OPTN

Public Comment Proposal

Review of National Liver Review Board (NLRB) Diagnoses and Update to Alcohol-Associated Diagnoses

OPTN Liver and Intestinal Organ Transplantation Committee

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Review of National Liver Review Board (NLRB) Diagnoses and Update to Alcohol-Associated Diagnoses

Affected Policies:	*Policy 9.5.I.i: Initial Assessment and Requirements for HCC Exception Requests* *Policy 9.5.I.vii: Extensions of HCC Exceptions*
Affected Guidance:	*Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exceptions for Hepatocellular Carcinoma (HCC);* *Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review*
Sponsoring Committee:	*Liver and Intestinal Organ Transplantation*
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Executive Summary

This proposal includes two distinct aspects intended to improve the liver allocation system. The two parts of the proposal are improvements to the National Liver Review Board (NLRB) and updates to the diagnoses on the transplant candidate registration form (TCR) and transplant recipient registration form (TRR) to better capture alcohol-associated liver diseases (ALD).

This proposal includes the addition of NLRB guidance for candidates with hepatocellular carcinoma (HCC) who were treated with immunotherapy and a clarification of the waiting period for candidates with a history of resected HCC. The proposal also updates guidance for candidates with encephalopathy to include new references and clearer language. Finally, the proposal clarifies the policy requirements for submitting a chest CT for candidates with an HCC exception.

Separate from the changes to NLRB guidance and policy, the proposal also includes an update to the list of diagnoses on the TCR and TRR. The current list of diagnoses for alcohol-associated liver diseases is outdated and does not allow for consistent data collection. The proposal updates the possible response options to allow transplant programs to provide accurate information on liver transplant candidates and will allow for more complete data collection and analysis.

These changes will make the liver allocation system more efficient and equitable, while also allowing for accurate data collection to inform future allocation changes.

Background

Ongoing Review of NLRB Diagnoses

When being listed for a liver transplant, candidates receive a calculated MELD or PELD score, which is based on a combination of the candidate's clinical lab values.[1] These scores are designed to reflect the probability of death on the waitlist within a 3-month period, with higher scores indicating a higher probability of mortality and increased urgency for transplant. Candidates who are less than 12 years old receive a PELD score, while candidates who are at least 12 years old receive a MELD score. Candidates that are particularly urgent are assigned status 1A or 1B.

When a transplant program believes that a candidate's calculated MELD or PELD score does not accurately reflect a candidate's medical urgency, they may request a score exception. The NLRB is responsible for reviewing exception requests and either approving or denying the requested score.

The NLRB was approved by the OPTN Board of Directors (the Board) at their June 2017 meeting and was implemented on May 14, 2019.[2] The NLRB was designed to create an efficient and equitable system for reviewing exception requests for candidates across the country.

Under the NLRB, candidates who meet the criteria outlined in OPTN policy for one of the nine standardized diagnoses are eligible to have their exception automatically approved. In addition, each of the three specialty review boards (Pediatric, Adult - Hepatocellular Carcinoma (HCC), and Adult - Other Diagnosis) has an associated guidance document. The guidance documents contain information for review board members and transplant programs on diagnoses and clinical situations not included as one of the standardized diagnoses in policy. They provide recommendations on which candidates should be considered for a MELD or PELD exception and are based on published research, clinical guidelines, medical experience, and data. The documents are intended to help ensure consistent and equitable review of exception cases and are not OPTN policy.

Because these documents are consulted by transplant programs and NLRB reviewers when applying for and reviewing exception requests, they have the ability to impact which candidates are approved for a MELD or PELD exception. Therefore, it is necessary that the OPTN Liver and Intestinal Organ Transplantation Committee (the Committee) systematically and proactively review the documents to ensure they continue to align with current clinical consensus and updated data. Whereas previous updates to NLRB policy and guidance were based on community feedback as it was provided, this proposal was developed using a more systematic and proactive review process. Rather than waiting to consider a change once an issue was identified, the Committee began a process to examine current guidance and policy for a specific subset of NLRB diagnoses using a set schedule.

As a result of this process, the Committee is proposing updates to the guidance for HCC and encephalopathy, as well as HCC policy. The review process included reviewing recent literature, correcting any ambiguity in current guidance, reviewing cases that were appealed to the Appeals Review Team (ART), consultation with subject matter experts, and review of updated data, as needed. In addition to the changes included in this proposal, the Committee reviewed current guidance for hepatic

[1] The calculation for the MELD and PELD scores can be found in OPTN Policy, Available at https://optn.transplant.hrsa.gov/.
[2] *Proposal to Establish a National Liver Review Board*, OPTN Liver and Intestinal Organ Transplantation Committee, June 2017, Available at https://optn.transplant.hrsa.gov/

hydrothorax, ascites, and gastrointestinal bleeding and is not recommending any changes at this time. The Committee also considered updating the guidance for HCC candidates beyond downstaging criteria but decided not to pursue any changes as the available data was insufficient.

Updating Alcohol-Associated Diagnoses on TCR/TRR

In 2016, ALD overtook chronic hepatitis C virus (HCV) as the leading indication for liver transplantation.[3] In 2012, ALD accounted for 19% of waitlist additions and 15% of liver transplant recipients.[4] By 2016, those numbers had increased to 30% and 24%, respectively.[5] This increase aligns with the higher prevalence of alcohol use, high-risk drinking, and alcohol use disorder between 2001-2002 and 2012-2013, as seen in the results of the National Epidemiological Survey on Alcohol Related Conditions.[6] In addition, preliminary research has shown that alcohol consumption has increased during the COVID-19 pandemic, portending a correlated increase in ALD in the future.[7,8]

Despite ALD being the leading indication for liver transplantation, recent research has shown that there is significant inconsistency when entering the diagnosis for candidates with ALD.[9] This research reported that of the 124 recipients with alcoholic hepatitis at the participating centers, only 43 (35%) had alcoholic hepatitis as the listing diagnosis in the OPTN database.[10]

In addition, most transplant programs require a six-month abstinence period prior to transplantation for candidates with ALD to determine if liver function could return without the need for transplant. [11,12] However, there remains ongoing dialogue within the liver transplant community about the utility and effectiveness of the six-month abstinence rule.[13]

In particular, a diagnosis of alcoholic hepatitis, which is defined as the acute onset of jaundice as a result of excessive alcohol consumption, is associated with increased short-term mortality.[14] In fact, 75%-90% of deaths for patients with severe alcoholic hepatitis occur within two months, making the six-month rule infeasible for these candidates.[15] Recent research has demonstrated that recipients (n=147) with

[3] George Cholankeril and Aijaz Ahmed, "Alcoholic Liver Disease Replaces Hepatitis C Virus Infection as the Leading Indication for Liver Transplantation in the United States," *Clinical Gastroenterology and Hepatology* 16, no. 8 (2018): pp. 1356-1358, https://doi.org/10.1016/j.cgh.2017.11.045.
[4] Ibid.
[5] Ibid.
[6] Bridget F. Grant et al., "Prevalence of 12-Month Alcohol Use, High-Risk Drinking, and DSM-IV Alcohol Use Disorder in the United States, 2001-2002 to 2012-2013," *JAMA Psychiatry* 74, no. 9 (January 2017): p. 911, https://doi.org/10.1001/jamapsychiatry.2017.2161.
[7] Elyse R. Grossman, Sara E. Benjamin-Neelon, and Susan Sonnenschein, "Alcohol Consumption during the COVID-19 Pandemic: A Cross-Sectional Survey of US Adults," *International Journal of Environmental Research and Public Health* 17, no. 24 (September 2020): p. 9189, https://doi.org/10.3390/ijerph17249189.
[8] Michael S. Pollard, Joan S. Tucker, and Harold D. Green, "Changes in Adult Alcohol Use and Consequences During the COVID-19 Pandemic in the US," *JAMA Network Open* 3, no. 9 (2020), https://doi.org/10.1001/jamanetworkopen.2020.22942.
[9] Brian P. Lee et al., "Underestimation of Liver Transplantation for Alcoholic Hepatitis in the National Transplant Database," *Liver Transplantation* 25, no. 5 (2019): pp. 706-711, https://doi.org/10.1002/lt.25448.
[10] Ibid.
[11] Michael R. Lucey, Philippe Mathurin, and Timothy R. Morgan, "Alcoholic Hepatitis," *New England Journal of Medicine* 360, no. 26 (2009): pp. 2758-2769, https://doi.org/10.1056/nejmra0805786.
[12] Brian P. Lee et al., "Outcomes of Early Liver Transplantation for Patients With Severe Alcoholic Hepatitis," *Gastroenterology* 155, no. 2 (2018), https://doi.org/10.1053/j.gastro.2018.04.009
[13] Tiffany Wu et al., "Controversies in Early Liver Transplantation for Severe Alcoholic Hepatitis," *Annals of Hepatology* 17, no. 5 (2018): pp. 759-768, https://doi.org/10.5604/01.3001.0012.3134.
[14] Brian P. Lee et al., "Outcomes of Early Liver Transplantation for Patients With Severe Alcoholic Hepatitis," *Gastroenterology* 155, no. 2 (2018), https://doi.org/10.1053/j.gastro.2018.04.009.
[15] Ibid.

severe alcoholic hepatitis who were transplanted early (without the six month abstinence period) had positive post-transplant outcomes, including 94% one-year survival and 84% three-year survival. In the same study, the probability of post-transplant alcohol use was 25% at one year post-transplant and 34% at three years post-transplant.[16] Sustained alcohol use after transplant was the strongest predictor of death.[17]

Nonetheless, controversy remains in the liver transplant community about the effectiveness of the six month abstinence rule and the feasibility of listing patients for early transplantation with severe alcoholic hepatitis for liver transplantation. This ongoing discussion is hindered by the lack of available data on candidates with ALD, which is partly caused by outdated and unclear diagnoses on the TCR and TRR.

Purpose

Ongoing Review of NLRB Diagnoses

The purpose for updating HCC guidance and policy, as well as encephalopathy guidance, is to continue to improve the NLRB by creating a more efficient and equitable system for reviewing MELD and PELD exception requests. These changes ensure that guidance and policy language remain clear and aligned with current research so that the appropriate candidates receive MELD or PELD exceptions.

Updating Alcohol-Associated Diagnoses on TCR/TRR

The purpose for updating the alcohol-associated diagnoses on the TCR and TRR is to allow for more accurate data collection and analysis in the future. By updating the diagnoses on the TCR and TRR, more candidates will be categorized with the correct diagnosis, leading to a more complete and reliable OPTN database.

Overview of Proposal

Ongoing Review of NLRB Diagnoses

This proposal includes changes to the guidance for candidates with HCC, the guidance for candidates with hepatic encephalopathy, and a clarification to HCC policy.

HCC Guidance

There are two updates to HCC guidance included in this proposal:

- Adding guidance for candidates treated with immunotherapy
- Clarifying the guidance for candidates with a prior history of resection

The current HCC guidance document does not provide any recommendation for how the NLRB should consider HCC candidates treated with immunotherapy, despite immunotherapy being an approved

[16] Ibid.
[17] Ibid.

treatment for HCC.[18] However, the use of immunotherapy in treating liver transplant candidates with HCC has historically been discouraged, due to reports of rejection and graft loss in candidates treated with immunotherapy prior to transplantation.[19]

Initial data on candidates treated with immunotherapy is sparse and the lack of available guidance on how to handle these candidates when a transplant program is requesting a MELD exception on their behalf has led to confusion among NLRB reviewers. The Committee was specifically concerned that the lack of available guidance would lead to these exception cases being inappropriately denied and inadvertently preclude a subset of candidates from accessing a MELD exception.[20]

A single-center study recently reported positive outcomes for nine liver transplant recipients with HCC who were treated with immunotherapy.[21] None of the nine recipients suffered severe graft rejection, tumor recurrence, or death at a median post-transplant follow-up of 16 months.[22] Despite only having this single-center data available, the Committee is proposing the addition of language to the HCC guidance document that will make it clear that the use of immunotherapy as a treatment method for a candidate with HCC should not preclude that candidate from being considered for a MELD exception.

The proposed language acknowledges that the available data is preliminary. The new guidance is intended to provide a pathway to an exception for candidates treated with immunotherapy. The Committee anticipates additional research to be available on this patient population in the future and expects to add a more robust recommendation once that research has been published.

In addition to adding guidance for candidates treated with immunotherapy, the proposal also includes a clarification for HCC candidates with a prior history of resection. One section of the current guidance document states that candidates with a history of HCC more than two years ago, that was completely treated and who then develop new or recurrent lesions, should be considered the same as candidates with no history of HCC. In effect, this guidance is intended to recommend that these candidates wait the standard six month period before receiving their full MELD exception (MMaT-3).

However, a subsequent section of the guidance states that candidates with cirrhosis who present with T2 resectable HCC who undergo complete resection and develop T1 or T2 recurrence can be considered for a MELD exception without a six month waiting period.

These two sections of guidance are contradictory for any candidate who presented with T2 resectable HCC more than two years ago who was completely resected and then recurs. In this case, it is unclear if the candidate would need wait six months for a full MELD exception, as the HCC presented more than two years ago but it was completely resected.

To address this discrepancy and to avoid further confusion, the proposal adds new language to the guidance document that makes it clear that candidates with a history of HCC more than two years ago

[18] Parissa Tabrizian, Sander S. Florman, and Myron E. Schwartz, "PD-1 Inhibitor as Bridge Therapy to Liver Transplantation?," *American Journal of Transplantation* 21, no. 5 (February 2021): pp. 1979-1980, https://doi.org/10.1111/ajt.16448.
[19] Ibid.
[20] See NLRB Subcommittee meeting summary, March 11, 2021. Available at https://optn.transplant.hrsa.gov/
[21] Parissa Tabrizian, Sander S. Florman, and Myron E. Schwartz, "PD-1 Inhibitor as Bridge Therapy to Liver Transplantation?," *American Journal of Transplantation* 21, no. 5 (February 2021): pp. 1979-1980, https://doi.org/10.1111/ajt.16448.
[22] Ibid.

that was resected and recurs do not need to wait six months to receive a full MELD exception score. This clarification retains the incentive for resection that currently exists.
The Committee is seeking feedback on the proposed changes to HCC guidance.

Hepatic Encephalopathy Guidance

During the development of this proposal, the NLRB Subcommittee reviewed a number of diagnoses to ensure they remained updated and aligned with current research.[23] While the Committee is not recommending changes for the majority of the diagnoses reviewed, the proposal does include a non-substantive revision to the guidance for candidates with hepatic encephalopathy. The proposed language includes updated references and states that while the presence of hepatic encephalopathy is associated with mortality independent of the MELD score, there is no reliable, objective assessment of its severity and therefore should not be an indication for a MELD exception.

The Committee is seeking feedback on the proposed change to encephalopathy guidance.

HCC Policy

HCC candidates meeting specific criteria in OPTN policy are eligible to have their MELD or PELD exception request automatically approved. One of the requirements for an HCC candidate to have a MELD or PELD exception request automatically approved is the completion of a chest CT prior to the initial exception request.

However, members of the Committee noted that during their tenure as NLRB reviewers, a significant number of HCC exception extension requests were denied because reviewers thought that a chest CT is required prior to each extension. To remedy this situation, the proposal includes clarifying policy language that makes it clear that a chest CT is only required prior to the initial exception. The intent of the new language is to decrease the number of extension requests denied because reviewers misunderstand the chest CT requirement.

The Committee is seeking feedback on the proposed clarification to HCC policy, as well as whether any transition procedures should be adopted when implementing this policy clarification.

Updating Alcohol-Associated Diagnoses on the TCR/TRR

The Committee is proposing a number of changes to the diagnoses on the TCR/TRR to allow for better data collection on candidates with ALD. The proposed changes are summarized in Table 1 below.

[23] The Committee also reviewed current guidance for hepatic hydrothorax, gastrointestinal bleeding, and ascites. No changes are being proposed to the guidance for these diagnoses.

Table 1: Updating Diagnoses on TCR/TRR

Current Diagnosis	New Diagnosis
Alcoholic Cirrhosis	Alcohol-associated cirrhosis without acute alcohol-associated hepatitis
Alcoholic Cirrhosis with Hepatitis C	N/A: diagnosis will be inactivated
Acute Alcoholic Hepatitis	Acute alcohol-associated hepatitis with or without cirrhosis

The first change to note is the transition away from the use of the term "alcoholic" to the more accepted term "alcohol-associated." This change was made in both of the new diagnoses. The proposed changes also include updating "alcoholic cirrhosis" to "alcohol-associated cirrhosis without acute alcohol-associated hepatitis" and changing "acute alcoholic hepatitis" to "acute alcohol-associated hepatitis with or without cirrhosis." In addition, the Committee is proposing the inactivation of "alcoholic cirrhosis with hepatitis C."

The intent of the new diagnoses is to make it easier for transplant programs to distinguish between those candidates with chronic alcohol-associated cirrhosis and those candidates with acute alcohol-associated hepatitis. This is an important distinction between two patient groups – the former with a chronic form of ALD and the latter with acute onset of alcohol-associated hepatitis and therefore unlikely to be able to wait through a six-month abstinence period. These updated diagnoses are clearer, more accurate, and will allow for better data collection on this specific subset of liver transplant candidates.

The proposed changes will occur on the TCR and TRR, which are OMB-approved forms. The new diagnoses, while intended to improve data collection, are not themselves new data fields and will not increase the data submission burden on transplant programs. The diagnosis data field already exists on both the TCR and TRR and this information is already collected and submitted by transplant programs. The actions included in this proposal simply involved updating the terminology for two diagnoses and inactivating one. These changes will be applied retrospectively to ensure historical consistency in the OPTN database.

The Committee is seeking public comment feedback on the proposed changes to the diagnoses for ALD.

NOTA and Final Rule Analysis

The OPTN issues the *Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review* and *Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exceptions for Hepatocellular Carcinoma (HCC)* for the operation of the OPTN.[24] This guidance will support the operation of the NLRB by assisting the reviewers with evaluating exception requests. The OPTN Final Rule requires the Board to establish performance goals for allocation policies, including "reducing inter-transplant program variance" in performance indicators.[25] The changes to these guidance documents will assist in reducing inter-transplant program variance in

[24] 2019 OPTN Contract Task 3.2.4: Development, revision, maintenance, of OPTN Bylaws, policies, standards and guidelines for the operation of the OPTN.
[25] 42 C.F.R. §121.8(b)(4)

the types of cases reviewed and approved by the NLRB by facilitating more consistent review of exception cases.

The committee submits the proposed changes to policy under the authority of the OPTN Final Rule, which states "The OPTN Board of Directors shall be responsible for developing…policies for the equitable allocation for cadaveric organs."[26] The Final Rule requires that when developing policies for the equitable allocation of cadaveric organs, such policies must be developed "in accordance with §121.8," which requires that allocation policies "(1) Shall be based on sound medical judgment; (2) Shall seek to achieve the best use of donated organs; (3) Shall preserve the ability of a transplant program to decline an offer of an organ or not to use the organ for the potential recipient in accordance with §121.7(b)(4)(d) and (e); (4) Shall be specific for each organ type or combination of organ types to be transplanted into a transplant candidate; (5) Shall be designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement;…(8) Shall not be based on the candidate's place of residence or place of listing, except to the extent required by paragraphs (a)(1)-(5) of this section." This proposal:

- **Is based on sound medical judgment[27]** because it is an evidenced-based change relying on the collective clinical experience of the Committee and the NLRB reviewers.
- **Is designed to…promote patient access to transplantation[28] by** giving similarly situated candidates equitable opportunities to receive an organ offer, by making the requirements for extending the exception more clear and thus more consistently applied.
- **Is not based on the candidate's place of residence or place of listing[29]**

This proposal also preserves the ability of a transplant program to decline an offer or not use the organ for a potential recipient,[30] and it is specific to an organ type, in this case liver.[31]

Although the proposal outlined in this briefing paper addresses certain aspects of the Final Rule listed above, the Committee does not expect impacts on the following aspects of the Final Rule:

- **Seeks to achieve the best use of donated organs[32]**
- **Is designed to avoid wasting organs[33]**
- **Is designed to avoid futile transplants[34]**
- **Promotes the efficient management of organ placement[35]**

The Committee submits the proposed changes to diagnoses on the TCR and TRR for community feedback under the authority of the OPTN Final Rule, which states "An organ procurement organization or transplant hospital shall…submit to the OPTN…information regarding transplant candidates, transplant recipients, [and] donors of organs…"[36] and that the OPTN shall:

[26] 42 CFR §121.4(a).
[27] 42 CFR §121.8(a)(1).
[28] 42 CFR §121.8(a)(5).
[29] 42 CFR §121.8(a)(8).
[30] 42 CFR §121.8(a)(3).
[31] 42 CFR §121.8(a)(4).
[32] 42 CFR §121.8(a)(2).
[33] 42 CFR §121.8(a)(5).
[34] Id.
[35] Id.
[36] 42 CFR §121.11(b)(2).

(i) Maintain and operate an automated system for managing information about transplant candidates, transplant recipients, and organ donors, including a computerized list of individuals waiting for transplants;

(ii) Maintain records of all transplant candidates, all organ donors and all transplant recipients;

(iii) Operate, maintain, receive, publish, and transmit such records and information electronically, to the extent feasible, except when hard copy is requested; and

(iv) In making information available, provide manuals, forms, flow charts, operating instructions, or other explanatory materials as necessary to understand, interpret, and use the information accurately and efficiently.[37]

This proposal will allow the OPTN to collect more complete data on liver transplant candidates and recipients and maintain such data in the OPTN dataset.

Implementation Considerations

Member and OPTN Operations

The proposed changes to alcohol-associated diagnoses will need to be implemented in UNet[SM].

Relevant guidance documents and policy language will need to be updated. No changes in UNet[SM] are required for the updated guidance and policy clarification. All changes will be communicated to the community prior to implementation. Transplant programs and NLRB reviewers will need to be aware of the changes.

Operations affecting Histocompatibility Laboratories

This proposal will have no operational impact on histocompatibility laboratories.

Operations affecting Organ Procurement Organizations

This proposal will have no operational impact on organ procurement organizations.

Operations affecting Transplant Hospitals

Transplant programs will need to be familiar with the proposed changes to NLRB policy and guidance when submitting exception requests for candidates.

Transplant programs will also need to be aware of the updated diagnoses to ensure accurate data entry.

[37] 42 CFR §121.11(a)(1)(i)-(iv).

Operations affecting the OPTN

The proposed changes to diagnoses on the TCR and TRR will need to be implemented in UNet[SM]. Relevant guidance documents and policy language will need to be updated. The OPTN will communicate any changes prior to becoming effective and will provide educational resources as appropriate.

Potential Impact on Select Patient Populations

This proposal will impact the HCC patient population. With the proposed changes to HCC guidance, it is more likely that HCC candidates who were treated with immunotherapy will be approved for a MELD exception. In addition, the updated HCC guidance will allow candidates with a history of HCC who were resected more than two years ago to be approved for a MELD exception without waiting six months. The proposed changes to encephalopathy guidance will not impact any specific patient population. The HCC policy clarification is intended to reduce the number of HCC exception extension cases inappropriately denied by the NLRB. No populations were identified as likely to be treated less favorably under the new policy and therefore no transition procedures are recommended.[38]

The updated alcohol-associated diagnoses will not impact a select patient population.

Projected Fiscal Impact

Projected Impact on Histocompatibility Laboratories

There is no expected fiscal impact for histocompatibility laboratories.

Projected Impact on Organ Procurement Organizations

There is no expected fiscal impact for organ procurement organizations.

Projected Impact on Transplant Hospitals

There is no expected fiscal impact for transplant hospitals.

Projected Impact on the OPTN

This proposal will require a very small IT implementation effort, estimated to be 36 hours, to update the diagnoses on the TCR and TRR. A small amount of additional effort (estimated 30 hours) will be required to update the guidance documents and policy language, as well as communicate the proposed changes to the transplant community. A very small amount of ongoing effort (estimated 25 hours) will be needed to monitor the changes after implementation.

[38] 42 C.F.R. § 121.8(d).

Post-implementation Monitoring

Member Compliance

The Final Rule requires that allocation policies "include appropriate procedures to promote and review compliance including, to the extent appropriate, prospective and retrospective reviews of each transplant program's application of the policies to patients listed or proposed to be listed at the program."[39]

The proposed language will not change the current routine monitoring of OPTN members. Site surveyors will continue to review a sample of medical records, and any material incorporated into the medical record by reference, to verify that data reported through UNet[SM] for standardized MELD or PELD exception or exception extension qualifying criteria are consistent with source documentation in the candidate's medical record.

Policy Evaluation

The Final Rule requires that allocation policies "be reviewed periodically and revised as appropriate."[40] Changes made to the policy and guidance will be monitored as requested by the NLRB Subcommittee as part of the ongoing NLRB review.

Conclusion

This proposal includes changes to HCC guidance and policy, as well as guidance for candidates with hepatic encephalopathy. The updates to HCC guidance include adding language for candidates treated with immunotherapy and clarifying guidance for candidates with a history of resected HCC more than two years ago. These changes will ensure that candidates are appropriately considered for an HCC exception. The proposal also includes an update to guidance for hepatic encephalopathy to ensure the language remains aligned with current research. The proposal also clarifies that a chest CT is only required at the time of the initial HCC exception request.

Separately, the proposal includes updating alcohol-associated diagnoses on the TCR and TRR. The updated diagnoses will allow for more complete and accurate data entry, leading to better data analysis in the future.

[39] 42 CFR §121.8(a)(7).
[40] 42 CFR §121.8(a)(6).

Policy and Guidance Language

Proposed new language is underlined (example) and language that is proposed for removal is struck through (~~example~~). Heading numbers, table and figure captions, and cross-references affected by the numbering of these policies will be updated as necessary.

9.5.I Requirements for Hepatocellular Carcinoma (HCC) MELD or PELD Score Exceptions

Upon submission of the first exception request, a candidate with hepatocellular carcinoma (HCC) will receive a score according to Policy *9.5.I.vii: Extensions of HCC Exceptions* if the candidate meets the criteria according to *Policies 9.5.I.i through 9.5.I.vi.*

9.5.I.i Initial Assessment and Requirements for HCC Exception Requests

Prior to applying for a standardized MELD or PELD exception, the candidate must undergo a thorough assessment that includes *all* of the following:

1. An evaluation of the number and size of lesions before local-regional therapy that meet Class 5 criteria using a dynamic contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI)
2. A CT of the chest to rule out metastatic disease. This is only required prior to applying for an initial exception. A CT of the chest is not required for exception extensions.
3. A CT or MRI to rule out any other sites of extrahepatic spread or macrovascular involvement
4. An indication that the candidate is not eligible for resection
5. An indication whether the candidate has undergone local-regional therapy
6. The candidate's alpha-fetoprotein (AFP) level

The transplant hospital must maintain documentation of the radiologic images and assessments of all OPTN Class 5 lesions in the candidate's medical record. If growth criteria are used to classify a lesion as HCC, the radiology report must contain the prior and current dates of imaging, type of imaging, and measurements of the lesion.

For those candidates who receive a liver transplant while receiving additional priority under the HCC exception criteria, the transplant hospital must submit the *Post-Transplant Explant Pathology Form* to the OPTN within 60 days of transplant. If the *Post-Transplant Explant Pathology Form* does not show evidence of HCC or liver-directed therapy for HCC, the transplant program must also submit documentation or imaging studies confirming HCC at the time of assignment.

The Liver and Intestinal Organ Transplantation Committee will review the submitted documentation or imaging studies when more than 10 percent of the *Post-Transplant Explant Pathology Forms* submitted by a transplant program in a one-year period do not show evidence of HCC or liver-directed therapy for HCC.

9.5.I.vii Extensions of HCC Exceptions

A candidate with an approved exception for HCC is eligible for automatic approval of an extension if the transplant program enters a MELD or PELD Exception Score Extension Request that contains the following:

1. Documentation of the tumor using a CT or MRI
2. The type of treatment if the number of tumors decreased since the last request
3. The candidate's alpha-fetoprotein (AFP) level

A CT of the chest to rule out metastatic disease is not required after the initial exception request.

The candidate's exception extension will then be automatically approved unless *any* of the following occurs:

- The candidate's lesions progress beyond T2 criteria, according to *9.5.I.ii: Eligible Candidates Definition of T2 Lesions*
- The candidate's alpha-fetoprotein (AFP) level was less than or equal to 1,000 ng/mL on the initial request but subsequently rises above 1,000 ng/mL
- The candidate's AFP level was greater than 1,000 ng/mL, the AFP level falls below 500 ng/mL after treatment but before the initial request, then the AFP level subsequently rises to greater than or equal to 500 ng/mL
- The candidate's tumors have been resected since the previous request
- The program requests a score different from the scores assigned in Table 9-10.

When a transplant program submits either an initial exception request or the first extension request for a liver candidate at least 18 years old at the time of registration that meets the requirements for a standardized MELD score exception, the candidate appear on the match run according to the calculated MELD score.

A candidate who meets these requirements for a MELD or PELD score exception for HCC will receive a score according to *Table 9-10* below.

Table 9-10: HCC Exception Scores

Age	Age at registration	Exception Request	Score
At least 18 years old	At least 18 years old	Initial and first extension	Calculated MELD
At least 18 years old	At least 18 years old	Any extension after the first extension	3 points below MMaT
At least 12 years old	Less than 18 years old	Any	40
Less than 12 years old	Less than 12 years old	Any	40

Guidance to Liver Transplant Programs and the National Liver Review Board for:

Adult MELD Exceptions for Hepatocellular Carcinoma (HCC)

Background

A liver candidate receives a MELD[41] or, if less than 12 years old, a PELD[42] score that is used for liver allocation. The score is intended to reflect the candidate's disease severity, or the risk of 3-month mortality without access to liver transplant. When the calculated score does not reflect the candidate's medical urgency, a liver transplant program may request an exception score. A candidate that meets the criteria for one of nine diagnoses in policy is approved for a standardized MELD exception.[43] If the candidate does not meet criteria for standardized exception, the request is considered by the Review Board.

The OPTN Liver and Intestinal Organ Transplantation Committee (hereafter, "the Committee") has developed guidance for adult MELD exceptions for Hepatocellular Carcinoma (HCC). This guidance document is intended to provide recommendations for the review board considering HCC cases which are outside standard policy.

This guidance replaces any independent criteria that OPTN regions used to request and approve exceptions, commonly referred to as "regional agreements." Review board members and transplant centers should consult this resource when considering MELD exception requests for adult candidates with the following diagnoses.

Recommendation

- Patients with the following are contraindications for HCC exception score:
    - Macro-vascular invasion of main portal vein or hepatic vein
    - Extra-hepatic metastatic disease
    - Ruptured HCC
    - T1 stage HCC

While in most cases, ruptured HCC and primary portal vein branch invasion of HCC would be contraindications, some patients who remain stable for a prolonged (minimum of 12 months) interval after treatment for primary portal vein branch invasion or after ruptured HCC may be suitable for consideration.

[41]Model for End-Stage Liver Disease
[42]Pediatric End-Stage Liver Disease
[43]Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

Evidence for the use of immunotherapy as a down-staging or bridging therapy is preliminary. However, based on the published data in transplant and non-transplant setting, the use of immunotherapy does not preclude consideration for an HCC exception.[44]

- Patients who have a history of prior unresectable HCC more than 2 years ago which was completely treated with no evidence of recurrence, who develop new or recurrent lesions after 2 years should generally be considered the same as those with no prior HCC, in order to determine the current stage suitability for an initial MELD exception, and initial MELD exception score assignment.

- Patients beyond standard criteria who have continued progression while waiting despite LRT are generally not acceptable candidates for HCC MELD exception.

- Patients with AFP>1000 who do not respond to treatment to achieve an AFP below 500 are not eligible for standard MELD exception, and must be reviewed by the HCC review board to be considered. In general, these patients are not suitable for HCC MELD exception but may be appropriate in some cases.

- Patients with HCC beyond standard down-staging criteria who are able to be successfully downstaged to T2 may be appropriate for MELD exception, as long as there is no evidence of metastasis outside the liver, or macrovascular invasion, or AFP >1,000. Imaging should be performed at least 4 weeks after last down-staging treatment. Patients must still wait for 6 months from the time of the first request to be eligible for an HCC exception score.

- Patients with cirrhosis who presented with stage T2 resectable HCC (one lesion >2 cm and <5 cm in size, or two or three lesions >1 cm and <3 cm in size, based on resection specimen pathology) who underwent complete resection but developed T1 (biopsy proven), or T2 HCC (LI-RADS 5) following complete resection should be considered for MELD score exception, without a six month delay period. This includes candidates who initially presented with T2 resectable HCC and who underwent complete resection more than 2 years ago.

Patients with cirrhosis and HCC beyond T2 but within generally accepted criteria for down-staging (such as up to 5 lesions, total tumor volume <8 cm based on resection pathology) who underwent complete resection with negative margins and developed T1 (biopsy proven) or T2 recurrence (LI-RADS 5) may also be considered for MELD score exception for HCC. Because the larger tumor size, the 6 month delay is appropriate to ensure favorable tumor biology.

[44] Parissa Tabrizian, Sander S. Florman, and Myron E. Schwartz, "PD-1 Inhibitor as Bridge Therapy to Liver Transplantation?," *American Journal of Transplantation* 21, no. 5 (February 2021): pp. 1979-1980, https://doi.org/10.1111/ajt.16448.

Recommendations for Dynamic Contrast-enhanced CT or MRI of the Liver

Table 1: Recommendations for Dynamic Contrast-enhanced CT of the Liver

Feature:	CT scans should meet the below specifications:
Scanner type	Multidetector row scanner
Detector type	Minimum of 8 detector rows and must be able to image the entire liver during brief late arterial phase time window
Slice thickness	Minimum of 5 mm reconstructed slice thickness; thinner slices are preferable especially if multiplanar reconstructions are performed
Injector	Power injector, preferably dual chamber injector with saline flush and bolus tracking recommended
Contrast injection rate	3 mL/sec minimum, better 4-6 mL/sec with minimum of 300 mg I/mL or higher, for dose of 1.5 mL/kg body weight
Mandatory dynamic phases on contrast-enhanced MDCT	1. Late arterial phase: artery fully enhanced, beginning contrast enhancement of portal vein 2. Portal venous phase: portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins 3. Delayed phase: variable appearance, greater than 120 seconds after initial injection of contrast
Dynamic phases (Timing)	Use the bolus tracking or timing bolus

Table 2: Recommendations for Dynamic Contrast-enhanced MRI of the Liver

Feature	MRIs should meet the below specifications:
Scanner type	1.5T Tesla or greater main magnetic field strength. Low field magnets are not suitable.
Coil type	Phased array multichannel torso coil, unless patient-related factors precludes its use.
Minimum sequences	Pre-contrast and dynamic post gadolinium T1-weighted gradient echo sequence (3D preferable), T2 (with and without fat saturation), T1-weighted in and out of phase imaging.
Injector	Dual chamber power injector with bolus tracking recommended.
Contrast injection rate	2-3 mL/sec of extracellular gadolinium chelate that does not have dominant biliary excretion, preferably resulting in vendor-recommended total dose.

Feature	MRIs should meet the below specifications:
Mandatory dynamic phases on contrast-enhanced MRI	1. Pre-contrast T1W: do not change scan parameters for post contrast imaging. 2. Late arterial phase: artery fully enhanced, beginning contrast enhancement of portal vein. 3. Portal venous phase: portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins. 4. Delayed phase: variable appearance, greater than 120 seconds after initial injection of contrast.
Dynamic phases (Timing)	The use of the bolus tracking method for timing contrast arrival for late arterial phase imaging is preferable. Portal vein phase images should be acquired 35 to 55 seconds after initiation of late arterial phase. Delayed phase images should be acquired 120 to 180 seconds after the initial contrast injection.
Slice thickness	5 mm or less for dynamic series, 8 mm or less for other imaging.
Breath-holding	Maximum length of series requiring breath-holding should be about 20-seconds with a minimum matrix of 128 x 256. Technologists must understand the importance of patient instruction about breath-holding before and during scan.

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Guidance to Liver Transplant Programs and the National Liver Review Board for:

Adult MELD Exception Review

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a complication of chronic liver disease ~~associated with significant morbidity. There is an absence of evidence of sufficient quality to support MELD exception for complications of HE.[45,46,47,48]~~ with an associated mortality independent of MELD scoring. Presently, no additional MELD priority for HE is recommended in the absence of a widely available, reliable, objective assessment of its severity. [49, 50,51,52]

~~[45]Cordoba J., M. Ventura-Cots, M. Simón-Talero, et al. "Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF)." Hepatology 60 (2014): 275-81.~~

~~[46]García-Martínez, R., M. Simón-Talero, J. Córdoba. "Prognostic assessment in patients with hepatic encephalopathy." Dis Markers 31 (2011): 171-9.~~

~~[47]D'Amico, G., G. Garcia-Tsao, L. Pagliaro. "Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies." Hepatology 44 (2006): 217-31.~~

~~[48]Brandman, D., S.W. Biggins, B. Hameed, et al. "Pretransplant severe hepatic encephalopathy, peritransplant sodium and post-liver transplantation morbidity and mortality." Liver Int 32 (2012): 158-64.~~

[49] Kerbert, Annarein J., Enric Reverter, Lara Verbruggen, Madelon Tieleman, Miguel Navasa, Bart J. Mertens, Sergio Rodríguez-Tajes, et al. "Impact of Hepatic Encephalopathy on Liver Transplant Waiting List Mortality in Regions with Different Transplantation Rates." *Clinical Transplantation* 32, no. 11 (2018). https://doi.org/10.1111/ctr.13412.

[50] Chiranjeevi Gadiparthi et al., "Waitlist Outcomes in Liver Transplant Candidates with High MELD and Severe Hepatic Encephalopathy," *Digestive Diseases and Sciences* 63, no. 6 (February 2018): pp. 1647-1653, https://doi.org/10.1007/s10620-018-5032-5.

[51] Cristina Lucidi et al., "Hepatic Encephalopathy Expands the Predictivity of Model for End-Stage Liver Disease in Liver Transplant Setting: Evidence by Means of 2 Independent Cohorts," *Liver Transplantation* 22, no. 10 (2016): pp. 1333-1342, https://doi.org/10.1002/lt.24517.

[52] Robert J. Wong, Robert G. Gish, and Aijaz Ahmed, "Hepatic Encephalopathy Is Associated with Significantly Increased Mortality among Patients Awaiting Liver Transplantation," *Liver Transplantation*, 2014, https://doi.org/10.1002/lt.23981.