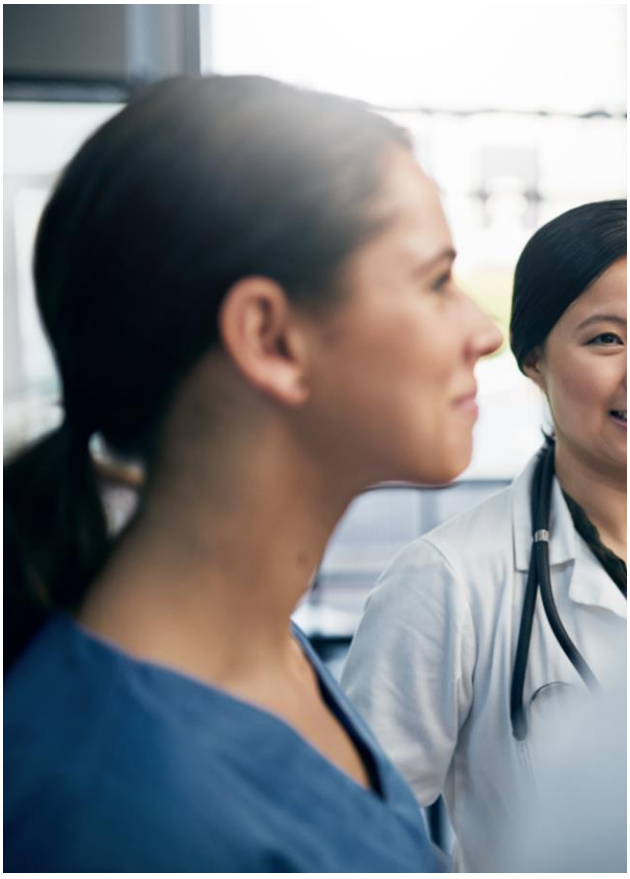

Clinical Handbook for Alcohol-associated Liver Disease

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Amanda Stypulkowski
Program Manager, Transplant Systems
Trillium Gift of Life Network (Ontario Health)

Amy Chambers
Transplant Recipient Coordinator
London Health Sciences Centre

Dr. Anton Skaro
Associate Professor, General HPB and Transplant Surgeon
London Health Sciences Centre

Dr. Anouar Teriaky
Assistant Professor of Medicine,
Western University
Medical Director Liver Transplant,
London Health Sciences Centre

Ashlee Worrall
Transplant Coordinator
London Health Sciences Centre

Dr. Bernard Le Foll
Clinician Scientist; Head, Translational Addiction Research Laboratory
Centre for Addiction and Mental Health

Cathy Vandersluis
Vice President, Patient Centred Care
London Health Sciences Centre

Caitin Don
Transplant Coordinator
University Health Network

Cheryl Beriault
Transplant Recipient Coordinator
University Health Network

Dr. Christian Hendershot
Director, Clinical and Translational Addiction Research Program
University of North Carolina at Chapel Hill

Clare Payne
Vice President, Clinical Transplant Systems
Trillium Gift of Life Network (Ontario Health)

Dr. Darin Treleaven
TGLN Chief Medical Officer, Transplant; Medical Director of the Kidney Transplant Program; Nephrologist
St. Joseph's Healthcare Hamilton

Diana Hallett
Director, Transplant Services
Trillium Gift of Life Network (Ontario Health)

Fareed Hameed
Lead, Transplant Programs (Tissue)
Trillium Gift of Life Network (Ontario Health)

Heather Sadler
Social Worker
London Health Sciences Centre

Isabel Sales
Relapse Prevention Therapist
University Health Network

Jill Quance
Transplant Coordinator
University Health Network

Joanne Zee
Senior Clinical Director, Multi-Organ Transplant, Nephrology and Endocrinology
University Health Network

Dr. Josée Lynch
Assistant Professor, Department of Psychiatry, University of Toronto,
Addiction Psychiatrist
University Health Network

Kelly Thomas
Social Worker
London Health Sciences Centre

Lauren Carrique
Social Worker, Multi Organ Transplant Program
University Health Network

Dr. Les Lilly
Medical Director, GI Transplantation
University Health Network

Lorraine Stuyt
Substance Use Counsellor
London Health Sciences Centre

Lucy Truong
Manager, Transplant Programs
Trillium Gift of Life Network (Ontario Health)

Dr. Nazia Selzner
Associate Professor of Medicine, University of Toronto Medical Director Live Donor Transplant, Transplant Hepatologist
University Health Network

Ryan Kalladeen
Manager, Transplant Systems Planning and Integration
Trillium Gift of Life Network (Ontario Health)

Dr. Viraj Mehta
Addiction Psychiatrist
London Health Sciences Centre

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Disclaimer

The content in this Handbook has been developed through collaborative efforts between Trillium Gift of Life Network and experts from Ontario's liver transplant programs. It is based on available literature and expert opinions at the time of development. The Handbook is not intended to be an exhaustive analysis of all liver transplant literature and practices, and may not reflect all available research and consensus from all experts. Other relevant scientific findings may have been published since completion of the Handbook and it may be superseded by an updated publication on the same topic. While every reasonable effort has been made to ensure the accuracy and validity of the information provided, TGLN and the expert contributors assume no responsibility for any errors or omissions in the content.

List of Abbreviations

AASLD	American Association for the Study of Liver Diseases
ACU	Acute Care Unit
ALD	Alcohol-associated liver disease
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BASD	Bile Acid Synthetic Defects
CAMH	Centre for Addiction and Mental Health
CBC	Complete Blood Count
CCO	Cancer Care Ontario
CDT	Carbohydrate-deficient transferrin
CMV	Cytomegalovirus
CPK	Creatine phosphokinase
CSF	Cerebrospinal Fluid
CT	Computed Tomography
EBV	Epstein-Barr Virus
EASL	European Association for the Study of the Liver
EBV	Epstein-Barr virus
ECFAA	Excellent Care for All Act
ED	Emergency department
ESLD	End-stage liver disease
EtG	Ethyl glucuronide
GFR	Glomerular filtration rate
GGT	Gamma-Glutamyl Transferase
GSD	Glycogen Storage Disease
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HSV	Herpes Simplex Virus
HTLV	Human T-Lymphotropic Virus
IGRA	Interferon-Gamma Release Assays
ICU	Intensive Care Unit
INR	International Normalized Ratio
LDL	Low-Density Lipoprotein
MOHLTC	Ministry of Health and Long-Term Care
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
Na MELD	Sodium Model for End-Stage Liver Disease
NAT	Nucleic Acid Testing
NHSBT	National Health Service Blood and Transplant
OH	Ontario Health
PT/PTT	Prothrombin/Prothrombin Time
SAH	Severe-acute Alcoholic Hepatitis
Tb	Tuberculosis

TGLN	Trillium Gift of Life Network (Ontario Health)

Trillium Gift of Life Network

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I. Purpose

The *Clinical Handbook for Alcohol-associated Liver Disease* has been developed in response to the *2010 Auditor General's Report on Organ and Tissue Transplantation*, the *2009 Organ and Tissue Wait Times Expert Panel Report*, recommendations arising from the *ALD Pilot Program*, and as part of the Ministry of Health and Long-Term Care's commitment to quality healthcare and better outcomes.
The *Clinical Handbook* aims to identify opportunities to enhance integration of services across the ALD patient care continuum; facilitate efforts to improve existing processes within Ontario's liver transplant centres by reducing unnecessary practice variations and optimizing resource utilization; and inform policy frameworks and implementation approaches to the care of liver transplant patients in Ontario.
The *Clinical Handbook* includes the following tools to guide the development of policies, procedures, and processes:

1. Clinical pathways for typical chronic ALD and SAH liver transplant patients from the time of referral to post-transplantation monitoring and care. The clinical pathways outline the general process that Ontario patients follow when moving through the transplant system.
2. Services that correspond to each stage of the respective patient pathways.

To foster partnership and strengthen clinician engagement, the clinical pathways and service bundles were developed using opinions from clinical experts from all Ontario adult liver transplant centres, and the Centre for Mental Health and Addictions (CAMH), guided by national and international evidence-based guidelines. As a result, the *Clinical Handbook* is a compendium of evidence-based rationale and clinical consensus on guidelines for liver transplant patients.

This document has been prepared as a tool for hospitals and individual providers to support the development of clinical patient pathways for their organizations. The *Clinical Handbook* is not intended to replace the professional skill and judgement of healthcare providers, nor limit the development of new and innovative transplant solutions.

II.Improving Quality of Care

At the forefront of Canada's health-care system is a commitment to provide the highest standard of hospital and physician services. In Ontario, the Excellent Care for All Act (ECFAA) supports this by creating greater public accountability, increasing the focus on quality, bringing patient satisfaction to the forefront and basing patient care decisions on the best scientific evidence available. These dimensions of quality are supported by the following six domains:

- Improve **effectiveness** and reduce variation in clinical outcomes.
- Improve **appropriateness** by reducing practice variations.
- Improve **timeliness** across the continuum of care.
- Improve **efficiency** by reducing unwarranted variation in resource utilization.
- Improve or maintain **equity** to appropriate health services.
- Improve **patient centeredness** of health services.

Specific recommendations for the transplantation system were outlined in the *2010 Auditor General`s Report on Organ and Tissue Transplantation* and the *2009 Organ and Tissue Wait Times Expert Panel Report*, both of which highlighted the need for a more efficient and equitable allocation system, improved referral practices and more effective oversight for organ transplantation. Since then, new liver and kidney allocation systems have been implemented, standardized practices for referral introduced, and performance indicators and evaluation metrics developed. Such initiatives are aimed at improving both access to transplantation services by reducing geographical differences in wait times and establishing tools for patients and practitioners to ease the transplant process.

Further improvements to quality can be achieved by maximizing system efficiency. Data shows that short and long-term graft survival rates are favourable, but continued improvement remains the goal of all transplant centres (1). Patient quality of life can also be enhanced by reducing re-hospitalization and complications (including malnutrition, diabetes, severe debility, infection, and surgical complications). In one UK-based study it was found that although risk-adjusted mortality following liver transplantation was higher in the first 90 days in the UK and Ireland compared to US-based populations, for patients who survived the first year, the risk of mortality in the former was lower than their US counterparts (2). Given the significant economic costs of liver transplantation and subsequent re-hospitalization, and desire to further improve outcomes and quality of life, it is imperative that every effort is taken to maximize quality throughout the patient care continuum.

In its report, the Expert Panel specifically raised concern that Ontario did not have standard best practice guidelines for the pre- and post-care of transplant patients, stating that such guidelines are

important since they would identify the care that transplant centres and the local community should provide. The Panel recommended:

- Ontario's transplantation community compile and/or develop pre- and post-care best practice standards and guidelines by organ, and ensure that healthcare providers use these standards and guidelines to inform their care.
- Ontario Health (Trillium Gift of Life Network) (heretofore referred to as TGLN (OH)) and the transplantation community establish a system to monitor the use of best practice standards and guidelines for adult and paediatric organ transplantation, and the outcomes of these procedures (3).

These recommendations align with the Excellent Care for All Act (ECFAA) with its increased emphasis on continuous quality improvement supported by evidence informed best practices and standards of care. In order to fulfill these goals, TGLN (OH) undertook the development of *Clinical Handbooks* for each type of organ transplantation performed in Ontario, including liver transplantation. As a specialized subgroup of end-stage liver disease patients, ALD patients present a unique challenge in multi-disciplinary and multi-resource care in order to provide the most optimal outcomes. In addition to promising results achieved by a pilot program to treat ALD patients with a novel multidisciplinary approach, the *Clinical Handbook for Alcohol-associated Liver Disease* has been developed to help promote lessons learned in providing the best care for ALD patients.

The clinical pathways and corresponding services set out in this handbook and the steps taken to monitor their implementation and outcomes are intended to improve the appropriateness and efficiency of transplant care by reducing unnecessary practice variations and optimizing resource utilization, as well as enhancing integration across the patient care continuum.

Clinical Pathways and Practice Guidelines

Clinical pathways are tools used to manage quality in healthcare by standardizing processes. The objectives are to reduce unnecessary variations in practice, improve interdisciplinary cooperation, integrate care, and ultimately, improve clinical outcomes. They are especially useful in complex care systems, such as liver transplant, where care may be delivered by multiple providers at multiple sites over an extended period. Liver transplant referrals require a minimum set of tests and consultations to be completed, as per the *Provincial Transplant Referral Form.* Patients may receive testing as outpatients at referring centres or in hospital as inpatients depending on the severity of their condition. Transplant centres review referrals and may liaise with referring centres to complete additional tests as necessary before scheduling patients for a transplant assessment. During the transplant assessment process, patients are provided with transplant specific education and transplant specialists determine whether patients are eligible to be wait listed. While on the wait list, patients receive ongoing assessments by the transplant centre, which require blood testing and laboratory work, often from community healthcare providers. Once a patient is matched with a potential donor liver, if not already an inpatient, they are admitted and cared for by the transplant centre before, during, and immediately following their transplant surgery. Once transplanted, recipients receive ongoing care from a variety of providers including transplant specialists, hepatologists, family physicians, and other medical

practitioners based on their needs. The involvement of multiple providers creates considerable opportunity for variations in practice and resource utilization as the patient moves through the pathway.

The success of practice guidelines and clinical pathways has been documented in a variety of areas. For example, in the treatment of community-acquired pneumonia across nineteen teaching and community hospitals in Canada, implementation of a clinical pathway reduced the use of institutional resources without causing adverse effects on the well-being of patients (4). Other individual clinical pathways, for stroke management, inguinal hernia repair, laparoscopic surgery, pancreaticoduodenectomy, and the management of fractured femoral neck, have been shown to reduce length of stay and total costs of acute hospital admission while maintaining quality of care, improving patient outcomes, interdisciplinary co-operation and staff satisfaction (5).

A systematic review of published literature and analysis of twenty-seven studies involving 11,398 participants found that patients managed according to clinical pathways encountered a reduction in in-hospital complications as compared to usual care. Furthermore, the review presented evidence of decreased lengths of stay and reductions in hospital costs when clinical pathways were implemented (4). More generally, reviews of best practice clinical guideline dissemination and implementation strategies have shown that in the majority of cases, improvements in care are observed (6). In one study of 59 clinical guidelines, the authors concluded that “guidelines improve clinical practice and achieve health gains when introduced in the context of rigorous evaluations” (7). Specific to liver disease, a recent US-based study evaluated quality of care delivered to patients admitted to hospital with gastrointestinal haemorrhage before and after implementation of quality improvement initiative (8). The initiative included a clinician education program and a standardized paper order set to enable promotion of AASLD guideline-based care for patients with chronic liver disease and gastrointestinal haemorrhage (9). Implementation of this initiative was associated with decreased 30-day readmission and for readmissions due to gastrointestinal haemorrhage (8).

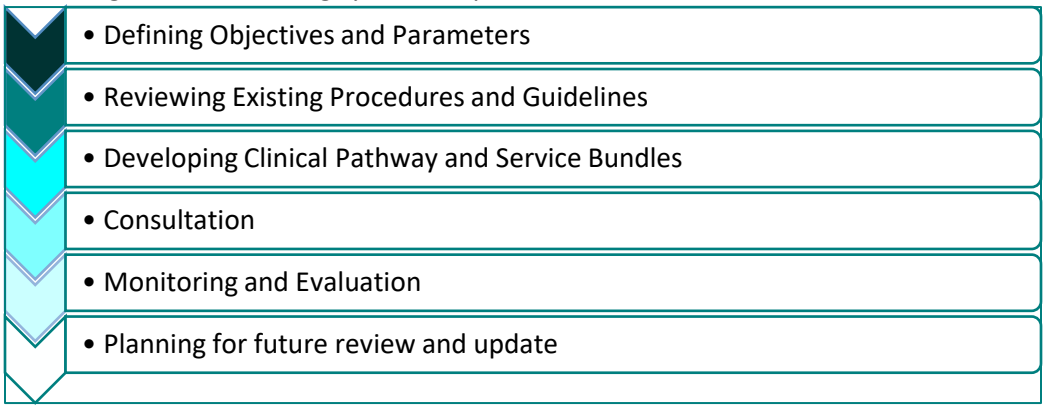
Ultimately, clinical guidelines can improve the experience of patients as they navigate through the transplant process by facilitating integrated care plans along the continuum. With the goal of optimizing care at all stages of the patient continuum, it is intended that this *Clinical Handbook* will facilitate efforts to improve existing processes in the care of ALD transplant patients in Ontario.

III. Methods

In developing the *Clinical Handbook for Alcohol-associated Liver Disease*, TGLN (OH), the ALD Committee, and the Provincial Liver/Small Bowel Working Group took a quality-driven approach for translating evidence into action. The overarching aim was to produce a *quality-driven*, *evidence-based* clinical pathway and service bundles using an *efficient* and *transparent* methodology for *action-ready* recommendations with *multi-disciplinary applicability*:(10).

- **Quality-driven** means placing quality improvement at the forefront of clinical pathway and service bundles development, using current best evidence and multidisciplinary consensus to prioritize recommendations. Selection of key action statements is driven by opportunities to promote best practices, reduce unnecessary variations in care, and minimize inappropriate care or resource utilization.
- **Evidence-based** means supporting all decisions with the best available research evidence identified through systematic literature review and expert consensus (i.e. AASLD, EASL, and physician & surgeons from all centres).
- **Efficient** clinical pathway and service bundles make maximum use of available resources to create a timely product, moving from conception to publication within a reasonable timeframe.
- **Transparent methodology** is explicit, reproducible, and applied consistently so guideline users can link recommendations to the corresponding level of evidence, benefit-harm-cost relationship, and the roles of values and patient preferences in decision making.
- **Action-ready** recommendations tell providers what to do, to whom, under what specific circumstance, using unambiguous language that facilitates implementation and measurement.
- **Multi-disciplinary** validity and applicability means that all stakeholders (e.g., primary care, specialists, allied health, nursing, consumers) are part of the development and implementation processes.

To achieve these goals the following systematic process was used:



The following sections describe each of these steps in further detail.

Defining Objectives and Parameters

Objectives

In defining the objectives for developing a clinical pathway and service bundles, the Working Group was guided by the following key question:

How can Ontario's transplant system provide the best quality of care to achieve the best possible outcomes for liver transplant patients?

The ALD Committee and Working Group agreed that the *Clinical Handbook* was an opportunity to develop and implement best practice guidelines throughout the transplant patient continuum, and determined that it must answer the following questions:

- **Who** should be defined as the patient population(s)?
- **What** practices and services should be employed in the treatment of transplant patients?
- **Where** can transplant patients expect to receive their treatment?
- **When** in their continuum of care can transplant patients expect to receive certain aspects of their care?

These guiding questions ensured that the patients' best interests remained at the centre of the development of the clinical pathway and service bundles.

Parameters

From the outset, the ALD Committee and Working Group identified the clinical population as being all adult ALD patients in Ontario who are potentially eligible to receive a liver transplant.

To ensure a seamless transition between different stages of the transplant process, the *Clinical Handbook* encompasses a patient's full continuum of care, beginning at the time of referral to a transplant program and continuing through transplantation and long-term, post-transplant management. In most cases, once a patient is referred and placed on the provincial wait list, the patient remains in the transplant care continuum until end of life.

These parameters guided the development of the *Clinical Handbook* to ensure that full and proper consideration was given to all patient populations throughout their transplant continuum of care.

Reviewing Existing Procedures and Guidelines

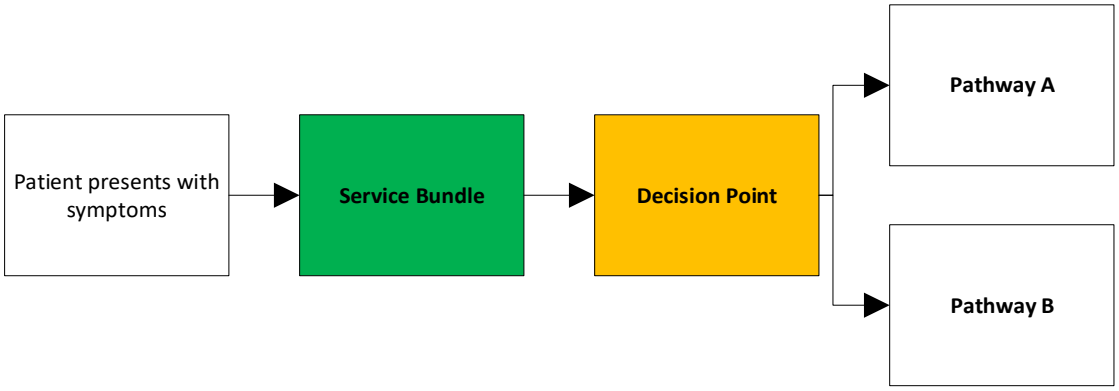
The *Clinical Handbook* contains a set of recommended practices reviewed and agreed upon by the ALD Committee and Working Group, and through wider consultation with the transplant community. In keeping with the ECFAA commitment to evidence-based care, considerable attention has been paid to ensure that the practices recommended here are supported by the best available evidence. A review was carried out of existing practices at each of Ontario's adult liver transplant programs, as well as published clinical guidelines currently utilized in the management of liver transplant patients throughout the world. This involved a detailed review of the following:

- Standard Operating Procedures from each of Ontario's liver transplant programs
- Clinical guidelines from the following organizations:
    - AASLD Evaluation for Liver Transplantation in Adults: 2013 Practice Guidelines by the AASLD and the American Society of Transplantation (2014)
    - AASLD Long-Term Management of the Successful Adult Liver Transplant: 2012 Practice Guideline by AASLD and the American Society of Transplantation (2013)
    - AASLD Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases (2020)
    - ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries (2017)
    - AST Indications for Liver Transplantation in Adults: Recommendations of the Austrian Society for Gastroenterology and Hepatology (ÖGGH) in cooperation with the Austrian Society for Transplantation, Transfusion and Genetics (ATX) (2016)
    - EASL Clinical Practice Guidelines: Management of Alcoholic Liver Disease (2018)
    - EASL Clinical Practice Guidelines: Liver Transplantation (2016)
    - NHSBT Liver Transplantation: Selection Criteria and Recipient Registration (2022)

The analysis was used to determine what services and procedures were carried out during a patient's care continuum at each of Ontario's liver transplant centres. A full list of services was then compiled and compared with the clinical guidelines to determine if they could be considered best practice.

Developing Clinical Pathway and Service Bundles

The clinical pathway model is structured around the parameters defined for the episode of care. The model describes the pathway of each patient case, from their initial presentation with symptoms warranting consideration of a transplant, through the subsequent components of care that they receive, before reaching an endpoint in their care. An exception to an endpoint of care would be in the post-transplant care phase, which would continue in partnership with the community until the time of the patient's death. The pathway presents the critical decision points and phases of treatment within the continuum of care. Decision points provide patient-specific criteria for whether a particular case proceeds down one branch of the pathway or another. Once patients move down a particular branch, they then receive a set of recommended practices that are clustered together as a bundle. Service bundles represent the major phases of care that patients receive during the transplant process. **Figure 1** provides an illustrative example of a service bundle and assessment point:



Through the development of the clinical pathway, the Working Group identified five service bundles corresponding to the key stages in the patient care continuum:

3. **Pre-Transplant before Listing: Referral and Transplant Assessment -** the period before placement on the transplant wait list. It includes the referral package and services required during transplant eligibility assessment.
4. **Pre-Transplant after Listing: Wait List Period -** the period after placement on the wait list, but before the transplant operation.
5. **Preoperative Assessment and Transplant Surgery -** the period from when an organ is matched to the patient, including the preoperative assessment and the surgical procedure.
6. **Post-Transplant: During Hospital Admission -** the period following the transplant operation while the patient is in hospital before discharge.
7. **Post-Transplant: After Discharge** - the period following hospital discharge.

Services for each stage were then categorized into the following two groups:

- **Bundled services:**

  These are services that are an essential part of the patient pathway and have a standard expected duration and frequency. For these services, a minimum standard frequency for the typical transplant patient at each phase of the care continuum was assigned. For example, a hepatology consult is a bundled service that should take place at least one time before listing and as required after listing during the wait list period. It is important to note that the set frequencies do not limit every patient's specific service needs. For example, although the bundles may state that patients should receive one social work consult prior to being placed on the wait list, some patients may require this more often.

- **Unbundled Services:**

  These are services that can potentially be provided to transplant patients but cannot be predicted and/or assigned a standard frequency for a given patient population. Included in this group are services whose frequency varies considerably across centres or services that are required for a patient based on the physician's overall assessment of their health and needs. These services should be provided at the physician's discretion. For example, patients with abnormal renal function should prompt further investigation, including possible evaluation for simultaneous liver-kidney transplantation (11). Therefore, this service is recognized as a potential service that a patient can receive, but is not assigned a standard frequency and duration.

Using the expertise of Ontario clinicians, published guidelines, and available data, TGLN (OH) provided each transplant program with a draft of the developed service bundles. TGLN (OH) solicited feedback from each of the liver transplant centers in Ontario and ensured they had an opportunity to respond to the content in the *Clinical Handbook*. The centres were asked the following key questions:

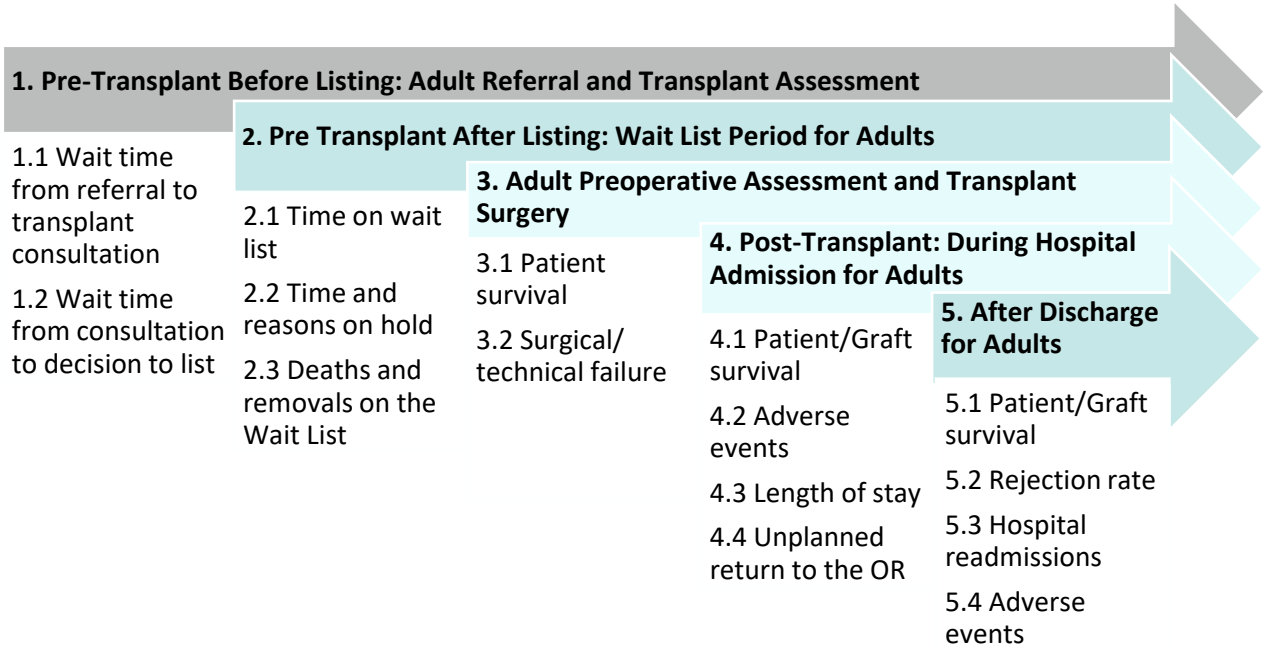
- Are there any services identified that should not be included in the service bundles?
- Are there any services that were not identified in the service bundles but should be included?
- How are the services outlined in the service bundles similar or dissimilar to current practice at your centre?
- What resources would be required to implement these practices?
- Are there any barriers to implementing these practices at your centres? Are there any enablers to implementing these practices at your centres?

To ensure transparency in the consultation process, all feedback was collated, with a summary provided to each of the transplant centres detailing the action taken on proposed changes to the service bundles. Centres were then given an opportunity for final review of the revised bundles and asked to submit any final comments.

Monitoring and Evaluation

Efforts to regularly monitor and evaluate the liver transplantation system in Ontario are taken to improve the transplant process and identify opportunities for further improvement. With the expertise of the Provincial Working Groups, TGLN (OH) has identified key performance indicators for each stage of the patient care continuum that will help clinicians and administrators monitor quality of care and identify associated opportunities for improvement within their centres.

The following diagram provides a sample of the key process and outcome for each phase of the care continuum.



Indicators during the pre-transplant phases of the care continuum focus on timely transplant assessment, consultation, and wait list management to promote patient safety and timely access to transplant. For the surgical and post-transplant phases, the focus is on patient outcomes, such as patient death, graft failure, length of stay and hospital readmissions and adverse events. Although these are baseline quality indicators that will be collected for all transplant patients, TGLN (OH) has worked with the ALD Committee, and Liver/Small Bowel Working Group to develop definitions that would be most relevant for liver transplant patients.

As part of the TGLN (OH)'s quality improvement framework, performance indicators will be reported and distributed to transplant programs. Transplant programs may use the reports to evaluate their own processes at each stage of the care continuum and enable centres to track, audit, and evaluate the implementation of the clinical pathway and best practice services within their centres. Through such monitoring, variances can be identified, progress monitored, and practices refined over time to improve patient outcomes.

TGLN (OH), in collaboration with the ALD Committee, and Liver/Small Bowel Working Group will utilize the performance indicators to monitor and evaluate the transplant system as a whole. Both groups may review the current state of the system and make recommendations to support practice changes where notable variations have been identified. Indicators will be reviewed regularly to ensure they remain relevant and align with quality objectives to promote ongoing improvement at both hospital and system levels.

Plan for Future Review and Update

The clinical pathway and service bundles will be revised when appropriate to ensure developments in liver transplant best practice are reflected. Upon the release of new or updated best practice guidelines, new evidence, or policy changes TGLN (OH) will conduct a review of the *Clinical Handbook*. If no guidelines are published, the *Clinical Handbook* will be reviewed every 4 years by the ALD Committee and Provincial Liver/Small Bowel Working Group. Comments received will be incorporated and reviewed by both groups as necessary.

IV. Overview of End-Stage Liver Disease

According to the Canadian Liver Foundation, it is estimated that approximately 25% of Canadians may be affected by some type of liver disease. The most prevalent forms – viral hepatitis (hepatitis B and C), non-alcoholic fatty liver disease, alcoholic liver disease, and liver cancer – are rising, leading to increased mortality and morbidity (12). For example, a retrospective population-based cohort study in Ontario, Canada analyzed annual standardized incidence and prevalence of chronic liver disease and cirrhosis in the general population, and found that the incidence of cirrhosis has increased over the past two decades, and more so in younger birth cohorts and women (13). In patients whose condition leads to end-stage liver disease (ESLD), transplantation may become their only chance for survival and/or acceptable quality of life (14).

A liver transplant is the surgical replacement of a person's severely diseased or damaged liver with a healthy liver from a human donor. It is performed when ESLD, liver failure or liver cancer cannot be treated by any other medical or surgical means. Patients who may need a transplant usually have one of three problems; irreversible damage to the liver due to cirrhosis, acute liver failure, or hepatocellular carcinoma (HCC) – a type of liver cancer – when the patient's cancer has failed other surgical or medical interventions. Occasionally, other types of liver disease leading to cirrhosis require transplantation, such as metabolic diseases that affect the body's normal physiological functions.

Liver transplantation is generally reserved for patients who are estimated to have poor prognosis i.e. an elevated risk of dying from liver failure in the following year without the transplant, have good prognosis for long-term survival should they receive a new liver (≥60% 5-year survival), and who cannot be helped by conventional medical therapy. It not only improves the quality of life for patients, but has shown to be a life-prolonging procedure. In Canada, it is the second most common organ transplant operation following kidney transplantation.

In an effort to improve access to transplantation, patients with more challenging indications are increasingly being considered for transplantation with the help of improving perioperative management and immunosuppression protocols. Additionally, improving surgical techniques and technologies have expanded the eligible donor pool. This has resulted in an overall favourable success rate for liver transplantation in Canada. As shown in table 1, one-year survival rates are around 90%, and five-year survival rates are over 80%. (15).

Table 1: Unadjusted 3-month and 1-, 3- and 5-year Patient Survival Rates for Deceased-Donor Liver Transplant Recipients, First Graft, Canada (excluding Quebec), 2009 to 2020 (percentage)												
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**
3 Months	94.5	96.6	94.2	96.1	94.7	96.9	94.3	97.7	96.6	97.4	96.3	96.5
1 Year	91.9	92.4	91.1	93.3	89.8	91.4	89.5	92.7	93.4	94.4	94.1	—
3 Years	84.1	87.4	85.1	88.4	85.5	86.2	81.9	87.9	87.6	—	—	—
5 Years	80.2	80.5	82.7	84.9	80.5	83.0	78.4	—	—	—	—	—
10 Years	72.7	71.1	—	—	—	—	—	—	—	—	—	—

Source: Canadian Organ Replacement Register, 2018, Canadian Institute for Health Information

For liver transplant patients, long-term exposure to immunosuppression, infection, malignancy and renal failure are some of the key concerns in the transplant community in improving long-term outcomes (15).

V. Liver Transplantation for ALD in Ontario

Data and Volumes

Alcohol-associated liver disease (ALD) is the second leading cause of acute and chronic liver failure in Ontario, comprising nearly a quarter of patients waiting on the deceased donor wait list, and approximately a fifth of annual liver transplantations performed in Ontario. For select patients with ALD, liver transplantation can be a life-saving intervention.

In most Canadian and international jurisdictions, liver transplant eligibility policies have traditionally called for at least six months of abstinence from alcohol and illicit drug use in order to demonstrate patient willingness and ability to remain abstinent post-transplant. In 2017, TGLN (OH) partnered with clinical, bioethical, medical, and administrative representatives to review the evidence supporting a six-month alcohol abstinence policy, along with the psychosocial requirements for liver transplant eligibility in regards to ALD.

The ALD Pilot Program was conducted from May 2018 to March 2021 in collaboration with London Health Sciences Centre (LHSC) and University Health Network (UHN), with input from a wide variety of experts including transplant medical teams, addictions psychiatry, social work, third-party addiction specialists, and others. The ALD Pilot Program supported patients from a medical and psychosocial perspective, and included new protocols for managing patients with two types of ALD (chronic and severe acute alcoholic hepatitis). Furthermore, the protocols developed for the pilot called for long-term monitoring of adherence to post-transplant therapy. The main purpose of the pilot was to gather the evidence required to determine what changes, if any, should be made to Ontario's Adult Referral and Listing Criteria for Liver Transplantation.

Table 2 shows the overall ALD Pilot Program activity from May 2018 – March 2021.

Referrals	Consultations	Listings	Transplants
916	516	122	62

Source: TGLN, 2021

Table 3 shows the graft and patient survival outcomes for patients who were transplanted through the ALD Pilot Program.

Outcome	30 days	90 days	365 days
Graft Survival	96.8%	93.6%	91.0%
Patient Survival	96.8%	93.6%	91.0%

Source: TGLN, 2021

Trillium Gift of Life Network (Ontario Health)

Trillium Gift of Life Network (TGLN) was an agency of the Ontario Ministry of Health and Long-Term Care established in 2002 with responsibility for coordinating the donation of organs and tissue in Ontario. Its mandate was extended to include transplantation in 2011/12 following recommendations from the *2010 Auditor General`s Report on Organ and Tissue Transplantation* and the *2009 Organ and Tissue Wait Times Expert Panel Report* for an integrated donor and transplant system. With the establishment of Ontario Health under the *Connecting Care Act, 2019*, TGLN transferred into Ontario Health on April 1, 2021.

TGLN (OH)'s transplant strategy aims to support the development of a sustainable end to end transplant system and to continually strive to improve the dimensions of quality, safety, effectiveness, access, patient centered care – all to enable better patient outcomes. This includes developing a provincial transplant system that provides equitable access through standardized processes and planning to enable better patient outcomes, and harmonizing the patient journey across the transplant continuum from pre-transplant through to post-transplant care.

Strategies to further enhance the provincial liver transplant system are facilitated by TGLN through the Provincial Liver/Small Bowel Working Group, which includes medical and administrative membership from each of Ontario's liver transplant programs. The Working Group's mandate is to consider all aspects related to the transplant patient's journey and recommend evidence-based policies and practices to ensure equitable access to quality patient care.

TGLN and the Provincial Liver/Small Bowel Working Group has implemented the following key initiatives aimed at improving patient access and equity, and the quality of care along the patient continuum:

- **Provincial Liver Allocation Algorithm**
  As there are not enough donor livers to meet the demand, every effort is made to ensure that allocation is as fair and equitable as possible. The Working Group regularly reviews and updates the liver allocation algorithm to ensure that it gives fair consideration of candidates' circumstances and medical needs, as well medical utility, by trying to increase the length of time patients and organs survive.

- **Referral and Listing Criteria**

In its report, the Auditor General recommended that TGLN, in conjunction with transplant hospitals and physicians, should "determine the best way to communicate referral criteria to non-transplant physicians, so that individuals who would benefit from a transplant (including from a quality-of-life perspective) are added to the wait list."

- TGLN has since taken measures to improve the referral process so that all patients who meet the criteria can be referred for transplant specialist consultation and assessment. These include:
    - Standardized referral form for external referrals to ensure appropriate information is sent to transplant centres;
    - Standardized referral and listing criteria to increase transparency and help support equitable access to transplant.

- **Performance Measurement and Monitoring**
  In May 2013, TGLN finalized a set of performance indicators to be developed as part of its quality framework for system monitoring and improvement. This includes thirteen key metrics from the Auditor General recommendations such as patient wait time, organ yield, deaths and removal on the wait list, patient and graft survival, and organ disposition.

The ALD Committee, previously known as the ALD Planning Committee was first established to develop the criteria, protocols, performance evaluation metrics, and standards to implement the ALD Pilot Program which ran from May 2018 through March 2021. Following completion of the pilot program, the committee was re-designated as the ALD Committee, with an updated mandate. The ALD Committee considers all aspects related to the ALD transplant patient's journey. The group provides recommendations based on the best available evidence and/or expertise to ensure equitable access to quality patient care including:

1. Developing policies and procedures that support best practices for ALD patients throughout the patient care continuum
2. Identifying barriers and solutions to timely patient referral to transplant programs
3. Developing effective education and communication materials for referring transplant health care professionals, ALD patients, and their caregivers
4. Identifying key clinical findings and metrics for monitoring and evaluation of the ALD patient journey from referral through to post-transplant

The development of the *Clinical Handbook for Alcohol-associated Liver Disease* is part of the ongoing provincial initiative to facilitate Ontario's goals of consistently delivering high quality liver transplant care across the province.

Transplantation Process

Pre-Transplant Before Listing: Adult Referral and Transplant Assessment
This phase refers to the period before placement on the liver transplant wait list. It includes the referral package and services required during transplant eligibility assessment.
Liver transplantation should be considered for patients with end-stage liver failure that is either not amenable to further treatment or progresses despite medical and surgical therapy. Guidelines for medical practitioners to utilize when referring a patient to a transplant program for assessment are outlined in *Ontario's Adult Referral and Listing Criteria for Liver Transplantation* (**Appendix A**). The criteria identify the requirements which have to be met for evaluation to be considered, and lists conditions that constitute absolute contraindications to liver transplantation.

The *Adult Liver Transplant Referral Form* (**Appendix B**) includes the patient information, medical history, and lab and diagnostic testing results required for the referral package. Once a referral is received, the referral package is reviewed to determine whether candidates are eligible for a transplant assessment. Candidates will undergo further testing and consultation to evaluate their eligibility for transplant. The evaluation is aimed at assessing the degree of liver failure and management to date, the chances of recovery from surgery, maximizing short- and long-term survival, and assessing the potential impact of transplantation on quality of life. Evaluation of the suitability of liver transplant candidates includes medical, surgical, immunologic, and psychosocial assessments.

For candidacy, patients will have to fulfill various medical and psychosocial criteria. Blood is drawn for serological and infectious disease testing as patients should be free of active infection, whether of viral, bacterial or fungal origin. Testing of HBV and HCV serology is particularly important, due to their association with decreased post-transplant outcome (11). Other infectious screening criteria, including for HIV, CMV, and EBV are outlined by the AASLD in its listing criteria for liver transplantation (11). Patient evaluation should also investigate other risk factors and contraindications. Impaired renal function is an independent predictor of mortality following liver transplantation and should be assessed by estimation of GFR (11). Liver dysfunction is also a predictor of adverse outcome following transplant and should be assessed regularly using standard liver function tests and advanced consultation and testing on an individual basis (15).

Screening for other common risks to transplantation should also be completed during the transplant assessment. For example, active malignancy is an absolute contraindication to liver transplant and patients should be screened for cancer at the time of evaluation (16). Furthermore, the risk of malignancy post-transplant is elevated, especially cutaneous cancers, and so should be monitored at regular intervals at the recommendation of their healthcare team (16).

Given the importance of adherence to therapy in transplant outcomes, all patients should have a pre-transplant psychosocial evaluation to assess for cognitive impairment, mental illness, risk of non-adherence to therapy and drug or alcohol abuse, and social and emotional supports (11). Patients should also receive transplant education so that they can make an informed decision about whether or not to proceed with transplant. Education should include the risks of the operation, side effects, implications of long-term monitoring including biopsies, immunosuppression, post-transplant morbidities, follow-up, short and long-term outcomes, and mortality estimates.

A full list of consultations, diagnostics and lab tests for patients undergoing assessment is outlined in the service bundle called ***Pre-transplant Before Listing: Adult Referral and Transplant Assessment***. The referral and transplant assessment process is carried out at both referring centres and transplant centres either as an outpatient or inpatient, and may take several months to complete.

Pre-Transplant After Listing: Wait List Period for Adults

This phase refers to the time period after placement on the wait list, but before the transplant operation.
Once the transplant team has agreed to pursue transplantation, patients are placed on the Ontario Liver Transplant Wait List. Donor organs are allocated on principles of equity and fairness, taking into consideration blood type, medical urgency, organ suitability, medical status, and wait time.

During the wait list phase, patients will continue to be monitored by the transplant program to ensure their ongoing eligibility for transplant. A full list of consultations, diagnostics and lab tests is outlined in the service bundle called ***Pre-transplant After Listing: Wait List Period for Adults***. Depending upon the patient's condition, day to day management of the patient and blood testing will be completed by the referring centre for outpatients and in hospital for inpatients, which are sent and reviewed by members of the multidisciplinary transplant team.

If a patient develops a new medical issue or is temporarily unable to receive a transplant while on the wait list, they will be placed on hold. For example, if a patient develops an infection that is a contraindication to transplant, they will be placed on hold until it has been resolved. Candidates with an on-hold status are not eligible for organ allocation, but will continue to accrue wait time.

Adult Preoperative Assessment and Transplant Surgery

This phase refers to the time period from when the patient is alerted that an organ match has been found and accepted by the Transplant program, to the pre-operative assessment and the surgical procedure.

TGLN (OH) notifies the candidate's transplant program of potential deceased organ donor matches, and the transplant program contacts the patient once an organ has been accepted for a specific patient based on the criteria outlined above. Patients not in hospital will be asked about the current state of their health and if no new medical problems have developed, they will be admitted to the hospital for transplant. All patients will receive a final assessment for surgical suitability before undergoing transplant surgery. The final assessment for transplant surgery can include surgical, hepatology and anesthesia consultations as well as lab and diagnostic testing. Each program has expertise in transplantation, advanced liver disease, and the flexibility to consult with other medical specialities and multidisciplinary teams to inform complex care practices beyond the scope of existing recommendations.

A full list of consultations, diagnostics and lab tests is outlined in the service bundle called ***Adult Preoperative Assessment and Transplant Surgery***. A multidisciplinary clinical team completes the patient assessment, prepares the patient for transplant, and performs the transplant surgery. The timing of a liver transplant surgery varies depending on the complexity of the procedure.

Post-Transplant: During Hospital Admission for Adults

This phase refers to the time period following the transplant surgery until the day of hospital discharge. Transplant programs are responsible for patient management during the post-transplant, hospital admission phase. During this phase, clinical teams closely monitor patients to ensure the necessary testing and interventions are completed. They are closely monitored in either the ACU, step-down, or ICU where they will remain until stabilized before being transferred to the designated ward. A full list is outlined in the service bundle for ***Adult Post-Transplant: During Hospital Admission for Adults***. Patients begin their immunosuppression therapy which is based on the transplant recipient's immunological risk and donor factors. Agents are used in combination to achieve sufficient immunosuppression, while minimizing the toxicity associated with individual agents. Most patients receive triple-drug immunosuppressive therapy, consisting of calcineurin inhibitors, purine antimetabolites, and steroids.

Most patients can be transferred to the designated ward within 2-5 days, once hemodynamically stable and no longer requiring critical care management and surveillance. Patients remain in the hospital until they no longer require in-hospital care and/or monitoring.

Post-Transplant: After Discharge for Adults

This phase refers to the time period following hospital discharge.

Following discharge from hospital, the transplant team and appropriate healthcare providers monitor patients through outpatient clinic visits, ensuring the necessary testing is completed, interpreting lab and diagnostic results, and collaborating with other members of the multidisciplinary team as required. The transplant team also monitors and adjusts immunosuppression therapy to prevent organ rejection. Between 20-25% of liver transplant recipients will have at least one episode of acute cellular rejection in the first year after transplantation, with the highest risk period within the first 4 to 6 weeks post-transplant (17). Chronic rejection occurs in approximately 5% or less of patients (17). Since symptoms are often asymptomatic, routine testing for rejection is standard practice (16,17). Abnormally elevated liver function tests are usually the first sign of rejection. When rejection is suspected, standard procedure calls for liver biopsy to confirm rejection (17).

Liver transplant recipients should also be screened for infections, which are most likely to occur in the weeks immediately after surgery and after augmentation of immunosuppression for rejection (16). There is higher risk related to viral replication or reactivation (e.g. CMV, EBV) in the first 6 months post-transplant in addition to increased risk of *Pneumocystis carinii* infection, and toxoplasmosis, hence the need for prophylactic antiviral and/or antimicrobial agents during this time period. Additionally, donor infections that were not captured during the donor screening process, such as hepatitis or mycobacteria can surface during this period. Assessments for infection should consider immunosuppression regimen, timing, environmental and donor exposures, recipient history and use of antimicrobials and vaccinations (15). Beyond 6 months after transplantation, conventional infection rates seen in the general population tend to occur. The most common infections between 3 and 24 months are intra-abdominal, lower respiratory tract or infections by community-acquired pathogens such as streptococcus pneumonia (16). Other key causes of morbidity and mortality post-transplant include malignancy, renal dysfunction, hypertension, hyperlipidemia, amongst others and require routine screening, evaluation and treatment.

A full list of tests and diagnostics for this phase of care is outlined in the service bundle for adult ***Post-Transplant: After Discharge for Adults***.

VI. Clinical Pathway for Alcohol-associated Liver Disease

The clinical pathway outlines the process that the typical Ontario patient can expect when moving through the transplant system. It is categorized into the following five key stages of the patient care continuum:

1. Pre-Transplant Before Listing: Adult Referral and Transplant Assessment	• The period before placement on the transplant wait list.
2. Pre-Transplant After Listing: Wait List Period for Adults	• The period after placement on the wait list, but before the transplant operation
3. Adult Preoperative Assessment and Transplant Surgery	• The period from when the patient is called in for the transplant operation, the preoperative assessment and the surgical procedure
4. Post-Transplant: During Hospital Admission for Adults	• The period following the transplant operation while patient is in hospital before discharge
5. Post Transplant: After Discharge for Adults	• The period following hospital discharge

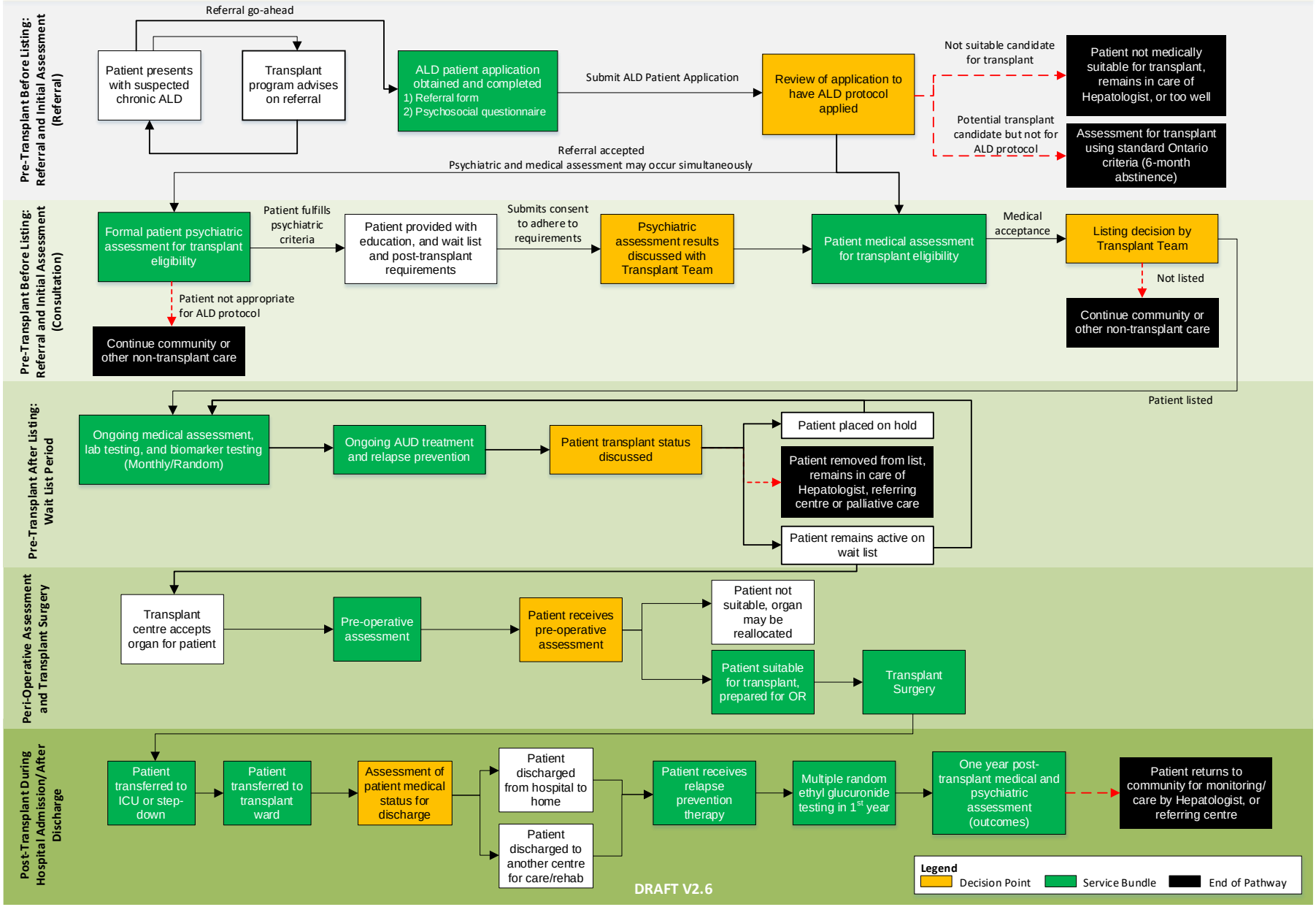
The pathway is intended to be a general guide to the transplant process and identify what patients can expect to receive during the specific time periods. It presents decision points and phases of treatment (service bundles) within an episode of care. Because the decision points determine whether or not a patient moves to the next stage of the transplant process, **Appendix B** outlines the criteria for patient referral and listing. The list of services for each service bundle are detailed in **Section VII**.

The clinical pathway and service bundles should be used in tandem to guide the care of ALD transplant patients in Ontario. Due to the complexity of ALD and its etiology and effects, two clinical pathways have

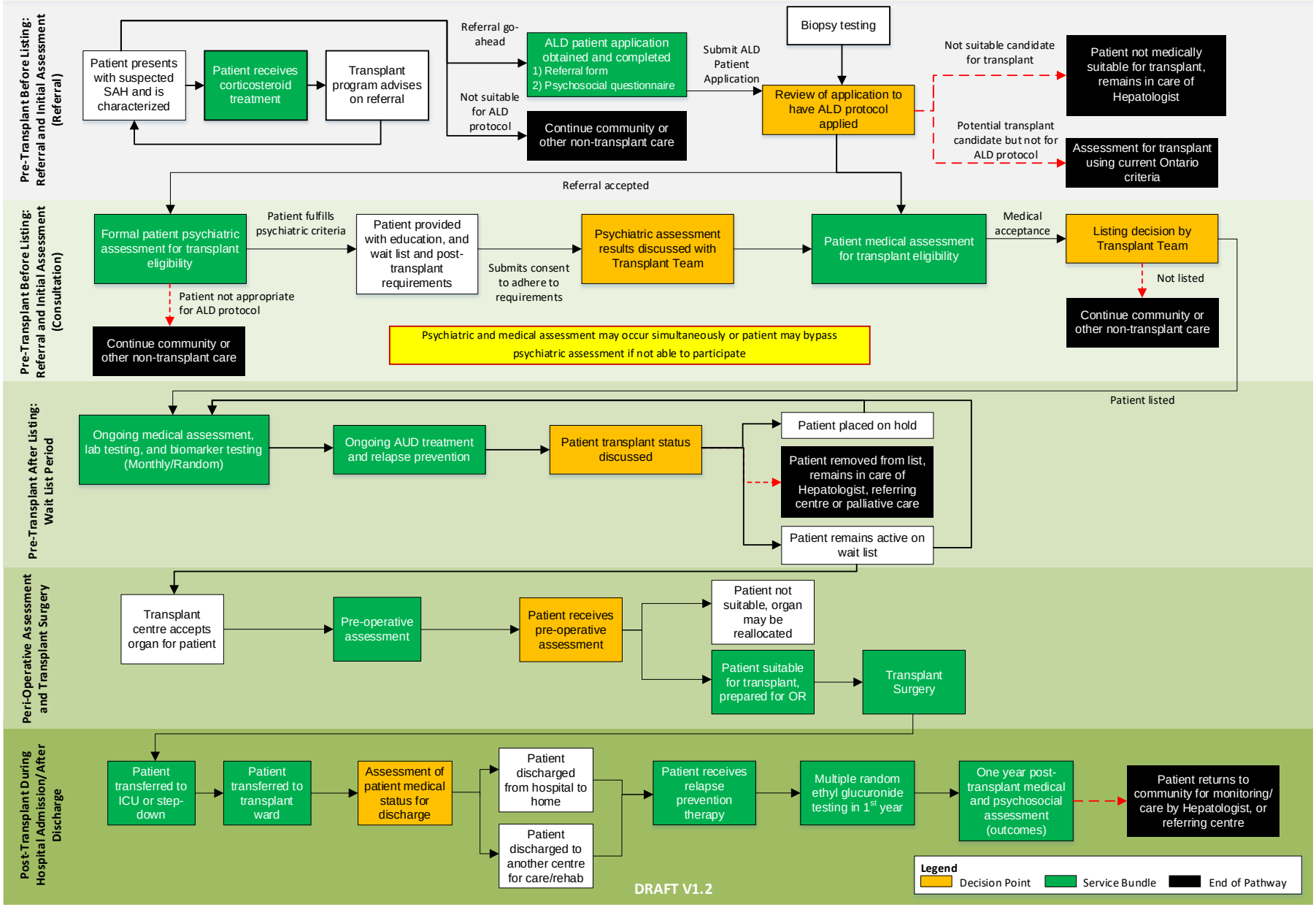
been developed for patients with end-stage liver disease; one for patients with chronic ALD, and the other for those patients diagnosed with severe-acute alcoholic hepatitis.

NOTE: The following clinical pathway and service bundles represent a baseline for patient requirements along the transplant care continuum. Depending on the diagnosis and/or complexity of the transplant patient, fewer or additional clinical services (e.g. tests, imaging, therapy sessions) may be required.

Clinical Pathway for Chronic Alcohol-Associated Liver Disease (ALD)



ALD Clinical Pathway for Severe Acute Alcoholic Hepatitis (SAH)



VII. Service Bundles

The Service Bundles outline the full scope of services and the frequencies with which they may be provided to the typical transplant patient at each stage of their transplant care continuum. The timing of when these services should be administered during the care continuum is indicated in the Clinical Pathway. Although all services will be provided as part of the transplant process, not all will be carried out at the transplant centre.

Because of differences in service needs for adult and paediatric patients, separate service bundles have been created for each group.

Unbundled services, which refer to services which cannot be predicted and/or do not have a standard frequency for a given patient population are not listed.

The Services Bundles do not intend to replace the professional skill and judgment of healthcare providers, but rather ensure minimum standards of care are met for all patients regardless of where care is being provided. They cannot be used to apply to all patients in all circumstances and cannot be used as a legal resource.

ALD Transplant Patient Bundle

Pre-Transplant Before Listing: Adult Referral and Transplant Assessment

Clinical Care: The transplant programs are responsible for determining whether the patient is medically suitable to receive a transplant. Once the referral is received, the transplant programs work to complete the required consultations, diagnostics, and lab testing to enable the multidisciplinary clinical team to assess the patient for transplant eligibility.

The assessment schedule is dependent upon the patient's condition and will be carried out as either an inpatient or outpatient. Patients are registered in the TGLN registry. Patient management during this phase is supported by the following personnel:

- RN, APN, hepatologist, transplant surgeon and other specialists as needed
- Allied health care (social work, physiotherapy, occupational therapy, pharmacy, and nutrition)
- Administrative support

In addition to the recommendations below, all transplant hospitals are expected to have their own protocols on how to treat complications common to all liver failure patients. Each program has expertise in end-stage liver failure management and the flexibility to consult with other medical specialties and multidisciplinary teams to inform complex care practices beyond the scope of existing recommendations.

Clinic Visits and Consultations	
Addictions psychiatry consult	One time and as required
Dietitian consult	As required
Hepatology consult	One time and as required
Metabolics/genetics consult	As required
Oncology consult	As required
Physiotherapist consult (including prehab)	As required
Social work consult	One time and as required
Surgical consult	One time
Transplant Coordinator consult (and education)	One time

Cancer Screening	
Cancer antigen (Ca) 19-9	As per CCO guidelines
Colonoscopy (>50 years)	As per CCO guidelines
Mammogram (females)	As per CCO guidelines
Prostate-specific antigen (PSA) (males)	As per CCO guidelines
PAP smear (females)	As per CCO guidelines

Autoimmune Screening	
α1-antitrypsin serum	As required
Anti-nuclear antibody	As required
Anti-smooth muscle antibody	As required

Treatment	
Pre-existing Infections (Tb, HCV, HBV) Treatment	As required

Tests/Assessments	
Abdominal girth	As required
Abdominal ultrasound	One time
Cardiac imaging: myocardial perfusion, non-invasive stress test (MIBI)	As required
Chest X-ray	One time
CT Scan	As required
Electrocardiogram	One time
Echocardiography	One time
Frailty test	As required
Gastroscopy/endoscopy	As required
Height, weight => BMI	One time
Liver biopsy	As required
Pulmonary function tests (with arterial blood gas)	As required

Infectious Profile	
Aspergillosis	As required
Candida	As required
CMV Antibody (IgG)	One time
EBV Antibody (IgG)	One time
Hepatitis A antibody	As required
Hepatitis B core antibody	One time
Hepatitis B DNA	As required
Hepatitis B surface antibody	One time
Hepatitis B surface antigen	One time
Hepatitis C antibody	One time
Hepatitis C RNA	As required
Hepatitis E virus	As required
HIV	One time
HSV	As required
HTLV I & II	As required
Toxoplasmosis	As required
Tuberculosis (skin test or IGRA)	As required
Varicella	One time

Pre-Transplant Before Listing: Adult Referral and Transplant Assessment

Lab Testing	
α-Fetoprotein	One time
24 hour urine creatinine clearance	As required
ABO/cross and type	One time
Albumin	One time
Alcohol test (EtG)	One time and as required
AST, ALT, ALP	One time
Bilirubin	One time
Blood gases (arterial)	One time
CBC	One time
Coagulation studies (PT, PTT, INR)	One time (not PT)
Creatinine	One time
Electrolytes (Na, K, Cl, HCO_3)	One time
Fe studies: ferritin, transferrin, caeruloplasmin	One time
GGT	As required
Glucose (random)	One time
Glycosylated haemoglobin	As required
HLA - Pre-transplant antibody testing	As required
Immunoglobulins (IgA, IgG, IgM)	As required
Lipid studies: triglycerides, HDL, LDL (fasting)	As required
Mg, Ca, PO_4	One time
Thyroid (TSH)	As required
Total protein	One time
Urea	As required
Urinalysis – routine	As required
Zn	As required

Pre-Transplant After Listing: Wait List Period for Adults

Clinical Care: The transplant programs are responsible for determining whether the patient is medically suitable to receive a transplant. Once the referral is received, the transplant programs work to complete the required consultations, diagnostics, and lab testing to enable the multidisciplinary clinical team to assess the patient for transplant eligibility.

The assessment schedule is dependent upon the patient's condition and will be carried out as either an inpatient or outpatient. Patients are registered in the TGLN registry. Patient management during this phase is supported by the following personnel:

- RN, APN, hepatologist, transplant surgeon and other specialists as needed
- Allied health care (social work, physiotherapy, occupational therapy, pharmacy, and nutrition)
- Administrative support

In addition to the recommendations below, all transplant hospitals are expected to have their own protocols on how to treat complications common to all liver failure patients. Each program has expertise in end-stage liver failure management and the flexibility to consult with other medical specialties and multidisciplinary teams to inform complex care practices beyond the scope of existing recommendations.

Clinic Visits and Consultations	
Clinical trials consult	As required
Discharge planning	As required
Hepatology consult	As required
Relapse prevention therapy	One time and as required
Social work consult	As required
Transplant education	As required
Transplant surgery consult	As required
Physiotherapist consult (including prehab)	As required

Tests/Assessments	
Chest X-ray	As required
Electrocardiogram	As required
HCC surveillance (known lesion): ultrasound	q6 months
HCC surveillance (known lesion): CT/MRI	q3 months
HCC screening: ultrasound or CT/MRI	q6 months
Height, weight, abdominal girth	As required
Non-invasive stress test (Echo, MIBI)	As required

Lab Testing	
Alcohol test (EtG or CDT test)	As required
Na MELD lab work	q3 months and as required
Routine lab blood work	q3 months and as required

Infectious Profile	
CMV Antibody (IgG)	As required, or annually if negative
EBV Antibody (IgG)	As required, or annually if negative
Hepatitis B DNA	As required
Hepatitis B surface antibody	As required
Hepatitis C antibody	As required
Hepatitis C RNA	As required
Hepatitis E	As required
HIV	As required
HSV	As required
HTLV I & II	As required
Toxoplasmosis	As required
Varicella	As required

Cancer Screening	
Colonoscopy (>50 years)	As per CCO guidelines

Treatment	
Pharmacotherapy	As required

Adult Preoperative Assessment and Transplant Surgery

Clinical Care: The transplant programs are responsible for determining whether the patient is medically suitable to receive a transplant. Once the referral is received, the transplant programs work to complete the required consultations, diagnostics, and lab testing to enable the multidisciplinary clinical team to assess the patient for transplant eligibility.

The assessment schedule is dependent upon the patient's condition and will be carried out as either an inpatient or outpatient. Patients are registered in the TGLN registry. Patient management during this phase is supported by the following personnel:

- RN, APN, hepatologist, transplant surgeon and other specialists as needed
- Allied health care (social work, physiotherapy, occupational therapy, pharmacy, and nutrition)
- Administrative support

In addition to the recommendations below, all transplant hospitals are expected to have their own protocols on how to treat complications common to all liver failure patients. Each program has expertise in end-stage liver failure management and the flexibility to consult with other medical specialties and multidisciplinary teams to inform complex care practices beyond the scope of existing recommendations.

Clinic Visits and Consultations	
Anaesthesia consultation	One time
Hepatology	As required
Transplant surgery	One time

Tests/Assessments	
Chest X-ray	One time
Electrocardiogram	One time
Weight	As required

Infectious Profile	
CMV: IgG	As required

Lab Testing	
ABO/cross and type	One time
Albumin	One time
ALP, AST, ALT	One time
Amylase	As required
Bilirubin	One time
Ca, Mg, PO_4	One time
CBC	One time
Coagulation Tests (PT, PTT, INR)	One time
Creatinine	One time
Electrolytes (Na, K, Cl, HCO_3)	One time
Fibrinogen	As required
GGT	As required
Glucose (point-of-care)	As required
Glucose (random)	One time
Total protein	As required

Post-Transplant: During Hospital Admission for Adults

Clinical Care: The transplant programs are responsible for determining whether the patient is medically suitable to receive a transplant. Once the referral is received, the transplant programs work to complete the required consultations, diagnostics, and lab testing to enable the multidisciplinary clinical team to assess the patient for transplant eligibility.

The assessment schedule is dependent upon the patient's condition and will be carried out as either an inpatient or outpatient. Patients are registered in the TGLN registry. Patient management during this phase is supported by the following personnel:

- RN, APN, hepatologist, transplant surgeon and other specialists as needed
- Allied health care (social work, physiotherapy, occupational therapy, pharmacy, and nutrition)
- Administrative support

In addition to the recommendations below, all transplant hospitals are expected to have their own protocols on how to treat complications common to all liver failure patients. Each program has expertise in end-stage liver failure management and the flexibility to consult with other medical specialties and multidisciplinary teams to inform complex care practices beyond the scope of existing recommendations.

Clinic Visits and Consultations	
Acute pain service	Ongoing as required
Diabetes education	As required
Dietician consult	As required
Discharge planning	As required
Hepatology	Ongoing
Pharmacy	As required
Physiotherapy/rehabilitation consult	Ongoing as required
Relapse prevention therapy	As required
Social work consult	As required
Transplant surgery	Ongoing

Tests/Assessments	
Chest X-ray	As required
Electrocardiogram	As required
Liver biopsy	As required
Transplant ultrasound	As required

Monitoring	
Weight	Daily

Lab Testing	
Albumin	As required
ALP, ALT, AST	Daily
Bilirubin	Daily
Blood gases (arterial)	As required
Ca, Mg, PO_4	Daily
CBC	Daily
Coagulation studies: PT,PTT,INR	Daily
Creatinine	Daily
Electrolytes: Na, K, Cl, HCO_3	Daily
GGT	As required
Glucose (POC)	As required
Glucose (random)	As required
Immunosuppression levels	As required
Lactate	As required
Total Protein	As required
Urea	As required

Post Transplant: After Discharge for Adults

Clinical Care: The transplant programs are responsible for determining whether the patient is medically suitable to receive a transplant. Once the referral is received, the transplant programs work to complete the required consultations, diagnostics, and lab testing to enable the multidisciplinary clinical team to assess the patient for transplant eligibility.

The assessment schedule is dependent upon the patient's condition and will be carried out as either an inpatient or outpatient. Patients are registered in the TGLN registry. Patient management during this phase is supported by the following personnel:

- RN, APN, hepatologist, transplant surgeon and other specialists as needed
- Allied health care (social work, physiotherapy, occupational therapy, pharmacy, and nutrition)
- Administrative support

In addition to the recommendations below, all transplant hospitals are expected to have their own protocols on how to treat complications common to all liver failure patients. Each program has expertise in end-stage liver failure management and the flexibility to consult with other medical specialties and multidisciplinary teams to inform complex care practices beyond the scope of existing recommendations.

Clinic Visits and Consultations	
Addictions consult	As required
Dermatology consult	As required
Hepatology consult	As required
Physiotherapy / rehabilitation consult	As required
Pharmacy consult	As required
Social work consult	As required
Relapse prevention therapy	As required
Transplant education	As required

Tests/Assessments	
Abdominal ultrasound	As required
Abdominal/chest computed tomography (CT)	As required
Bone density scan	GP care
Echocardiography	As required
Gastroscopy	As required
Liver biopsy	As required
Magnetic resonance cholangiopancreatography (MRCP)	As required

Prevention	
Influenza vaccine	As per public health recommendations
Pneumococcal vaccine	As per public health recommendations

Cancer Screening	
Colorectal Screening: Colonoscopy and Biopsy	As per CCO guidelines

Lab Testing	
α-fetoprotein	As required
Albumin	As required
Alcohol test (EtG and/or CDT)	As required
ALP, ALT	As required
Amylase	As required
Bilirubin	As required
Ca, Mg, PO_4	As required
CBC (including platelets)	As required
Coagulation studies: PT,PTT,INR	As required
Creatinine	As required
Electrolytes: Na, K, Cl, HCO_3	As required
GGT	As required
Glucose (random)	As required
Immunosuppression levels	As required

Infectious Profile/Screening	
HBV serology: HBsAg, HBV DNA	As required
HCV serology: RNA (quantitative and genotype)	As required
If IRD Donor Used	
HIV (NAT, Serology)	At 1 month and 3 months
HCV (NAT, Serology)	At 1 month and 3 months
HBV (Anti-HBs, Anti-HBc, HBsAg)	At 12 months
If IRD Donor was HCV Ab-positive or HCV NAT-positive	
HCV (NAT)	At 2 weeks and 6 weeks
HIV (NAT, Anti-HBc, HBsAg (± HBV NAT)	At 1 month and 3 months
HBV (Anti-HBs, Anti-HBc, HBsAg)	At 12 months

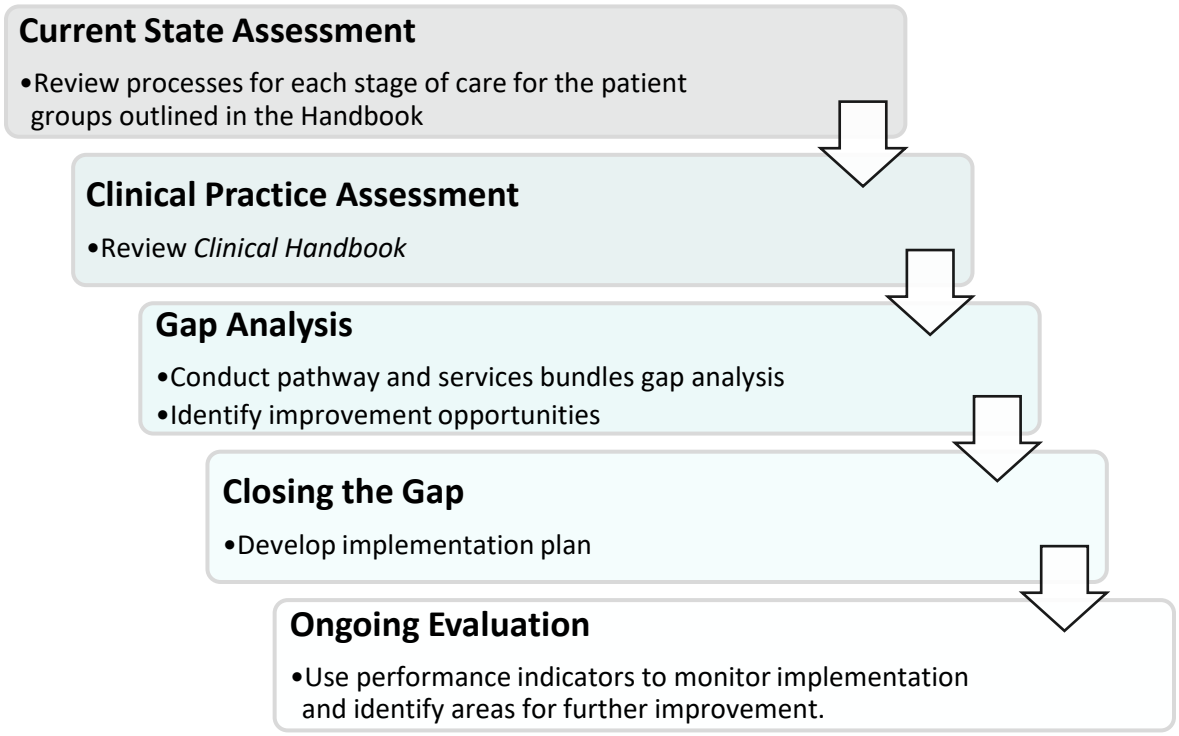
VIII. Implementation

The *Clinical Handbook* is a compendium of evidence-based and clinical consensus guidelines created with the goal of improving quality of transplant care delivery and patient outcomes as measured through performance indicators. This toolkit is not intended to replace the professional skill and judgement of healthcare providers, nor inhibit the development of new and innovative transplant solutions.
Successful implementation of the Handbook can be facilitated by leveraging the following components:

- **Building a shared vision for clinical practice:** The *Clinical Handbook* is an opportunity to share clinical consensus guidelines that will allow the system to provide even higher quality care, while increasing system efficiencies.
- **Engaging leadership for change:** Senior leaders can support the vision for change by providing a clear message about the implications of guideline implementation.
- **Supporting clinical engagement:** From the outset, staff, physicians and other clinicians should be provided with sufficient information that will help them understand the importance of this initiative, including its impact on patient care.

To achieve a shared vision for clinical practice, transplant centres are encouraged to review their current processes in relation to the clinical pathway and identify any variation that exists. As transplantation is a complex system, when a variation is identified, transplant centers are encouraged to work within their centers to understand the variation in developing their local clinical pathway. To help with the review process the following roadmap to implementation has been suggested.

Roadmap to Liver Transplant Clinical Pathway and Service Bundles Implementation



The *Clinical Handbook* provides an opportunity to build a shared vision for clinical practice for liver transplantation to improve quality of care, while maximizing the effective use of available resources. In order to make informed and accurate decisions, the importance of high-quality data cannot be emphasized enough. As outlined in **Section III**, TGLN has developed a list of quality indicators that can be used to evaluate each stage of the patient care continuum. Such indicators will enable centres to track, audit, and evaluate the implementation of the clinical pathway and service bundles at an organizational level. Through such monitoring, variances can be identified, progress monitored, and practices refined over time to improve patient outcomes.

The Liver/Small Bowel Working Group and ALD Committee will utilize performance metrics to review clinical practices and make recommendations to support practice changes where notable variations in practice have been identified. The *Clinical Handbook* will be reviewed regularly by both groups, and when appropriate, updated with new recommended practices, evidence, and policy changes.

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X. Appendices

Appendix A. Ontario's Adult Referral and Listing Criteria for Liver Transplantation

PATIENT REFERRAL CRITERIA:

The patient referral criteria are criteria which a Health Care Provider would utilize to refer a patient to a transplant centre for assessment. The criteria identified below are the currently agreed upon conditions for which a patient should be considered for referral for liver transplant assessment.

1) **Chronic Liver Disease:** Referral for adult liver transplantation should be considered for patients with decompensated chronic liver disease. Such patients generally have one or more of the following:
    - End-stage of chronic liver disease with hepatic decompensation
        - Ascites or complications thereof such as hepatic hydrothorax and (resolved) spontaneous bacterial peritonitis, jaundice, hepatic encephalopathy or portal hypertensive GI bleed. These patients will typically have a Sodium Model of End-stage Liver Disease score (Na MELD) score of greater than or equal to 11 or a Child-Pugh B score of greater than or equal to 7;
    - Other Complications of End-stage Liver Disease or Portal Hypertension such as
        - Hepatopulmonary syndrome (HPS);
        - Hepatocellular carcinoma (HCC).

2) **Fulminant hepatic failure**

3) **Metabolic Disorders:** Referral for adult liver transplantation may also be considered for patients with metabolic disorders of hepatic origin. This may include conditions such as hereditary transthyretin amyloidosis, hyperoaxaluria type I and others.

Early referral is essential to allow the patient to be evaluated and to survive (in a condition that still allows major surgery) until a suitable organ becomes available.

PATIENT LISTING INDICATIONS:

Each patient is assessed individually for his/her suitability for liver transplantation by one of the two provincial liver transplant programs (London or Toronto). The criteria identified below are the currently agreed upon general and specific conditions for which a patient may be eligible to be waitlisted for liver transplantation in Ontario.

1) **General:** Listing for liver transplantation may be considered for patients if the following requirements are met:

- Therapeutic options, other than liver transplantation, have been exhausted;
- Absence of obvious contraindication for transplant; and,
- Expected 5-year survival ≥ 60% (co-morbidity, compliance).

2) **End-Stage Chronic Liver Disease:** Listing for liver transplantation may be considered for patients with decompensated cirrhosis with a Sodium MELD (Na MELD*) score of greater or equal to 15. Patients with Na MELD scores of 11 - 15 (or, under exceptional circumstances, less) may be considered only with the presence of factor(s) indicating poor prognosis that is/are not adequately captured by their Na MELD score (e.g. recurrent cholangitis, refractory ascites).

   * Na MELD is a scoring system for assessing the severity of chronic liver disease; the higher the score, the more severe the liver disease and the lower the patient's 90-day survival without a liver transplant.

3) **Hepatocellular Carcinoma (HCC):** Patients with hepatocellular carcinoma may be considered for liver transplantation. However, they must be carefully selected to minimize the chance of recurrence after surgery. Of note, exception points for allocation purposes will be granted only if the HCC meets the following criteria: one HCC nodule greater than or equal to 2cm or multiple HCC nodules greater than or equal to 1cm or one HCC nodule greater than 1cm and less than or equal to 2cm that cannot be treated by intent to cure other than liver transplantation or any recurrent HCC nodule greater than or equal to 1cm. In addition to meeting one of the aforementioned criteria patients must meet all of the following criteria to be granted exception points for allocation: Total Tumour Volume (TTV) less than or equal to 145cm3 and Alpha Fetoprotein (AFP) less than or equal to 1,000, diagnostic imaging for HCC (if imaging not diagnostic than a biopsy is required), no evidence of vascular invasion or extrahepatic spread and no HCC mixed with predominance of cholangiocarcinoma features on histology.

   HCC patients not fulfilling the specified criteria (outlined above) do not receive exception points but can be actively listed as per their calculated SMC.

4) **Alcohol-associated Liver Disease (ALD):** Patients with alcohol-associated liver disease may be considered for liver transplantation. These patients must be carefully assessed for higher risk of return to problematic alcohol use to help ensure optimal outcomes in addition to meeting standard transplant listing and contraindication criteria. The transplant team should be guided in its assessment by the following criteria:

   a) the patient does not meet criteria for moderate to severe Alcohol Use Disorder (AUD) likely to result in a return to problematic drinking in the post-transplant period;
   b) the patient is willing to commit to abstinence from alcohol;
   c) the patient is willing to commit to AUD treatment pre/post-transplant when recommended by transplant psychosocial team;
   d) history of no more than one previously failed AUD treatment where failure is defined as a return to problem drinking that would meet criteria for AUD;
   e) absence of comorbid active substance use disorder, excluding cannabis use and tobacco use disorder;
   f) absence of untreated and refractory severe psychiatric co-morbidity (including personality disorder) likely to interfere with treatment adherence;

g) other than in relation to alcohol use, no history of recurrent problems with adherence to medical treatment and repeated inability to follow up with/unable to contact patient;
h) the patient has a dedicated support person available to assist them throughout the process and stable housing.

In addition to the above, patients identified as having Chronic ALD should have the ability to engage in the ALD psychosocial assessment and demonstrate capacity to consent to protocol requirements. For those patients who are diagnosed as having Severe Alcoholic Hepatitis (SAH) they must meet the additional criterion as having SAH as their first liver-decompensating event leading to diagnosis of acute liver disease.

If an ALD patient does not meet the above criteria, they may be re-assessed when there is a change (including a change in their psycho-social profile) that in the transplant team's opinion would merit re-considering whether they meet the above criteria.
Furthermore, if an ALD patient does not meet the criteria above, the patient may be listed if they have demonstrated a sustained period abstinence from alcohol of six months or more and have demonstrated a commitment to sustained abstinence.

5) **Fulminant Hepatic Failure:** Patients with fulminant hepatic failure may be considered for liver transplantation if they meet the Kings College Criteria or other validated criteria and have no contraindication (see below) for transplant.

6) **Metabolic Diseases**: Liver transplantation may be offered as therapy for patients with certain metabolic diseases of hepatic origin (e.g. hereditary transthyretin amyloidosis, Maple Syrup Urine Disease, hyperoaxaluria type I, etc.).

7) **Other Conditions**: Selected patients with certain rare conditions may be considered for liver transplantation. Such conditions may include:
   - Selected cholangiocarcinoma (within the Mayo Clinic protocol)
   - Selected neuroendocrine liver tumours
   - Fibrolamellar HCCs
   - Selected hepatoblastomas

PATIENT LISTING CONTRAINDICATIONS:

The contraindications for liver transplantation identified below are the currently agreed upon conditions in which the presence of one or more would result in the patient not being eligible to be waitlisted for liver transplantation in Ontario.

1) **Co-Morbidities:** Patients with any co-morbidity that decreases the likelihood of surviving 5 years post-transplant to below 50% or for whom the peri-operative risk is deemed unacceptably high are not candidates for liver transplantation.

2) **Nutritional State:** For a patient with a calculated body mass index (BMI) [estimated dry weight (kg) divided by height (cm)] that exceeds 40 kg/m^2, liver transplantation is a relative contraindication due

to excessive morbidity and potential excess mortality. For patients with a BMI > 45 kg/m^2, liver transplantation should be contraindicated except in exceptional circumstances.

For a patient with a body mass index (BMI) < 18.5 kg/m^2, liver transplantation is a relative contraindication, and aggressive nutritional support should be implemented.

3) **Infections:** Patients are not candidates for liver transplantation if they display the following:
    1. Active or uncontrolled extrahepatic infection (including sepsis)
    2. Uncontrolled HIV infection (i.e. detectable viral load and/or CD4 count <100) or AIDS.

4) **Malignancy**: Patients with extrahepatic malignancy are not candidates for liver transplantation. In general, patients must be cancer free for at least 2 - 5 years after curative therapy, depending on the cancer type. This may be assessed on an individual patient basis depending on the type and stage of the tumour.

5) **Vascular Abnormalities**: Patients with extensive thrombosis of the Portal Vein, Superior Mesenteric Vein and Splenic Vein, or other extensive vascular anomalies or pathologies precluding sufficient revascularization of the graft are not candidates for liver transplantation.

6) **Psychosocial Considerations:** Patients who display any of the following are not candidates for liver transplantation:
    1. Unstable psychiatric disorder, especially one likely to interfere with compliance;
    2. Any illicit drug misuse within six months;
    3. Previous documentation or current unwillingness or inability to follow the advice of health professionals;
    4. Social support/compliance issues prohibiting adherence to post-operative medications and/or follow-up care.

NOTE: The referral form presented here includes information for patients to be referred for liver transplantation. Depending on the diagnosis and/or complexity of the patient, fewer or additional clinical information (e.g. tests, imaging) may be required.

Appendix B. Adult Liver Transplant Referral Form

- For a complete list of conditions suitable for referral for adult liver transplantation, refer to the TGLN website: http://www.giftoflife.on.ca/en/professionals.htm

To refer a candidate for adult liver transplantation, complete this form and attach all applicable documents.

Submit the completed form, including all applicable documents to the appropriate transplant centre listed below:

London Health Sciences Centre	**University Health Network**
Liver Transplant Team	**Liver Transplant Assessment Clinic**
University Hospital	**Toronto General Hospital**
339 Windermere Road	**200 Elizabeth Street, NCSB11C–1222**
London, Ontario N6A 5A5	**Toronto, Ontario M5G 2N2**
Tel: (519) 685-8500 ext. 33354	**Tel: (416) 340-4800 ext. 6521**
Fax: (519) 663-3858	**Fax: (416) 340-4779**

The completion of this form will facilitate your patient's investigations and subsequent consideration for transplantation. Thank you for your cooperation in providing this material.

TO BE COMPLETED BY TRANSPLANT PROGRAM/HEPATOLOGIST:

(Na)MELD: _____ **HCC:** ☐ Yes ☐ No

URGENCY: ☐ High (within two weeks) ☐ Normal (next available appointment)

Date: _____ **Initials: _____**

TO BE COMPLETED BY TRANSPLANT PROGRAM UPON RECEIPT OF FORM:

Date Referral Form Received: _____

PATIENT DEMOGRAPHIC INFORMATION

Patient Name:_____ **Health Card #:_____** **Version Code: ___**

Date of Birth: _____ **Sex:** ☐ Male ☐ Female **Patient Phone #:**

_(___)____-_____

Address/City:_____**Postal Code:**_____

Patient Location: ☐ At Home ☐ In Hospital ☐ Other: _____

Need for interpreter: ☐ Yes ☐ No **If Yes, language** _____

PATIENT CLINICAL INFORMATION

Patient ABO: ☐ A ☐ B ☐ AB ☐ O ☐ Unknown

Diagnosis: ☐ Cirrhosis ☐ Liver Cancer ☐ Other: _____

Other Conditions: ☐ Diabetes ☐ Heart Disease ☐ Other: _____

Diagnosis due to (select all that apply):

☐ HCV ☐ HBV ☐ NASH ☐ AIH ☐ PBC ☐ PSC

☐ Alcohol; Period of Alcohol Abstinence: _____ ☐Other:

_____

Complications:

☐ Ascites

☐ Controlled with diuretics ☐ Requires regular paracentesis

☐ SBP, last episode: _____ ☐ Variceal Bleed, last episode:

_____

☐ Encephalopathy, last episode: _____ ☐ Acute Kidney Injury (AKI)

☐ Other: _____

Dialysis:

Is patient currently on Dialysis? ☐ Yes ☐ No

Does patient require Dialysis during assessment at this centre? ☐ Yes ☐ No

LAB RESULTS AND CONSULT ATTACHMENTS

Date of Lab Results: _____

☐Bilirubin $_{\text{total}}$**:** _____ umol/l ☐ INR: _____ ☐ Creatinine: _____ umol/l

☐ Platelet count: _____ x10^9/l ☐ Sodium: _____ umol/l

Please attach copies of the following reports, WHERE APPLICABLE:

Tests:

☐ Ultrasound, CT, MRI – Liver and Portal Vein ☐ Esophago-gastro-duodenoscopy (EGD)

Additional Tests (if available):

☐ Colonoscopy ☐ Pulmonary Function test ☐ Cardiac Test

☐ Consult Notes/Clinic Letters ☐ OR reports

☐ Other: _____

ADDITIONAL COMMENTS

REFERRING PHYSICIAN

Referring Physician Name: _____

Referring Physician Organization: _____

Billing #: _____ **Phone #:** _____

Address/City: _____ **Postal Code:** _____

Referral Form submitted to: ☐London Health Sciences Centre ☐University Health Network

Signature: _____ **Date Submitted:** _____

Version Control

Version	Summary of Changes	Date Approved
1.0	First publication	February 2, 2023