

Public Comment Proposal

Regional Review Board Guidance for Adult Congenital Heart Disease Exception Requests

OPTN/UNOS Thoracic Organ Transplantation Committee

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Contents

Executive Summary	2
What problem will this resource address?	3
Why should you support this resource?	3
How was this resource developed?	4
How well does this resource address the problem statement?	9
Which populations are impacted by this resource?	9
How does this resource impact the OPTN Strategic Plan?	10
How will the OPTN implement this resource?	10
How will members implement this resource?	10
Transplant Hospitals	10
Will this resource require members to submit additional data?	11
How will members be evaluated for compliance with this resource?	11
How will the sponsoring Committee evaluate whether this resource was successful post implementation?	11
Guidance Document	12
Regional Review Board (RRB) Guidance for Adult Congenital Heart Disease (CHD) Exception Requests	13
Background	13
Recommendations	13
Category 1: Single ventricle heart disease	14
Category 2: Dual ventricle heart disease	17
Conclusion	17

Regional Review Board Guidance for Adult Congenital Heart Disease Exception Requests

Affected Policies: N/A
Sponsoring Committee: Thoracic Organ Transplantation
Public Comment Period: July 31, 2017 – October 2, 2017

Executive Summary

The OPTN Board of Directors recently approved the Thoracic Organ Transplantation Committee's (Committee) Modification to the Adult Heart Allocation proposal during their December 2016. During the development of the proposal, the Committee received feedback from the heart transplant community during both rounds of public comment voicing concerns that adult congenital heart disease (ACHD) candidates may be disadvantaged by the proposed policy.¹ The Committee considered the following issues in congenital heart disease (CHD) candidates:

- Higher urgency statuses are device-driven
- Variability in review board decision-making for ACHD exception requests
- Challenging to objectively quantify severity of illness

The Committee acknowledged that some ACHD candidates may have higher mortality and may not be candidates for mechanical support options, but ultimately did not change proposed policy. Short-term, the exception and review process will accommodate these candidates, who can apply for an exception in any status as their medical urgency and potential for benefit would warrant. The Committee recognized that CHD expertise may be inconsistent across the regional review boards (RRBs), thus potentially making evaluation and award of ACHD exception requests vulnerable to variability. To help mitigate these inconsistencies, the Committee created guidance for the RRBs with the goal of outlining objective criteria to standardize the evaluation and decision-making of ACHD exception requests.

This proposal aligns with the OPTN strategic goal of improving equity in access to transplants by providing objective criteria to RRBs, potentially making evaluation and award of exception requests for ACHD candidates more consistent, especially for those boards that lack a CHD expert. In addition, developing standardized exception criteria creates an intelligible pathway for more medically urgent ACHD 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 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 Board of Directors recently approved the Thoracic Organ Transplantation Committee's (Committee) Modification to the Adult Heart Allocation proposal during their December 2016 meeting. During the development of the proposal, the Committee received feedback from the heart transplant community during both rounds of public comment voicing concerns that ACHD candidates may be disadvantaged by the proposed policy.² The Committee considered the following issues in CHD candidates:

- Higher urgency statuses are device-driven
- Variability in review board decision-making for ACHD exception requests
- Challenging to objectively quantify severity of illness

Higher urgency statuses are device-driven

For both anatomic and physiologic reasons, these candidates are both less frequently helped by mechanical support and higher risk when mechanical support is used than non-CHD candidates.^{3,4}

Variability in review board decision-making for ACHD exception requests

The evaluation and award of exception requests for ACHD candidates may vary from region to region because there is variable, limited, and inconsistent congenital heart disease (CHD) expertise on regional review boards.

Challenging to quantify severity of illness

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

The Committee acknowledged that some ACHD candidates may have higher mortality and may not be candidates for mechanical support options, but ultimately did not change proposed policy. Short-term, the exception and review process will accommodate these candidates, who can apply for an exception in any status as their medical urgency and potential for benefit would warrant. The Committee recognized that CHD expertise may be inconsistent across the RRBs, thus potentially making evaluation and award of ACHD exception requests vulnerable to variability.

Why should you support this resource?

To help mitigate these inconsistencies, the Committee agreed to draft guidance for the RRBs with the goal of outlining objective criteria to standardize the evaluation and decision-making of ACHD 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 ACHD candidates' assignment to status 4, the historical waitlist mortality of ACHD patients was consistent with other populations within status 4.⁵ Improved data collection envisioned within the new policy should result in better assessment of whether specific subpopulations of ACHD are disadvantaged by the status 4 assignment and may, in the long term, result in policy changes to address any disadvantages. As an interim measure, the Committee determined guidance 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.

² OPTN/UNOS Board Briefing. *Proposal to Modify the Adult Heart Allocation System*. https://optn.transplant.hrsa.gov/media/2006/thoracic_brief_201612.pdf .

³ Peng, Griselli, O'sullivan, Crossland, Chaudhari, Wrightson, Butt, Roysam, Parry, Macgowan, Schueler, and Hasan. "Mechanical Circulatory Support for Failing Systemic Right Ventricle Using Left Ventricular Assist Device - An Option To Decide and Bridge?" *The Journal of Heart and Lung Transplantation* 33, no. 4 (2014): S58-59.

⁴ Villa, Chet R., and David L. S. Morales. "The Total Artificial Heart in End-Stage Congenital Heart Disease." *Frontiers in Physiology* 8 (2017): Frontiers in Physiology, 2017, Vol.8.

⁵ 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*.

This guidance suggests objective criteria to define a pathway to the higher urgency statuses for ACHD. The transplant community explicitly requested such criteria during both rounds of public comment. Per the community’s concerns, this guidance provides:

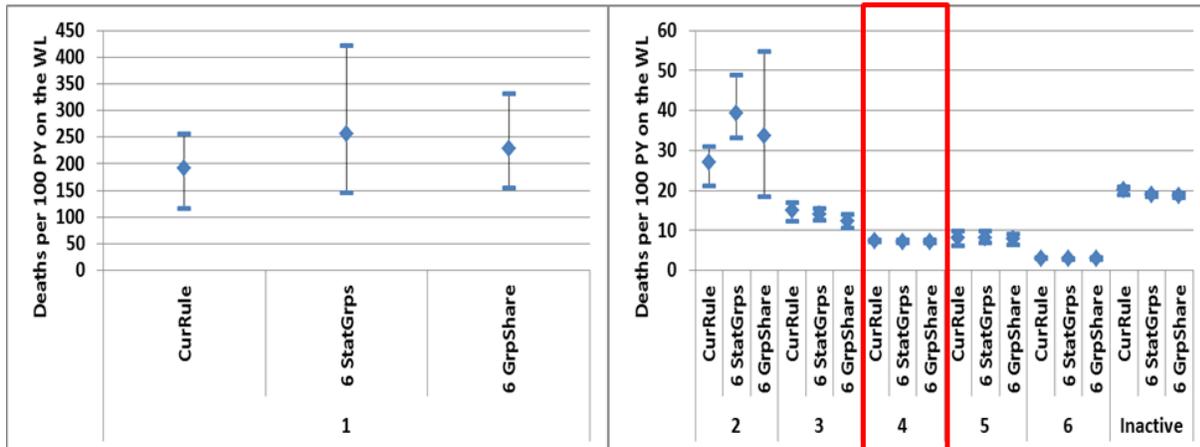
- Guidelines regarding which statuses would be appropriate for specific conditions
- Rationale and context that justify the recommendations, potentially helping review boards without a CHD expert
- Specific, objective criteria the RRBs can use in evaluating exception requests, potentially increasing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

If utilized, the RRBs should be able to recognize more medically urgent ACHD 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, the Committee received feedback that CHD 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. Therefore, they made a conscientious decision to keep candidates stratified in the same statuses originally proposed, as supported by evidence and the thoracic simulated allocation model (TSAM) (Figure 1). It important to note that status 4 is not limited to CHD candidates. Specific CHD diagnoses were not stratified in the TSAM cohort analyzed but are included in status 4. The TSAM results showed waitlist mortality rates were similar under current rules and under allocation by statuses.⁶

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



However, after the second round of public comment, the Committee agreed to consider drafting guidance for regional review boards to standardize the evaluation of CHD 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 pitfalls of developing guidance, in advance of implementation of the heart allocation policy changes. During public comment, several commenters requested guidance specifically, or questioned how exceptions for ACHD candidates would be handled. The Committee understood that the RRBs have requested more “guidance” in the past to standardize decision-making; especially because of the often limited CHD expertise on the review boards. Finally, this would be an opportunity to engage some of the individuals and organizations, including the American College of Cardiology (ACC), critical of the handling of adult CHD and other status 4 candidates in the new allocation policy, as well as advocacy groups that did not submit feedback on the modifications to the adult heart allocation system policy changes. Conversely, one of the goals of the modifications to

⁶ Scientific Registry of Transplant Recipients. *HR2015_01*, 2015.

the adult heart allocation policy proposal was to reduce exceptions by better stratifying candidates according to medical urgency. Although this guidance could also help transplant programs determine which ACHD patients may be appropriate for an exception request, it runs counter to the goal of reducing the number of exceptions. It concedes that the exception process continues to be an important way for ACHD candidates to access the higher urgency statuses (which will not be unique to this patient population). As with all guidance, these recommendations are voluntary, do not carry the weight of policy, and therefore are not enforceable, so it will not necessarily change behavior. Ultimately, the Committee developed guidance and communicated this intent to the OPTN Board of Directors while presenting the modifications to the adult heart allocation system proposal for consideration.

The Subcommittee considered expanding the scope of this guidance to include hypertrophic and restrictive cardiomyopathy (HCM/RCM) and amyloid candidates, also assigned to the new status 4. However, there was a consensus that the candidate populations differ markedly and the required expertise for these disparate patient groups was distinct. Therefore, this guidance is specific to ACHD candidates; a separate workgroup is addressing guidance for HCM/RCM candidates. This guidance is scheduled to go out during the next public comment cycle. The Committee may consider developing guidance for amyloid candidates in the future.

As there were only a few pediatric specialists on the Subcommittee, a pediatric congenital heart disease physician was recruited to bolster expertise and provide an external perspective. These members formed a small workgroup (CHD workgroup). The group identified several professional societies and advocacy groups to engage during public comment, including the International Society for Heart and Lung Transplantation, the Adult Congenital Heart Association, and the Heart Failure Society of America. In addition, the Committee will seek additional perspective and support from the OPTN/UNOS Pediatrics Committee.

Members were not aware of any standard classification system for ACHD patients proposed by professional societies, thus the CHD workgroup performed literature searches to find evidence in peer-reviewed journals to support their positions. They 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 absence of conclusive evidence in literature or in data, the workgroup reached clinical consensus based on expertise to determine its final recommendations.

The workgroup began by evaluating draft criteria composed by an ad hoc workgroup from Region 5. This workgroup was formed during the fall 2016 regional meetings in response to concerns raised during the pre-plenary thoracic breakout session and consisted of three CHD experts (from one adult and two pediatric heart transplant programs). It drafted criteria for ACHD candidates based on clinical consensus regarding the severity of illness. These criteria categorized CHD diagnoses into three broad categories: 1. single ventricle disease with extra-cardiac complications, 2. single ventricle disease with pump failure, and 3. dual ventricle disease. Pathways qualifying for higher status were proposed for each category.

Table 1: Region 5 Workgroup’s Strawman of RRB Guidelines for Stratifying CHD Candidates

Category		Suggested Status	Rationale
Category 1	Single ventricle heart disease with protein losing enteropathy, plastic bronchitis, excessive cyanosis, or other extra-cardiac chronic complication not directly related to ventricular or valvular function, but potentially cured by heart transplant.	<ul style="list-style-type: none"> Propose these patients should be status 4 by default. Propose that these patients, if admitted to the listing institution for complications of their illness, would be suitable for status 3, without regard for change in their cardiac support. 	Many of these listed patients have single ventricle heart disease, and poor quality of life, but may be at lower risk of dying while listed (compared with single ventricle patients with heart failure). However, they do not respond to inotropes, and MCS is not a helpful option for their treatment. Their continued deterioration during long listing times (proneness to infection, malnutrition, deteriorating lung function, coagulopathy, etc) contributes to their higher peri-transplant mortality.
Category 2	Single ventricle heart disease with failing pump function (myocardial or valvular heart disease not amenable to surgical correction).	<ul style="list-style-type: none"> Propose that these patients should be status 4 by default. This group would fit with status 3 if prescribed dischargeable inotropic support. This same group should be allowed to be status 2 if on multiple inotropes as an inpatient (and Swan Ganz Monitoring should not be required, as it is frequently irrelevant and often complicated by thrombosis). 	This definition can be refined to refer to those single ventricle heart disease with “typical” failure, whether primarily diastolic, systolic, irreparably valvular, or combined. These patients are exceptionally fragile, may not respond favorably to initiation of inotropic support, and are at substantially higher risk of death if they receive MCS (if they are candidates for MCS at all).
Category 3	Failing dual ventricle heart disease (e.g. Tetralogy of Fallot, CCTGA, repaired DORV, coronary anomalies, Ebsteins anomaly, etc. <i>Propose using the same definition of congenital heart disease used in the newest version of the pediatric listing system.</i>	<ul style="list-style-type: none"> Propose that these patients should be status 4 by default, unless meeting additional criteria. 	These patients, when listed for heart transplant, are generally high-risk candidates for temporary or durable MCS. While a patient with 2-ventricle CHD on oral therapies may be suitable for status 4 due to risk stratification, further increases in the listing criteria can be similar to other patients without congenital heart disease.

This categorization formed the starting point for the guidance document workgroup. Initial draft modifications included further subdividing the dual ventricle patients into those with a systemic right or a systemic left ventricle. While it was felt that this might provide more granular guidance, there was a countervailing concern, especially among the pediatric practitioners on the Subcommittee, that the guidance was becoming too detailed and prescriptive. The Subcommittee expressed concern that an overly complex guidance might not be as helpful.

The external CHD expert agreed that simplifying the guidance may be the best strategy. In addition, he expressed a concern that the distinction between single ventricle patients with and without pump failure was clinically difficult, often subjective, and likely beyond the expertise of the review boards. This simplification did prompt concerns from some Subcommittee members that the guidance might become insufficiently helpful to RRBs that lack a CHD specialist. As a compromise, the workgroup members agreed to collapse the categories to condense the guidance, but to keep examples and rationale to help educate RRB members. All workgroup members and members of the Subcommittee supported this strategy.

The Subcommittee presented draft criteria to the Committee during the March 23, 2017 full committee meeting. The Committee acknowledged the challenges in further stratifying this group by waitlist mortality or medical urgency due to lack of data, but recommended the criteria be more specific, similar to previous guidance drafted by the Subcommittee.⁷ The Subcommittee deliberated the Committee’s recommendation to make the guidance more specific and therefore, potentially more helpful to regional review boards. While this would better standardize how review boards evaluate exceptions for these candidates, the pediatric specialists on the Subcommittee reiterated it was difficult to select hemodynamic criteria or laboratory testing that would make the guidance any better than originally proposed. UNOS staff prompted the group to reconsider whether the guidance is specific enough to address the problems it was meant to address: variability in regional review board decision-making, leading to inequitable access, and adult-trained physicians determining pediatric exception requests. After making minor adjustments to the criteria, the Subcommittee was satisfied with the changes, as outlined below.

Exception Request Guidance for Single Ventricle ACHD Candidates

The Subcommittee proceeded to evaluate the guidance initially proposed to ensure there was consensus that the suggestions would be appropriate for all *single ventricle* patients:

Table 2: Draft RRB Guidance for Single Ventricle CHD Exception Requests

If a candidate meets this criteria:	Then the candidate is eligible for:
<ul style="list-style-type: none"> • Has complications of his/her VAD (single-ventricle VADs are currently classified into Status 2 in the new policy) 	Status 1 exception
<ul style="list-style-type: none"> • Admitted to the transplant hospital that registered the candidate on the waiting list and either: <ul style="list-style-type: none"> ○ Is on multiple inotropes ○ Is mechanically ventilated <p>Continuous monitoring of hemodynamic data, including cardiac output, as with a pulmonary artery catheter or other device is not required in these patients, because it is often not relevant and may be complicated by thrombosis or infection.</p>	Status 2 exception

⁷ OPTN/UNOS Thoracic Organ Transplantation Committee. “Guidance Regarding Adult Heart Status 1A(b) Device-Related Complications”. Accessed June 29, 2017. <https://optn.transplant.hrsa.gov/resources/guidance/guidance-regarding-adult-heart-status-1a-b-device-related-complications/>.

If a candidate meets this criteria:	Then the candidate is eligible for:
<ul style="list-style-type: none"> • Admitted to the transplant hospital that registered the candidate on the waiting list and is experiencing complications of his/her illness, without regard for change in his/her cardiac support <p>OR</p> <p>Has dischargeable inotropic support</p>	<p>Status 3 exception</p>

Status 1 Exception Criteria

The CHD workgroup and Subcommittee agreed unanimously that single ventricle patients experiencing complications of their VAD have no other options and are equally as urgent as other candidates in status 1.^{8,9,10} Single ventricle patients with VADs are currently assigned to status 2 in the approved policy.¹¹

Status 2 Exception Criteria

The Subcommittee debated whether ACHD candidates on multiple inotropes (a status 3 criterion) were as medically urgent as other candidates in status 2 and whether it would be sufficient for the guidance to simply note that pulmonary artery catheters are not indicated in single ventricle patients. Ultimately, the Subcommittee concluded that (1) this was a very small group of patients, and (2) they are exceptionally fragile and often may not respond favorably to initiation of inotropic support.¹² However, in order to limit overuse of this pathway, the Subcommittee agreed to add the specific inotropes and dosages to be consistent with policy language. In addition, the Subcommittee proposed adding mechanical ventilation as a criterion for higher status because single ventricle patients are often higher-risk for VADs, making mechanical ventilation an appropriate, if sub-optimal, treatment for heart failure in this population.

Status 3 Exception Criteria

The Region 5 workgroup initially included “dischargeable inotropic support” as a status 3 exception criterion in their proposed criteria, but the Subcommittee opted to eliminate it because, as per the approved policy, (1) a candidate must be admitted to the transplant hospital that registered the candidate on the waiting list for all status 1, 2 and 3 exception requests, and (2) all patients with single-ventricle CHD and a VAD are already status 2.¹³

Exception Request Guidance for Dual Ventricle ACHD Candidates

The Subcommittee then vetted the categorization of dual ventricle patients. Members agreed to adopt the same approach to simplify the dual ventricle categories as was done with the single ventricle categories and collapse them into a single category. The Subcommittee agreed the following guidance would be appropriate for all dual-ventricle patients:

- Most two-ventricle candidates *are generally not eligible* for an exception to a higher status and are appropriately classified in Status 4 (where all CHD candidates are currently categorized)
- A candidate that meets either of the following criteria is eligible for a Status 3 exception:
 - Failing biventricular heart disease with either a systemic right ventricle or other risk factors for VAD support including heterotaxy syndrome or multiple previous sternotomies

⁸ Mackling, Tracey, Tejas Shah, Vivian Dimas, Kristine Guleserian, Mahesh Sharma, Joseph Forbess, Monica Ardura, Jami Gross-Toalson, Ying Lee, Janna Journeycake, and Aliessa Barnes. "Management of Single-Ventricle Patients With Berlin Heart EXCOR Ventricular Assist Device: Single-Center Experience." *Artificial Organs* 36, no. 6 (2012): 555-59.

⁹ Vanderplyum, Rebeyka, Ross, and Buchholz. "The Use of Ventricular Assist Devices in Pediatric Patients with Univentricular Hearts." *The Journal of Thoracic and Cardiovascular Surgery* 141, no. 2 (2011): 588-90.

¹⁰ Brancaccio, Gianluca, Fabrizio Gandolfo, Adriano Carotti, and Antonio Amodeo. "Ventricular Assist Device in Univentricular Heart Physiology." *Interactive Cardiovascular and Thoracic Surgery* 16, no. 4 (2013): 568-69.

¹¹ OPTN/UNOS Thoracic Organ Transplantation Committee. "Guidance Regarding Adult Heart Status 1A(b) Device-Related Complications"

¹² Nakano, Nelson, Sucharov, and Miyamoto. "Myocardial Response to Milrinone in Single Right Ventricle Heart Disease." *The Journal of Pediatrics* 174 (2016): 199-203.e5.

¹³ 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 .

- Admitted to the transplant hospital that registered the candidate on the waiting list **and** is on multiple inotropes

These candidates are generally high-risk candidates for temporary or durable mechanical circulatory support. While the original Region 5 workgroup proposed that most of these candidates are appropriately assigned to status 4 per new policy, there was consensus on the CHD workgroup that patients are both higher risk for mechanical support and may have difficulty meeting the stringent hemodynamic and other sub-criteria required to qualify for Status 3 in the new policy.

While the guidance restates policy in some cases and may be redundant, the new allocation policy is complex and its application to CHD patients may not be immediately evident. Public comment for the heart allocation proposal indicated confusion regarding how policy applies to CHD patients continues to exist. RRBs may therefore get exception requests for scenarios already captured within the new policy language. Therefore, the guidance reiterates how policy applies to CHD candidates and includes policy citations in the guidance document as reference.

The Subcommittee reviewed the draft guidance during their April 27th meeting, made some additional clarifications to the guidance document narrative, and voted (10-yes, 0-no, 0-abstentions) to recommend to the full Committee that this guidance go out for public comment. The Committee made several clerical changes to the guidance narrative and voted (15-yes, 0-no, 0-abstentions) to send the proposal out for public comment in July 2017.

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 RRBs 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 convey a program's ACHD candidate has an urgency comparable to that of other candidates at the requested status.

Variability in review board decision-making for ACHD exception requests

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

Challenging to objectively quantify severity of illness

This resource provides more discrete recommendations for specific CHD conditions, therefore recognizing more medically urgent CHD diagnoses groups and those with limited therapeutic options.

While this guidance addresses some of the community's concerns, it does not carry the weight of policy, in that this guidance is not enforceable. It also diminishes the Committee's original goal of reducing the number of exceptions, especially for this patient population. It may encourage more exception requests.

Which populations are impacted by this resource?

As of June 30, 2017, there were 161 ACHD candidates on the waitlist.¹⁴ Table 4 shows the number of adult (defined as listed at age 18 or greater) registrations on the waiting list for a heart with a diagnosis

¹⁴ United Network for Organ Sharing Research Department. *Heart CHD Registrations by Status and Exception*. OPTN/UNOS Descriptive Data Analyses. Prepared for the Heart Subcommittee. July 5, 2017.

recorded on the transplant candidate registration form (TCR) in the CHD category by waiting list status and whether or not the status 1A and 1B candidates were waiting with exceptions.

Table 4: Heart CHD Registrations by Status and Exception

Status	1a or 1b Exception	N
Status 1a	No	6
Status 1a	Yes	9
Status 1b	No	58
Status 2	No	55
Inactive	No	33
Total		161

This guidance will affect ACHD candidates whose transplant programs request exceptions under the new adult heart allocation policy.

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 RRBs, potentially making evaluation and award of exception requests for ACHD candidates more consistent, especially for those boards that lack a CHD expert.
3. *Improve waiting listed candidate, living donor, and transplant recipient outcomes:* Developing standardized exception criteria creates an intelligible pathway for more medically urgent ACHD 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.
5. *Promote the efficient management of the OPTN:* There is no impact to this goal.

How will the OPTN implement this resource?

If public comment is favorable, the Committee plans to bring this guidance to the Board of Directors in December 2017. Upon Board approval, the OPTN/UNOS will publish this guidance to the resources section of both the OPTN and other websites concurrently to 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 regional 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 UNetSM.

How will members implement this resource?

Review board members should consult this resource when assessing exception requests

Transplant Hospitals

Heart programs should consider this guidance when submitting exception requests for their adult congenital heart disease candidates. However, these guidelines are for voluntary use by members and are not prescriptive of clinical practice.

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?

Adult CHD 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 ACHD patients.

Guidance Document

1 Regional Review Board (RRB) Guidance for Adult Congenital 2 Heart Disease (CHD) Exception Requests

3

4 The OPTN Board of Directors recently approved the Thoracic Organ Transplantation Committee's
5 Modification *to the Adult Heart Allocation* proposal during their December 2016 meeting in St. Louis, MO.
6 One of the major components of the new allocation system was the creation of three additional medical
7 urgency statuses, for a new total of six. This new six-status system stratifies heart transplant candidates
8 according to waiting list mortality.

9 During the development of the adult heart allocation policy, the Committee received feedback from the
10 heart transplant community that adult congenital heart disease (ACHD) candidates may be
11 disadvantaged by the new system, as they are a very heterogeneous candidate group and they may not
12 always be optimal candidates for devices or inotropes.

13 The Committee acknowledged that some ACHD candidates may have higher waiting list mortality. The
14 new allocation policy includes hemodynamic criteria in addition to criteria based on levels of support.
15 Measurement of hemodynamics among patients with CHD can be complicated by altered anatomy and
16 rendered meaningless. In addition, ACHD patients may not be candidates for the inotropic or mechanical
17 support options. Thus CHD candidates may have difficulty meeting criteria for higher status according to
18 policy, despite waitlist mortality equivalent to other candidates at higher status. Instead, the exception and
19 review process will continue to accommodate these candidates, who can still apply for an exception at
20 any status as their medical urgency and potential for benefit would warrant, including status 1, short-term.
21 The Committee drafted this guidance with the goal of helping regional review boards (RRBs) standardize
22 decision-making for ACHD exception requests.

23

24 Regional Review Board (RRB) Guidance for Adult Congenital 25 Heart Disease (CHD) Exception Requests

26 27 Background

28 The majority of adult heart transplants occur for candidates diagnosed with ischemic cardiomyopathy.
29 Heart failure in such candidates is often treated with inotropes or mechanical support, and the need for
30 these support modalities is an important predictor of survival while waitlisted for an organ. Candidates
31 without predominant systolic heart failure, including those with congenital heart disease (CHD),
32 hypertrophic, or restrictive cardiomyopathies (HCM, RCM) are often poorly served by these types of
33 support. Since the listing status of heart transplant candidates may be dependent on the utilization of
34 mechanical support or inotropes, this subgroup of patients may have limited access to higher urgency
35 statuses using standard criteria.

36 Overall mortality for ACHD places them clearly within status 4 of the new allocation system, so this
37 allocation scheme does acknowledge that on average, these candidates have higher waiting list mortality
38 than candidates with dilated cardiomyopathy.¹ But, there are likely subsets of candidates with CHD in
39 status 4 who will have worse outcomes and merit listing at a higher urgency. Despite a detailed review of
40 available OPTN data, as well as results from the thoracic simulation allocation model (TSAM) that
41 informed the modifications to the adult heart allocation system, the Committee was unable to classify
42 specific ACHD candidates into higher urgency statuses based on reliable, objective hemodynamic or
43 other data in a nationwide sample. Therefore, the Committee recognized that these candidates may need
44 to be handled through the exception pathway and regional review board system. In evaluating exception
45 requests, the RRBs are tasked with determining whether the “candidate has an urgency and potential for
46 benefit comparable to that of other candidates at the requested status.”² While this provides a measure of
47 individual assessment for each candidate, there is the risk that it will also result in unintended variation
48 and disparate listing criteria based on the region of listing rather than the severity of heart failure.
49 Accordingly, the Committee believes that an attempt to define broad groups of CHD candidates who are
50 likely to have higher mortality and merit higher urgency listing would assist the review boards in their
51 assessments and improve the consistency across the entire review process.

52 Recommendations

53 The following guidelines are intended to broadly classify ACHD candidates and, based on a
54 comprehensive review of the current literature, suggest appropriate status upgrades under specific
55 clinical circumstances. As part of its review, the Committee acknowledges that while the
56 recommendations are, to the extent possible, based on published, peer-reviewed data as well as
57 Scientific Registry of Transplant Recipients (SRTR) modeling, there is also a component of expert
58 consensus that is not as robust. Therefore, these recommendations should not be interpreted as stringent
59 as policy but more so a guide for each individual candidate. The Committee expects that the RRBs will
60 play an important role in objectively assessing medical urgency and potential for benefit in individual
61 candidates by placing candidates within a status that corresponds to their most likely level of waiting list
62 mortality as compared with other candidates in that status.

63 Adult candidates with CHD who are listed for transplant are a particularly heterogeneous group. They
64 represent a small proportion of adults listed for transplant (approximately 2% in any given year), and have
65 a range of diagnoses, including single ventricle circulation at various stages of palliation, failed two
66 ventricle circulations, and failure not directly attributable to altered systolic function.³ Each diagnosis may
67 have drastically different predictors of waiting list mortality; for example, Fontan candidates with protein-
68 losing enteropathy (PLE) may have normal filling pressures and normal cardiac output, but have a high
69 risk of infection and decompensation, while a candidate with tetralogy of Fallot may have a combination of

¹ First proposal/TSAM

² OPTN/UNOS Policy 6.3: Adult and Pediatric Status Exceptions.

³ Davies RR, Russo MJ, Yang J, Quaegebeur JM, Mosca RS, Chen JM. Listing and transplanting adults with congenital heart disease. *Circulation*. 2011;123:759–767.

70 biventricular failure and arrhythmia risk. The task of the RRBs is to attempt to estimate the medical
71 urgency and potential for benefit in each candidate, something that is particularly challenging in this
72 population, and may be made more challenging by the relative lack of experience with these diagnoses
73 among many adult heart failure practitioners. While reliance on objective measures of heart failure
74 severity, including hemodynamics and laboratory values, is intuitively attractive, there is little data
75 (especially in single ventricle candidates) to support the use of objective measures in predicting waiting
76 list mortality among ACHD. The inability to reliably predict survival among candidates with Fontan failure
77 remains a critical challenge in choosing when to list these complex candidates. Clearly, waiting for non-
78 cardiac end organ injury, including renal failure or profound liver insufficiency, results in poor post-
79 transplant outcomes and indicates that listing and transplant have occurred too late.⁴ Therefore, reliance
80 on the occurrence of end-organ dysfunction may not be appropriate in evaluating candidates for higher
81 listing urgency.

82 In order to provide some standardization to the analysis of these candidates, the Committee recommends
83 two broad category groupings based on the number of ventricles:

- 84 • Single ventricle heart disease candidates
- 85 • Dual ventricle heart disease candidates

86 Each category is discussed more fully below. It is important to note that in all cases, candidates must be
87 admitted to the transplant hospital that registered the candidate on the waiting list to be eligible for
88 exceptions to status 1-3.

89 **Category 1: Single ventricle heart disease**

90 Most candidates, in the absence of the conditions below, are appropriately categorized in status 4 or
91 status 2 (when supported by a ventricular assist device). Table 1 provides useful guidance for RRBs
92 asked to approve upgraded listing urgency by exception for ACHD with single ventricle physiology.

⁴ Davies RR, Sorabella RA, Yang J, Mosca RS, Chen JM, Quaegebeur JM. Outcomes after transplantation for “failed” Fontan: A single-institution experience. *J Thorac Cardiovasc Surg.* 2012;143:1183–1192.e4.

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Table 1: Recommended criteria for status exceptions

If the candidate meets this criteria:	Then the candidate is eligible for:
Is admitted to the transplant hospital that registered the candidate on the waiting list and is experiencing complications of their VAD (<i>single-ventricle VADs are currently classified into status 2 in policy</i>) ⁵	Status 1 exception
<p>Is admitted to the transplant hospital that registered the candidate on the waiting list and is <i>either</i>:</p> <ul style="list-style-type: none"> • Supported by <i>one</i> of the following: <ul style="list-style-type: none"> ○ A continuous infusion of at least one high-dose intravenous inotrope: <ul style="list-style-type: none"> ▪ Dobutamine greater than or equal to 7.5 mcg/kg/min ▪ Milrinone greater than or equal to 0.50 mcg/kg/min ▪ Epinephrine greater than or equal to 0.02 mcg/kg/min ○ A continuous infusion of at least two intravenous inotropes: <ul style="list-style-type: none"> ▪ Dobutamine greater than or equal to 3 mcg/kg/min ▪ Milrinone greater than or equal to 0.25 mcg/kg/min ▪ Epinephrine greater than or equal to 0.01 mcg/kg/min ▪ Dopamine greater than or equal to 3 mcg/kg/min • Mechanically ventilated <p>Continuous monitoring of hemodynamic data, including cardiac output, with a pulmonary artery catheter or other device, is <i>not</i> required in these candidates.</p>	Status 2 exception
Is admitted to the transplant hospital that registered the candidate on the waiting list and is experiencing complications related to their congenital heart disease (including but not limited to: protein-losing enteropathy, plastic bronchitis, or circuit thrombosis), without regard for change in the candidate's cardiac support	Status 3 exception

94

95 Adult single ventricle candidates are nearly all candidates with Fontan circulation, but smaller subsets
 96 may also be palliated through other stages, including a superior cavopulmonary connection (bidirectional
 97 Glenn procedures, hemiFontan procedures) or volume-loading palliative surgeries such as
 98 aortopulmonary shunts or pulmonary artery bands.

99 Some of these candidates will have “typical” heart failure symptoms, whether primarily diastolic, systolic,
 100 irreparably valvular, or combined. While the hemodynamics in these candidates, with low ejection
 101 fractions or higher filling pressures, may appear superficially similar to non-ACHD candidates with dilated
 102 cardiomyopathy, single ventricle candidates are exceptionally fragile, may not respond favorably to
 103 initiation of inotropic support, and are at substantially higher risk of death if they receive mechanical
 104 circulatory support, or they may not be candidates for mechanical circulatory support at all. In candidates

⁵ Policy notice

105 without mechanical circulatory support options, mechanical ventilation may be used as a treatment for
106 heart failure, but mechanical ventilation is an important risk factor for higher mortality in children with
107 Fontan palliation, and this likely applies to adults as well.⁶

108 In addition to “typical” heart failure candidates, all candidates with palliated single-ventricle circulations
109 are at-risk for extra-cardiac complications not directly related to ventricular or valvular dysfunction. In most
110 of these cases, traditional treatments for systolic heart failure (including inotropes and mechanical
111 circulatory support) provide limited benefit and may be harmful.^{7,8} On the other hand, recent data
112 suggests that as a group, Fontan candidates with preserved ventricular function may have worse
113 outcomes than those with impaired ventricular function.⁹ Protein-losing enteropathy is associated with
114 relatively high mortality, and much of this excess mortality is attributable to infectious and other non-
115 hemodynamic complications.¹⁰ Specific and clear predictors of mortality in the complex and
116 heterogeneous group of candidates with extra-cardiac complications and preserved ventricular function
117 are not available in the literature, although candidates with high pulmonary vascular resistance (PVR),
118 elevated cavopulmonary circuit pressures, and low cardiac output are likely at increased risk.¹¹ However,
119 there is a broad spectrum of severity in most of these disease processes, especially protein-losing
120 enteropathy and plastic bronchitis, and normal PVR or filling pressures does not exclude a high risk of
121 poor outcomes. In addition, these candidates have a lower quality of life due to the extra-cardiac
122 manifestations of cavopulmonary circuit failure. They may be at lower short-term risk of mortality on the
123 waiting list, but they do not respond to inotropes, and mechanical circulatory support is often not helpful in
124 treatment. Optimal timing of listing and transplantation remains elusive, but it does appear that many
125 candidates are transplanted late in their disease course and the onset of end-organ function suggests the
126 window for successful transplantation may have already passed.^{12,13} Continued deterioration during long
127 listing times (proneness to infection, malnutrition, deteriorating lung function, coagulopathy, etc.)
128 contributes to their higher peri-transplant mortality.¹⁴ However, because of the spectrum of
129 manifestations, the presence of a complication (e.g. protein-losing enteropathy) alone likely does not
130 merit listing at a higher urgency status than the currently assigned status 4. Conversely, where
131 complications require hospitalization (e.g. for ongoing albumin infusions or monitoring of severe cyanosis
132 and polycythemia), higher urgency is likely justified.

133

⁶ Kovach JR, Naftel DC, Pearce FB, Tresler MA, Edens RE, Shuhaiber JH, Blume ED, Fynn-Thompson F, Kirklin JK, Zangwill SD. Comparison of risk factors and outcomes for pediatric patients listed for heart transplantation after bidirectional Glenn and after Fontan: An analysis from the Pediatric Heart Transplant Study. *J Heart Lung Transpl.* 2012;31:133–139.

⁷ Gewillig M and Brown SC. The Fontan circulation after 45 years: update in physiology. *Heart* 2016; 102: 1081-1086.

⁸ John AS, Johnson JA, Khan M, Driscoll DJ, Warnes CA, Cetta F. Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. *J Amer Coll Cardiol*; 64: 54-62.

⁹ Griffiths ER, Kaza AK, Wyler von Ballmoos MC, Loyola H, Valente AM, Blume ED, del Nido P. Evaluating failing Fontans for heart transplantation: predictors of death. *Ann Thorac Surg.* 2009;88:558–63.

¹⁰ John

¹¹ Ibid.

¹² Davies, *Outcomes after transplantation*

¹³ Kovach

¹⁴ Davies, *Outcomes after transplantation*

134 **Category 2: Dual ventricle heart disease**

135 The following may be useful guidance for RRBs asked to approve upgraded listing urgency by exception.

136 Most candidates, in the absence of the conditions below, are appropriately categorized in status 4 (where
137 all CHD candidates are currently categorized).

138 For a candidate to be considered eligible for a status 3 exception, a candidate must be admitted to the
139 transplant hospital that registered the candidate on the waiting list and meet *either* of the following criteria:

- 140 • Has heart failure with risk factors for VAD support including a systemic right ventricle, failing
141 pulmonary ventricle, heterotaxy syndrome or multiple previous sternotomies
- 142 • Is supported by *one* of the following:
 - 143 ○ A continuous infusion of at least one high-dose intravenous inotrope:
 - 144 ▪ Dobutamine greater than or equal to 7.5 mcg/kg/min
 - 145 ▪ Milrinone greater than or equal to 0.50 mcg/kg/min
 - 146 ▪ Epinephrine greater than or equal to 0.02 mcg/kg/min
 - 147
 - 148 ○ A continuous infusion of at least two intravenous inotropes:
 - 149 ▪ Dobutamine greater than or equal to 3 mcg/kg/min
 - 150 ▪ Milrinone greater than or equal to 0.25 mcg/kg/min
 - 151 ▪ Epinephrine greater than or equal to 0.01 mcg/kg/min
 - 152 ▪ Dopamine greater than or equal to 3 mcg/kg/min

153 Candidates with two-ventricle CHD include those with a systemic right ventricle (e.g. congenitally
154 corrected transposition of the great arteries, [ccTGA], transposition of the great arteries [TGA] following
155 an atrial switch procedure) as well as those with systemic left ventricles (e.g. tetralogy of Fallot, repaired
156 double-outlet right ventricle, major coronary anomalies [such as anomalous left coronary artery from the
157 pulmonary artery, ALCAPA], Ebstein's anomaly, etc.). Most candidates in these categories have heart
158 failure as the consequence of ventricular dysfunction. Therefore, they may superficially resemble the
159 "typical" adult heart failure candidate with dilated or ischemic cardiomyopathy. However, the use of either
160 temporary or durable mechanical circulatory support in these populations is associated with significantly
161 higher risks. Among the factors resulting in high-risk are: anatomy (including heterotaxy syndrome), the
162 presence of a systemic right ventricle (associated with technical challenges during implant and likely
163 poorer outcomes), multiple previous sternotomies, and often multiple previous aortic procedures.¹⁵ Each
164 of these make VAD implantation more challenging and increase the risk of subsequent complications.

165 **Conclusion**

166 Some adult candidates with CHD may represent a higher risk group awaiting heart transplantation when
167 compared to candidates with dilated cardiomyopathy. They qualify for status 4 based entirely on the
168 etiology of heart failure. However, they often have limited options (or higher risk options) for mechanical
169 support. Attainment of higher urgency status through standard criteria (which require both impaired two-
170 ventricle hemodynamics and specific levels of either inotropic or mechanical support) may be restricted.
171 Unfortunately, there are no clear hemodynamic or laboratory data that indicate candidates at high risk.
172 When non-cardiac end organ injury (such as renal or liver failure) has occurred, transplantation is
173 extremely high-risk and may be prohibitive. Obtaining higher urgency status for candidates prior to the
174 occurrence of such injury should guide RRBs.

175 RRB members should consult this resource when assessing exception requests for ACHD candidates.
176 Adult heart transplant programs should also consider this guidance when submitting exception requests
177 for adult candidates with CHD. However, these guidelines are not prescriptive of clinical practice.

#

¹⁵ Peng E, O'Sullivan JJ, Griselli M, Roysam C, Crossland D, Chaudhari M, Wrightson N, Butt T, Parry G, MacGowan GA, Schueler S, Hasan A. Durable ventricular assist device support for failing systemic morphologic right ventricle: early results. *Ann Thorac Surg*. 2014;98:2122–2129.