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Public Comment Proposal

Review Board Guidance for Hypertrophic and Restrictive Cardiomyopathy Exception Requests

OPTN/UNOS Thoracic Organ Transplantation Committee

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Contents

Executive Summary 1
What problem will this resource address? 2
Why should you support this resource? 3
How was this resource developed? 3
How well does this resource address the problem statement? 6
Which populations are impacted by this resource? 7
How does this resource impact the OPTN Strategic Plan? 7
How will the OPTN implement this resource? 8
How will members implement this resource? 8
Transplant Hospitals 8
Will this resource require members to submit additional data? 8
How will members be evaluated for compliance with this resource? 8
How will the sponsoring Committee evaluate whether this resource was successful post implementation? 8
Guidance Document 9

Review Board Guidance for Hypertrophic and Restrictive Cardiomyopathy Exception Requests

Affected Policies: *N/A*
Sponsoring Committee: *Thoracic Organ Transplantation*
Public Comment Period: *January 22, 2018 – March 23, 2018*

Executive Summary

The OPTN/UNOS Board of Directors recently approved the Thoracic Organ Transplantation Committee's (Committee) proposal to Modify the Adult Heart Allocation System during its December 2016 meeting.[1] During the development of the proposal, the Committee received feedback from the heart transplant community voicing concerns that hypertrophic cardiomyopathy (HCM) and restrictive cardiomyopathy (RCM) candidates may be disadvantaged by the proposed policy.[2] The Committee considered the following issues in HCM and RCM candidates:

- HCM/RCM physiology may not benefit from mechanical circulatory support devices (MCSDs), and the higher statuses are device driven
- A lack of uniform expertise in HCM/RCM physiology results in variability in Regional Review Board (RRB) decisions across the country
- Objectively quantifying the severity of illness is challenging

The Committee acknowledged that some HCM/RCM candidates may have higher mortality and may not be candidates for mechanical support options, but ultimately did not change proposed policy due to lack of objective data to support these assumptions. Instead, the exception and review process will accommodate these candidates, who can apply to the review board for an exception in any status as their medical urgency and potential for benefit would warrant. The Committee recognized that HCM/RCM expertise may be inconsistent across the review boards, thus potentially making evaluation and award of HCM/RCM exception requests vulnerable to variability. To help mitigate these potential inconsistencies, the Committee created guidance for the review boards with the goal of outlining objective criteria to standardize the evaluation and decision-making of HCM/RCM exception requests. Improved data collection required by the new policy should result in better assessment of whether specific subpopulations of HCM/RCM are disadvantaged by the status 4 assignment and may result in future policy changes to address any disadvantages.

This proposal aligns with the OPTN strategic goal of improving equity in access to transplant by providing objective criteria to review boards, potentially making evaluation and award of exception requests for HCM/RCM candidates more consistent, especially for those boards that lack an HCM/RCM expert. In addition, developing standardized exception criteria creates an intelligible pathway for more medically urgent HCM/RCM candidates to obtain access to higher urgency statuses, under which they may be transplanted more quickly, thereby potentially reducing waitlist mortality for those candidates.

[1] OPTN/UNOS Policy Notice. *Proposal to Modify the Adult Heart Allocation System*. Accessed June 27, 2017. https://optn.transplant.hrsa.gov/media/2028/thoracic_policynotice_201612.pdf .
[2] OPTN/UNOS Board Briefing. *Proposal to Modify the Adult Heart Allocation System*. Accessed June 27, 2017. https://optn.transplant.hrsa.gov/media/2006/thoracic_brief_201612.pdf.

What problem will this resource address?

The OPTN/UNOS Board of Directors recently approved the Thoracic Organ Transplantation Committee's (Committee) proposal to Modify the Adult Heart Allocation System during its December 2016 meeting.[3] During the development of the proposal, the Committee received feedback from the heart transplant community voicing concerns that hypertrophic cardiomyopathy (HCM) and restrictive cardiomyopathy (RCM) candidates may be disadvantaged by the proposed policy.[4] The Committee considered the following issues in HCM and RCM candidates:

- HCM/RCM physiology may not benefit from mechanical circulatory support devices (MCSDs), and the higher statuses are device driven
- A lack of uniform expertise in HCM/RCM physiology results in variability in RRB decisions across the country
- Objectively quantifying the severity of illness is challenging

Higher statuses are device driven
For both anatomic and physiologic reasons, these candidates are less frequently helped by mechanical support, and are at higher risk when mechanical support is used than dilated cardiomyopathy candidates.[5,6,7,8,9]

Variability in review board decision-making for HCM/RCM exception requests
The evaluation and award of exception requests for HCM/RCM candidates may vary from region to region because there is variable, limited, and inconsistent HCM/RCM expertise on review boards; this inexpertise may also lead to delay in patients being referred to transplant.[10,11,12,13]

Quantifying the severity of illness is challenging
Because of limited data and challenges in reproducibly quantifying the severity of disease in a highly heterogeneous population, a variety of HCM/RCM candidates (likely with different mortality risks) have been grouped together within the new policy.

The Committee acknowledged that some HCM/RCM candidates may have higher waitlist mortality and may not be candidates for mechanical support options, but ultimately did not change proposed policy due to lack of objective data to support these assumptions. Instead, the exception and review process will accommodate these candidates, who can apply to the review board for an exception in any status as their medical urgency and potential for benefit would warrant. The Committee recognized that HCM/RCM

[3] OPTN/UNOS Policy Notice. *Proposal to Modify the Adult Heart Allocation System.* https://optn.transplant.hrsa.gov/media/2028/thoracic_policynotice_201612.pdf
[4] OPTN/UNOS Board Briefing. *Proposal to Modify the Adult Heart Allocation System*. https://optn.transplant.hrsa.gov/media/2006/thoracic_brief_201612.pdf .
[5] Patel SR, Saeed O, Naftel D, Myers S, Kirklin J, Jorde UP, Goldstein DJ. Outcomes of restrictive and hypertrophic cardiomyopathies after LVAD: An INTERMACS analysis. *Journal of Cardiac Failure*, Volume 23, Issue 12, 2017, Pages 859-867.
[6] Topilsky Y, Pereira NL, Shah DK et al. Left ventricular assist device therapy in patients with restrictive and hypertrophic cardiomyopathy. *Circ Heart Fail* 2011;4(3):266-275.
[7] Muthiah K, Phan J, Robson D et al. Centrifugal continuous-flow left ventricular assist therapy for patients with hypertrophic cardiomyopathy: a case series. *American Society for Artificial Internal Organs.* 2013;59:183-187.
[8] Sivathasan C,, Tan TEE, Sim D, and Kerk KL. "Burnt out" dilated hypertrophic cardiomyopathy causing acute LVAD thrombosis. *Clinical Case Reports* 3, No. 6 (2015): 376-78.
[9] Grupper A, Park SJ, Pereira NL, Schettle SD, Gerber Y, Topilsky Y, Edwards BS, Daly RC, Stulak JM, Joyce LD, and Kushwaha SS. Role of ventricular assist therapy for patients with heart failure and restrictive physiology: Improving outcomes for a lethal disease. *Journal of Heart and Lung Transplantation* 34, no. 8 (2015): 1042-049.
[10] Rowin EJ, Maron BJ, Kiernan MS, Casey SA, Feldman DS, Hryniewicz KM, Chan RH, Harris KM, Udelson JE, Denofrio DC, Roberts WS, and Martin MS. Advanced heart failure with preserved systolic function in nonobstructive hypertrophic cardiomyopathy: Under-recognized subset of candidates for heart transplant. *Circulation: Heart Failure* 7, no. 6 (2014): 967-75.
[11] Pasqualucci D, Fornaro A, Castelli G, Rossi A, Arretini A, Chiriatti C, Targetti M, Girolami F, Corda M, Orrù P, Matta G, Stefàno P, Cecchi F, Porcu M, and Olivotto I. Clinical spectrum, therapeutic options, and outcome of advanced heart failure in hypertrophic cardiomyopathy. *Circulation: Heart Failure* 8, no. 6 (2015): 1014-021
[12] Gilstrap LG, Niehaus E, Malhotra R, Ton VK, Watts J, Seldin DC, Madsen JC, and Semigran MJ. Predictors of survival to orthotopic heart transplant in patients with light chain amyloidosis. *Journal of Heart and Lung Transplantation* 33, no. 2 (2014): 149-56.
[13] OPTN/UNOS Public Comment. *Proposal to Modify the Adult Heart Allocation System*. https://optn.transplant.hrsa.gov/governance/public-comment/modify-adult-heart-allocation-2016-2nd-round/

expertise may be inconsistent across the review boards, thus potentially making evaluation and award of HCM/RCM exception requests vulnerable to variability. To help mitigate these inconsistencies, the Committee created guidance for the review boards with the goal of outlining objective criteria to standardize the evaluation and decision-making of HCM/RCM exception requests.

Why should you support this resource?

To help mitigate the problems associated with accommodating HCM/RCM candidates through exceptions, the Committee drafted guidance for the review boards with the goal of outlining objective criteria to standardize the evaluation and decision-making of HCM/RCM exception requests. Evidence-based assessment of waitlist mortality drove the assignment of particular criteria into statuses in the new allocation policy. While the Committee acknowledges the community's consternation with HCM/RCM candidates' assignment to status 4, the historical waitlist mortality of these candidates was consistent with other populations within status 4.[14] Improved data collection required by the new policy should result in better assessment of whether specific subpopulations of HCM/RCM are disadvantaged by the status 4 assignment and may result in future policy changes to address any disadvantages. As an interim measure, the Committee determined guidance to the review boards was an appropriate step to address the heart transplant community's concerns while additional data collection is ongoing and the impact of the new policy is assessed.

This guidance provides objective criteria to define a pathway to the higher urgency statuses for candidates with HCM or RCM. The transplant community explicitly requested such criteria during public comment. Per the community's concerns, this guidance provides:

- Guidelines regarding which statuses would be appropriate for specific conditions
- Rationale and context that justify the recommendations, potentially helping review boards without an HCM/RCM expert
- Specific objective criteria the review boards can use in evaluating exception requests, potentially increasing standardization of decision-making

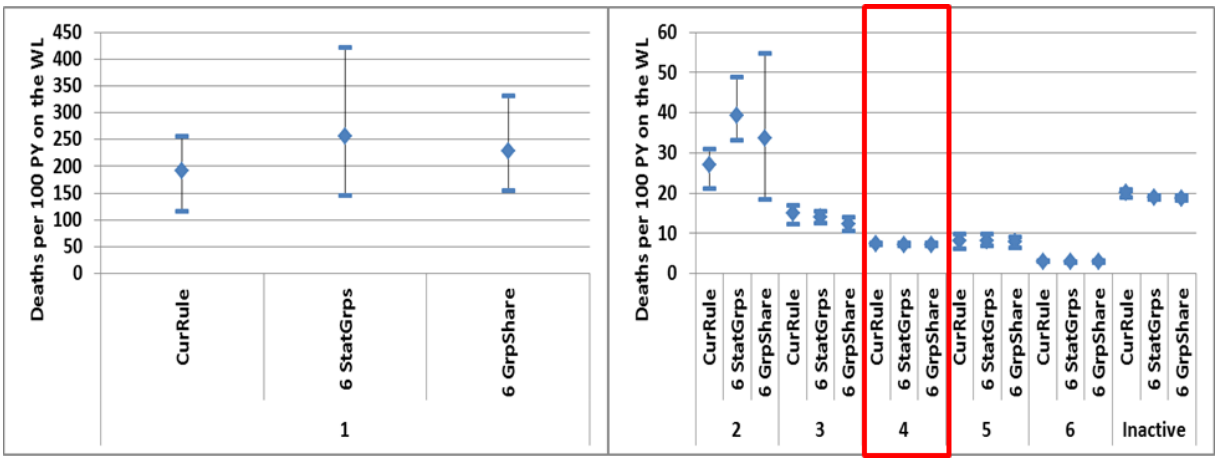
If utilized, the review boards should be able to recognize more medically urgent HCM/RCM candidates requesting exceptions and can grant access to the higher urgency statuses. Therefore, they may be transplanted more quickly.

How was this resource developed?

During public comment for the proposal to Modify the Adult Heart Allocation System, the Committee received feedback that HCM/RCM candidates face unique challenges and warrant a higher status due to limited mechanical and inotropic therapies. The Committee took these concerns seriously. Ultimately, after considering whether to alter policy, the Committee re-committed to the adult heart allocation system policy changes' primary goal of reducing waiting list mortality rates. Candidate status assignments were based on waitlist mortality rates, and the mortality rates of HCM/RCM patients were consistent with other candidates within status 4 (Figure 1). Based on this evidence and the thoracic simulated allocation model (TSAM) (Figure 1), status 4 was the most appropriate listing status for these patients.

[14] Scientific Registry of Transplant Recipients. "*HR2015_01: Data Request from the Heart Subcommittee of the OPTN Thoracic Organ Transplantation Committee". Inferential Data Analyses. Prepared for the Heart Subcommittee, 2015.*

Figure 1: Waitlist mortality rates by simulation and new status groups, adult candidates



A thorough evaluation of exception requests did not demonstrate sufficient data to enable further stratification of HCM/RCM diagnoses. It is important to note that status 4 is not limited to HCM/RCM candidates.

The Committee agreed to consider drafting guidance for review boards to standardize the evaluation of HCM/RCM exception requests and define objective clinical criteria that would provide a pathway for these candidates to access higher urgency statuses.

The Heart Subcommittee (Subcommittee) discussed the advantages and disadvantages of developing guidance in advance of the implementation of the heart allocation policy changes. During public comment, several commenters requested guidance specifically, or questioned how exceptions for HCM/RCM candidates would be handled. The Committee understood that the review boards have requested more "guidance" in the past to standardize decision-making, especially because of the often limited HCM/RCM expertise on the review boards. The exception process continues to be an important way for HCM/RCM candidates to access the higher urgency statuses (which will not be unique to this patient population). As with all guidance, these recommendations are voluntary and do not carry the weight of policy, and therefore may not change behavior as much as a policy change. Finally, this would be an opportunity to engage some of the individuals and organizations, including the American College of Cardiology (ACC) and the Hypertrophic Cardiomyopathy Association (HCMA), vocal advocates for HCM/RCM candidates during both rounds of public comment of the Proposal to Modify the Adult Heart Allocation System.[15]

As there were few specialists on the Subcommittee with extensive experience treating HCM/RCM and amyloidosis patient populations, several external cardiologists from HCMA-recognized Centers of Excellence, as well as amyloidosis specialists, were invited to join a project workgroup to bolster expertise and provide an external perspective.[16] Patient advocates also participated. The group identified several professional societies and advocacy groups to engage during public comment, including the International Society for Heart and Lung Transplantation (ISHLT), the HCMA, the Heart Failure Society of America, and the Amyloidosis Foundation. In addition, the Committee sought additional perspective and support from the OPTN/UNOS Patient Affairs Committee. The workgroup performed literature searches to find evidence in peer-reviewed journals to support its recommendations. It also met via teleconference with the Subcommittee on multiple occasions to reach clinical consensus on questions that may not be explicitly answered by data or literature alone. Finally, in the absence of conclusive evidence in literature or in data, the workgroup reached clinical consensus based on expertise to determine its final recommendations.

The workgroup's discussions included:

[15] OPTN/UNOS Board Briefing. Proposal to Modify the Adult Heart Allocation System.
[16] Hypertrophic Cardiomyopathy Association. *Recognized Centers of Excellence*. Accessed November 15, 2017. http://www.4hcm.org/coe

- Scope of the guidance
- Guiding philosophy for developing criteria
- Criteria for HCM/RCM exceptions

The workgroup's discussions on each of these topics are summarized below.

Scope of the Guidance

The workgroup discussed limiting the guidance to just HCM candidates or expanding to include RCM candidates, or to also include amyloidosis candidates with HCM and RCM candidates. There was some discussion about including re-transplant, but as that is a different criterion under status 4, the workgroup elected to not include guidance for that group in this document. One member felt that HCM, RCM, and amyloidosis patient populations were distinctly different, with different concerns that might each deserve dedicated guidance. Another member felt the HCM and RCM populations should be combined. The group determined the guidance should focus on candidates with HCM and RCM. The workgroup further debated how to "restrict" the use of restrictive cardiomyopathy. They debated using "primary," "congenital," or idiopathic," and agreed "idiopathic" was sufficient. There was some debate regarding including amyloidosis patients. Some subgroups are more similar to HCM and RCM patients, such as transthyretin (TTR) amyloidosis patients, and the workgroup therefore agreed to include guidance for such candidates.

Therefore, this guidance is not targeted towards patients with restrictive physiology, based on other primary disease (e.g. coronary artery disease or transplant coronary artery vasculopathy) or chronic rejection. The proposed guidance is limited to patients with:

- HCM with NYHA Class IV heart failure[17]
- Primary restrictive cardiomyopathy of idiopathic or genetic origin
- Infiltrative (e.g. cardiac amyloidosis [TTR or AL])
- Radiation RCM

Even amongst those groups, the candidates are very heterogeneous. The HCM advocate suggested stratifying the HCM patient population into the three subgroups of potential heart failure: systolic dysfunction, diastolic dysfunction, and low output. Stratifying the population this way might reveal criteria to help support elevating these subgroups to higher statuses. This member also suggested considering genetic testing results.

The workgroup continued to struggle with stratifying more medically urgent cohorts within this heterogeneous group, and determining the medical urgency equivalencies between HCM subgroups and the patients in the higher urgency statuses. For example, there are some end-stage HCM patients with dilated ventricles that could be supported with mechanical devices. The workgroup reiterated that the goal was to provide guidance for the HCM patient population that will allow the grant exceptions to higher risk patients that need to be elevated to the higher urgency statuses.

Guiding Philosophy for Developing Criteria

Workgroup members discussed principles to consider when developing guidance for this patient population. While there was agreement that, when possible, the exception criteria should provide candidates with the opportunity to register in a higher status as a preemptive measure to increase the chance of transplant, doing so would contradict the approach the Thoracic Committee took when developing the statuses: candidates are stratified by waitlist mortality. Current and approved pending policy permits transplant programs to request exceptions for status 1, 2, or 3 if the candidate is admitted to the hospital and there is medical evidence to illustrate that the candidate has an urgency and potential for benefit comparable to that of other candidates at the requested status. The workgroup felt that it is justifiable to provide these candidates with access to higher statuses not due to their relative waitlist mortality, but due to the ability to demonstrate a comparable potential for benefit as other candidates in statuses 1, 2, and 3.

[17] American Heart Association. *Classes of Heart Failure*. Accessed January 8, 2018. http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp#.Wk5TJVWnHIU

Patients with HCM/RCM might have potential benefit at least comparable to patients in the higher statuses. For many of the HCM/RCM candidates, they may be younger and with disease isolated only to the heart, thus benefit may be great.

Criteria for HCM/RCM Exceptions

The working group discussed clinical criteria necessary for HCM/RCM exceptions. Subject matter experts felt the following elements helped illustrate the severity of disease:

- Formal diagnosis of HCM; idiopathic, non-amyloid RCM; or amyloidosis
- Restrictive physiology
- Cardiac index
- Marker of advanced disease (e.g. pulmonary vascular resistance)
- Inotropes with a pulmonary capillary wedge pressure of a certain threshold
- VO_2
- Diastolic dimension
- Ejection fraction
- Indicators of end organ failure
- Hospital admission
- Quality of life/limited treatment or support options

The working group agreed that transplant programs should provide information regarding these categories to the review board when submitting exception requests for HCM/RCM candidates. Standardizing the information that is provided to the review boards will help the review boards make consistent decisions on these exception requests. Ultimately, the guidance is simple and not overly prescriptive, but provides the review boards and transplant programs with objective parameters to follow when submitting and considering exception requests for these candidates.

During public comment, a few commenters indicated there may be geographic disparities around this patient population and access to expertise. The HCMA felt very strongly that a transplant program in one region applying for an exception on behalf of a candidate might be treated very differently as compared to a transplant program in another region applying for an exception on behalf of a candidate. They wanted to make sure that the candidates would be treated the same, particularly when the review board members may have more or less expertise.

The group reconsidered continuous or daily intravenous diuretic therapy as an exception criterion. One work group member thought it was appropriate and wondered if the group wanted to add additional criteria. However, the consensus was to remove it along with mechanical ventilation and VO_2 max testing.

How well does this resource address the problem statement?

This proposal is informed primarily by clinical consensus, due to the lack of data to support elevating this diverse patient population to higher urgency statuses as well as the lack of data regarding specific clinical, hemodynamic, or laboratory data that might assist with identifying a higher risk population. The review boards operate based on medical judgment and clinical consensus; hence, guidance developed via clinical consensus for a body whose decisions are made by clinical consensus is reasonable. When relevant, OPTN descriptive analyses and TSAM results referenced in the modifications to the adult heart allocation system proposal were considered, as well as current peer-reviewed literature. In addition, the Subcommittee reviewed relevant feedback pertaining to this patient population from both public comment cycles.

Higher urgency statuses are device-driven

This resource suggests specific medical criteria that, if met, would suggest that a program's HCM/RCM candidate may have an urgency comparable to that of other candidates at the requested status despite not being supported by an MCSD.

Variability in review board decision-making for HCM/RCM exception requests

This resource provides rationale and context to justify the recommendations, potentially helping review boards without a HCM/RCM expert. It offers specific, objective criteria the review boards can use in evaluating exception requests, potentially increasing standardization of decision-making.

Challenging to objectively quantify severity of illness

This resource provides more granular recommendations for specific HCM/RCM conditions, therefore recognizing more medically urgent HCM/RCM diagnosis groups with limited therapeutic options.

While this guidance addresses some of the community's concerns, it does not carry the weight of policy.

Which populations are impacted by this resource?

As of October 31, 2017, there were 160 HCM or RCM candidates on the OPTN heart waiting list.[18] Table 2 shows the number of adult (defined as listed at age 18 or greater) registrations on the waiting list for a heart with a diagnosis of HCM/RCM recorded on the transplant candidate registration form (TCR), and whether or not the status 1A and 1B candidates were waiting with exceptions.

Table 2: Heart HCM/RCM Registrations by Status and Exception

Status	1a or 1b Exception	Number of Registrations
Status 1a	**No**	**13**
Status 1a	**Yes**	**3**
Status 1b	**No**	**59**
Status 2	**No**	**59**
Inactive	**No**	**26**
Total		**160**

The population being addressed by this guidance document is anticipated to remain small, especially as the Committee's recommendations limits the RCM candidate population to exclude any patient with restrictive physiology from another primary etiology (e.g. coronary artery disease) or those who require re-transplant.

How does this resource impact the OPTN Strategic Plan?

1. *Increase the number of transplants:* There is no impact to this goal.
2. *Improve equity in access to transplants*: This guidance provides objective criteria to review boards, potentially making evaluation and award of exception requests for HCM/RCM candidates more consistent, especially for those boards that lack expertise in the evaluation and management of these patients.
3. *Improve waitlisted patient, living donor, and transplant recipient outcomes:* Developing standardized exception criteria creates an intelligible pathway for more medically urgent HCM/RCM candidates to obtain access to higher urgency statuses, under which they may be transplanted more quickly, thereby potentially reducing waitlist mortality for those candidates.
4. *Promote living donor and transplant recipient safety:* There is no impact to this goal.

[18] United Network for Organ Sharing Research Department. *Heart Hypertrophic and Restrictive Cardiomyopathy Registrations by Status and Exception*. OPTN/UNOS Descriptive Data Analyses. Prepared for the Heart Subcommittee. October 31, 2017.

5. *Promote the efficient management of the OPTN:* This guidance will provide review boards with objective criteria for HCM/RCM candidates, which can help make review board decisions more consistent.

How will the OPTN implement this resource?

If the Board approves this proposal, the OPTN/UNOS will publish this guidance to the resources section of the OPTN website and other necessary pages when the policy changes to the adult heart allocation system are fully implemented. UNOS staff will work with the Committee to develop a training pertaining to the new heart allocation policy, specific to review board representatives and alternates. The content of this guidance will be included as part of that training. This proposal will not require programming in UNet^{sm}.

How will members implement this resource?

Transplant Hospitals

Heart programs should consider this guidance when submitting exception requests for their HCM/RCM candidates. However, these guidelines are for voluntary use by members and are not prescriptive of clinical practice. Review board members should consult this resource when assessing exception requests.

Will this resource require members to submit additional data?

No, this proposal does not require additional data collection.

How will members be evaluated for compliance with this resource?

Guidance from the OPTN does not carry the weight of policies or bylaws. Therefore, members will not be evaluated for compliance with the guidance in this document.

How will the sponsoring Committee evaluate whether this resource was successful post implementation?

HCM/RCM patients and any such exceptions will be monitored with other exception requests in concert with the post-implementation monitoring of the heart allocation proposal. In monitoring the new allocation policy, the Committee will monitor pre- and post-transplant outcomes as well as access to transplant for specific sub-populations of transplant candidates including HCM/RCM patients every six months for 2-3 years as the Committee sees fit.

Guidance Document

All the language in the guidance document below is proposed new language; underlines have been omitted for easier reading.

Review Board Guidance for Hypertrophic/Restrictive (HCM/RCM) Cardiomyopathy Exception Requests

Summary and Goals

The OPTN/UNOS Board of Directors recently approved the Thoracic Organ Transplantation Committee's (Committee) Proposal to Modify the Adult Heart Allocation System during its December 2016 meeting.[19] One of the major components of the new allocation system was the creation of three additional medical urgency statuses, for a new total of six. This new six-status system stratifies heart transplant candidates according to waiting list mortality.

During the development of the adult heart allocation policy, the Committee received feedback from the heart transplant community that hypertrophic and restrictive cardiomyopathy (HCM/RCM) candidates may be disadvantaged by the new system, as they are a heterogeneous candidate group and they may not always be optimal candidates for devices or inotropes. Specific examples include HCM patients with end-stage diastolic heart failure, but with preserved systolic function. For these patients with small left ventricular cavities, low cardiac output and high filling pressures, inotropes may provide little benefit and possibly cause harm.[20,21] Similarly, placement of a mechanical circulatory support cannula into a small, stiff left ventricle may not provide adequate unloading, and may precipitate right ventricular failure, suction events, thrombosis and low flow alarms.[22,23,24,25]

The Committee acknowledged that some HCM/RCM candidates may have a higher waiting list mortality. The new allocation policy includes hemodynamic criteria in addition to criteria based on levels of support. While these hemodynamic criteria will likely apply to most HCM/RCM candidates with advanced disease, improvements in hemodynamic parameters after initiation of inotropes may not require high doses or dual therapies. Thus strict criteria regarding drug doses may be unnecessary and may precipitate destabilizing arrhythmias. Therefore, HCM/RCM candidates may have difficulty meeting criteria for higher status according to policy, despite potentially having waitlist mortality equivalent to other candidates at higher statuses.[26] Instead, the review board exception and review process will continue to accommodate these

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[19] OPTN/UNOS Policy Notice. *Proposal to Modify the Adult Heart Allocation System*. Accessed June 27, 2017. https://optn.transplant.hrsa.gov/media/2028/thoracic_policynotice_201612.pdf .

[20] Rowin, J., Ethan, Maron, J., Barry, Kiernan, S., Michael, Casey, A., Susan, Feldman, S., David, Hryniewicz, M., Katarzyna, Chan, H., Raymond, Harris, M., Kevin, Udelson, E., James, Denofrio, C., David, Roberts, S., William, and Maron, S., Martin. "Advanced Heart Failure With Preserved Systolic Function in Nonobstructive Hypertrophic Cardiomyopathy: Under-Recognized Subset of Candidates for Heart Transplant." *Circulation: Heart Failure* 7, no. 6 (2014): 967-75.

[21] Pasqualucci, Fornaro, Castelli, Rossi, Arretini, Chiriatti, Targetti, Girolami, Corda, Orrù, Matta, Stefàno, Cecchi, Porcu, and Olivotto. "Clinical Spectrum, Therapeutic Options, and Outcome of Advanced Heart Failure in Hypertrophic Cardiomyopathy." *Circulation: Heart Failure* 8, no. 6 (2015): 1014-021.

[22] Topilsky Y, Pereira NL, Shah DK et al. Left ventricular assist device therapy in patients with restrictive and hypertrophic cardiomyopathy. *Circ Heart Fail* 2011;4(3):266-275.

[23] Muthiah K, Phan J, Robson D et al. Centrifugal continuous-flow left ventricular assist therapy for patients with hypertrophic cardiomyopathy: a case series. *American Society for Artificial Internal Organs.* 2013;59:183-187.

[24] Sivathasan, Cumaraswamy, Teing E. E. Tan, David Sim, and Ka Lee Kerk. "Burnt Out" Dilated Hypertrophic Cardiomyopathy Causing Acute LVAD Thrombosis." *Clinical Case Reports* 3, no. 6 (2015): 376-78.

[25] Grupper, Park, Pereira, Schettle, Gerber, Topilsky, Edwards, Daly, Stulak, Joyce, and Kushwaha. "Role of Ventricular Assist Therapy for Patients with Heart Failure and Restrictive Physiology: Improving Outcomes for a Lethal Disease." *Journal of Heart and Lung Transplantation* 34, no. 8 (2015): 1042-049.

[26] OPTN/UNOS Policy Notice. *Proposal to Modify the Adult Heart Allocation System.*

candidates, who can apply for an exception at any status as their medical urgency and potential for benefit would warrant, including status 1. The Committee drafted this guidance with the goal of helping review boards standardize decision-making for HCM/RCM exception requests.

Contents

Summary and Goals 9

Contents 10

Background 11

Recommendations 14

- Diagnoses Included within this Guidance 14
- Diagnoses Not Included Within This Guidance 14
- Criteria 15
- Extensions 17

Conclusion 17

Review Board Guidance for Hypertrophic/Restrictive (HCM/RCM) Cardiomyopathy Exception Requests

Background

Hypertrophic cardiomyopathy (HCM) is a common genetic cardiomyopathy with a prevalence in the general population of 1:500.[27,28] Mutations in genes encoding proteins of the cardiac sarcomere are responsible for HCM and result in a heterogeneous phenotypic expression and clinical course.[29,30] The penetration of a mature sudden death risk stratification algorithm and the implantable cardioverter defibrillator (ICD) have decreased sudden death events and shifted the pendulum toward greater recognition of heart failure, including an increasing subgroup with advanced heart failure symptoms who are candidates for transplantation.

The most common mechanism responsible for heart failure symptoms in HCM is dynamic left ventricular (LV) outflow tract obstruction, due to mitral valve-ventricular septal contact. Obstructive HCM patients with advanced symptoms refractory to medical therapy are candidates for invasive septal reduction therapies (i.e. surgical myectomy or alcohol septal ablation), which are highly effective at substantially improving (or eliminating) heart failure symptoms. Therefore, obstructive HCM patients are not generally candidates for heart transplant listing.

Although relatively uncommon, non-obstructive HCM patients can develop end-stage advanced heart failure. Approximately 50% of these patients demonstrate phenotypic transformation from diastolic dysfunction to LV pump failure with systolic dysfunction (ejection fraction (EF) ≤50%) and adverse LV remodeling involving wall thinning and/or ventricular chamber enlargement due to diffuse myocardial scarring.[31] The remaining non-obstructive HCM patients with refractory heart failure symptoms demonstrate preserved systolic function (ejection fraction (EF) $\geq$ 50%) with a non-dilated LV cavity associated with impaired cardiac output, often associated with impaired LV filling, and pulmonary hypertension. This subset of HCM patients with preserved LV function may progress to New York Heart Association (NYHA) Class IV heart failure with refractory symptoms and poor hemodynamics and are unable to be clinically stabilized on intravenous inotropes and are not candidates for mechanical support devices.[32]

Restrictive cardiomyopathy (RCM) includes genetic disorders of the sarcomere and cytoskeleton, infiltrative cardiomyopathies secondary to glycogen storages diseases, and amyloid deposition disease from either bone-marrow derived light chains (primary systemic amyloidosis (AL)) or from mutational or

[27] Maron BJ, Gardin JM, Flack JM et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults: echocardiographic analysis of 4111 subjects in the CARDIA Study Coronary Artery Risk Development in (Young) Adults. *Circ* 1995;92:785-789.
[28] Gersh BJ, Maron BJ, Bonow RO et al. 2011 ACCF/AHA Guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;124:37-85. DOI: 10.1161/CIR.0b013e318223e2bd
[29] Maron, Martin S., Maron, Barry J., Harrigan, Caitlin, Buros, Jacki, Gibson, C. Michael, Olivotto, Iacopo, Biller, Leah, Lesser, John R., Udelson, James E., Manning, Warren J., and Appelbaum, Evan. "Hypertrophic Cardiomyopathy Phenotype Revisited After 50 Years With Cardiovascular Magnetic Resonance." *Journal of the American College of Cardiology* 54, no. 3 (2009): 220-28.
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wild-type transthyretin protein made in the liver (transthyretin (TTR) cardiac amyloidosis).[33,34,35] Patients may also have an idiopathic RCM (restrictive physiology without any contributing etiology such as atherosclerosis), which may ultimately be genetic-based or secondary to radiation.[36] RCM manifests as dilated atria, non-dilated thickened ventricles, with diastolic dysfunction/restrictive physiology, exhibiting interdependence, low stroke volumes and often atrial arrhythmias. As with HCM, there is progressive exercise intolerance, end-organ dysfunction, including development of pulmonary hypertension, and ultimately heart failure requiring transplant.

In end-stage heart failure, mechanical support options are limited for the vast majority of patients with HCM or RCM and non-dilated ventricles and/or biventricular disease.[37] Total artificial heart surgery is a treatment option, but is limited to few specialized centers, with significant perioperative morbidity and mortality in low volume centers.[38] Given that current allocation schemes give higher transplant priority to patients placed on mechanical support, it is particularly challenging for HCM/RCM patients to advance in priority on the transplant list. This issue has raised concern that HCM/RCM patients who experience progressive heart failure symptoms are subject to a measure of inequality with respect to pathway to transplant, especially in areas of marked organ shortage where the majority of transplants are for patients who are listed at the highest urgency statuses. Upgrade on the heart transplant waiting list typically requires application for exception status and use of inotropes at specified doses that may not improve cardiac output in these unique subgroup of cardiomyopathy patients and may expose patients to significant arrhythmias. Lastly, recent data has suggested that transplant list mortality for HCM patients may not be low as previously considered.[39]

Data on heart transplantation in these populations yield the following insights:

- Patients with HCM are typically younger with fewer co-morbidities as compared to non-HCM candidates and have equal or superior long-term survival.[40,41,42]
- A subset of HCM patients with preserved LV function may progress to NYHA Class IV heart failure with refractory symptoms and poor hemodynamics and are unable to be clinically stabilized on intravenous inotropes and are not candidates for mechanical support devices.[43]

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- Data extrapolated from children with RCM indicate that high waitlist mortality is associated with need for inotrope use, along with need for intra-aortic balloon pump (IABP), ventricular assist devices (VAD) or extracorporeal membraneous oxygenator therapies (VA ECMO).[44] Other data in adults with RCM indicate that the RCM diagnosis alone is a marker for worse waitlist outcomes.[45]
- Based on an analysis of the OPTN database from 2009-16, patients with RCM are less likely to receive a VAD as bridge to transplant by 28.2%, with a multivariate risk score for poor waitlist survival including frailty, renal dysfunction, elevated pulmonary capillary wedge pressure > 20 mmHg and need for inotrope at listing.[46]
- Successful heart transplant in patients with cardiac amyloidosis (or heart-liver transplant for patients with mutational TTR) depends on experienced amyloid centers making timely referrals to transplant centers with appropriate comprehensive diagnostic capabilities for assessment of systemic involvement timely organ availability and experience with chemotherapy prior to and shortly after organ transplant.[47,48,49] A key variable in survival of patients with amyloidosis is organ transplant based on progressive heart failure *in the context* of a progressive systemic medical illness.
- There is sparse literature on the outcomes of patients with radiation induced cardiomyopathy, especially as patients with restrictive/non-dilated cardiomyopathy were combined with systolic dysfunction.[50,51,52] Overall, post-transplant outcomes in patients with prior radiation appear to be worse than those without prior radiation, mostly related to post-transplant lung cancer and other complications, irrespective of prior restrictive physiology.
- In end-stage heart failure, mechanical support options are limited for the vast majority of patients with HCM or RCM and non-dilated ventricles and/or biventricular disease.[53] Total artificial heart (TAH) surgery is a treatment option, but is limited to few specialized centers, with significant perioperative morbidity and mortality in low volume centers.[54]

Given that current allocation schemes prioritize patients in cardiogenic shock requiring mechanical support, it is particularly challenging then for HCM/RCM patients to advance in priority on the transplant list. This issue has raised concern that HCM/RCM patients who experience progressive heart failure symptoms, and who may be on the precipice of cardiogenic shock, may be subject to a measure of inequality with respect to pathway to transplant. Upgrade on the heart transplant waiting list typically requires application for exception status and use of inotropes at specified doses that may modestly improve cardiac output in these unique subgroup of cardiomyopathy patients, but may precipitate destabilizing arrhythmias without adequate back up mechanical support option.

Within the diverse spectrum of cardiovascular diseases, which can progress to advanced heart failure, patients with HCM, RCM and amyloid represent a subgroup with unique considerations with respect to priority for transplant listing. Many of these patients develop low output heart failure, often in the setting of

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[47] Castano, 2015.
[48] Gray Gilstrap, 2014.
[49] Varr, Liedtke, Arai, Lafayette, Schrier, and Witteles. "Heart Transplantation and Cardiac Amyloidosis: Approach to Screening and Novel Management Strategies." *Journal of Heart and Lung Transplantation* 31, no. 3 (2012): 325-31.
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[51] Saxena, 2014.
[52] Depasquale, Nasir, and Jacoby. "Outcomes of Adults with Restrictive Cardiomyopathy after Heart Transplantation." *Journal of Heart and Lung Transplantation* 31, no. 12 (2012): 1269-275.
[53] Topilsky, 2011.
[54] Arabia, Gregoric, Kasirajan, Moriguchi, Naftel, Myers, and Kirklin. "(237) - Total Artificial Heart (TAH): Survival Outcomes, Risk Factors, and Adverse Events in Intermacs." *Journal of Heart and Lung Transplantation* 35, no. 4 (2016): S95.

normal (or near normal) systolic function. Unfortunately, the opportunity to improve end-stage heart failure clinical symptoms and/or hemodynamics is limited compared to other cardiovascular diseases since intravenous inotropes are often ineffective (or not well tolerated) in these patients and mechanical support as a bridge to transplant can be technically challenging with higher complication rates and may provide inadequate unloading.[55,56] Taken together, these considerations, as well as the recent observation that transplant list mortality may not be as low as previously considered for HCM, raise important considerations to providing alternative organ allocation schemes which address more specifically these considerations.

The following recommendations are intended to provide objective criteria to guide decision-making in granting access to higher urgency statuses for those HCM, RCM or amyloid patients who meet specific clinical and/or hemodynamic variables and in the process provide an aspect of greater equality in transplant priority listing.

Recommendations

In all cases, candidates must be admitted to the transplant hospital that registered the candidate on the waiting list to be eligible for exceptions to status 1-3.

Diagnoses Included within this Guidance

The criteria described herein is appropriate for the following diagnoses groups:

- HCM diagnosis based on 2011 American College of Cardiology Foundation/American Heart Association Hypertrophic Cardiomyopathy Guidelines:[57]

  "…a disease state characterized by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient, with the caveat that patients who are genotype positive may be phenotypically negative without overt hypertrophy. Clinically, HCM is usually recognized by maximal LV wall thickness _15 mm, with wall thickness of 13 to 14 mm considered borderline, particularly in the presence of other compelling information (e.g., family history of HCM), based on echocardiograph".

  Primary restrictive cardiomyopathy, of idiopathic or genetic origin, or secondary to radiation
- Infiltrative cardiomyopathy (e.g. cardiac amyloidosis (TTR or AL), based on American Heart Association criteria 2006/International Society of Heart and Lung Transplantation 2016 guidelines[58]

Diagnoses Not Included Within This Guidance

While all patients are potentially eligible for exception status based on individual circumstances, this guidance document is intended to apply only to patients with primary HCM/RCM and small ventricular chamber size. Application of these criteria to candidates with the following clinical conditions is therefore not warranted:

- Patients with restrictive physiology as a secondary consequence of other cardiac disease. Therefore, coronary artery disease or transplant coronary artery vasculopathy or chronic rejection, for example, do not fall under this guidance.
- Review boards should use caution in applying these criteria to patients with a primary diagnosis of HCM, but who are otherwise candidates for mechanical support. The guidance was intended

[55] Topilsky, 2011.
[56] Grupper et al., 2015.
[57] Gersh et al., 2011.
[58] Mehra, Canter, Hannan, Semigran, Uber, Baran, Danziger-Isakov, Kirklin, Kirk, Kushwaha, Lund, Potena, Ross, Taylor, Verschuuren, and Zuckermann. "The 2016 International Society for Heart Lung Transplantation Listing Criteria for Heart Transplantation: A 10-year Update." *Journal of Heart and Lung Transplantation* 35, no. 1 (2016): 1-23.

for candidates with restricted ventricular chamber size (non-dilated left ventricular end-diastolic dimension indexed to body surface area [BSA]) and normal systolic function (eg. EF > 45%) who are therefore poor candidates for ventricular assist devices.

Criteria

Most candidates, in the absence of the conditions below, are appropriately categorized in status 4. Table 1 provides useful guidance for review boards asked to approve upgraded listing urgency by exception for hypertrophic, primary or infiltrative or radiation-induced restrictive cardiomyopathy.

Table 1: Recommended criteria for HCM/RCM status exceptions

If the candidate meets this criteria:	Then the candidate may be eligible for:
Is admitted to the transplant hospital that registered the candidate on the waiting list, has ongoing symptoms of NYHA class IV heart failure symptoms, and meets *all* of the following: 1. Continuous monitoring of hemodynamic data, including cardiac output, with a pulmonary artery catheter 2. Within 24 hours prior to submitting the exception request, *all* of the following are true: a. Candidate reached maximally-tolerated inotropic dosages, as evidenced by documented intolerance at higher dosages (e.g. hypotension, vasodilation, hemodynamically unstable atrial or ventricular arrhythmias) b. Candidate has *either* of the following: *At least 2* indicators of hemodynamic instability as shown below • One indicator of hemodynamic instability *and* at least one indicator of end-organ dysfunction as shown below **<u>Hemodynamic instability indicators:</u>** • Systolic blood pressure < 90 mmHg • Left or right atrial pressure, left or right ventricular end-diastolic pressure, or pulmonary capillary wedge pressure greater than 20 mmHg • Persistently low cardiac index ≤ 2.2 L/min/m2 • $Sv0_2$ < 50% **<u>End organ dysfunction indicators:</u>** • Elevated arterial lactate to 2.5 mmol/L • Increase in serum creatinine > 50% above baseline • Increase in total bilirubin > 50% above baseline • AST or ALT > 2x upper limit of normal	**Status 2 exception**
Is admitted to the transplant hospital that registered the candidate on the waiting list, has ongoing symptoms of NYHA class IV heart failure symptoms, and meets *all* of the following: 1. Has *one* of the following: • Invasive pulmonary artery catheter • Daily hemodynamic monitoring to measure cardiac output and left ventricular filling pressures 2. Is supported by continuous inotropic infusion to improve end-organ perfusion/function 3. Prior to initiation of inotropes, demonstrated evidence of decompensated heart failure, as evidenced by *at least two* of the following: • Systolic blood pressure < 90 mmHg • Left or right atrial pressure, left or right ventricular end-diastolic pressure, or pulmonary capillary wedge pressure greater than 20 mmHg • Cardiac index < 1.8 L/min	**Status 3 exception**

Extensions

According to policy, candidates at higher statuses due to temporary support modalities must generally demonstrate a failure-to-wean the temporary support in order to extend the status beyond specified periods. Because of the complexity of managing patients with HCM/RCM, a failure to wean should not be required in all patients. However, it is recommended that the requesting center demonstrate a failed attempt to wean inotrope support.

Conclusion

In summary, patients with HCM/RCM represent a small, but perhaps growing cohort of patients who advance to end-stage heart failure and require heart transplantation. The new heart allocation policy was created on the basis of TSAM modeling which indicated that these patients should be prioritized as Status or Tier 4. However, there is great heterogeneity within these disease categories. Some candidates may have urgency comparable to higher status candidates with other etiologies without meeting standard policy criteria for those statuses. This guidance document provides a more standardized approach to the evaluation of exception requests in such candidates. It should minimize variability in access to transplantation and limit the extent to which some candidates with HCM/RCM might be disadvantaged under the current allocation scheme.

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