health consults</td>
<td>$408</td>
<td>$1,030</td>
<td>$795</td>
</tr>
<tr>
<td>Imaging</td>
<td>$408</td>
<td>Not specified</td>
<td>$218</td>
</tr>
<tr>
<td>Pathology</td>
<td>$2,043</td>
<td>Not specified</td>
<td>$540</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$260</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Family support, accommodation, travel</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$1,600</td>
</tr>
<tr>
<td><strong>Work-up total</strong></td>
<td><strong>$4,159</strong></td>
<td><strong>$2,114</strong></td>
<td><strong>$6,234</strong></td>
</tr>
<tr>
<td>Acceptance – multi-disciplinary team meeting</td>
<td>$1,000</td>
<td>$4,433</td>
<td>$394</td>
</tr>
<tr>
<td>Acceptance – consent</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$341</td>
</tr>
<tr>
<td>Acceptance total</td>
<td>$1,000</td>
<td>$4,433</td>
<td>$735</td>
</tr>
<tr>
<td>Work-up and acceptance total</td>
<td>$5,159</td>
<td>$6,547</td>
<td>$5,569</td>
</tr>
</tbody>
</table>

**Inpatient / outpatient pre-NFC treatment monitoring**

The SCHN(W) costs include both inpatient and outpatient expenses. One short admission in which a procedure in theatre is performed is included. Overall 87% of pre-transplant costs are attributed to the inpatient stay (Table 24). In contrast, neither RCHB nor RCHM has significant inpatient costs, although RCHB does identify $3,300 of emergency department costs which, on the basis of their estimated costs per visit, represents five attendances. In addition, RCHB has a large outpatient pharmacy expense, which has not been identified by the other units.

Review of the cost spreadsheet for the recent RCHB admissions confirmed significant pharmacy costs including two scripts for nutritional supplements at $921 each as well as the costs of dispensing many medications over a six month period. RCHM identifies actual outpatient costs incurred whilst the patient is on the waiting list, including 32 hours of work time for the transplant coordinator.
Table 24: Estimated costs for work-up and acceptance onto Nationally Funded Centres Program

<table>
<thead>
<tr>
<th>Service</th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department</td>
<td>Not specified</td>
<td>$3,300</td>
<td>Not specified</td>
</tr>
<tr>
<td>Outpatient multidisciplinary team meeting</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$2,786</td>
</tr>
<tr>
<td>Outpatient medical</td>
<td>$360</td>
<td>$5,750</td>
<td>$4,120</td>
</tr>
<tr>
<td>Outpatient nursing</td>
<td>$50</td>
<td>$561</td>
<td>$1,618</td>
</tr>
<tr>
<td>Outpatient allied health</td>
<td>$120</td>
<td>$561</td>
<td>Not specified</td>
</tr>
<tr>
<td>Outpatient imaging</td>
<td>$710</td>
<td>$887</td>
<td>$550</td>
</tr>
<tr>
<td>Outpatient pathology</td>
<td>$175</td>
<td>$7,312</td>
<td>Not specified</td>
</tr>
<tr>
<td>Inpatient medical</td>
<td>$6,221</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Inpatient nursing</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Inpatient allied health</td>
<td>$1,921</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Inpatient imaging</td>
<td>$323</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Inpatient pathology</td>
<td>$485</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Inpatient pharmacy</td>
<td>$216</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Inpatient theatre</td>
<td>$667</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Overhead</td>
<td>Not specified</td>
<td>$344</td>
<td>Not specified</td>
</tr>
<tr>
<td>Total</td>
<td>$11,246</td>
<td>$18,154</td>
<td>$13,323</td>
</tr>
</tbody>
</table>

**Theatre / surgery**

The structure and value of the estimated costs for the three sites diverged significantly. RCHB provided just one figure for the total cost but it was possible to determine from the detailed spreadsheets that the ward admission prior to theatre involved $3,719 of expense. In addition, it was possible to determine the hourly rates for the three surgeons and three anaesthetists presented in Table 25. The cost of an eight-hour operation (10 hours of anaesthetic time) would be $29,728 for the surgeons and $18,000 for the anaesthetists, at least double the fee-for-service costs at RCHM. The specialist surgical and anaesthetic costs at SCHN(W) seem inexplicably low. The $1,616 per hour for running the theatre at RCHB is reasonably close to the identified costs at RCHM for the theatre, recovery, theatre staff and consumables.
Table 25: Estimated costs for theatre and transplant surgery

<table>
<thead>
<tr>
<th>Service</th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-theatre care</td>
<td>Not specified</td>
<td>$3,719</td>
<td>$350</td>
</tr>
<tr>
<td>Theatre staff</td>
<td>$11,107 (includes surgeon expense)</td>
<td>$1616/hour (includes theatre costs)</td>
<td>$5,457</td>
</tr>
<tr>
<td>Surgeons</td>
<td>See above</td>
<td>1 surgeon @ $800/hour;</td>
<td>3 FFS surgeons @ total cost of $11,000;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 surgeons each @ $1,458/hour</td>
<td>1 fellow @ $734</td>
</tr>
<tr>
<td>Anaesthesists</td>
<td>$7,153</td>
<td>3 anaesthetists each @ $600/hour</td>
<td>3 anaesthetists @ total cost of $11,076</td>
</tr>
<tr>
<td>Consumables</td>
<td>$3,726</td>
<td>Not specified</td>
<td>$3,725</td>
</tr>
<tr>
<td>Implantable devices</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$300</td>
</tr>
<tr>
<td>Theatre costs</td>
<td>Not specified</td>
<td>See above</td>
<td>$2,500</td>
</tr>
<tr>
<td>Recovery</td>
<td>$458</td>
<td>Not specified</td>
<td>$1,200</td>
</tr>
<tr>
<td>Pathology</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$350</td>
</tr>
<tr>
<td>Transport</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$1,088</td>
</tr>
<tr>
<td>Total theatre</td>
<td>$22,444</td>
<td>$67,240</td>
<td>$37,780</td>
</tr>
<tr>
<td>Other attributed costs</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$14,875 (2 replacement lists)</td>
</tr>
</tbody>
</table>

The 2012-13 Victorian costs distinguish RCHM and Austin Health costs although for the most part in this analysis they have, for convenience, been combined. However, in the theatre costs section it is necessary to highlight a claim by Austin Health for $14,875 being for the "salary and wages - additional two lists required to replace cancelled surgery due to transplant". The logic behind this is unclear as these costs have not been incurred. In addition, no similar allowance has been made before in the NFC Program and so the claim should at this stage be disallowed.

Also as noted above the residual increase in RCHM theatre costs is due to a large extent to enhanced remuneration for the transplant surgeons and Austin Health anaesthetist. The level of the fee-for-service payment does not appear excessive and is certainly much less than RCHB levels.

Other procedures

None of the hospitals identified "other procedure" costs in 2007, so their inclusion here is a new source of expense. SCHN(W) identified a number of additional investigations not costed elsewhere, which appear relevant and appropriate (Table 26). RCHM identified the costs of a return to theatre during the transplant admission, which is consistent with a high proportion of cases not having a primary closure of the abdominal wall at the end of the abdominal transplant surgery. RCHB did not explicitly include an amount for this matter. Review of the spreadsheet for one of the recent
admissions did have a return to theatre for 100 minutes of surgery, the cost of which amounted to $13,240. In addition, a further PICU stay of 1.65 days was needed. These costs are included by way of information, rather than as a contribution to the overall cost analysis.

<table>
<thead>
<tr>
<th>Service</th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiogram/biopsy</td>
<td>$360</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>ECG</td>
<td>$240</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>Echo</td>
<td>$240</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>EEG</td>
<td>$240</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>Return to theatre</td>
<td>$0</td>
<td>$13,240</td>
<td>$1,700</td>
</tr>
<tr>
<td>Return to theatre PICU</td>
<td>$0</td>
<td>$10,449 (1.65 days)</td>
<td>$0</td>
</tr>
<tr>
<td>Total</td>
<td>$1,080</td>
<td>$23,669</td>
<td>$1,700</td>
</tr>
</tbody>
</table>

## Paediatric intensive care unit

As previously, the total estimated cost for RCHB was provided without a direct attribution of the unit costs upon which it was based. The length of stay presented in Table 27 is the average of the transplants performed in the last three years, with three extreme outliers excluded. The RCHB cost / bed day and imaging and pathology expenses were extracted from the spreadsheet of costs for the recent admissions. The SCHN(W) data also presented in Table 27 reflect the extent of the detail provided in its cost submission.

As described above there is a wide difference between the units in the expected length of PICU stay and also in the estimated bed day cost. International experience and advice from the expert international reviewer suggests that the average expected PICU stay is about 10 days, which reflects RCHB experience and the RCHM submission.

By way of comparison the costs for the NFC for the surgical management of hypolastic left heart syndrome in 2010 were $3,072 at SCHO(W) and $3,000 at RCHM. From that base, the average cost for a 10 day PICU stay was about $45,000 when specialist medical, allied health and investigation costs were included. It is not possible to verify that the bed day cost at RCHB includes the bundled up costs for pharmacy and specialist surgical and medical review. The imaging and pathology costs at RCHB and RCHM are quite close in aggregate, when the expected length of stay is taken into account, however these costs seem high in the SCHO(W) submission. It is likely that there would be some pharmacy costs, although potentially these are to some extent bundled into the bed day cost at RCHB and RCHM. The daily tacrolimus levels are now performed at RCHM, so the costs identified by Austin Health are still incurred albeit by another entity and have been retained.

As estimate of SCHO(W) costs with a 10 day PICU length of stay have been made, which is in effect two thirds of the submitted costs.
Table 27: Estimated paediatric intensive care unit costs

<table>
<thead>
<tr>
<th></th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay</td>
<td>15 days</td>
<td>10.6 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Cost / bed day (includes ICU staff, consumables)</td>
<td>$4,300</td>
<td>$6,333</td>
<td>$3,500</td>
</tr>
<tr>
<td>Total bed day cost</td>
<td>$64,459</td>
<td>Not specified</td>
<td>$35,000</td>
</tr>
<tr>
<td>Specialist medical</td>
<td>$7,992</td>
<td>Not specified</td>
<td>$7,012</td>
</tr>
<tr>
<td>Specialist nursing</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$1,320 (liver coordinator)</td>
</tr>
<tr>
<td>Specialist allied health</td>
<td>Not specified</td>
<td>Not specified</td>
<td>$1,181</td>
</tr>
<tr>
<td>Imaging</td>
<td>$28,345</td>
<td>$145 / day</td>
<td>$2,650</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td>$500 / day</td>
<td>$4,179</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$9,282</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Total</td>
<td>$110,077</td>
<td>$51,519</td>
<td>$51,342</td>
</tr>
<tr>
<td>Adjusted estimated expense with 10 day PICU stay</td>
<td>$73,385</td>
<td>$51,519</td>
<td>$51,342</td>
</tr>
</tbody>
</table>

Ward costs

The limitations with the data identified above apply to ward costs as well. RCHB identified bed day costs for both a general ward and the renal unit, a distinction not made by the other sites. The combined bed day costs equal $102,933, which is more than twice the next highest amount. The RCHB submission also identified additional inpatient expense for pathology, imaging and pharmacy, which have also been included here. The difference in cost between SCHN(W) and RCHM is largely a factor of the total bed day costs, with SCHN(W) length of stay being 50% longer than RCHM and the rate being 36% greater. As noted above international experience points to much shorter ward stays in the order of 15 days, consequently an estimate of costs has been made using that length of stay. The analysis provides for 15 days of ward, medical, pharmacy costs and 16.75 days of allied health and special nursing care costs which reflect the higher intensity of use at the start of the ward admission and all the attributed pathology and imaging expense.

The bed day rates listed here are comparable after indexation to those that underpinned the NFC surgical management of hypoplastic left heart syndrome procedure estimates, which were $1,128 for SCHN(W) and $850 for RCHM (Table 28).
Table 28: Estimated ward costs

<table>
<thead>
<tr>
<th></th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay</td>
<td>37 days</td>
<td>26.3 days</td>
<td>25 days</td>
</tr>
<tr>
<td>Cost / bed day (nursing,</td>
<td>$1,295 / day</td>
<td>$1,483 / day</td>
<td>$950 / day</td>
</tr>
<tr>
<td>consumables)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bed day costs</td>
<td>$47,195</td>
<td>$102,933</td>
<td>$23,750</td>
</tr>
<tr>
<td>Medical</td>
<td>$10,588</td>
<td>Not specified</td>
<td>$12,438</td>
</tr>
<tr>
<td>Liver coordinator / special nursing</td>
<td>$360</td>
<td>Not specified</td>
<td>$19,680</td>
</tr>
<tr>
<td>Allied health</td>
<td>$10,326</td>
<td>Not specified</td>
<td>$3,672</td>
</tr>
<tr>
<td>Imaging</td>
<td>$19,971</td>
<td>$3,660</td>
<td>$1,100</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td>$4,532</td>
<td>$14,315</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$10,679</td>
<td>$9,990</td>
<td>$1,122</td>
</tr>
<tr>
<td>Total</td>
<td>$99,848</td>
<td>$121,115</td>
<td>$74,072</td>
</tr>
<tr>
<td>Adjusted estimated expense with 15 day ward stay</td>
<td>$55,262</td>
<td>$72,597</td>
<td>$51,505</td>
</tr>
</tbody>
</table>

Post-discharge care

In 2007 SCHN(W) identified $92,275 in post-discharge monitoring, which represented ongoing management for a whole year after discharge of which $20,699 was accrued in the first three months. Neither RCHB nor RCHM included post-discharge costs in their 2007 submissions.

There is a wide margin of difference between the estimated costs subsequent to discharge for the three sites, with the outpatient expense alone varying by more than a factor of three (Table 29). Variation is attributable to differences in medical review costs and imaging, pathology and pharmacy costs. SCHN(W) and RCHM also identified the cost of a short readmission related to the transplant procedure, with the total cost being relatively moderate compared with other NFC related admissions. The RCHB submission did not explicitly identify outpatient costs, so the data presented here were built up from the spreadsheet from recent admissions and clinical protocols.
Table 29: Estimated costs of outpatient supervision prior to discharge from Nationally Funded Centres

<table>
<thead>
<tr>
<th></th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical review</td>
<td>$8,040</td>
<td>$4,129 (7 visits)</td>
<td>$2,400</td>
</tr>
<tr>
<td>Allied health</td>
<td>$1,270</td>
<td>$0</td>
<td>$2,464</td>
</tr>
<tr>
<td>Imaging</td>
<td>$5,520</td>
<td>$0</td>
<td>Not specified</td>
</tr>
<tr>
<td>Pathology</td>
<td>$1,877</td>
<td>$599</td>
<td>$325</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$1,320</td>
<td>$3,156</td>
<td>Not specified</td>
</tr>
<tr>
<td>Outpatient total</td>
<td>$18,027</td>
<td>$7,884</td>
<td>$4,789</td>
</tr>
</tbody>
</table>

Ward admission

<table>
<thead>
<tr>
<th></th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed day costs</td>
<td>$665</td>
<td>Not specified</td>
<td>$950</td>
</tr>
<tr>
<td>Nursing / allied health</td>
<td>$350</td>
<td>Not specified</td>
<td>$400</td>
</tr>
<tr>
<td>Medical</td>
<td>$204</td>
<td>Not specified</td>
<td>$888</td>
</tr>
<tr>
<td>Imaging</td>
<td>$435</td>
<td>Not specified</td>
<td>$129</td>
</tr>
<tr>
<td>Pathology</td>
<td>$431</td>
<td>Not specified</td>
<td>$334</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$170</td>
<td>Not specified</td>
<td>$520</td>
</tr>
<tr>
<td>Ward admission total</td>
<td>$2,255</td>
<td>Not specified</td>
<td>$3,212</td>
</tr>
<tr>
<td>Total post-discharge</td>
<td>$20,282</td>
<td>Not specified</td>
<td>$7,888</td>
</tr>
</tbody>
</table>

Travel and accommodation

Neither RCHB nor SCHN(W) provided a detailed justification for the estimated accommodation and travel expense. RCHM claimed 49 days of costs per patient, made up of a 35 day inpatient stay and 14 days when the patient needs to remain in reasonable proximity to the hospital in the immediate post-discharge period (Table 30). RCHM accommodation is costed at $200 / day and meals at $30 /day. It appears that this cost is factored into all admissions although only a proportion of patients are not from Melbourne, currently about 50% of cases.

Travel also appears to have been costed for all patients and families rather than just the expected interstate caseload of about a quarter. Consequently, a more representative amount is $4,485 for meals and accommodation and $675 for interstate travel, a total of $5,160.
Table 30: Estimated cost of travel and accommodation for patients and family

<table>
<thead>
<tr>
<th></th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accommodation</td>
<td>$4,063</td>
<td>$9,409</td>
<td>$9,813</td>
</tr>
<tr>
<td>Meals</td>
<td></td>
<td>$1,470</td>
<td></td>
</tr>
<tr>
<td>Travel &amp; other expenses</td>
<td>$1,658</td>
<td>$4,561</td>
<td>$2,700</td>
</tr>
<tr>
<td>Total</td>
<td>$5,721</td>
<td>$13,970</td>
<td>$13,983</td>
</tr>
<tr>
<td>Adjusted total</td>
<td>n/a</td>
<td>n/a</td>
<td>$5,160</td>
</tr>
</tbody>
</table>

Indirect costs - management and overhead costs

The NFC Guidance document identifies in particular two main streams of indirect costs - firstly, management costs which reflect the additional personnel costs incurred by the hospital to manage the Program and secondly, health service administration and overhead costs, which are calculated as a percentage of direct patient care costs.

SCHN(W) identified program management costs of $8,656 for general management and clerical and medical costs. It also separately identifies additional liver transplant CNC / coordinator expense of $1,606. Likewise, RCHB identified a coordinator expense, but in this case of $25,700 per transplant, which with a caseload of 10 represents an annual amount of $257,000, which would approximate the salary of two EFT coordinators, including an all-hours on-call. RCHM in its built-up costing identified $23,749 of wage expense attributable to this role. With a caseload of 10 transplants this would provide an annual salary of $120,000 to $130,000 for each of two coordinators at each site, which would appear to be appropriate and desirable.

The indirect costs for RCHM also included the estimated costs for Austin Health. Program management costs of $3,200 for RCHM and $21,479 at Austin Health were identified for the unit head, manager, administrative staff, transplant coordinators, training and development and data base management. This would allow the appointment of administration and database staff and a 0.3 EFT head of unit. It is in the expected range for a program of this type.

The NFC Guidance document specifies that overhead expense should be a percentage of direct patient costs. New costing systems at RCHM now suggest a rate of 20% is warranted (Table 31).

With most centres realising survival rates post-transplant of 90% or more, there is increasing attention in the literature towards the long-term outcomes of children after liver transplantation, with issues including quality of life, neurocognitive and learning outcomes and behavioural problems. RCHM identified the cost of undertaking important neuro-developmental research into the progress of transplant patients. A similar amount was factored into the costings for the surgical management of hypoplastic left heart syndrome NFC Program.

Future research also needs to identify factors associated with poorer long-term outcomes aside from patient survival, such as the degree of illness and malnutrition at the time of transplant, the time spent waiting for a donor liver, the type of graft and relationship to post-transplant complications. Having access to assured annual funding of about $7 million through the NFC Program provides a solid platform for the development of a comprehensive research program which should provide leverage in accessing other research funds. It is also noted that current NFC policy precludes the direct funding of research.
Table 31: Estimated costs using adjusted direct patient costs

<table>
<thead>
<tr>
<th>Care pathway</th>
<th>SCHN(W)</th>
<th>RCHB</th>
<th>RCHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral</td>
<td>Outside NFC Program</td>
<td>Outside NFC Program</td>
<td>Outside NFC Program</td>
</tr>
<tr>
<td>Work-up and acceptance</td>
<td>$5,159</td>
<td>$6,547</td>
<td>$5,569</td>
</tr>
<tr>
<td>Pre-transplant monitoring</td>
<td>$11,246</td>
<td>$18,154</td>
<td>$13,323</td>
</tr>
<tr>
<td>Theatre</td>
<td>$22,444</td>
<td>$67,240</td>
<td>$37,780</td>
</tr>
<tr>
<td>Other procedures</td>
<td>$1,080</td>
<td>$23,669</td>
<td>$1,700</td>
</tr>
<tr>
<td>PICU</td>
<td>$73,385</td>
<td>$51,519</td>
<td>$51,342</td>
</tr>
<tr>
<td>Ward</td>
<td>$99,848</td>
<td>$121,115</td>
<td>$74,072</td>
</tr>
<tr>
<td>Post-discharge care</td>
<td>$20,282</td>
<td>$0</td>
<td>$7,888</td>
</tr>
<tr>
<td>Transport and accommodation</td>
<td>$5,721</td>
<td>$13,970</td>
<td>$7,065</td>
</tr>
<tr>
<td>On-call</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td><strong>Direct patient costs</strong></td>
<td><strong>$239,165</strong></td>
<td><strong>$302,214</strong></td>
<td><strong>$198,739</strong></td>
</tr>
<tr>
<td>Administrative overhead (20%)</td>
<td>$47,833</td>
<td>$60,443</td>
<td>$42,263</td>
</tr>
<tr>
<td>Program management</td>
<td>$10,262</td>
<td>$25,700</td>
<td>$24,679</td>
</tr>
<tr>
<td>Neuro-developmental review</td>
<td>$5,000</td>
<td>$5,000</td>
<td>$5,000</td>
</tr>
<tr>
<td><strong>Total estimated cost</strong></td>
<td><strong>$302,260</strong></td>
<td><strong>$393,357</strong></td>
<td><strong>$270,681</strong></td>
</tr>
</tbody>
</table>

Summary of financial analysis

Ideally, with three NFC sites there should be an opportunity to make detailed comparisons of costs. Given the information provided this was not possible for all stages of the care pathway, however using the submissions made to the 2007 review and with adjustments made on the basis of international contemporary experience it has been possible to analyse the costs of paediatric liver transplantation. The estimated cost for RCHM is $270,681 which is reasonably proximate to the SCHN(W) amount of $302,260, with a higher estimate for RCHB due to high theatre costs and the accounting of ward and PICU costs. The NFC Guidance document requires that the lower estimate forms the basis for future reimbursement.

The new estimated cost of one paediatric liver transplant is based on the lowest estimated cost and is set out in Table 32.
Table 32: Estimated cost of NFC paediatric liver transplantation

<table>
<thead>
<tr>
<th>Type of cost</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct costs</td>
<td>$198,739</td>
</tr>
<tr>
<td>Indirect costs</td>
<td>$71,942</td>
</tr>
<tr>
<td>Total costs</td>
<td>$270,681</td>
</tr>
</tbody>
</table>

Recommendation 6
That paediatric liver transplants provided through the Nationally Funded Centres Program are funded at a rate of $270,681 for each transplant.
OTHER FINANCIAL MATTERS

Equipment costs

SCHN(W) and RCHM identified the current state of equipment used exclusively for paediatric liver transplants (Table 33). All of the major equipment would be expected to have a life span of 10 years except for the flow probes that can be used for about 50 cases.

Table 33: Equipment costs, paediatric liver transplant items

<table>
<thead>
<tr>
<th>Item</th>
<th>Purchase price</th>
<th>Age at 1/1/2013</th>
<th>Annual repair and maintenance costs</th>
<th>Replacement due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound machine</td>
<td>$48,000</td>
<td>2.4 years</td>
<td>$4,000</td>
<td>7.6 years</td>
</tr>
<tr>
<td>Thromboelastogram</td>
<td>$21,000</td>
<td>4.3 years</td>
<td>$3,000</td>
<td>5.7 years</td>
</tr>
<tr>
<td>Transit time flow meter</td>
<td>$40,000</td>
<td>3 years</td>
<td>$2,200</td>
<td>7.0 years</td>
</tr>
<tr>
<td>Microscope</td>
<td>$68,380</td>
<td>3.1 years</td>
<td>$1,000</td>
<td>6.9 years</td>
</tr>
<tr>
<td>Medistim flow meter</td>
<td>$55,000</td>
<td>3.0 years</td>
<td>-</td>
<td>7.0 years</td>
</tr>
<tr>
<td>Medistim flow probes</td>
<td>$28,412</td>
<td>1.5 years</td>
<td>-</td>
<td>3.5 years</td>
</tr>
<tr>
<td>Thromboelastograph</td>
<td>$35,402 + service agreement of $14,125</td>
<td>4.2 years</td>
<td>-</td>
<td>5.8 years</td>
</tr>
</tbody>
</table>

RCHM – equipment requiring replacement as more than 10 years old

<table>
<thead>
<tr>
<th>Item</th>
<th>Age at 1/1/2013</th>
<th>Replacement due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoscope TEG Machine Model 5000</td>
<td>2 needed at $27,747 each. Total cost $55,494 excl GST</td>
<td></td>
</tr>
<tr>
<td>Cell Saver Elite System</td>
<td>$34,000 excl GST</td>
<td></td>
</tr>
</tbody>
</table>

Therefore RCHM has immediate equipment cost requirements of $89,494 and SCHN(W) has identified annual repair and maintenance costs of $10,200.

However it should be noted that NFC Guidance requires that equipment purchases through the NFC Program must be used for a minimum of 70% of time on NFC patients. In addition only equipment valued at more than $25,000 per item in terms of current purchase price or replacement cost is eligible for consideration.

Living donor related transplants

At SCHN(W) up to 25% of paediatric liver transplants are from living related donors. RCHB has also had a recent increase in the number of transplants from living related donors. It estimates that the inpatient costs for adult donors on the LDLT Program are in the order of $32,800. Outpatient costs are estimated at 35% of the total inpatient cost (based upon the cost of living donor work-up for donors in the renal program), which would bring the total cost to $44,280. Further, a number of work-ups are often needed to find a suitable donor, so this amount is the minimum estimated cost.
Austin Health, based on one living donor transplant some years ago, estimated their costs are $6,875 for each work-up with an average expected two work-ups for each candidate. The work-up is a five stage process with extensive involvement of medical specialists, as well as allied health staff and the transplant coordinator. There are also $1,200 of pathology costs and $1,800 of imaging costs.

The estimated inpatient cost at Austin Health is $22,818. According to the hospital this procedure codes as DRG Z01B "OR procedure with diagnoses of other contacts with health service without catastrophic or severe complications" which currently in Victoria has a case weight of only 0.9708, thereby only providing a reimbursement in the order of $4,000. The hospital will also incur sizeable post-discharge follow-up and monitoring expense over the succeeding year.

There is currently no dedicated income stream to cover the donor costs associated with securing a living donor graft for paediatric transplantation. Instead, it appears that facilities are expected to be reimbursed through usual funding mechanisms, which as demonstrated by the Austin Health example above may significantly under-reimburse them for the actual costs of providing the service.

According to the NFC guidance document (para 4.4, page 6) reimbursable costs for NFCs are for a specific NFC site and for a specific patient. On that basis, costs associated with the donor procedure do not explicitly fall within the define reimbursable costs. Further, the guidance document states funding will generally not be considered for different clinical pathways (which LDLT constitutes). However, the guidance document does state that consideration will be given to funding the elements of preliminary care which are regarded as highly specialised, high cost and / or need to be undertaken by the NFC team.

The review team believes that securing a dedicated funding stream for LDLT donor costs is important to ensure paediatric patients receive LDLT when clinically indicated. To ensure that this impost does not impact the best management of the child it is appropriate for the NFC Program to identify a suitable mechanism to reimburse the hospital for this cost.

### Recommendation 7

That the Nationally Funded Centres Reference Group considers mechanisms to fund the assessment, work-up, surgery and outpatient care for living related donor surgery undertaken by adult liver transplant hospitals to provide donor organs for the Nationally Funded Centres paediatric liver transplantation sites.

### Organ retrieval costs

The Australian Organ and Tissue Authority was established in 2009 to spearhead a national approach to achieving a significant and lasting increase in the number of organ and tissue transplants in Australia. To that end, and as part of a comprehensive suite of measures, the Commonwealth made available funds to cover activity based staffing and infrastructure costs associated with organ and tissue donation at public and private hospitals.

All NFC sites identified that the cost of organ retrieval represented a significant impost in terms of workforce availability and costs as they are not funded for NFC retrievals. Austin Health estimates that it incurs on average $9,929 in costs for the retrieval of transplant organs. This amount is consistent with cost estimates made by Alfred Health in the assessment of costs for the paediatric lung and heart-lung transplantation NFC. It determined that for in-state retrieval the average cost was $5,379 and for an out-of-state retrieval it was $13,870, the average of which is $9,625. This does not include the cost of hiring a private jet, which is on occasions required.

Hospitals which undertake a significant proportion of organ retrievals are a vital resource in ensuring that national organ donation and transplantation rates are met, so they need active and transparent
support to maintain this effort. They are currently not fully reimbursed for their costs through any existing funding mechanism.

**Recommendation 8**

That the Nationally Funded Centres Reference Group considers undertaking further work in collaboration with the Australian Organ and Tissue Authority regarding opportunities for funding organ retrieval that is being undertaken to provide organs for the Nationally Funded Centres sites.

**Future costs**

As the transplant Program matures and accepted indications for transplantation change, smaller, sicker, more complex patients are being transplanted. The increasing complexity of patients is accompanied by an associated requirement for additional expertise not included in the original model of care, including interventional radiology to undertake liver biopsies, insertion of ports, dilatation of bile duct and vascular stenoses, and more complex anaesthesia to manage portopulmonary hypertension and hypertrophic cardiomyopathy. There may also be in the future the question of combined organ transplants, with the kidney or intestine.

The NFC costing pro forma allows for a detailed estimate of costs based on current practice, but cannot immediately take account of changes in practice or additional costs. However the NFC Guidance document makes clear that a rapid review, rather than full triennial review, can be undertaken if a comprehensive evaluation is not required.
MANAGEMENT OF PATIENTS WITH BILIARY ATRESIA

Biliary atresia is the cause of liver failure in the majority of paediatric patients awaiting liver transplantation. Biliary atresia is not a single disease entity with a predictable natural history and stereotypical response to surgery. Rather, the aetiology of the condition is heterogeneous and complex. Although developmental and virus-associated biliary atresia represent a substantial portion of cases, many cases of isolated biliary atresia have no obvious definable aetiology. When diagnosed at birth the treatment of choice for extra-hepatic biliary atresia is the Kasai portoenterostomy. Approximately 80% of patients achieve bile drainage to some degree if the procedure is performed before 60 days of age. This delays primary liver transplantation, with transplant-free survival at four years estimated at 46% in patients who receive this initial treatment option. The deferral of liver transplantation has many surgical and medical advantages, including the size of the older recipients, exposure to a far broader deceased donor organ pool, completion of immunisation schedules, longer exposure with seroconversion to community infections and better psychological preparation. The later in life the liver transplant can be performed, the lower its morbidity and mortality.

There is an established volume-quality relationship associated with performing the Kasai procedure. Studies from the UK and France show that patient outcomes associated with biliary atresia are improved by centralisation of care in specialised paediatric hepatology centres with expertise in both Kasai portoenterostomy and paediatric liver transplantation. In the UK, wide variation in survival of the native liver after Kasai portenterostomy led to the centralised referral of British patients with biliary atresia to three paediatric liver units able to the manage the child from diagnosis to transplantation. This policy, implemented in 1999, proved to be efficient and was associated with improvement in outcomes for patients with biliary atresia, with clearance of jaundice improving from 44% to 57% after policy implementation. The policy is no longer in place, but centralised referral to selected centres in the UK continues and subsequent analysis of UK data to 2009 has demonstrated improved native liver survival and patient survival has been maintained.

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90 Wildhaber B. Biliary atresia. ISRN Surgery 2012; Article ID 132089.
The success of Kasai portoenterostomy has also been demonstrated to improve when care is provided by units with expertise in both the Kasai procedure and in liver transplantation. Both UK and French data have found this association.\(^{97,98,99}\)

After a Kasai portoenterostomy children are managed according to a clinical pathway that seeks to maximise the patient’s clinical status until liver transplantation is required. A number of best practice peri-operative and post-operative management elements are yet to be determined. In particular, the role of laparoscopic surgical techniques versus laparotomy, the use of pharmacological management including corticosteroids and choleretic agents, methods for the prevention and treatment of cholangitis, options (if any) for limiting hepatic fibrosis and optimal nutritional management are areas of research inquiry.\(^{100}\) Further, there are a number of technical variants to the procedure that are being explored.\(^{101}\)

Management of biliary atresia with the Kasai portoenterostomy is not formally limited to a defined number of surgical centres in Australia at present. Expert reviewer feedback indicates that there are two important "upstream" issues that may affect live paediatric liver transplantation. The first of these is the likelihood of early rather than delayed presentation for paediatric liver transplant. Secondly, recipient heptectomy can be complicated in patients with previous hepatic surgical procedures who may have extensive adhesions and scar tissue resulting in higher complication rates and higher blood loss at operation.

Whilst outside the scope of this review, the review team suggests that service concentration for Kasai portoenterostomy in Australia should be explored to establish whether services are achieving outcomes comparable to international best practice.

**Recommendation 9**

That the Nationally Funded Centres Reference Group explores service concentration for Kasai portoenterostomy in Australia.

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101 Wildhaber B. Biliary atresia. ISRN Surgery 2012; Article ID 132089.
NEW AND EMERGING TECHNOLOGIES

Laparoscopic donor hepatectomy

Laparoscopic donor hepatectomy is an emerging surgical technique used in LDLT. This technique has been associated with reduced morbidity in donors of LDLT, however clinical experience with the technique is still evolving and early reported results indicate that the left lateral segment grafts obtained laparoscopically using this technique are inferior in terms of recipient complication rates and overall graft survival rates\(^{102}\)\(^{103}\). Further, surgeon experience with the technique affects surgical outcomes and sufficient case volumes are required to achieve high quality patient outcomes\(^{104}\).

Laparoscopic living donor hepatectomy is likely to become a more established and accepted method of harvesting the left lateral segment for paediatric liver transplants both internationally and nationally. However, the number of LDLT procedures performed in Australia is relatively small compared with many centres internationally. This may delay the introduction of laparoscopic donor hepatectomy in Australia.

The review team considers that the impact of laparoscopic living related donor hepatectomy should be assessed at the next review of the NFC Paediatric Liver Transplant Program.

Multiple organ transplantation

A small subgroup of patients are emerging that may require a liver transplant as part of a multiple organ transplantation procedure\(^{105}\)\(^{106}\):

- liver-small bowel;
- liver-small bowel-stomach;
- liver-small bowel-stomach-pancreas;
- liver-small bowel-stomach-kidney;
- liver-heart;
- liver-kidney;
- liver-lung;
- liver-pancreas;
- liver-kidney-heart;
- liver-kidney-intestine;

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103 Lai Q et al. Laparoscopy in liver transplantation: the future has arrived. HPB Surgery 2012; Article 148387.
- liver-kidney-pancreas;
- liver-lung-heart;
- liver-pancreas-intestine; and
- liver-kidney-intestine-pancreas.

Multiple organ transplantation has been the subject of ethical debate. The major ethical principles underlying allocation of organs are justice (equity in distribution) and utility (medical benefit and efficiency)\textsuperscript{107}. Donor organs are scarce and multiple organ transplantation potentially benefits one individual at the expense of benefit to a number of individuals. Some argue that for this reason multiple organ transplantation is unjust and inefficient. However, the alternative view is that failure to provide individuals who require multiple organ transplantation with the same opportunity for survival as individuals who require single organ transplantation is also unjust and discriminatory\textsuperscript{108}.

The increased survival of very low birth weight and extremely low birth weight children with short gut syndrome and liver failure resulting from necrotising enterocolitis, malrotation and midgut volvulus may result in increased demand for multiple organ transplantation, particularly small bowel - liver transplantation\textsuperscript{109, 110}. At this stage the impact of multiple organ transplantation, particularly combined liver and small bowel transplantation, is unable to be defined but may be assessed at the next NFC Paediatric Liver Transplant Program review.


\textsuperscript{108} Arnon R. Liver and combined lung and liver transplantation for cystic fibrosis. Paediatric Transplantation 2011; 15: 254-64.


SCHEDULE 1: EXPERT REVIEWER COMMENTS ON REPORT

Professor Stephen Munn MB ChB FRACS FACS

Summary

This review, conducted in 2012, has highlighted the overall success of the Paediatric Liver Transplant NFC Program in Australia in terms of delivering a consistently high standard of care with excellent outcomes by world standards. Centre reports produced for the review, along with direct questioning has exposed some issues related to: eligibility criteria for paediatric transplantation; discrepancies in the use of living donors; management of the waiting list; wide variations in cost-accounting between centres; and some residual concerns about succession planning. In addition, whilst outcome data was supplied to the review group in a timely fashion and was very useful, it was not uniform in character. This issue is longstanding as it was first identified in 1997 and will require early attention. Within the Australian context of large geographical distances between population centres, it seems reasonable to maintain the same number of paediatric liver transplant centres provided outcomes remain uniformly good. The NFC umbrella would seem conducive to achieving the recommendations of the review.

Volumes and Outcomes

In the period 2006-2010, inclusive, there were 141 paediatric liver transplants performed in the three NFC sites representing about 1.3 transplants per million of population per year (pmp/yr). By way of comparison this is slightly lower than the paediatric liver transplantation rate in the United States of America (USA) or NZ where the rates for the same period were 1.8 and 1.9 pmp/yr, respectively. Whilst there is a slight difference in the proportion of under 15 year olds in the population of Australia (19%) compared with USA and NZ (20%) it is at least possible that proportionately fewer children are being referred for liver transplant assessment in Australia. Possible explanations include: a lower overall incidence of liver diseases, such as biliary atresia; a lower referral rate for newer indications for paediatric liver transplantation, such as metabolic diseases; or geographic and/or sociological barriers to referral. Once referred for transplantation assessment, 70% of children are listed for transplantation and the waiting list mortality rates do not appear to be excessive. Post-transplant survival rates at one and five years for all three programs are excellent ranging from 93-100% and 86-93% respectively, not dissimilar to the NZ figures of 98% and 98%, respectively. Post-transplant complication rates, including biliary and vascular problems were not excessive by international standards and rarely resulted in graft loss. Re-transplantation rates were not uniformly reported but appear to be <10% within 5 years of transplantation which is in keeping with best international practice.

Length of stay ("LOS") data showed significant variation from centre to centre. Children spent from 10-15 days in the paediatric intensive care unit and from 17-37 days on the ward following liver transplantation (on average). This produced total LOS averages of between 27 and 52 days. Data from the SPLIT registry in the USA indicated an average total LOS of 24 days and NZ data indicates an average of 5 days in the intensive care unit and 21 days in the ward for an average total LOS of 26 days. A more detailed statistical analysis would be necessary but it appears likely that the total LOS and intensive care LOS at SCHN(W) may be outlying values compared to international data.

The review included international data suggesting that low volume paediatric liver transplant centres may experience excess post-transplant mortality rates. The threshold used in this analysis was <7 transplants per year. In the period analyzed, the average numbers of transplants performed at each centre were: SCHN(W) – 13, RCHB – 6, RCHM – 9. In theory, there could be cause for concern about the centre volume at the RCHB site. However, local outcome data defies the international supposition about a volume effect. It would be fair to note, however, that volumes would be
marginal if divided amongst only paediatric surgeons doing no other liver or transplant surgery. This could potentially be a problem at SCHN(W) once the principal surgeon retires.

**Access to Liver Allografts**

The majority of liver allografts used (around 80%) are portions of an adult liver. Such allografts are derived either by reducing the adult deceased-donor liver, splitting it (so that the larger portion can be used for an adult), or obtaining a portion of a living donor liver. The three NFC paediatric liver transplant units tend not to use living donors very often. During the 5 years under scrutiny only 15 LDLTs were performed (about 11% of transplants), the majority of these at a single site (SCHN(W)). By comparison, during the same 5 year period, LDLT was used for about 50% of paediatric liver transplants in NZ. There may be a number of explanations for this variation in practice, the most influential being access to deceased donor grafts of sufficient quality. The review did not reveal an excess waiting list mortality by international standards, however it was not zero. Other important factors include the ready availability of technical expertise (live donor hepatectomies require highly skilled, experienced, and committed liver surgeons), proximity of donor and recipient surgical sites (in all three NFC sites there is geographical separation of adult and paediatric liver transplant operating rooms), and philosophical ambivalence by donor surgeons about putting donors in harm’s way. A further possible disincentive is the lack of a clear funding pathway for the living donor operation.

Given that around 80% of the liver allografts used for children in Australia come from deceased donor livers, it seems surprising that decisions about splitting or cutting down adult livers rest almost solely with surgeons engaged by the adult liver transplant programs and that there is no standarized organ acquisition fee paid to defray procurement costs. In 2007, the average liver organ acquisition charge in the USA was around $USD 33,000. Whilst this seems high, much of the direct cost is attributable to transport, a fact common to Australia where it has been estimated that 50% of the total cost of organ acquisition is paid for transport. Interestingly, the organ acquisition charge in the USA and the cost of live donor hepatectomy are not dissimilar. It could be that the assignment of a single organ acquisition fee for a liver or liver segment allocated to a child could be set in such a manner as to cover derivation of the allograft from either a deceased or living donor. This might simplify and standardize the situation across Australia (and potentially NZ).

Whilst organ donor rates in Australia have increased in recent years, this increase has been, in large part, due to increased utilization of organs from donation-after-cardiac-death ("DCD") donors. Livers from such donors are of slightly inferior quality, especially in relation to the likelihood of post-transplant cholangiopathy, and thereby not frequently split or cut down for paediatric recipients. The fact that increases in deceased donation have not translated into increased availability of organs suitable for paediatric recipients highlights the pressure that will be put on the three NFC sites to increase access to living donation.

Indications for paediatric transplantation have altered over time, in part related to the improving outcomes of the procedure. An increasing number of metabolic diseases that cause extra-hepatic sequelae are seen as treatable by liver transplantation now that the peri-operative mortality rate is less than 5%. This expanded eligibility will mean that, if anything, increasing demands will be placed on NFC paediatric liver transplant centres to provide livers or liver segments for such patients. Such diseases include; Primary Oxalosis, Crigler-Najjar Type I, Familial Hypercholesterolaemia, Organic Acidaemias, Urea Cycle Defects, Factor VI Deficiency, Protein C Deficiency and Maple Syrup Urine Disease. Given that patients with such diseases do not suffer liver-related injury, use of standard prioritizing systems for organ allocation, such as the PELD score as a measure of liver disease severity, will not result in the timely transplantation of such patients. Alternative means of organ allocation (exception criteria) will need to be developed that allow for the fair and timely allocation of suitable livers or liver segments to children with such diseases. The three NFC centres will clearly play an important role in the development of these exception criteria.
Cost-accounting

Whilst the total cost of assessing and transplanting a child in any of the three NFC centres seems similar, the component costing seems very disparate. Examples of disparities include: Total operating theatre costs (range $22-67,000); Paediatric intensive care unit costs (range $51-110,000); and Ward costs (range $74-121,000). Some of these disparities can be accounted for, in part, by variation in lengths of stay. For example, SCHN(W) has the highest intensive care LOS and the highest cost associated with this stay but, per diem, the charges are still significantly higher (RCHB and RCHM charge from $3788-5134 per day whereas SCHN(W) charges $7338 per day). The point is well made in the report that such variations in accounting practices (especially inclusions and exclusions) make head-to-head comparison exceedingly difficult. Whilst it could be argued that aligning cost-accounting methods at the three NFC sites is too much to ask and that the lump sum approach to funding paediatric liver transplants makes detailed accounting somewhat moot, it is also true that the centres are asking for recognition of costs that are becoming an issue. These include: the pre-transplant inpatient hospital stay; live donor hepatectomy charges; and long-term follow-up expenses arising because of a growing total cohort of patients. One centre also wants recognition of opportunity losses associated with cancelling elective operating lists during liver transplant procedures. The reasonableness, or otherwise, of these calls for recognition of unmet expenses can only be determined if there is access to fairly detailed information about the composition of hospital charges or attributions.

Having complained about the costing systems it is nevertheless fair to say that the overall cost of a paediatric liver transplant in Australia compares well with international figures. The report concludes that total costs are about $289,000. In NZ the reimbursement for a paediatric liver transplant is about $AUD 220,000 and in the USA it is, averaged across the whole of the country, around $USD 280,000.

Succession planning

It was apparent from the site reviews and reports that attention is being paid to surgical and medical manpower issues. Nevertheless, the lead surgeons for some centres are approaching retirement age and consideration will need to be given not only to surgical manpower but also to surgical (and, indeed, wider) leadership of the Paediatric Liver Transplant Programs at all three centres. The context of the current programs includes potential increases in volumes (more metabolic disease cases, more deceased and living donors) and case complexity (program success has allowed consideration of higher risk surgical candidates and living donors make the surgical exercise more logistically demanding). This context demands wise and sustained leadership from persons whose skill sets need to include business acumen and knowledge about human resource processes. The grooming of successors for the above-named leaders will need to be underway in the very near future if stability and excellent outcomes are to be maintained.

Collection of outcome data

Whilst the important parameters such as patient and graft survival were provided promptly by each of the three NFC centres to the reviewers, it was much more difficult to obtain standardized data on post-transplant morbidities such as: vascular and biliary complications, rejection, infection and unplanned readmissions. This makes comparison of the centres difficult and, in particular, interpretation of the cost variations between them. Each NFC review conducted since 1997 has concluded that the standardization of such metrics is important and I would agree. The obvious agency to collect the data is the Australian and NZ Liver Transplant Registry ("ANZLTR") which is resourced to collect the data most pertinent to that required for internal or external audit purposes including those supplied to regulators and payors. It would be reasonable for a working group from the paediatric liver transplant centres to work with the coordinator of ANZLTR to set in place
electronic forms to prospectively collect the outcome data referred to above and on any other parameters deemed relevant (including pre-transplant exclusion rates).

**Conclusions**

The current service structure provided for eligible Australian children that could benefit from liver transplantation, namely three distinct NFC centres in Sydney, Melbourne and Brisbane seems to be functioning very well. Clients of these centres seem satisfied, staff recruitment and retention has not, to date, been an issue and benchmarking would indicate that a very satisfactory job is being done for a cost that compares well with international centres. It therefore seems very reasonable that these three NFC centres should continue to be funded to provide liver transplant services to children in Australia with continuing oversight provided by the NFC review process. Issues raised in the overall review and in this Expert Reviewer’s Comments should be seen only as a potential means to further standardize and streamline the operations and audit of the existing transplant units.
SCHEDULE 2: REPORT OF CONSULTATION WITH CLINICIANS AND FAMILIES

Methods of obtaining feedback

An important aspect of this review was seeking advice from referring units about their experiences in dealing with the NFCs currently providing paediatric liver transplantation, as well as their views on the service system configuration.

To obtain the views of referring clinicians, a survey with follow-up telephone calls was administered to clinicians in all States and Territories. Clinicians were nominated by the jurisdictions. A copy of the survey is at Attachment 1.

Survey responses were received from 18 clinicians from the following jurisdictions:

- ACT (three);
- NSW (five);
- Queensland (one);
- South Australia (four);
- Tasmania (two); and
- Western Australia (three).

In addition, face-to-face and telephone interviews were conducted with families of paediatric patients who had undergone paediatric liver transplantation (nine families) or were waiting for transplantation (two families). Interviews were conducted with families from the following jurisdictions:

- NSW (three);
- Queensland (three);
- Tasmania (one);
- Victoria (three); and
- Western Australia (two).

Below, we detail referring clinicians' perspectives as conveyed via the survey responses and interviews and patient family perspectives as conveyed via the face-to-face and telephone interviews.

Referring clinician feedback

Referral processes and waiting list management

Respondents from all States and Territories report high levels of satisfaction with processes for referring patients for assessment for liver transplantation.
According to some referring clinicians, there are well-established processes for referral to the NFCs, both for assessment for suitability for transplant and for care once the patient is accepted on the waiting list.

However, referring clinicians did report that there is a lack of clarity regarding the type of liver transplant that will be provided to the patient. Some clinicians expressed a view that criteria describing the type of liver transplant performed at each of the three NFCs were not standardised and that, as a result, there was inconsistency between the sites regarding whether the patient would receive a split liver, living donor, reduced, cadaveric or whole transplant.

Referring clinicians reported that they have well-established relationships with their interstate treating centre as a whole, including nursing and allied health staff. Processes for communication with the transplant team at referral and after assessment of the patient were reported to be of high quality.

Some stakeholders reported that clinicians from outside the field of gastroenterology generally had poor levels of knowledge and awareness regarding the causes of hepatic failure in neonates and young people, and tended to refer patients late. In response, NFCs could promulgate guidance for Neonatal Intensive Care Units and general paediatric units on the assessment and early management of liver failure.

Clinicians referring to each of the NFC sites report that the transplant teams at each site are very supportive and respond promptly to email, telephone or written requests for patient assessment. Protocols for work-up prior to referral are clear. Referring clinicians report that nursing and allied health support and communication from the NFC sites is also of very high quality.

*Ability to provide care within the home jurisdiction*

Jurisdictions felt that current NFC arrangements maximise the amount of support that can be delivered locally. Referring clinicians report that they are well supported by transplant centres to have ongoing involvement in the patient's care and have close communication with the paediatric transplant team when appropriate.

Referring clinicians utilising the NSW centre report that the transplant team provides post-transplant review protocols which are clear and well communicated to clinicians. This is viewed favourably by referring clinicians as it facilitates consistency and transparency in shared management of patients. Communication regarding what management can be provided locally is reported to be prompt and clear.

Referring clinicians using the Victorian centre report high levels of support, particularly from the paediatric hepatologist, and that the site makes every effort to manage patients a close to home as possible. All clinicians in the transplant team are reported to be available should referring clinicians require support.

No comments were received about the Queensland site regarding support to provide care close to home.

Respondents report that transplant teams maintain close contact with patients. Transplant teams at all three centres are reported to be always willing to provide telephone advice and to accept transfer where appropriate for patients, even at times of bed shortages in their institution.
Support for families

Referring clinicians report that the NSW and Victorian teams provide local clinic visits wherever possible, saving families inconvenience and costs associated with travel to Sydney or Melbourne. Families are reported to value this highly. Families valued both transplant teams’ support of local nursing, primary care and allied health providers to enable multidisciplinary supports to be more available locally. Queensland families however felt that the support available to them was constrained by the heavy workload of the liver transplant CNC / coordinators. It was felt that higher staffing level would substantially alleviate this problem. In addition, there was poor access to facilities and support outside that available in the transplantation unit. The families felt this should be improved.

Service concentration

Referring clinicians recognised that a critical volume of caseload is required to maintain world-class outcomes. Respondents expressed the view that case volumes in Australia are insufficient to sustain additional paediatric liver transplantation sites.

Although the majority of stakeholders were supportive of three NFC sites, some stakeholders expressed a view that two NFC sites would be more appropriate given current case volumes.

Other issues

Some referring clinicians questioned why poor availability of donor organs was not being addressed through increasing access to living related donor transplantation or to cadaveric transplantation.

A number of stakeholders expressed a view that living related donor transplants were under-utilised as a transplant option in paediatric patients and that numbers of living donor related transplants should be increased as a matter of priority.

Some reported that children with single organ and non-recurrent disease who experience excellent patient and graft survival should be given higher priority for grafts. One respondent felt that organ allocation protocols need review in order to address this issue.

Respondents questioned whether there was consistency of prioritisation of children between the three transplant centres and whether there was unequal access to a donor organ depending on which transplant site the family presented to.

Feedback from families

The consultation with families and support organisations addressed the following issues:

- their level of awareness of liver transplantation as a treatment option;
- issues associated with relocation to a surgical centre for the duration of treatment, including waiting list time; and
- their views on support services that families require whilst their child is in hospital for prolonged periods.

Overall experience

Families utilising all three sites were very grateful for access to liver transplantation and the outcomes of successful surgery were valued highly.
Families expressed the view that transplant extends life expectancy and gives the child a reasonable quality of life; this outweighs any negative aspects to treatment, including the need for subsequent surgery, frequent outpatient attendances, extensive medication management and invasive follow-up that was required.

Knowledge and awareness

All respondents reported that they became aware of transplantation as a treatment option through their usual treating paediatric health care provider when their child first became unwell.

Families reported a high level of satisfaction with the information they received at referral regarding transplantation and its advantages and disadvantages. Families reported that there was no alternative to transplantation, as without the procedure their child would have died.

Families were very aware of a lack of donors as the major barrier to successful transplantation being performed.

The level of knowledge of participants was high regarding long-term outcomes, graft and patient survival, the risk of rejection, the importance of high levels of compliance with immunosuppressant medications.

Medication compliance into adolescence

Participants raised transition of their child's management to an adult centre during their adolescence as an important issue affecting the long-term success of their child's transplant.

Some families were concerned about the risk of non-compliance with medications as their child approached adolescence. Most families were very concerned about the loss of contact with their child's treating paediatric transplant team, many of whom had developed a close relationship with staff over many years.

Families desired management of transition to adult services that commenced early and enabled co-management across paediatric and adult facilities during the transition, so that continuity of care could be maintained.

Access to services

Most families who participated had relocated to the transplant centre whilst awaiting transplant. Families were satisfied with the level of support they received whilst awaiting the transplant.

Difficulties associated with relocation included:

- being away from family, friends and community;
- extended time off work for working parents;
- often long commutes between home and the hospital for family members; and
- finding schooling and child care for other children in the family.

Respondents felt that the level of assistance provided for families was sufficient. No difficulties accessing transport and accommodation were reported.
Having a designated transplant coordinator and social worker were viewed as essential to assist families to navigate access to available supports. Families also reported that the support of other families who had greater experience of accessing services was vital to receive accurate information regarding the supports available to families.

Service concentration

Families recognised the need for service concentration and expressed a strong preference to travel to a high quality, specialised centre to receive treatment rather to have access to a less experienced service closer to home. However, where aspects of care could be provided locally it was the preference of most families to remain in their home jurisdiction with their usual paediatric team and paediatric facility.
Dear Doctor

Re: Nationally Funded Centre review for Paediatric Liver Transplant Program

Purpose of letter

The purpose of this letter is to invite you to contribute to a review of the Nationally Funded Centre ("NFC") for paediatric liver transplantation. The NFC for paediatric liver transplantation currently operates across three sites. The sites are:

- Royal Children's Hospital, Brisbane, Queensland,
- Royal Children's Hospital Melbourne, Victoria and
- The Sydney Children's Hospital Network (Westmead), New South Wales.

DLA Piper (Consultants: Dr Heather Wellington, Dr Kelly Shaw, Dr Paul Woodhouse), in conjunction with Professor Barry Duffy, Professor Hock Lim Tan and Professor Stephen Munn, have been contracted by SA Health on behalf of all States and Territories to undertake the review.

The NFC Program

NFCs are established to provide Australians with equitable access to certain high cost, low demand, new and emerging medical technologies. NFCs are approved by the Australian Health Ministers' Advisory Council ("AHMAC") and funded from a pool with contributions from all States and Territories according to a weighted population-based formula based.

The objectives of the NFC Program are to ensure that:

- there is maximal access to certain high cost, low demand, new and emerging technologies regardless of geographical location, in the context of workforce and resource availability;
- these technologies are provided efficiently and effectively;
- requirements for high quality and safe introduction and ongoing provision of these technologies have been defined and implemented; and
- health and cost outcomes of these technologies are monitored and evaluated.

There are currently five technologies being funded under the NFC Program, as follows:

- Norwood procedure and staged surgical palliation for hypoplastic left heart syndrome;
- Paediatric Cardiac Transplantation;
- Paediatric Liver Transplantation;
- Paediatric Lung and Heart-Lung Transplantation; and
- Pancreas Transplantation (adult program).

The Nationally Funded Centres ("NFC") Reference Group will recommend to the Australian Health Minister's Advisory Council ("AHMAC") the commissioning of a review of all NFCs three years after initial establishment. After the initial review, future reviews will normally also be every three years but may vary, subject to AHMAC approval.

The possible recommendations from a review will be to:

- continue the existing activities of the NFC at a reduced, equal or increased level for a further defined period with a further review to be conducted at the end of the period;
- decrease the number of NFC sites providing the service;
- increase the number of NFC sites providing the service; or
- cease NFC status effective by 30 June in the next calendar year from the date of the decision.

Opportunity to contribute to the review

As NFC sites are funded by all the States and Territories, health department officials in each of the jurisdictions are keen to ensure key clinicians have the opportunity to provide their views on relevant issues.

The review team is particularly interested in your views about the matters identified in the attachment to this letter, but would be pleased to receive any comments you think are pertinent to the review.

The views of individuals and/or organisations will remain confidential to the review team. The report and recommendations of this review will be thematic and will not identify individuals or organisations without their consent.

We would appreciate it if you could respond to this letter by close of business, Monday 3 September 2012. Please email your responses to kelly.shaw@pfhealth.com.au.

Further information

Please feel free to contact the following members of the project team if you wish to discuss this review by telephone or have additional comments that you would like to make or issues you wish to discuss in detail:

Dr Kelly Shaw (0448 552617, kelly.shaw@pfhealth.com.au)

Dr Paul Woodhouse (0430 338208, paul.woodhouse@westnet.com.au).

Yours sincerely

Dr Kelly Shaw
MBBS, MPH, PhD
Consultant
Direct 0448 552617
kelly.shaw@pfhealth.com.au
Questions for consideration about NFC paediatric liver transplant services

Q1. Have you or your unit referred any patients to the NFC for paediatric liver transplantation in the last 5 years? Yes/No

If yes, please provide approximate details in the table below:

<table>
<thead>
<tr>
<th>Site</th>
<th>Approximate number of patients referred</th>
<th>Approximate number of patients who received a transplant</th>
<th>Main reason for referring to this site</th>
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</thead>
<tbody>
<tr>
<td>Brisbane</td>
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<td>Melbourne</td>
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<tr>
<td>Sydney</td>
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</table>

Q2. From your experience, please provide feedback (about any relevant sites) regarding the following:

<table>
<thead>
<tr>
<th>Aspect of care</th>
<th>Brisbane</th>
<th>Melbourne</th>
<th>Sydney</th>
</tr>
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<tbody>
<tr>
<td>Support for referring clinicians to discuss transplant or palliation options with patients and parents</td>
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</tr>
<tr>
<td>Information about transplantation services available to you and patients and parents prior to referral</td>
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<tr>
<td>Consultation and communication with the transplant team at referral and after assessment of the patient</td>
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<tr>
<td>Specialist consultation services provided by the transplant unit for patients admitted to your health service</td>
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<tr>
<td>Care of the patient whilst on the waiting list</td>
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<tr>
<td>Communication with you about the patient whilst on the waiting list</td>
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<tr>
<td>Support for the family pre and post-transplant</td>
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<tr>
<td>Follow-up of the patient and communication with you by the transplant unit after discharge</td>
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</table>
Please provide any additional comments regarding the above aspects of care and how care could be improved:

Q3. How could the current system for management of children requiring a liver transplant be improved?

Q4. What are your views regarding the number of NFC sites (three sites) currently providing paediatric liver transplant services?

Q5. What are your views regarding the NFC status of paediatric liver transplantation and whether NFC status should be continued?

Thank you for taking the time to participate in this review. If you require further information or would like to discuss any aspect of the review please contact:

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Dr Paul Woodhouse (0430 338208, paul.woodhouse@westnet.com.au).
SCHEDULE 3: LITERATURE REVIEW

Provided as a separate volume.
REVIEW OF PAEDIATRIC LIVER TRANSPLANTATION SERVICES – LITERATURE REVIEW
NATIONALLY FUNDED CENTRES REFERENCE GROUP
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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANZLTR</td>
<td>Australian and New Zealand Liver Transplant Registry</td>
</tr>
<tr>
<td>BA</td>
<td>Biliary atresia</td>
</tr>
<tr>
<td>CAH</td>
<td>Chronic active hepatitis</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CT</td>
<td>Computerised Tomography</td>
</tr>
<tr>
<td>DCD</td>
<td>Donation after cardiac death</td>
</tr>
<tr>
<td>FCH</td>
<td>Free-standing children’s hospital</td>
</tr>
<tr>
<td>FHF</td>
<td>Fulminant hepatic failure</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IGF</td>
<td>Insulin-like growth factor</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalised Ratio</td>
</tr>
<tr>
<td>LDLT</td>
<td>Living donor liver transplantation</td>
</tr>
<tr>
<td>MARS</td>
<td>Molecular Absorbent Recirculating System</td>
</tr>
<tr>
<td>MELD</td>
<td>Model for End-Stage Liver Disease</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
</tr>
<tr>
<td>NFC</td>
<td>Nationally Funded Centre</td>
</tr>
<tr>
<td>OLT</td>
<td>Orthotopic liver transplantation</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
</tr>
<tr>
<td>PELD</td>
<td>Paediatric End-Stage Liver Disease</td>
</tr>
<tr>
<td>PSC</td>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>PTLD</td>
<td>Posttransplant lymphoproliferative disease</td>
</tr>
<tr>
<td>RSLT</td>
<td>Reduced-size liver transplantation</td>
</tr>
<tr>
<td>SLT</td>
<td>Split liver transplantation</td>
</tr>
<tr>
<td>SPLIT</td>
<td>Studies of Paediatric Liver Transplantation registry</td>
</tr>
<tr>
<td>TPN</td>
<td>Total parenteral nutrition</td>
</tr>
<tr>
<td>TSANZ</td>
<td>Transplant Society of Australia and New Zealand</td>
</tr>
<tr>
<td>UCSF</td>
<td>University of California San Francisco</td>
</tr>
<tr>
<td>UNOS</td>
<td>United Network of Organ Sharing</td>
</tr>
</tbody>
</table>
INTRODUCTION

Paediatric liver transplantation is a well-established therapy for paediatric patients with end-stage liver disease\(^1\).

In 1990 liver transplantation programs at the Royal Prince Alfred Hospital in NSW, The Princess Alexandra Hospital in Queensland and the Austin Hospital in Victoria were given Nationally Funded Centre (NFC) status. In 1993, adult liver transplantation was removed from the NFC Program but paediatric liver transplantation was given separate NFC status.

The three current NFC sites for paediatric liver transplantation are the Sydney Children’s Hospital Network (Westmead), the Royal Children’s Hospital (Brisbane) and the Royal Children’s Hospital (Melbourne).

Once established as a NFC, the clinical practice / technology is reviewed between every three and five years. Reviews of the paediatric liver transplantation NFC program were conducted in 2002 and 2007. These reviews concluded that the sites continued to meet the criteria for NFC funding.

DLA Piper has been engaged to undertake this current review of the NFCs for paediatric liver transplantation. The evidence base for contemporary best practice in paediatric liver transplantation continues to evolve. Therefore, as part of the review process, this targeted search of the health care and management literature regarding paediatric liver transplantation has been performed.

Literature review methods

In the health care literature, the MeSH terms ‘liver transplantation’ and ‘paediatrics’ were used to search the literature, together with truncated keywords to cover the various subheadings relevant to paediatric hepatology and surgery.

These search strategies were used with the international databases Medline, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), Social Sciences Citation Index, Biological Sciences, the Cochrane Library, MD Consult Journals, Web of Science and ProQuest. The ‘grey literature’ was also searched using the same keywords and acronyms. ‘Google®’ and ‘Google Scholar®’ were interrogated to identify materials of broad relevance. A summary of findings is presented below.

Structure of the current literature review

Drawing on the relevant materials identified, this review outlines the aetiology, clinical presentation and epidemiology of clinical conditions for which paediatric liver transplantation may be indicated, describes the current management of these conditions by paediatric liver transplantation, discusses the clinical course patients follow, complications associated with transplantation options, volume-quality relationships across surgical centres, and specialised resource requirements for provision of care.

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Current evidence regarding the role of paediatric liver transplantation in clinical medicine, international and national experience in performing the procedure, issues and challenges that are the subject of ongoing research are discussed. The impact of paediatric liver transplantation on patients and families, and ethical issues associated with treatment are also described.

PAEDIATRIC LIVER TRANSPLANTATION

Liver transplantation is the definitive treatment for end-stage liver disease in children and adults. Advances over the last two decades have resulted in improved patient and graft survival. These advances are attributed to improvements in a range of factors, including surgical techniques, surgical experience, immunosuppressive regimens, intraoperative anaesthetic management and pre- and post-operative care.

Children account for 10% to 18% of all liver transplants performed annually nationally and internationally. The majority receive their transplant before the age of 5 years. The paediatric patient group is distinct from adults receiving liver transplants in their aetiology of underlying disease, perioperative transplant management, anaesthetic and surgical approach and post-operative care.

Orthotopic liver transplant (OLT) (meaning the new liver is placed in the same location as the diseased liver) was first performed in humans in 1963. The operation was performed on a child with biliary atresia. Initial outcomes were poor and children generally did not survive more than 12 months postoperatively.

Survival increased significantly when cyclosporine was introduced into clinical practice. By 1983, OLT was considered a mainstream therapeutic approach for the management of end-stage liver disease.

Patient and graft survival have continued to improve over time and patient survival at one year is now in excess of 90%.

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5 ANZLTR. 22nd Australian and New Zealand Liver Transplant Registry Report, 2010.
A major obstacle to paediatric OLT has been a lack of availability of a size-matched small liver allograft. Over time, innovative surgical techniques have been introduced to address this problem. Reduced-size liver transplantation (RSLT), split liver transplantation (SLT) and living donor liver transplantation (LDLT) have increased the allograft pool in paediatric patients. The first successful LDLT was performed in Brisbane, Australia, by Dr Russell Strong\(^9\).

**CLINICAL INDICATIONS FOR TRANSPLANTATION**

Liver transplantation is indicated when end-stage liver disease progresses to\(^11\):

- hepatic encephalopathy;
- complications of portal hypertension (e.g. variceal bleeding or ascites that is medically difficult to manage);
- hepatic synthetic failure (e.g. prolonged prothrombin time or decreased serum albumin);
- and/or
- growth failure (as a consequence of progressive hepatic metabolic failure and anorexia).

Specific underlying causes of end-stage liver disease in children differ from those in the adult population. However, the main categories of underlying disease are the same (Table 1):

- chronic liver diseases;
- metabolic diseases;
- acute liver failure;
- malignancy; and
- other.

In paediatric patients the diseases under each category include, but are not limited, to the following (Table 1)\(^12\):

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\(^12\) Emre S. Current concepts in paediatric liver transplantation. Mount Sinai Journal of Medicine 2012; 79: 199-213.
Table 1: Paediatric liver diseases in which liver transplantation may be indicated

<table>
<thead>
<tr>
<th>Chronic liver diseases</th>
<th>Metabolic diseases</th>
<th>Acute liver failure</th>
<th>Malignancy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary atresia</td>
<td>α 1 antitrypsin deficiency</td>
<td>Poisoning</td>
<td>Hepatoblastoma</td>
<td>Budd-Chiari syndrome</td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>Crigler –najjar syndrome</td>
<td>Drug-induced</td>
<td>Hepatocellular carcinoma</td>
<td>Caroli disease</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>Cystic fibrosis</td>
<td>Viral hepatitis</td>
<td>Sarcoma</td>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td>Familial cholestasis</td>
<td>Galactosaemia</td>
<td>Autoimmune hepatitis</td>
<td>Haemangio-endothelioma</td>
<td>Neonatal haemochromatosis</td>
</tr>
<tr>
<td>Progressive familial intrahepatic cholestasis</td>
<td>Gaucher disease</td>
<td></td>
<td></td>
<td>Necrotising enterocolitis</td>
</tr>
<tr>
<td>Idiopathic neonatal hepatitis</td>
<td>Glycogen storage disease</td>
<td></td>
<td></td>
<td>Re-transplantation</td>
</tr>
<tr>
<td>Autoimmune liver disease</td>
<td>Hypercholesterolaemia</td>
<td></td>
<td></td>
<td>Short gut syndrome</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>Niemann-Pick disease</td>
<td></td>
<td></td>
<td>TPN associated</td>
</tr>
<tr>
<td>Fibrocystic disease of liver and kidneys</td>
<td>Tyrosinaemia</td>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
</tbody>
</table>

The most common primary disease affecting children requiring liver transplantation in Australia and New Zealand is biliary atresia, which accounts for 57% of all paediatric liver transplants (Figure 1)\textsuperscript{13, 14}.

\textsuperscript{13} ANZLTR. 22\textsuperscript{nd} Australian and New Zealand Liver Transplant Registry Report, 2010.

Figure 1: Primary diseases of paediatric patients receiving liver transplantation, Australasia\textsuperscript{15}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{Primary diseases of paediatric patients receiving liver transplantation, Australasia\textsuperscript{15}}
\end{figure}

BA=biliary atresia; MET=metabolic diseases; OTH=other diseases; FHF=fulminant hepatic failure; MAL=malignancy; PSC=primary sclerosis cholangitis; CC=cryptogenic cirrhosis; CAH:AI=chronic active hepatitis (autoimmune)

**Biliary atresia**

When diagnosed at birth the treatment of choice for extra-hepatic biliary atresia is the Kasai portoenterostomy\textsuperscript{16}. Approximately 80\% of patients achieve bile drainage to some degree if the procedure is performed before 60 days of age. This delays primary liver transplantation, with transplant-free survival at 4 years estimated at 46\% in patients who receive this initial treatment option\textsuperscript{17,18}.

**Paediatric hepatic tumours**

Paediatric liver tumours are rare, accounting for 1\% of childhood cancers. Hepatoblastoma is the most common and hepatocellular carcinoma the second most common malignant paediatric liver tumours\textsuperscript{19}. Hepatoblastoma is treated with chemotherapy followed by resection. OLT may be indicated when the tumour is non-responsive to chemotherapy, is unresectable or recurs after resection\textsuperscript{20}. Only a few published series have focussed on the outcomes of hepatocellular carcinoma

\textsuperscript{15} ANZLTR. 22\textsuperscript{nd} Australian and New Zealand Liver Transplant Registry Report, 2010.


\textsuperscript{17} Khalil B. Clinical practice: management of biliary atresia. European Journal of Paediatrics 2010; 169: 395-402.


in children. Available results suggest favourable outcomes of primary liver transplantation in children with hepatocellular carcinoma\textsuperscript{21}.

NATIONAL AND INTERNATIONAL CLINICAL ACTIVITY

Australia and New Zealand

The ANZLTR defines children as persons aged <16 years. Between 1985 and 2010, there were 3,510 Australasian patients who received a liver transplant – 2,871 adults and 639 children\textsuperscript{22}. The ages of paediatric liver transplant recipients ranged from 24 days to 15.9 years and 47\% were male (Table 2).

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>639</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age</td>
<td>4.6 (4.5) years</td>
</tr>
<tr>
<td>Median age</td>
<td>2.5 years</td>
</tr>
<tr>
<td>Age range</td>
<td>24 days to 15.9 years</td>
</tr>
<tr>
<td>Male</td>
<td>300 (47%)</td>
</tr>
<tr>
<td>Surviving</td>
<td>509 (80%)</td>
</tr>
</tbody>
</table>

The number of paediatric patients receiving liver transplantation has increased over time, but has not increased at the same rate as transplants performed in adults (Figure 2).


\textsuperscript{22} ANZLTR. 22\textsuperscript{nd} Australian and New Zealand Liver Transplant Registry Report, 2010.

\textsuperscript{23} Ibid
Figure 2: Number of new patients transplanted each year, Australasia, 1985 to 2010

The average age at which paediatric recipients receive their primary liver transplant has not changed significantly across different surgical eras of transplantation (Figure 3).

Figure 3: Age at primary transplant by surgical era, Australasia

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25 Ibid
Split grafts make a significant contribution to the total number of paediatric transplants performed and provided 18 of 46 grafts in 2010 (39%) and 162 of 731 grafts overall between 1985 and 2010 (22%) (Figure 4).

**Figure 4: Type of graft in paediatric patients by year, 1985 to 2010**

![Figure 4: Type of graft in paediatric patients by year, 1985 to 2010](image)

**US clinical activity**

There is no international paediatric liver transplant registry and international comparison data are not widely available. US paediatric liver transplantation clinical activity data are provided in this section in lieu of international data.

In the US, there are 127 liver transplant centres, 58 of which perform paediatric liver transplants. The US Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients (SRTR) record patterns of paediatric transplantation activity in the US. Between 2007 and 2009 there were 1,790 paediatric liver transplants performed in the US. Consistent with Australasian patterns, the majority were performed in children aged 5 years or less and approximately 50% of paediatric liver transplant recipients were male (Table 3).

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26 ANZLTR. 22nd Australian and New Zealand Liver Transplant Registry Report, 2010.
27 http://www.UNOS.org (accessed 3/5/12)
Table 3: Paediatric liver transplant recipients, US, 2007-2009\textsuperscript{28}

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>542</td>
<td>30.3%</td>
</tr>
<tr>
<td>1-5 years</td>
<td>692</td>
<td>38.7%</td>
</tr>
<tr>
<td>6-10 years</td>
<td>232</td>
<td>13.0%</td>
</tr>
<tr>
<td>11-17 years</td>
<td>324</td>
<td>18.1%</td>
</tr>
</tbody>
</table>

Consistent with Australasian clinical practice, the primary disease leading to paediatric transplantation in the US is cholestatic disease (Table 4).

Table 4: Primary disease leading to paediatric liver transplantation, US, 2007-2009\textsuperscript{29}

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestatic disease</td>
<td>809</td>
<td>45.2%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>282</td>
<td>15.8%</td>
</tr>
<tr>
<td>Acute hepatic necrosis</td>
<td>186</td>
<td>10.4%</td>
</tr>
<tr>
<td>Metabolic liver disease</td>
<td>184</td>
<td>10.3%</td>
</tr>
</tbody>
</table>

Whole paediatric liver transplantation rates are reported to be higher than Australian rates. Approximately 64\% of paediatric patients received a whole liver transplant, 20\% received a partial liver transplant and 16\% received a SLT in the US between 2007 and 2009 compared with 18\% of Australasian paediatric patients who received a whole liver transplant, 40\% who received a partial liver transplant and 43\% who received a SLT. However, data are not directly comparable as US data include paediatric patients over the age of 16 years whereas Australasian data do not.

At the time of paediatric liver transplantation in the US, 25.5\% of patients are hospitalised in ICU, 18\% are hospitalised but not in ICU and 56.5\% are not hospitalised\textsuperscript{30}.

The number of deceased donor liver transplants actually performed has remained steady over time, and the number of living donor transplants has decreased over time, from 120 in 2000 to 51 in 2009 (Figure 5). The median number of months waiting for a liver transplant was 2.6 months in 2009.


\textsuperscript{29} Ibid

PREOPERATIVE MANAGEMENT

Preoperative assessment

A multidisciplinary team evaluates the patient for suitability for transplant. The clinical assessment is undertaken by the transplant surgeon in conjunction with paediatric specialists in hepatology, cardiology, infectious diseases, psychiatry, anaesthesia, radiology, intensive care, transplant nurse coordinators, social work and nutrition.

The evaluation includes confirmation of the diagnosis and assessment of the severity of liver disease. Alternative treatment modalities are excluded. Specific assessment includes for:

- the presence of advanced portal hypertension (e.g. variceal haemorrhage, intractable ascites, spontaneous bacterial peritonitis, encephalopathy);
- worsening metabolic and synthetic function (including failure to thrive);
- development of extrahepatic complications (e.g. hepatorenal syndrome, hepatocellular carcinoma, osteoarthropathy).

Transplantation is not indicated if an acceptable alternative treatment is available or if contraindications such as a terminal condition or poor expected outcome exist.

Imaging studies are an important part of pre-transplant assessment in order to evaluate vascular and positional abnormalities, hepatic masses and other intra-abdominal pathologies. Doppler ultrasound is commonly used for initial assessment in children as it is non-invasive. MRI is preferred to CT by

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some centres as, although MRI requires anaesthesia and intubation, it does not require the radiation exposure of CT32.

**Listing for transplantation**

Once a paediatric patient is found to be a suitable candidate for a liver transplant, the patient is placed on a waiting list for transplantation. More potential recipients are on the waiting list than there are organs available each year33.

Patients who qualify for liver transplantation are assigned a score based on a ranking system. This system is called the Model for End-Stage Liver Disease (MELD) for adults and the Paediatric End-Stage Liver Disease (PELD) for patients younger than 12 years.

MELD uses a mathematical formula based on a patient's creatinine level, International Normalised Ratio (INR) for prothrombin time, and bilirubin. The MELD score quantifies the risk of death within 3 months (the higher the score, the higher the mortality).

The PELD score differs in that its calculation also includes albumin level, growth failure, and the patient's age when first placed on the waiting list and it does not include the creatinine level34. The PELD system ranks children based on the severity of illness by increments in predicted 3-month survival outcomes. Although PELD was originally implemented for paediatric patients up to 18 years of age, is significantly underestimated the degree of illness in many paediatric patients with end-stage liver disease. The PELD score was modified by UNOS as a result to children aged < 12 years35.

The PELD score is calculated as follows (laboratory values < 1 are set to 1 for the purposes of the PELD score calculation):

“PELD score = 0.480 x Loge (bilirubin mg/dL) + 1.857 x Loge (INR) - 0.687 x Loge (albumin g/dL) + 0.436 if patient is < 1 y (scores for patients < 1 y listed for liver transplantation; continue to include the value assigned for age of < 1 y until the patient is actually aged 2 y) + 0.667 if the patient has growth failure (<-2 standard deviation) x 10 (then round to the nearest whole number).

The Transplantation Society of Australia and New Zealand (TSANZ) determines eligibility criteria for patients to be listed for organ transplantation and protocols for the allocation of organs to patients once listed36. As part of the implementation of the ‘National Reform Agenda – A World’s Best Practice Approach to Organ and Tissue Donation for Transplantation’ and one of its key initiatives

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34 The Organ Procurement and Transplantation Network. National Data Reports. OPTN.


of ensuring safe, equitable and transparent national transplantation processes, TSANZ received funding from the Australian Organ and Tissue Authority to:

- develop nationally uniform eligibility criteria to ensure there are equitable and transparent criteria for listing patients for organ transplantation; and
- develop nationally uniform allocation protocols to ensure consistency across Australia in the criteria by which donated organs and tissues are allocated.

According to TSANZ, inclusion criteria for liver transplantation are for chronic liver disease with life-threatening complications:

- the principal indication in patients with end-stage liver disease is a Model for End-Stage Liver Disease (MELD) score of >15 in an adult or a Paediatric End-Stage Liver Disease (PELD) score of >17;
- patients may also be suitable candidates if they have small hepatocellular carcinomata (HCCs) that fulfil the University of California San Francisco (UCSF) criteria;
- additional indications include:
  - liver disease that would result in a 2 year mortality rate of >50% without liver transplantation;
  - diuretic resistant ascites;
  - recurrent hepatic encephalopathy;
  - recurrent spontaneous bacterial peritonitis;
  - recurrent or persistent gastrointestinal haemorrhage;
  - intractable cholangitis (in primary or secondary sclerosing cholangitis patients);
  - hepatopulmonary syndrome;
  - portopulmonary hypertension;
  - metabolic syndromes (with severe or life-threatening symptoms) that are curable with liver transplantation (e.g. familial amyloidosis, urea cycle disorders, oxalosis etc.);
  - polycystic liver disease with severe or life-threatening symptoms; and
  - acute liver disease unlikely to result in spontaneous recovery as determined by the King’s College Hospital criteria.

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Contraindications to listing for transplantation

Absolute contraindications to paediatric OLT include:\cite{EmreS2012}:

- metastatic cancer to the liver;
- extrahepatic malignancy (except some children with hepatoblastoma with metastases and neuroendocrine tumours will have OLT indicated);
- multi-organ failure that cannot be cured by OLT e.g. generalised mitochondrial disorder; and
- active, untreated bacterial, fungal or viral infection at the time of transplantation including uncontrolled systemic sepsis.

Relative contraindications are more variable and tend to be centre-specific. They may include:

- irreversible and devastating neurological injury;
- severe cardiopulmonary disease (except if suitable candidate for heart-liver and/or heart-liver-lung transplant); and/or
- psychosocial problems that may interfere with adherence to post-operative management.

TSANZ exclusions (medical or psychosocial) to listing for liver transplantation include those conditions or circumstances that would make a post-transplant survival rate of >50% at 5 years unlikely. The following would be reasons to exclude patients (paediatric and/or adult) from listing given this survivorship standard:\cite{TSANZ2011}:

- malignancy (prior or current, except for HCC within UCSF criteria);
- active infection (other than hepatitis B, hepatitis C, or HIV);
- coronary artery disease that is irremediable or associated with a poor prognosis;
- cerebrovascular disease that is irremediable or associated with a poor prognosis;
- severe metabolic syndrome (hypertension, morbid obesity, hyperlipidaemia, and type II diabetes, with or without obstructive sleep apnoea);
- patients with alcoholic liver disease who experience social instability, alcohol problems in first degree relatives, who are <50 years old, have had repeated alcohol cessation treatment failures, find it difficult to comply with medical care, currently are polydrug.

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\cite{TSANZ2011} TSANZ. Organ Transplantation from Deceased Donors: Consensus Statement on Eligibility Criteria and Allocation Protocols. 23 June 2011.
abusers and/or who have a coexisting severe mental disorder — such patients are very unlikely to remain abstinent in the post-transplant period;

- tobacco use is a relative contraindication to liver transplantation (because of an increased risk of malignancy and cardiovascular disease);

- inadequate or absent social support is a relative contraindication to liver transplantation (because of an increased risk of non-adherence); and

- severe neurocognitive impairment and/or developmental delay in a potential paediatric candidate.

**Timing of transplantation**

Allocation of deceased donor organs is undertaken using a distribution system that ensures impartiality to disease category, sex, race, age and socio-economic status. TSANZ outlines the following donor liver allocation criteria based on category of urgency.

Any liver becoming available from a deceased donor within Australia or New Zealand is first to be allocated to patients listed as urgent. There are three separate categories for urgent liver transplantation:

- **Status 1** Patients suitable for transplantation with acute liver failure who are ventilated and in an ICU at risk of imminent death. When such patients are listed, allocation to them is mandatory.

- **Status 2a** Patients suitable for transplantation with acute liver failure from whatever cause who are not yet ventilated but who meet the King’s College criteria. This includes patients who have acute liver failure because of vascular thrombosis in a liver allograft.

  In addition, this category includes paediatric candidates with severe acute or chronic liver disease who have deteriorated and are in a paediatric ICU. When such patients are listed, allocation to them is usual but not mandatory. It is subject to discussion between the directors (or delegates) of donor and recipient state (or NZ) liver transplant centres.

- **Status 2b** Paediatric patients suitable for transplantation who suffer from severe metabolic disorders or hepatoblastoma (after initial treatment) for whom a limited time period exists during which liver transplant is possible.

If no patient is listed in the urgent category then the local liver unit will allocate livers according to the following principles:

---


• the liver will go to the ABO blood group identical recipient with the highest MELD or PELD score; and

• if not allocated according to MELD or PELD score then the following factors will be considered:
  
  • the presence of a patient on the list with HCC whose HCC MELD score exceeds the standard MELD score of other patients on the list of the same ABO blood group;
  
  • the quality of the donor liver – poor quality donor livers may be utilised but may require transplantation into recipients with lower MELD scores to ensure success;
  
  • the presence of a paediatric patient on the waiting list in need of a split or reduced size liver provided the donor liver is of suitable quality;
  
  • if the donor is paediatric then for size reasons, paediatric recipients will have priority for that liver;
  
  • donor size – overly large size discrepancies result in poor outcomes; size matching may result in patients without the highest MELD or PELD scores being allocated a liver;
  
  • logistical concerns – transport, cold storage preservation time, surgeon and operating room staff skill mix and availability, along with the anticipated hepatectomy time may impact on allocation and result in patients without the highest MELD or PELD scores being allocated a liver; and
  
  • the presence of a patient on the waiting list who has a condition that will not result in a MELD, PELD or HCC MELD score that allows prioritisation – such patients will usually have severe, correctable extrahepatic disease that mandates some priority of allocation (e.g. familial amyloidosis, oxalosis, protein C deficiency) that is nevertheless a variance.

‘Marginal’ livers are used and allocated based on the above algorithm. No specific category of patient is excluded from the use of marginal organs.

**Preoperative care**

Pre-transplantation care needs to take into consideration the potentially prolonged waiting periods for donor organs to become available and to manage the specific care needs of children with end-stage liver disease.
Specialised pre-operative care needs relate to growth and development, cirrhotic complications and psychosocial problems. Nutritional failure is also an important clinical challenge with end-stage liver disease\(^\text{42}\).

Failure to thrive and malnutrition result from inadequate oral caloric intake due to early satiety, intractable gastro-oesophageal reflux secondary to organomegaly, tense ascites, poor enteric absorption of macronutrients such as fat, and micronutrients including calcium, phosphorus, magnesium, zinc, selenium and iron and/or fat-soluble vitamins (A, D, E, K), hypermetabolic state (resting energy expenditure up to 30% greater than normal), deranged use of endogenous substrate (decreased hepatic capacity for gluconeogenesis), physiological disturbance due to impaired synthesis of IGF-1\(^\text{43 44}\).

Impacts include growth failure, muscle wasting, fatty acid deficiency, osteopaenia and reduced neurocognitive development. Higher rates of perioperative infections and surgical complications such as poor wound healing are also observed. Further, higher rates of graft failure are experienced when growth failure is present\(^\text{45 46}\). The optimisation of nutritional status in paediatric patients has translated into improved survival after transplantation, fewer infections and a reduction in surgical complications\(^\text{47}\).

Portal hypertension is a significant clinical comorbidity associated with chronic liver disease. Treatment is important to prevent variceal bleeding which is associated with high morbidity and a mortality of up to 19%. Centres may screen children with cirrhosis by upper endoscopy to detect the presence of gastro-oesophageal varices. Management strategies vary but are indicated in a stepwise manner from least to most invasive, and may include serial oesophageal banding or bypass operations\(^\text{48 49}\).

\(^\text{47}\) McDiarmid S. Management of the paediatric liver transplant patient. Liver Transplantation 2001;7:S77-86.
Fluid overload, peripheral oedema, ascites and hydrothorax are managed by sodium restriction, diuretics and, if required, therapeutic drainage. Ongoing serum electrolytes monitoring is necessary to reduce risks associated with electrolyte disturbance.

Infections that occur pre-operatively may be life-threatening, particularly spontaneous bacterial peritonitis, bacterial or fungal sepsis, and cholangitis. Investigations may include diagnostic paracentesis and appropriate cultures. Treatment with antibiotic therapy is adjusted after results of sensitivity testing are received. Some surgical centres provide prolonged antibiotic prophylaxis, particularly for cholangitis.

Pre-transplantation management also includes updating immunisation schedules, including vaccination for hepatitis A and B, meningococcal and pneumococcal disease.

The paediatric patient is evaluated immediately prior to surgery in order to determine whether to accept a deceased-donor liver for transplant. The recipient should not have any infection, including upper respiratory tract infection, fever and elevated white cell count. Each of these may lead to postponement of surgery. Children with continuous episodes of cholangitis present a particular challenge to appropriate timing of transplant. Some surgical centres prefer LDLT in this patient group as surgery may be scheduled between episodes of infection.

PERIOPERATIVE MANAGEMENT

The transplant procedure in a child commences with a bilateral subcostal incision, careful mobilisation of the anatomic structures around the liver and excision of the diseased liver with or without the retro-hepatic vena cava.

Recipient hepatectomy can be complicated, especially in patients with previous hepatic surgical procedures (such as the Kasai procedure) who may have extensive adhesions and scar tissue that result in higher complication rates and higher blood loss at operation. Patients may also have congenital anatomic malformations that increase the surgical complexity of the procedure.

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52 Ibid
54 Ibid
The new liver is placed in the same location as the diseased liver. The implantation technique depends on the type of graft used.

**Reduced size liver transplantation**

This technique involves the procurement of an adult donor liver as a whole organ. This is then reduced with an appropriate segmental dissection based on the recipient’s body size. The reduction procedure is performed in the recipient hospital.

The technique involves performing either a right lobectomy or a right trisegmentectomy on the donor organ yielding either a left lobe or left lateral segment for transplantation. During implantation the graft’s arterial supply is taken from the aorta and the inferior vena cava is managed according to the type of graft. In a left lobe graft the donor inferior vena cava is left attached to the graft and anastomosed directly to the recipient’s suprahepatic and infra-hepatic vena cava. In a left lateral segment graft, the donor inferior vena cava is removed and a patch of left hepatic vein is sewn to the recipient’s hepatic vein confluence.\(^{57}\)

Intra- and post-operative complications include bleeding from the graft’s cut surface after reperfusion, subhepatic haematoma, fluid collection at the hepatic cut surface with secondary infection and bile leakage.\(^{58}\)\(^{59}\)

The grafts grow with the children and outcomes are comparable to those of whole-liver transplantation. Further, RSLT can potentially make use of a donor organ that would otherwise be wasted when there is a donor organ with laceration on one lobe of the liver.\(^{60}\)

**Split liver transplantation**

This technique procures the deceased donor liver as a whole liver and separates the liver to create two liver allografts. Classically, the left lateral segment (segments two and three) is used for a paediatric recipient and the larger right lobe or extended right lobe graft (segments four or five to eight) used for a larger recipient.

The technique was further developed by Broelsch and Rogiers, who performed liver partitioning in the donor hospital before cross-clamping in the donor. This technique is referred to as ‘in-situ’ splitting. Advantages of this refinement include a shorter ischaemia time (as the donor heart is still beating when splitting is performed) and upon reperfusion in the recipient, there is less blood lost from the cut surface of the liver graft.\(^{61}\)

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\(^{58}\) Broelsch C. Application of reduced-size liver transplants as split grafts, auxiliary orthotopic grafts and living related segmental transplants. Annals of Surgery 1990; 212: 368-77.


Postoperative complications are associated with the technical manipulations required for graft reduction and vascular and biliary reconstructions. These include haemoperitoneum, biliary leaks and obstruction and necrosis of the medial segment of the left lobe of the liver\textsuperscript{62,63}.

The use of split livers from deceased donors and partial grafts from living donors yields favourable graft viability. Earlier results of SLT appeared unsatisfactory, with a 20% increase in mortality\textsuperscript{64}. However, refinements in the surgical techniques and revised selection criteria for donors and recipients where splitting can be performed have led to outcomes comparable with other conventional techniques. Careful donor and recipient selection decreases the risk of primary non-function in split-liver grafts\textsuperscript{65}.

**Living donor liver transplantation**

This technique involves transplanting a segment or lobe of the liver from a living adult donor into a child. Advantages to recipients include that the surgery can be scheduled whenever it is indicated as the allograft is readily available. As a result, wait-list mortality can be reduced. Further, ischaemia time is short, reducing transplantation risks from ischaemia-reperfusion injury. Disease transmission is very rare as there is sufficient time for screening the donor\textsuperscript{66}.

The donor operative procedure consists of resection of the relevant liver portion and removal of the donor vessels for recipient vascular reconstruction. The common grafts that can be used from a living donor for transplantation include the left lateral segment, the left lobe (with or without the caudate lobe) and the right lobe. In all cases, the segment(s) to be removed must have dual vascular inflow from a branch of the portal vein and a branch of the hepatic artery, vascular outflow from one or more of the hepatic veins and biliary drainage\textsuperscript{67}.

Donors are usually healthy individuals related to the recipient, aged between 18 and 55 years and have normal liver function and ABO-compatible blood type. The donor should have no contraindications to major surgery, a single common hepatic artery and a left lateral segment volume greater than 1% of the recipient’s body weight. The procedure is generally safe for the donor (2% to 20% morbidity, 0.01% mortality)\textsuperscript{68}. However, the donor is subjected to a major surgery with associated risks and consequences, including splenic injury, postoperative biliary leaks and fluid collections at the cut surface of the liver. Donor evaluation, counselling and support with a social


\textsuperscript{64} Broelsch C. Application of reduced-size liver transplants as split grafts, auxiliary orthotopic grafts and living related segmental transplants. Annals of Surgery 1990; 212: 368-77.


\textsuperscript{67} Florman S. Live donor liver transplantation. Liver Transplantation 2006; 12: 499-510.

worker, coordinator and psychiatrist or psychologist assist to ensure that the donation is ethical and donors are properly informed\textsuperscript{69}.

The recipient procedure is equivalent to the left lateral segment RSLT procedure. The donor hepatic artery and, potentially donor portal vein, is lengthened using donor saphenous vein. Postoperative complications include hepatic vein stenosis, portal vein thrombosis and biliary complications\textsuperscript{70}.

**General surgical considerations\textsuperscript{71}**

There are differing surgical approaches to vascular surgery at transplantation. If the new liver is a whole liver, the intrahepatic portion of the inferior vena cava can be removed as well, or it can be left in the recipient and the new liver attached to the vena cava. If the new liver is from a living donor or is the result of a reduction or splitting of the deceased donor's liver, then the inferior vena cava must be left in place and the new liver will be anastomosed to the native vena cava. The preferred preservation time for the new liver is less than 12 hours, although the maximum time is approximately 24 hours.

The implantation requires the reestablishment of blood flow to the liver via the portal vein and hepatic artery and the reestablishment of blood flow away from the liver via the hepatic veins. After the blood flow has been restored, the bile duct's continuity with the gastrointestinal tract must be established.

Bile duct complications are still a significant factor that influences the success of OLT. Surgical techniques are applied on a case-by-case basis and are oriented towards not compromising the vascular supply of both recipient and donor bile ducts during procurement and transplantation.

Choledocho- or hepatico-jejunostomy are techniques that may be used for biliary anastomosis, particularly in children aged < 2 years, children receiving left lateral segment grafts and children with biliary atresia and primary sclerosing cholangitis. Otherwise end-to-end choledochocholedochostomy duct anastomosis may be used for bile duct reconstruction in larger patients with adequate size of the biliary system\textsuperscript{72}.

**Anaesthetic management**

Anaesthetic management of paediatric patients receiving transplantation is a specialised area of practice that involves an understanding of the impacts of liver disease on anaesthetic management.


\textsuperscript{70} Florman S. Live donor liver transplantation. Liver Transplantation 2006; 12: 499-510.

\textsuperscript{71} Bartlett A. Progress in surgical techniques in pediatric liver transplantation. Pediatric Transplantation 2010; 14: 33-40.

Although there are different aetiologies of end-stage liver disease, all share the same pathophysiology of liver failure. The pathophysiologic changes of end-stage liver disease and their anaesthetic implications are summarised as follows (Table 5)\textsuperscript{73}:

**Table 5: Anaesthetic implications of liver failure**

<table>
<thead>
<tr>
<th>Pathophysiologic change</th>
<th>Anaesthetic implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular – increased cardiac output, low systemic vascular resistance, increased mixed venous oxygenation, decreased aretrio-venous oxygen difference</td>
<td>Hypotension on administration of anaesthetic Decreased sensitivity to catecholamines and vasopressors</td>
</tr>
<tr>
<td>Pulmonary – hypoxia, impaired hypoxic pulmonary vasoconstriction, alveolar hypoventilation, decreased functional residual capacity</td>
<td>Adequate preoxygenation before induction Increased peak inspiratory pressure Positive end-expiratory pressure (PEEP) Cuffed endotracheal tube</td>
</tr>
<tr>
<td>CNS – encephalopathy, cerebral oedema, increased intracranial pressure</td>
<td>Avoid sedatives Fluid management complicated</td>
</tr>
<tr>
<td>Gastrointestinal – delayed gastric emptying, increased intra-abdominal pressure</td>
<td>Rapid sequence induction</td>
</tr>
<tr>
<td>Hepatic – portal hypertension, impaired synthetic function, decreased intravascular volume, decreased glycogen stores, decreased clotting factors</td>
<td>Impaired clearance of drugs Hypotension Glucose supplementation Large blood loss</td>
</tr>
<tr>
<td>Renal - prerenal uraemia, hepatorenal syndrome</td>
<td>Monitoring or urine output and central venous pressure</td>
</tr>
</tbody>
</table>

\textsuperscript{73} Yudkowitz F. Anesthetic issues in paediatric liver transplantation. Paediatric Transplantation 2005; 9: 666-72.
POSTOPERATIVE MANAGEMENT

Early postoperative care

Patients are transferred to ICU intubated and sedated for ongoing management by a paediatric intensivist. The initial focus includes resuscitation with fluids and blood products, as well as correction of metabolic abnormalities\textsuperscript{74}.

Following liver transplant surgery, patients frequently remain on a ventilator for the first 24 to 48 hours. Patients leave intensive care in a few days, depending on their recovery. Postoperative course is dependent on the medical condition of the patient prior to transplantation, the intraoperative course and the graft function\textsuperscript{75}.

Reintroduction of oral intake can begin within the week following surgery. Typically, hospital stays range from 1 to 2 weeks\textsuperscript{76}.

Prior to discharge, the transplant team provides follow-up care and medication instructions. The patient's and caregivers' questions are answered, and signs of rejection are discussed with the patient in an age-appropriate manner and with the family. The patient and family receive instructions regarding rehabilitation that includes exercise, proper nutrition, and the continuation of immunosuppression and other medications\textsuperscript{77}.

Post-discharge care

The role of parents in managing the child’s care after discharge is important to successful outcomes, including adherence with laboratory and clinical follow-up, even as child participation in their own care increases with age\textsuperscript{78}. Parents are responsible for managing the complex post-transplant treatment regimen and balancing treatment tasks with other child and family responsibilities\textsuperscript{79}.

Following liver transplantation, patients require at-home rehabilitation. Recommendations vary depending on the age of the patient. Follow-up visits commence soon after the patient returns home. Initially, outpatient visits may occur weekly or more often. Over time the frequency of follow-up visits usually decreases.


\textsuperscript{75} Yudkowitz F. Anesthetic issues in paediatric liver transplantation. Paediatric Transplantation 2005; 9: 666-72.


\textsuperscript{78} Lerret S. How ready are they? Paediatric Transplantation 2011; 15: 606-16.

An example of a routine investigation schedule following liver transplantation in childhood is as follows:

- **Quarterly**
  - Blood pressure, height/weight
  - Full blood count
  - Liver function tests (bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, \( \gamma \)-glutamyltransferase and albumin).
  - Urea and electrolytes, creatinine
  - Immunosuppressant level
  - Urine analysis

- **Annually**
  - Serology
  - Fasting lipids, urate
  - Immunoglobulins and autoantibodies

- **Biannually**
  - Abdominal ultrasound
  - Cr EDTA

- **5 Yearly**
  - Liver biopsy

The state of knowledge is scarce on discharge transition for paediatric patients in general and the paediatric transplant population specifically. Studies have documented the importance of discharge preparation and coordination processes as essential components of care for families of hospitalised children including children with medically complex clinical conditions.

**Immunosuppression management**

Immunosuppressive treatment involves balancing immunological efficacy whilst limiting the number and severity of side effects. This requires using a combination of medications.

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regimens used for immunosuppression vary between different paediatric transplant centres\textsuperscript{82}. The major classes of immunosuppressive drugs and their side-effects are summarised below (Table 6).

\textbf{Table 6: Immunosuppressive medications}\textsuperscript{83, 84}

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids (e.g. prednisone)</td>
<td>Osteoporosis, diabetes mellitus, adrenal insufficiency, growth failure, glaucoma, truncal obesity, increased susceptibility to infections</td>
</tr>
<tr>
<td>Calcineurin inhibitors (e.g. tacrolimus, cyclosporin)</td>
<td>Nephrotoxicity, hypertension, neuropsychiatric disturbance, hyperkalaemia</td>
</tr>
<tr>
<td>Antimetabolites (e.g. azathioprine, mycophenolate)</td>
<td>Bone marrow suppression, fatigue, alopecia</td>
</tr>
<tr>
<td>Mammalian target of rapamycin inhibitor (e.g. sirolimus, everolimus)</td>
<td>Bone marrow suppression, proteinuria, pleural effusion</td>
</tr>
<tr>
<td>Antibodies (e.g. atgam, cytogam)</td>
<td>Anaphylaxis, cytopenia, glomerulonephritis</td>
</tr>
<tr>
<td>Depleting antibodies (e.g. alemtuzumab)</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Monoclonal anti-T-cell receptor (OKT3) antibodies</td>
<td>Cytokine release syndrome (fever, aseptic meningitis, hypotension, pulmonary oedema, gastrointestinal disturbance)</td>
</tr>
<tr>
<td>Interleukin 2 receptor blockers (e.g. basiliximab)</td>
<td>Easy bruising or bleeding, weakness, flu-like illness, gastrointestinal disturbance</td>
</tr>
</tbody>
</table>

The majority of patients receive tacrolimus as part of their initial maintenance immunosuppression after transplant. Approximately 84\% receive steroids at the time of transplant. However, nearly 50\% of these patients are no longer on steroids at 1 year after transplant\textsuperscript{85}. By 5 years, 25\% or fewer are still on steroids (Figure 6)\textsuperscript{86}.

\textsuperscript{86} Ng V. Outcomes of 5-year survivors of paediatric liver transplantation. Paediatrics 2008; 122: e1128-35.
By one year, 47% of patients who receive a whole organ and 41% of those who receive living donor transplants will have experienced at least one rejection episode. The probability of an episode of acute cellular rejection occurring within 5 years is approximately 60% and chronic rejection occurs in approximately 5% of patients.

Concerns regarding steroid effects on post-transplant catch-up linear growth may influence clinical management towards low-dose or no steroids as part of the immunosuppressive regime. Cyclosporine and tacrolimus cause significant nephrotoxicity and their use is associated with a 5 year cumulative incidence of significant renal disease of 18% and 3-year and 10-year incidence of renal insufficiency of 33% and 77% respectively.

Long-term immunosuppression therapies place children surviving liver transplantation at increased risk of accelerated cardiovascular disease. Data from the Studies of Paediatric Liver Transplantation (SPLIT) registry indicate 7% of patients have hypercholesterolaemia, 10% have hypertriglyceridaemia and 13% have diabetes mellitus at five years post transplant. Surveillance, recognition and early management are required to prevent premature cardiovascular complications.

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89 Ng V. Outcomes of 5-year survivors of paediatric liver transplantation. Paediatrics 2008; 122: e1128-35.
90 Ibid
Newer immunosuppressants that are currently in development may have reduced side-effects and could provide additional therapeutic options in paediatric patients. Immunosuppressants in development include FK778 (synthetic malononitrilamide), Janus kinase inhibitors, FTY720 (fungal sphingosine-like metabolite), Belatacept, Alefacept and Eculizumab. However, these agents currently have few clinical studies with robust data to rationalise their use in conjunction with existing agents\(^9\).

**Planning for service transition**

The medical care of paediatric transplant recipients needs to transfer to an adult-oriented setting when the child reaches adulthood. This should be an active and organised process, taking into account chronological age as well as developmental and emotional maturity of the transplant recipient.

Available evidence suggests that adolescent patients who have received a transplant need to be actively supported to acquire the necessary self-management skills to successfully transition to care under an adult transplant service\(^9^4\)\(^9^5\).

**OUTCOMES OF TREATMENT**

**Complications**

Complications of liver transplantation include\(^9^6\):

- hepatic artery thrombosis;
- biliary complications;
- infection;
- nephrotoxicity;
- CNS toxicity;
- osteoporosis;
- cardiovascular disease;


\(^9^5\) Annunziato R. How do we know whether the kids will really be OK? Paediatric Transplantation 2011; 15: 668-70.

• lymphoproliferative disorders; and
• psychosocial stress.

Hepatic artery thrombosis is the most common complication after OLT. The incidence is between 5% and 30%. It most commonly occurs within 30 days of transplant. Factors that have been proposed as significant causes of hepatic artery thrombosis include:

• diameter of the hepatic artery (<3mm);
• type of arterial anastomosis;
• number of attempts at efficient arterial anastomosis;
• intraoperative administration of fresh frozen plasma; and
• postoperative anticoagulant administration.

Subsequent studies have also demonstrated risk factors as including prolonged cold ischaemia, cytomegalovirus mismatch, re-transplantation, low recipient weight, variant arterial anatomy, use of a whole liver graft with recipient arterial flow and low volume transplant centres.

A variety of treatment factors are thought to reduce hepatic artery thrombosis, including to maximise graft-to-recipient weight ratios; avoid redundancy, kinking or stretching of hepatic arteries; and routinely use low molecular weight heparin with antiplatelet treatment. However, some surgical centres are also pursuing microsurgical techniques in order to reduce hepatic artery thrombosis.

Treatment is by revascularisation, including interventional radiologic approaches using thrombolysis, transluminal angioplasty, balloon dilation or intraluminal stents. Between 67% and 100% of patients can be treated successfully without the need for re-transplantation.

Impediment to blood flow is associated with biliary complications and hepatic artery thrombosis is associated with up to 25% of all biliary complications. Complications may develop from day one.

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after surgery to several weeks after transplant and present as graft necrosis, bile duct necrosis resulting in anastomotic bile leak, sepsis, bile duct stricture and intrahepatic biloma\textsuperscript{104}.

If hepatic artery thrombosis occurs with bile duct necrosis and/or multiple intrahepatic strictures, re-transplantation is usually indicated. Most late anastomotic strictures are managed with percutaneous transhepatic or endoscopic retrograde cholangiopancreatography with a stent placement and repeat balloon dilations\textsuperscript{105, 106}. If unable to be managed through these interventional techniques surgical revision may be indicated\textsuperscript{107, 108}.

Primary non-function is early graft dysfunction that is characterised by absent postoperative synthetic functional recovery of the patient and graft. This results in either patient death or re-transplantation. Two-thirds of children with primary non-function die after graft loss\textsuperscript{109}. The incidence of primary non-function is generally lower with SLT and LDLT due to shorter cold ischaemia times and lower reperfusion injury\textsuperscript{110}.

Portal vein thrombosis occurs in approximately 5% to 10% of paediatric liver transplant recipients\textsuperscript{111, 112}. Risk factors include biliary atresia as the underlying indication for transplantation, hypoplastic portal vein, whole liver graft, haemoconcentration, splenectomy, severe acute rejection and a hypercoagulable state\textsuperscript{113, 114}. Treatment by early detection and prompt anastomotic revision and thrombectomy can result in graft salvage. Portal anastomotic stenosis can be treated by stent

placement or balloon dilation\textsuperscript{115}. Late portal vein thrombosis presents with ascites, enlarged spleen and thrombocytopenia. Treatment options include shunt surgeries or thrombolysis\textsuperscript{116}.

Long-term, patients frequently develop liver fibrosis after transplantation. Protocol biopsy for long-term monitoring in children after liver transplantation is controversial. However, clinical studies where children with normal liver function tests are followed over time with serial biopsies demonstrate increasing prevalence of fibrosis within the liver graft, from 31\% at one year after transplant to 70\% at 10 years\textsuperscript{117,118}.

Post-transplant malignancy is a significant long-term complication after liver transplantation. The true incidence of malignancy in long-term survivors after paediatric transplantation is unknown. In adults the relative risk of cancer in recipients is more than twice that of an age-matched population\textsuperscript{119}.

Post-transplant lymphoproliferative disease (PTLD) is the commonest malignancy following childhood transplant. In most instances PTLD is associated with Epstein-Barr virus infection of B cells. The more intense the immunosuppression, the higher the incidence of PTLD and the earlier it occurs. The cornerstone of successful treatment of PTLD is reduction or withdrawal of immunosuppression. The cumulative incidence of PTLD for children and adolescents who receive liver transplant is approximately 1.1\% at 6 months, 2.1\% at 2 months, 3\% at 2 years and 4.7\% at 5 years after transplant\textsuperscript{120}.

**Re-transplantation**

Graft survival has continued to improve over time. For deceased donor transplants, there is an approximate 88\% graft survival at 6 months, 85\% at 12 months, 78\% at 3 years, 73\% at 5 years and 62\% at 10 years. Graft survival for living donor transplants is higher than for deceased donor transplants (Figure 7). However, between 10\% and 30\% of paediatric patients will require re-transplantation at some stage over the course of their life\textsuperscript{121,122}.


\textsuperscript{116} Takatsuki M. Systemic thrombolytic therapy for late-onset portal vein thrombosis after LDLT. Transplantation 2004; 77: 1014-8.


\textsuperscript{118} Ng V. Outcomes of 5-year survivors of paediatric liver transplantation. Paediatrics 2008; 122: e1128-35.


\textsuperscript{120} The US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Annual Data Report, 2010.

\textsuperscript{121} Arnon R. Liver transplantation in children weighing 5kg or less. Paediatric Transplantation 2011; 15: 650-8.

\textsuperscript{122} Urahashi T. Paediatric liver retransplantation from living donors can be considered as a therapeutic option for patients with irreversible living donor graft failure. Paediatric Transplantation 2011; 15: 798-803.
Deceased

The most common indications for re-transplantation include vascular complications (42%), rejection (29%), biliary complications (7%), poor graft function (6%), recurrent primary biliary cirrhosis / primary sclerosing cholangitis / chronic active hepatitis: autoimmune (2%) and other causes combined (14%) (Figure 8).

Relative to primary transplantation, re-transplantation is associated with an increased rate of death; infants undergoing re-transplantation appear to have higher mortality than older children\textsuperscript{125}. There are also greater technical difficulties in total hepatectomy of the failed liver graft and the


\textsuperscript{124} ANZLTR. 22\textsuperscript{nd} Australian and New Zealand Liver Transplant Registry Report, 2010.

\textsuperscript{125} Arnon R. Liver transplantation in children weighing 5kg or less. Paediatric Transplantation 2011; 15: 650-8.
implantation of the new liver graft in paediatric recipients which contribute to higher morbidity and mortality.\textsuperscript{126}

**Mortality**

Patient survival after paediatric liver transplantation is approximately 94% at one year, 92% at five years and 83% at 10 years. This compares favourably with patient survival in US cohorts of approximately 93% at one year, 87% at five years and 81% at 10 years.\textsuperscript{127,128}

The half-lives for paediatric liver transplant patients surviving with a functioning liver at least one year have improved over time. Patient half-lives are longer for Australian and New Zealand paediatric recipients than those in the US and is estimated at over 20 years for all time points, compared with 10 to 15 years in the US (Figure 9). This has important implications for the resource requirements for delivery of aftercare. Once the cohort of recipients reaches a certain critical level, the resources required for delivery of ongoing individual patient care reach a steady state. As the half-life is still increasing, the steady state has not yet been reached.

**Figure 9: Half-lives for paediatric liver transplant patients surviving with a functioning liver at least one year, US, 1991 to 2007.**\textsuperscript{129}

In paediatric patients sepsis is the most frequent cause of death (20%), followed by cerebrovascular complications (14%), rejection (11%), primary malignancy (7%), cardiovascular complications (7%), respiratory disease (5%), recurrent malignancy (4%), gastrointestinal disease (4%), operative complications (2%) and other causes (27%)\textsuperscript{130}.

\textsuperscript{126} Urahashi T. Paediatric liver retransplantation from living donors can be considered as a therapeutic option for patients with irreversible living donor graft failure. Paediatric Transplantation 2011; 15: 798-803.

\textsuperscript{127} ANZLTR. 22\textsuperscript{nd} Australian and New Zealand Liver Transplant Registry Report, 2010.


\textsuperscript{129} Ibid

\textsuperscript{130} ANZLTR. 22\textsuperscript{nd} Australian and New Zealand Liver Transplant Registry Report, 2010.
Patient survival after paediatric liver transplantation has increased over time, from 61% 5-year survival between 1985 and 1989 to 5-year survival of 92% in the most recent surgical era (2005 to 2009) (Figure 10).

**Figure 10: Paediatric patient survival, Australasia, 1985 to 2010**

![Paediatric patient survival](image)

Patients whose primary disease is malignancy have poorer long-term survival (Figure 11).

**Figure 11: Paediatric patient survival by primary disease, Australasia, 1985 to 2010**

![Paediatric patient survival by primary disease](image)

The type of primary deceased donor graft (whole, reduced or split liver) does not affect patient survival in children and all are associated with similar patient survival (Figure 12).

131 Ibid

Figure 12: Patient survival by deceased donor graft type, Australasia, 1985 to 2010¹³³

Graft survival following re-transplantation is not as favourable as after first liver transplant (Figure 13).

Figure 13: Graft survival by graft number, Australasia, 1985 to 2010¹³⁴

Quality of life

Health-related quality of life includes physical health, mental health, social functioning, role functioning and general health perception. Health-related quality of life after paediatric transplantation is good but differs from that of the general population. Children may have poorer physical function and their families may experience higher levels of emotional distress and disrupted family activities compared with the general population. These findings are consistent with those for children with other chronic illnesses¹³⁵.

¹³³ ANZLTR. 22nd Australian and New Zealand Liver Transplant Registry Report, 2010.
¹³⁴ ANZLTR. 22nd Australian and New Zealand Liver Transplant Registry Report, 2010.
Health-related quality of life generally improves over time. In adolescents, health-related quality of life equals that of age-matched controls. Parents rate their adolescent children as normal within most spheres with the exception of physical health\textsuperscript{136}.

Survey data demonstrate that at an average of 14 years after transplant, 75\% of patients are satisfied with their quality of life and 81\% are satisfied with their health status. Patients who are younger when they receive their liver transplant tend to rate their quality of life higher than those whose transplants are performed later in childhood\textsuperscript{137}.

Delayed educational attainment and higher unemployment is observed long-term in patient cohorts. At between 10 and 15 years post-transplant, one third of recipients have received age-appropriate schooling, and 31\%, 23\% and 13\% were 1, 2 and 3 years behind in their schooling respectively\textsuperscript{138}.

The restoration of normal growth patterns in paediatric patients is an important element of post-transplant care and influences the quality of life of recipients. Multiple postoperative factors influence post-transplantation growth (e.g. poor liver function, post-transplant lymphoproliferative disease, high steroid dosage and acute rejection) and have a subsequent negative association with quality of life in affected patients\textsuperscript{139}.

\section*{QUALITY ISSUES}

\textbf{Volume-quality associations}

In the US, there are 127 liver transplant centres, 58 of which perform paediatric liver transplants. The minimum paediatric case volume in 2010 was one, the maximum was 192 and the median volume was 40. Thirteen centres performed fewer than 10 transplants a year (Figure 14).

\begin{footnotesize}
\begin{itemize}
\item\textsuperscript{136} Sundaram S. Adolescent health-related quality of life following liver and kidney transplantation. American Journal of Transplantation 2007; 7:982–9.
\item\textsuperscript{137} Dommergues J. Medical follow-up, personal experiences and everyday life of young adults after liver transplantation during childhood. Bulletin of the Academy of Medicine 2008; 192: 1641-54.
\item\textsuperscript{138} Ibid
\item\textsuperscript{139} Evans I. Post-transplantation growth among paediatric recipients of liver transplantation. Paediatric Transplantation 2005; 9: 480-5.
\end{itemize}
\end{footnotesize}
The relationship between surgical centre volume and patient outcomes has primarily been investigated in cross-sectional studies.

Studies in adult liver transplant cohorts have assessed whether higher volume surgical centres achieve better patient outcomes. Analyses performed in the 1990s demonstrated that liver transplant centres with higher annual procedure volumes tended to achieve lower postoperative mortality rates than centres with lower annual volumes. However, more recent analyses have failed to confirm these findings, suggesting that the volume–outcomes relationship for liver transplantation may have changed over time. Currently, there are no formal minimum annual volume requirements in place for adult liver transplant centres. Instead, individual transplant centres are periodically subject to outside performance review.

Data regarding volume-quality associations for paediatric liver transplantation are more limited. A recent retrospective analysis of US SRTR data over a 7.5-year period analysed centre outcomes for

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High-volume paediatric liver transplant centres achieved significantly lower aggregate 1-year patient death ratios than low-volume centres (odds ratio = 0.77; p = 0.03).

Low-volume OC centres, which represent 41.6% of all paediatric liver transplant centres and perform 10% of all paediatric liver transplantation, had the least favourable aggregate 1-year patient death rates of all groups (odds ratio = 1.2; p = -0.03).

When freestanding children's hospitals (FCH – 23% of facilities), children's hospitals within adult hospitals (CAH – 32%) and other centres (OC – 46%) were considered separately, the authors found that a significant volume-outcomes association existed among OC centres but not among FCH or CAH centres (Figure 15).

In the US, paediatric cardiac surgery is the only procedure type that is subject to minimum annual hospital volume requirements by the Agency for Healthcare Research and Quality.

Higher volume centres are also more likely to perform multi-organ transplants (Figure 16). No volume quality data were identified regarding centre volume and multi-organ transplant outcomes in this review.

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ETHICAL ISSUES ASSOCIATED WITH TREATMENT

Non-adherence

Identifying ways to improve long-term post-transplant outcomes is important in maximising the effectiveness and efficiency of liver transplantation as a therapy for end-stage liver disease. Studies demonstrate that clinical outcomes are dependent in part on a patient’s ability to adhere to postoperative treatment requirements, including complex and usually lifelong immunosuppression.

The prevalence of failure to take immunosuppression correctly has been estimated at between 15% and 25% in paediatric populations\textsuperscript{152,153}. In adolescents, rates of non-adherence are higher – an estimated 50% of patients failing to take medications correctly\textsuperscript{154}.

Ethical issues associated with non-adherence arise when decisions regarding listing patients who are non-adherent for re-transplantation are made. The decision whether or not to re-list patients who lost their graft because of technical problems, primary non-function or hyperacute rejection is comparatively straightforward and there is consensus among clinicians about the appropriateness of re-transplantation for these indications\textsuperscript{155,156}. Re-transplant for non-adherent patients is debated.
among transplant teams because patients may not change their behaviour and adhere to the stringent immunosuppressive regimen after re-transplantation and keep their second graft healthy. Further it is not easy to detect non-adherence and the underlying reasons it occurs\(^{157}\).

A recent systematic review of the literature regarding re-transplantation for non-adherence found only one original research paper that met inclusion criteria\(^{158}\). Findings demonstrated that recurrence of non-adherence is highly prevalent in spite of screening and post-transplantation management; and clinical outcomes are poorer in patients being re-transplanted for non-adherence compared with patients undergoing re-transplantation for other indications.

Factors against re-transplantation for non-adherence include consideration of the following\(^{159}\):

- organ scarcity: patients on the waiting list could be disadvantaged;
- outcomes after re-transplantation appear to be inferior when indicated for non-adherence; and
- past non-adherent behaviour is a predictor of future non-adherent behaviour.

Factors in favour of re-transplantation after non-adherence include the following\(^{160}\):

- patients admitting to non-adherence cannot be punished for their honesty;
- there is evidence that behaviour change is possible;
- everybody deserves a new chance in life.

**Multiple organ transplantation**

Multiple organ transplantation is required for a subgroup of liver transplant recipients in whom the underlying disease process has led to end-stage disease or significant impairment of multiple organs. Multiple organ transplantation procedures involving liver transplantation include\(^{161}\):

- liver-heart;
- liver-intestine;
- liver-kidney;


\(^{158}\) Dobbels F. Should we retransplant a patient who is non-adherent? Paediatric Transplantation 2012; 16: 4-11.

\(^{159}\) Ibid.

\(^{160}\) Dobbels F. Should we retransplant a patient who is non-adherent? Paediatric Transplantation 2012; 16: 4-11.

• liver-lung;
• liver-pancreas;
• liver-kidney-heart;
• liver-kidney-intestine;
• liver-kidney-pancreas;
• liver-lung-heart;
• liver-pancreas-intestine; and
• liver-kidney-intestine-pancreas.

The major ethical principles underlying allocation of organs are justice (equity in distribution) and utility (medical benefit and efficiency). Donor organs are scarce and multiple organ transplantation potentially benefits one individual at the expense of benefit to a number of individuals. Some argue that for this reason multiple organ transplantation is unjust and inefficient. However, the alternative view is that failure to provide the individual who requires multiple organ transplantation with the same opportunity for survival as individual who require single organ transplantation is also unjust and is discriminatory.

Marginal donors

Segmental liver grafts from donation after cardiac death (DCD) in paediatric liver transplantation have been safely used, including for treating acute liver failure. Some studies have also demonstrated good initial outcomes with ABO incompatible liver transplants in infants. In neonates or small infants, there is a scarcity of size-matched organs which limit treatment options, particularly for urgent transplantation in neonates or infants with fulminant liver failure or primary non-function.

Although the use of DCD or ABO incompatible grafts may provide a marginal donor treatment option to patients with acute liver transplantation or to reduce the time on the waiting list, they are

more susceptible to initial dysfunction and the risk of re-transplantation is higher\textsuperscript{167, 168}. Their use, particularly in paediatric patients, is debated because of the higher associated morbidity and mortality\textsuperscript{169}.

Similarly, living donor liver transplantation is a subject of ethical debate due to the impacts on the live donor of partial hepatectomy, including the morbidity and risk of mortality that is associated with the donation\textsuperscript{170}.

**FUTURE THERAPIES**

New hopes for the future include extracorporeal liver support devices (e.g. the molecular adsorbent recirculating system [MARS®] and Prometheus®), hepatocyte transplantation, liver-directed gene therapy, genetically engineered enzymes and therapeutic modalities targeting fibrogenesis\textsuperscript{171}.

**Liver support devices**

Liver support devices (e.g. the bioartificial liver and the extracorporeal liver-assist device) are systems that perfuse blood or plasma through a hepatocyte-containing device to remove cytotoxic elements. For example, the Molecular Absorbent Recirculating System (MARS), developed in Germany, removes toxic substances from the blood, acting like an artificial liver. The device transports the patient's blood through a filter, where it is mixed with a "sticky" albumin. Albumin binds many compounds (e.g. bilirubin, uremic toxins) and has many nonspecific binding sites for various toxins along with heavy metals. The toxins in the blood then attach to the albumin molecules, thus removing them.

Although the development of an artificial liver is an area of active research, this device is not currently available. However, some prototypes have undergone phase one clinical evaluation but with mixed results.

**Hepatocyte transplantation**

Hepatocyte transplantation is being evaluated as an adjunct treatment for acute hepatic failure. To date harvested human and animal hepatocytes have shown only modest success. The major obstacles to xenotransplantation have been the potential spread of infection from animal to human recipient and hyperacute and vascular rejection due to the cross-species


transplant. Although hepatocyte transplantation appears to be promising, its future role is unknown.

SUMMARY

Liver transplantation is the definitive treatment for end-stage liver disease in paediatric and adult patients. The procedure is well-established in paediatric practice and is associated with highly favourable outcomes in paediatric patients.

Children account for 10% to 18% of all liver transplants performed annually nationally and internationally. The majority receive their transplant before the age of 5 years. The paediatric patient group is distinct from adults receiving liver transplants in their aetiology of underlying disease, perioperative transplant management, anaesthetic and surgical approach and post-operative care.

The most common clinical indication for paediatric liver transplantation is biliary atresia, which accounts for up to 57% of all paediatric liver transplants. Although other surgical options can be used to delay primary liver transplantation, transplant is the definitive treatment of the disease once progression to end-stage liver disease has occurred.

A major obstacle to paediatric OLT has been a lack of availability of a size-matched small liver allograft. Over time, innovative surgical techniques have been introduced to address this problem. Reduced-size liver transplantation (RSLT), split liver transplantation (SLT) and living donor liver transplantation (LDLT) have increased the allograft pool in paediatric patients.

The number of paediatric patients receiving liver transplantation has increased over time internationally and within Australia and New Zealand as a result of these surgical techniques. There are now approximately 40 to 45 paediatric liver transplants performed in Australia each year. The majority of patients receive split grafts.

Preoperative assessment determines appropriateness of liver transplantation. TSANZ eligibility criteria are used for listing patients for transplantation. Organ allocation protocols are used to determine the urgency of transplantation once listed. Pre-transplantation management is complex and involves addressing the specific impacts of end-stage liver disease on growth and development, complications of cirrhosis and psychosocial problems.

Intraoperative management is also complex and involves a high degree of specialisation in the anaesthetic management of the patient with end-stage liver disease. The implantation technique used to perform the transplant depends on the type of graft that is used.

Postoperative management involves intensive care and ward management. Prior to discharge the patient and their caregivers requires preparation for the demands of long-term after-care. High quality discharge planning and support is important to successful outcomes, particularly to adherence with laboratory and clinical follow-up and in the prevention of non-compliance.

Immunosuppression management is highly specialised and ongoing. Treatment involves balancing immunological efficacy whilst limiting the number and severity of side effects. Compliance with immunosuppression is an important factor for long-term graft survival.
Patient and graft survival have continued to improve over time and patient survival at one year is now in excess of 90%. In excess of 50% of patients survive past 25 years. However, between 10% and 30% of paediatric patients will require re-transplantation at some stage over the course of their life. Vascular complications are the most common indication for re-transplantation. The most frequent cause of death is sepsis, followed by cerebrovascular complications, rejection and primary malignancy respectively.

Survival is similar in all patient groups regardless of the underlying cause of end-stage liver disease. The exception is patients with hepatic malignancy in whom survival long-term is poorer.

Patient survival is similar long-term regardless of the type of primary deceased donor graft the patient receives. However, long-term graft survival after re-transplantation is not as high as survival in primary transplantation grafts.

There is some evidence that demonstrates a volume-quality association between the number of paediatric liver transplants performed annually in a surgical centre and patient mortality. Centres performing in excess of 15 transplants a year appear to have better outcomes than those performing seven or fewer a year.

Health-related quality of life of patients after paediatric liver transplantation is good but differs from that of the general population. Children experience poorer physical function and families have higher levels of emotional distress and disruption. Long-term, patients experience delays in educational attainment and poorer employment outcomes compared with the general population.

Future therapies that may be alternatives to liver transplantation include extracorporeal liver support devices and hepatocyte transplantation. Although both show some promise, the future role of either therapy is uncertain and both are still experimental.