

Public Comment Proposal

Modify Heart Policy for Intended Incompatible Blood Type (ABOi) Offers to Pediatric Candidates

OPTN Heart Transplantation Committee

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Modify Heart Policy for Intended Incompatible Blood Type (ABOi) Offers to Pediatric Candidates

Affected Policies:

5.3.E: Pediatric Heart Acceptance Criteria to Receive Intended Blood Group Incompatible Hearts

6.6.A: Allocation of Hearts by Blood Type

6.6.B: Eligibility for Intended Blood Group Incompatible Offers for Deceased Donor Hearts

10.4.A: Eligibility for Intended Blood Group Incompatible Offers for Deceased Donor Lungs

Sponsoring Committee:

Heart Transplantation

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Executive Summary

In July 2016, the Organ Procurement and Transplantation Network (OPTN) sought to improve pediatric heart candidates' waitlist mortality rates by implementing policy changes expanding access to heart offers from a donor with an incompatible blood type.¹ While the earlier changes have been beneficial, pediatric heart candidates continue to experience high waitlist mortality rates when compared to adult heart candidates. The OPTN Heart Transplantation Committee (hereafter, the Committee) proposes taking another incremental step to improve waitlist mortality rates by allowing candidates registered prior to turning 18 years old to receive offers of intended incompatible blood type (ABOi) donor hearts, lungs, and heart-lungs. In addition, eligibility for ABOi donor organs will be extended to pediatric status 2 heart candidates, as well as all pediatric lung candidates under the proposal, essentially removing status as an eligibility consideration.

¹ OPTN, Thoracic Organ Transplantation Committee and Pediatric Transplantation Committee, "Proposal to Change Pediatric Heart Allocation Policy," June 23, 2014.

Purpose

The purpose of this proposal is to expand access to ABOi donor hearts and heart-lungs to all pediatric heart and lung candidates, regardless of age, heart status, or lung composite allocation score. The OPTN Heart Transplantation Committee recommends:

- Increasing the eligibility age for access to ABOi donor hearts from being registered on the waiting list prior to turning two years old, to prior to turning 18 years old
- Permitting access to all active pediatric heart statuses, which would add pediatric status 2 candidates
- Aligning lung policy governing eligibility for ABOi donor lungs with the changes proposed for heart policy

Background

Heart transplantation in pediatric candidates is a well-established treatment for those with end-stage heart disease.² Pediatric heart candidates have worse waitlist mortality outcomes than adults, in part due to the unavailability of suitable donors.³ This is especially true for candidates who are less than one year old, but also true for older pediatric candidates as well. Among the methods employed to expand the donor pool for pediatric candidates has been to transplant disregarding acceptable blood group matches, an approach known as ABOi transplantation.⁴

However, clinical practice has demonstrated that in some cases successful ABOi transplants can occur in candidates who would not qualify under current OPTN policy. Successful ABOi transplants have been performed in candidates who were two years old and older, or had isohemagglutinin titers greater than 1:16.⁵ As with previous modifications approved by the OPTN Board of Directors, there are opportunities to align of pediatric heart policy more closely with clinical practice in beneficial ways.

OPTN Policy Establishes Eligibility Criteria for Accepting an ABOi Donor Offer

The OPTN's current ABOi policy is designed to benefit the very young heart candidates. First, such candidates have limited access to donor hearts. Second, it has been demonstrated that "newborn infants do not produce isohemagglutinins, and serum Anti-A or Anti-B antibody titers usually remain low until the age of 12 to 14 months."⁶ In both 2010 and 2016, the OPTN implemented policy changes to the pediatric heart allocation system designed to increase pediatric candidates' access to donor hearts. All

² Black, C.S, A Khushnood, H Holtby, and L Hepburn. "Cardiac Transplantation in Children." *BJA education* 19, no. 4 (2019): 105–112.

³ Fenton, Matthew. "Blood group-incompatible heart transplantation in children-an idea worth spreading," *The Lancet* 5, issue 5 (2021): 313-314.

⁴ Fenton, Matthew. "Blood group-incompatible heart transplantation in children-an idea worth spreading," *The Lancet* 5, issue 5 (2021): 313-314.

⁵ Irving, Claire A., Andrew R. Gennery, Vaughan Carter, Jonathan P. Wallis, Asif Hasan, Massimo Griselli, and Richard Kirk. "ABO-Incompatible Cardiac Transplantation in Pediatric Patients with High Isohemagglutinin Titers." *The Journal of Heart and Lung Transplantation* 34, no. 8 (2015): 1095–1102. <https://doi.org/10.1016/j.healun.2015.03.013>.

⁶ West, Lori J, Stacey M Pollock-Barziv, Anne I Dipchand, K. Jin Lee, Carl J Cardella, Leland N Benson, Ivan M Rebeyka, and John G Coles. "ABO-Incompatible Heart Transplantation in Infants." *The New England Journal of Medicine* 344, no. 11 (2001): 793–800. <https://doi.org/10.1056/NEJM200103153441102>.

of the changes more closely aligned OPTN policy with clinical practices and scientific advances involving ABOi transplantation at the time. In 2017, the OPTN implemented changes to pediatric lung policy that largely mirrored the ABOi eligibility criteria implemented in heart policy.⁷

Currently, to access ABOi donor hearts pediatric candidates must be registered on the heart waiting list as status 1A or 1B prior to turning two years old. They must also indicate a willingness to accept an ABOi donor heart, and report isohemagglutinin titer information to the OPTN. Different criteria exist based on candidate age at the time of the match run. Candidates who meet the criteria and who are less than one year old at the time of the match run are classified as primary blood type matches for purposes of the allocation tables. Candidates who meet the criteria and who are least one year old at the time of the match run are eligible if their reported isohemagglutinin titers are less than or equal to 1:16 for A or B blood type antigens, and they did not receive blood therapies that could reduce the titer value. The titers must be reported from a sample collected within the previous 30 days. Candidates who meet the eligibility and who are at least one year old at the time of the match run are classified as secondary blood type matches for purposes of the allocation tables.

Majority of Candidates Have Indicated Willingness to Accept ABOi Donor Organ

From January 1, 2017 through October 31, 2021, there were 2,586 pediatric waitlist list additions for status 1A and 1B. Of those, 1,320 (51 percent) were less than three years old at the time of registration.⁸ The transplant programs caring for the 1,320 candidates indicated they were willing to accept an ABOi heart offer on behalf of 59 percent of the candidates. During the same time period, there were a total of 2,290 pediatric heart transplants, of which 233 (10 percent) were ABOi transplants.⁹

Reluctance to accept an ABOi heart offer is more pronounced among transplant programs when it involves candidates who were one or two years old when registered. During the time period reviewed, a willingness to accept an ABOi heart was indicated on behalf of only 62 of the 354 (18 percent) pediatric heart waitlist additions who were one or two years old. Transplant programs were more likely to indicate they were willing to accept an ABOi heart on behalf of candidates who were less than one year old. Still, more of these candidates may have been able to accept an ABOi heart because it is likely that their isohemagglutinin production had not started given their age. Of the 1,077 pediatric candidates who were less than one year old when registered on the waiting list from January 1, 2017 through October 31, 2021, 746 (69.2 percent) indicated a willingness to accept an ABOi offer.

Pediatric Heart Candidates Have Worse Waitlist Mortality Rates Than Adult Candidates

While the OPTN policy changes have been beneficial, pediatric candidates continue to experience worse waitlist mortality than adult candidates. As mentioned, a primary reason continues to be the scarcity of donor hearts available for younger pediatric candidates. For instance, the International Society for Heart and Lung Transplantation's (ISHLT) 2022 report concerning pediatric heart transplantation states that because of size match considerations, the majority of donors for infant recipients have also been infants

⁷ Proposal to Modify Pediatric Lung Allocation Policy, OPTN Thoracic Transplantation Committee, March 2017, <https://optn.transplant.hrsa.gov/policies-bylaws/public-comment/modify-pediatric-lung-policy/> (accessed December 7, 2022).

⁸ OPTN, Data request prepared for the Pediatric-Heart Workgroup, March 31, 2022, pp. 4-5.

⁹ OPTN, Data request prepared for the Pediatric-Heart Workgroup, March 31, 2022, p. 11.

who are less than one year old.¹⁰ The report also states that 95 percent of all donors for infant recipients were less than three years old.¹¹ Therefore, continuing to find ways to increase pediatric candidates’ access to donor hearts remains critical.

Table 1 illustrates the number and percentage of waiting list removals by reasons and by age at listing for heart candidates listed from January 1, 2017 through June 30, 2022. As the table shows, removal as a result of death or being too sick to transplant accounted for higher percentages of removals for candidates less than one year old, one to two years old, and three to four years old than for the other candidate age groups. For example, pediatric candidates who were less than one-year old accounted for the highest proportion of waitlist removals due to death or being too sick to transplant (22 percent). Candidates aged one and two year olds had the second highest proportion of removals due to death or too sick to transplant (15 percent). Candidates who were three and four year olds accounted for the third highest proportion of waitlist removals due to death or being too sick to transplant (12 percent).

Table 1: Waiting List Removal Reason by Age at Listing for Heart Candidates Listed Between January 1, 2017 and June 30, 2022

Candidate Age at Listing (Years)	Candidates	Transplanted Percentage	Other Percentage	Death / Too Sick Percentage	Still Waiting Percentage
Less than 1	1,240	61.3%	11.9%	22.2%	4.7%
1-2	396	62.6%	13.6%	14.6%	9.1%
3-4	283	69.6%	9.5%	11.7%	9.2%
5-11	682	72.7%	4.8%	7.8%	14.7%
12-17	1,084	81.4%	5.3%	5.2%	8.2%
18-34	2,416	71.9%	11.1%	7.1%	9.9%
35-49	4,636	68.6%	12.0%	7.6%	11.8%
50-64	10,670	70.9%	9.8%	9.5%	9.9%
65 and older	4,279	72.8%	9.1%	11.6%	6.5%
Total	25,686	70.8%	10.0%	9.8%	9.5%

Source: OPTN data as of October 14, 2022. Data subject to change based on future data submission or correction.

The Committee’s proposal should be especially helpful for pediatric candidates who are three and four years old. As mentioned, approximately 12 percent of candidates in the age range are removed from the waiting list because of death or because their transplant program determined the candidates are too sick to benefit from a transplant. Current policy precludes candidates at this age from accepting intended incompatible donor hearts. The Committee’s proposal opens the door for access to such donor hearts at the discretion of each candidate’s transplant team.

Table 2 illustrates the number and percentage of pediatric candidates who were less than one year old at the time of listing and willing to accept an ABOi donor heart. As shown in the table, the percentage of

¹⁰ Singh, Tajinder P, Wida S Cherikh, Eileen Hsich, Michael O Harhay, Don Hayes, Michael Perch, Luciano Potena, Aparna Sadavarte, Andreas Zuckermann, and Josef Stehlik. “The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-Fifth Pediatric Heart Transplantation Report-2022; Focus on Infant Heart Transplantation.” *The Journal of Heart and Lung Transplantation* 41, no. 10 (2022): 1357–65. <https://doi.org/10.1016/j.healun.2022.07.019>.

¹¹ Singh, Tajinder P, et. al., “The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-Fifth Pediatric Heart Transplantation Report-2022; Focus on Infant Heart Transplantation,” 1357–65.

candidates less than one year old for whom a willingness to accept an ABOi donor heart has fluctuated between 65 percent and 75 percent since 2017. The table also illustrates the number and percentage of pediatric candidates who were at least one year old and less than two years old at listing and willing to accept an ABOi donor heart have remained relatively the same since 2017 as well.

Table 2: Willingness to Accept an ABOi Donor Heart by Candidate Age, January 1, 2017 – September 12, 2022¹²

Pediatric heart waitlist additions less than one year old by year of listing	# willing to accept an ABOi heart	% willing to accept an ABOi heart	# not willing to accept an ABOi heart	% not willing to accept an ABOi heart	Total
2017	147	67.1%	72	32.9%	219
2018	150	64.7%	82	35.3%	232
2019	164	70.7%	68	29.3%	232
2020	167	69.3%	74	30.7%	241
2021 ^a	122	75.3%	40	24.7%	162
Total	750	69.1%	336	30.9%	1,086
Pediatric heart waitlist additions at least one year old and less than two years old by year of listing	# willing to accept an ABOi heart	% willing to accept an ABOi heart	# not willing to accept an ABOi heart	% not willing to accept an ABOi heart	Total
2017	12	13.5%	77	86.5%	89
2018	18	21.7%	65	78.3%	83
2019	12	19.0%	51	81.0%	63
2020	8	11.6%	61	88.4%	69
2021 ^a	12	24.0%	38	76.0%	50
Total	62	17.5%	292	82.5%	354

^a Represents ten months.

Approximately 31 percent of candidates who were less than one year old at the time of listing were categorized as not willing to accept an ABOi donor heart. The Committee is asking the heart community to provide feedback as to why some transplant programs are reluctant to indicate a willingness for their candidates who are less than one year old to accept an ABOi donor heart. The Committee is also asking for recommendations designed to increase the percentage of candidates willing to accept ABOi donor hearts.

Table 3 identifies the number of pediatric ABOi transplants performed involving Anti-A and Anti-B titers reported at transplant and by the age of the recipient. There were 119 transplants of recipients who were less than one year old at the time of transplant and who had reported Anti-A titers. Of those, only three transplants were performed where the reported titer was greater than 1:16. Only one transplant was performed involving an Anti-B titer and titer value greater than 1:16.

¹² OPTN Website, Data and Calculators, Donor: Donation Year by Donor Age, Organs Discarded, Donors Recovered: January 1, 1998 – September 30, 2022, <https://optn.transplant.hrsa.gov/data/view-data-reports/build-advanced/#>, (accessed October 17, 2022).

Table 3: Pediatric ABOi Transplants by Anti-A and Anti-B Titers Reported at Time of Transplant by Age

Titer ratio	Number of transplants of recipients less than 1-year old with anti-A titers reported	Number of transplants of recipients older than 1-year old with anti-A titers reported	Number of transplants of recipients less than 1-year old with Anti-B titers reported	Number of transplants of recipients older than 1-year old with Anti-B titers reported	Total
1:0	12	2	32	3	49
1:1	28	0	22	3	53
1:2	23	0	20	4	47
1:4	26	1	10	2	39
1:8	17	4	5	3	29
1:16	10	1	1	2	14
1:32	3	0	0	0	3
1:64	0	0	1	0	1
Total transplants with reported titers	119	8	91	17	235
Not available	89	17	117	8	231

Table 3 also illustrates that there are some transplant programs willing to perform pediatric ABOi transplants of candidates who are less than one year old, and who have Anti-A titers of 1:16 or 1:32, and others who have Anti-B titers of 1:16 or 1:64.¹³ However, the figure also shows that few programs are willing to perform transplants at similar titers when the candidate is at least one year old. While the findings may be less than robust, the consensus of the Workgroup was that the information provides some sense of the extent to which transplant programs would consider ABO-incompatible transplants and titer levels.¹⁴

There appears to be a willingness to expand the use of ABOi hearts beyond the current eligibility criteria established in policy. However, existing age and titer requirements limit the amount and type of research of ABOi transplantation outcomes involving older pediatric candidates and recipients in the United States. Research about ABOi transplantation events that occur outside of the United States are also somewhat limited but that is the result of the small population of such transplants. Some of the research has reported success based on the recipient’s post-transplant survival, and indicates that intended incompatible blood type heart transplants may be an option for older children after careful selection and preparation.¹⁵

Overview of Proposal

The Committee proposes expanding current eligibility criteria governing intended incompatible blood type heart, lung, and heart-lung transplantation by increasing the eligibility age to include candidates who are registered on the heart or lung waiting lists prior to turning 18 years old. The proposal also expands eligibility to include pediatric heart status 2 candidates and pediatric lung priority 2 candidates.

¹³ Descriptive Data Request, “Pediatric Candidates and Recipients by ABO Compatibility Data Request,” Prepared for Heart Pediatric ABOi Offers Workgroup Conference Call, March 31, 2022, p. 34.

¹⁴ Meeting summary for March 31, 2022 meeting, OPTN Pediatric Heart Workgroup for ABOi Offers.

¹⁵ Urschel, Simon, and Lori J West. “ABO-Incompatible Heart Transplantation.” *Current Opinion in Pediatrics* 28, no. 5 (2016): 613–19. <https://doi.org/10.1097/MOP.0000000000000398>.

Access to a larger donor pool potentially increases the number of pediatric heart transplants and an improvement in waitlisted patient outcomes, both of which represent strategic goals of the OPTN.

Candidates registered prior to turning two years old and who are less than one year old at the time of the match run will continue to be classified as primary blood type and will need to report their titers as before. Candidates who are at least one year old at the time of the match run will continue to meet the titer cutoff of 1:16 or less, and will need to report their titers every 30 days. Additionally, the proposal increases the eligibility age for ABOi lungs to candidates registered prior to turning 18 years old. This proposal builds on previous OPTN efforts expanding the donor pool for pediatric candidates. The proposal does not include policy changes that would impact adult heart candidates.

The OPTN Heart Transplantation Committee sponsored the project. The Committee bolstered their understanding of pediatric heart issues by collaborating with the Pediatric Committee. A workgroup was formed consisting of members of the Heart and Pediatric Committees to review research findings associated with ABOi pediatric heart transplantation and to consider whether evidence exists supporting policy changes that might lead to increases in donor organ utilization and improved pediatric heart waitlist and post-transplant survival. The workgroup shared its considerations with the Heart Committee, whose members propose the policy modifications.

The isohemagglutinin titer cut-off of less than or equal to 1:16 will apply for candidates who are registered on the waiting list when they are at least one year old, but less than 18 years old. Currently, transplant programs must report the most recent measurement of a candidate's Anti-A titer and the date that sample was collected, or a candidate's Anti-B titer and the date that sample was collected. A program must also report whether a candidate has received any treatments that would have reduced the titer value within the last 30 days of when the blood sample was collected.

During their discussions, the Workgroup members considered whether a titer cut-off of less than or equal to 1:8 would be appropriate for this group. The case was made that if the titer ratio is the primary component for consideration, then maintaining the existing cut-off of less than or equal to 1:16 while expanding the age to less than 18 years old might be the simplest approach. It was suggested that, in some ways, a teenager with a titer of 1:16 is reassuring because it means that the candidate has maintained that titer ratio over multiple years.

As the Heart Committee was finalizing the proposed policy, they contacted the Lung Committee regarding the proposed changes and potential impact the changes might have on pediatric heart-lung candidates. Currently, the same general eligibility criteria for intended blood group incompatible offers apply to status 1A and 1B heart candidates who also need a lung, as well as priority 1 and 2 lung candidates who also need a heart. Hence, policy is intended to treat both types of candidates fairly in terms of access to deceased donor organs.

Heart Committee members realized that their proposed changes would result in older pediatric heart candidates having access to deceased donor lungs; whereas older pediatric candidates would not experience a likewise increase in their access to donor hearts. Members of the Heart and the Lung committees discussed the potential differences resulting from the proposed changes to heart policy and determined that an appropriate resolution was to increase the eligibility age of the lung policy to maintain the alignment with the proposed heart policy. Ultimately, the consensus of the OPTN Lung Committee members was that maintaining alignment between heart and lung ABOi eligibility criteria was appropriate. The Lung Committee agreed that changing *Policy 10.4.A: Eligibility for Intended Blood*

Group Incompatible Offers for Deceased Donor Lungs will benefit heart, lung, and heart-lung pediatric candidates. Lung Committee members indicated that lung transplants involving ABOi lungs are uncommon. In fact, a total of 15 heart-lung transplants involving pediatric recipients have occurred since 2017. Including the change in lung eligibility with the Committee's ABOi proposal was considered a minor change by both Committees. Furthermore, maintaining alignment between heart and lung ABOi policies avoids potential implementation issues related to the heart-lung match runs.

During the Heart Committee's consideration of the changes in lung policy, a member asked if there have been any concerns expressed about heart-lung transplants involving ABOi donor organs. It was pointed out that there is very little experience with such transplants. In addition, the members discussed that while it is not clear that all heart-lung programs are overly enthusiastic about transplanting across blood type incompatibility, especially at older ages, the policy allows the practice to occur if and when the transplant program deems it appropriate. Programs are not required to perform such transplants under the proposed changes. The Committee members were reminded that the proposal will be submitted for public comment and the community will be asked to provide information about potential safety issues.

The proposed policy changes do not require heart transplant programs to perform transplants of pediatric candidates using intended incompatible blood type donor hearts. During work on the proposal, it was pointed out that transplants of pediatric candidates using ABOi donor hearts is rare, even at relatively large transplant programs. Such transplants require a lot of in-servicing staff training and preparatory work. Based on these factors, it could be difficult for some transplant programs to fully take advantage of the opportunity to transplant their candidates using ABOi donor hearts. The changes acknowledge these concerns by maintaining the transplant programs' discretion for determining what is clinically appropriate for their candidates, while seeking to increase the pool of pediatric candidates who might benefit from intended incompatible blood type donor hearts and heart-lungs.

The changes are also expected to enhance the heart community's knowledge about the impacts associated with intended incompatible blood type transplants in older pediatric candidates, thereby better informing future policy revisions. For instance, a Workgroup member stated that candidates who are at least one year old, but less than two years old with the low titer ($\leq 1:8$) should be viewed differently than the group being discussed who are at least two years old but less than 18 years old because there is limited national data proving beyond a doubt that allocation to the older candidates would be safe. Therefore, data gathering and monitoring outcomes are important activities associated with the proposal.

NOTA and Final Rule Analysis

The Committee submits this proposal for OPTN Board of Directors consideration under the authority of NOTA, which requires the OPTN to "establish...medical criteria for allocating organs and provide members of the public an opportunity comment with respect to such criteria..."¹⁶ and to "recognize the differences in health and in organ transplantation issues between children and adults throughout the system and adopt criteria, policies, and procedures that address the unique health care needs of children..."¹⁷ In addition, the Committee submits the proposal under the authority of the OPTN Final Rule, which states "[t]he OPTN Board of Directors shall be responsible for developing...policies for the

¹⁶ 42 U.S.C. § 274(b)(2)(B).

¹⁷ 42 U.S.C. § 274(b)(2)(M).

equitable allocation for cadaveric organs.”¹⁸ The Final Rule requires that when developing policies for the equitable allocation of cadaveric organs, such policies must be developed “in accordance with §121.8,” which requires that allocation policies “(1) Shall be based on sound medical judgment; (2) Shall seek to achieve the best use of donated organs; (3) Shall preserve the ability of a transplant program to decline an offer of an organ or not to use the organ for the potential recipient in accordance with §121.7(b)(4)(d) and (e); (4) Shall be specific for each organ type or combination of organ types to be transplanted into a transplant candidate; (5) Shall be designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement;...(8) Shall not be based on the candidate’s place of residence or place of listing, except to the extent required by paragraphs (a)(1)-(5) of this section.”¹⁹ This proposal:

- **Is based on sound medical judgment**²⁰ because it is an evidence-based change relying on the following evidence:
 - Transplantation policies implemented in Canada and the United Kingdom that do not use age or isohemagglutinin titers in determining eligibility to receive an ABOi heart transplant.²¹
 - Medical judgment of the Heart and Pediatric committee members who based their decisions on OPTN data analyses and their collective clinical experience in treating pediatric heart transplant candidates.²² The committee members relied on their clinical experience and judgment in making determinations regarding the use of isohemagglutinin titer values and candidate age as factors for prioritization.
- **Seeks to achieve the best use of donated organs**²³ by ensuring organs are allocated and transplanted according to medical urgency. Analysis of OPTN waitlist data has demonstrated that candidates who are less than one year old at the time of listing have higher waitlist mortality rates than other age groups of pediatric candidates, whether they have indicated a willingness to accept an ABOi donor heart or not.²⁴ The proposal will ensure prioritization of pediatric ABOi candidates who are less than one year old at the time of the match run.
- **Is designed to avoid wasting organs by decreasing the number of organs recovered but not transplanted which maximizes the gift of organ donation by using each donated organ to its full potential.** The proposed changes are expected to expand the pool of eligible donor hearts.²⁵ For instance, modifying eligibility requirements for ABOi heart offers to include candidates who were registered on the heart waiting list prior to turning 18 years old is intended to mitigate the non-utilization of recovered hearts solely based on an age boundary that does not necessarily reflect current clinical practice.
- **Is designed to avoid futile transplants** because research has found that ABOi and ABOc recipients shared similar post-transplant survival.²⁶ For example, a study published in 2012 using

¹⁸ 42 C.F.R § 121.4(a)(1).

¹⁹ 42 C.F.R. § 121.8(a).

²⁰ 42 C.F.R. § 121.8(a)(1).

²¹ Daly, Kevin P, “The ABO-Incompatible Paradigm Shifts Only as Far as Allocation Policy Allows,” *The Journal of Heart and Lung Transplantation* 39, no. 7 (2020): 636–38. <https://doi.org/10.1016/j.healun.2020.04.017>.

²² OPTN Descriptive Data Request, “Pediatric Candidates and Recipients by ABO Compatibility Data Request,” Prepared for Heart Pediatric ABOi Offers Workgroup Conference Call, March 31, 2022.

²³ 42 C.F.R. § 121.8(a)(2).

²⁴ OPTN data as of June 9, 2022. Data subject to change based on future data submission or correction.

²⁵ Urschel, et. al., “Clinical outcomes of children receiving ABO-incompatible versus ABO-compatible heart transplantation: a multicenter cohort study,” *The Lancet*, Vol. 5, May 2021, 341-349.

²⁶ Beeman, Arun, and Nagarajan Muthialu, “ABO-Incompatible Heart Transplantation in Children—a Systematic Review of

data from the Pediatric Heart Transplant Society showed that the 85 pediatric recipients who were allocated an ABOi heart had comparable survival rates and rates of rejection in the first year post-transplant as ABO compatible recipients, despite a higher risk profile.²⁷ More recent study results involving more than 2,200 candidates who received a transplant before turning two years old reported similar graft survival, freedom from coronary allograft vasculopathy, and malignancy, as well as longer freedom from rejection.²⁸

- **Is specific for each organ**²⁹, in this case heart.
- **Is designed to...promote patient access to transplantation.**³⁰ The proposed changes seek to promote patient access by removing an age-related barrier to allow transplant programs to make decisions about accepting ABOi offers based on the medical condition of their patients, rather than how old the candidates are. For example, consider two pediatric patients with similar medical conditions who have not been registered on the hearting waiting list. One candidate is one-and-a-half years old and the other is three years old. Under current policy, if both candidates were registered on the same day, only the one-and-a-half year old would be eligible for ABOi offers because of age.
- **Is not based on the candidate's place of residence of place of listing.** The policy is open all pediatric heart, lung, and heart-lung candidates regardless of the location of the hospital that registered them on the waiting list. Transplant program practices vary, and some programs may choose not to perform ABOi transplants.

The changes recommended by the Committee also preserve the ability of a transplant program to decline an offer or not to use the organ for a potential recipient.³¹

This proposal aims to achieve equitable allocation, consistent with the requirements of 42 C.F.R. § 121.8(a), by creating less restrictive guidelines/requirements around ABOi heart transplants using evidence-based practices; therefore, potentially allowing pediatric and adults hearts to be transplanted that otherwise may not have been. The proposal will also promote patient access and efficient management of the OPTN system by considering patients who need a re-transplant, who have already had an ABOi heart transplant, for a second ABOi transplant.

Additionally, as pediatric candidates are uniquely able to receive ABOi transplants, reassessing the ABOi criteria for these candidates supports the OPTN's function under NOTA to "recognize differences in health and in organ transplantation issues between children and adults throughout the system and adopt criteria, policies, and procedures that address the unique health care needs of children."³²

Current Practice," *Indian Journal of Thoracic and Cardiovascular Surgery* 36, no. Suppl 2 (2020): 190–93.
<https://doi.org/10.1007/s12055-020-00971-8>.

²⁷ Urschel, Simon, Marie McCoy, Ryan S. Cantor, Devin A. Koehl, Warren A. Zuckerman, Anne I. Dipchand, Zdenka Reinhardt, et al., "A Current Era Analysis of ABO Incompatible Listing Practice and Impact on Outcomes in Young Children Requiring Heart Transplantation," *The Journal of Heart and Lung Transplantation* 39, no. 7 (2020): 627–35.
<https://doi.org/10.1016/j.healun.2020.02.008>.

²⁸ Urschel, et. al., "Clinical outcomes of children receiving ABO-incompatible versus ABO-compatible heart transplantation," 341-349.

²⁹ 42 C.F.R. § 121.8(a)(4).

³⁰ 42 C.F.R. § 121.8(a)(5).

³¹ 42 C.F.R. § 121.8(a)(3).

³² 42 U.S.C. § 274(b)(2)(M).

The Final Rule requires the OPTN to “consider whether to adopt transition procedures” whenever organ allocation policies are revised.³³ During their discussion of the proposed policy changes, the Committee considered whether any particular patient groups would be treated less favorably as a result of the changes. Particularly, the Committee discussed how the proposed revisions might affect pediatric heart-lung candidates and adult heart candidates who are small in stature and would benefit from access to smaller donor hearts. During its deliberations, the Committee members decided to reach out to the Lung Committee about potentially changing existing lung policy criteria governing ABOi lungs offers. The Lung Committee agreed, and the proposed policy was revised to maintain the consistency between heart and lung ABOi eligibility criteria. The Committee decided that adults who are small in stature already compete against adolescent pediatric candidates for donor hearts based on size and that the proposed changes are unlikely to exacerbate that competition.

Implementation Considerations

Member and OPTN Operations

Operations affecting Histocompatibility Laboratories

Histocompatibility laboratories that perform titer testing may experience an increase in the number of blood samples being submitted for analysis.

Operations affecting Organ Procurement Organizations

Organ Procurement Organizations (OPO) should educate their staff on the increased age eligibility requirements for intended incompatible blood type candidates.

Operations affecting Transplant Hospitals

After consulting with the candidate and the candidate’s family or responsible party, transplant hospitals should consider the appropriateness of indicating that the candidate is willing to accept an intended incompatible blood type donor organ. If willing, the transplant program will need to ensure that the blood samples are drawn at the required times, and reported to the OPTN based on the requirements established in OPTN policy. Transplant hospital staff will need to be trained on the new requirements.

Operations affecting the OPTN

The OPTN Contractor will need to implement changes to the OPTN Data System to accommodate the increased eligibility age associated with the proposed changes. Programming updates are also necessary to accommodate heart-lung candidate eligibility in the OPTN Waiting List System and the OPTN Donor Data and Matching System.

This proposal may require the submission of official OPTN data that are not presently collected by the OPTN. The collection of official OPTN data is subject to the Paperwork Reduction Act of 1995, which requires approval from the federal Office of Management and Budget (OMB). The OMB approval process may impact the implementation timeline.

³³ 42 C.F.R. § 121.8(d)(1).

Potential Impact on Select Patient Populations

The proposal improves access to transplantation for all pediatric heart candidates by increasing the age at the time of registration from “prior to turning two years old” to “prior to turning 18 years old.” In addition, the proposal expands eligibility to pediatric heart status 2 candidates, along with status 1A and status 1B candidates who are already eligible under OPTN policy. All pediatric heart, lung, and heart-lung candidates are expected to benefit from the proposed changes, including infants, children, and adolescents.

Projected Fiscal Impact

This proposal is projected to have a large fiscal impact on the OPTN, but only a minimal fiscal impact on organ procurement organizations (OPOs) or transplant hospitals. The proposal is anticipated not to have any fiscal impact on histocompatibility laboratories.

Projected Impact on the OPTN

The OPTN supported Workgroup and Committee meetings to research and develop the proposed policy changes. The OPTN’s activities included drafting, reviewing, and revising the policy modifications. The proposal will require information technology changes to eligibility requirements and procedures for incompatible heart, lung, and heart-lung cases. It is estimated that 890 hours are necessary to implement the changes.

Projected Impact on Organ Procurement Organizations

The proposal should not require new resources by OPOs, or substantial increases in existing resources. Under the proposed changes, OPOs may experience increased opportunities to allocate donor hearts that would not have been previously available due to the restrictions on intended incompatible blood type matching.

Projected Impact on Transplant Hospitals

The proposal is not expected to have a substantial fiscal impact on transplant programs, although there will be additional monthly titers required for some candidates. It is estimated that transplant programs may need three to six months for education and training as well as notifying patients impacted by the change. The changes are not expected to result in additional travel for transplant program staff or extended lengths of stay by the patients. As a result, additional staff should not be necessary, nor the costs associated with additional staff.

Projected Impact on Histocompatibility Laboratories

There is minimal fiscal impact for histocompatibility laboratories although there will be an increase in antibody titer testing.

Post-implementation Monitoring

Member Compliance

The Final Rule requires that allocation policies “include appropriate procedures to promote and review compliance including, to the extent appropriate, prospective and retrospective reviews of each

transplant program's application of the policies to patients listed or proposed to be listed at the program.”³⁴ This proposal will not change the current routine monitoring of OPTN members. Any data entered into OPTN computer systems may be reviewed by the OPTN, and members are required to provide documentation as requested.

Policy Evaluation

The following key metrics will be used to evaluate whether this policy has been successful in achieving its aims:

- Pediatric heart candidate waiting list mortality
- Heart non-utilization rates

These metrics will be compared pre- and post-implementation. If this policy is successful, it is expected that pediatric heart waiting list mortality will decrease and the non-utilization rate for deceased donor hearts will also decrease.

In addition, the Committee will review the following metrics, compared pre- and post-policy:

- The count and percent of pediatric heart candidates willing to accept an ABOi organ by age group and medical urgency status
- The count and percent of pediatric ABOi heart transplants by age group, medical urgency status, and blood type
- Anti-A and Anti-B titer at listing and at transplant for pediatric heart candidates by age group
- Median time to transplant for pediatric heart candidates by willingness to accept an ABOi transplant and medical urgency status
- Post-transplant survival for pediatric heart recipients by ABOi vs ABOc transplant

The Committee will review these metrics at six months, one year, and two years post-implementation.

Conclusion

Intended incompatible blood type heart eligibility criteria were last modified in July 2016. The amendments increased the qualifying isohemagglutinin titers and gave greater priority to heart candidates less than one year old and/or are eligible for intended incompatible donor heart. The changes resulted in some improvements for pediatric candidates, but as a group they continue to experience worse waitlist mortality rates when compared to most adult age cohorts.

Since the modifications were implemented in 2016, clinical practice and research findings in other countries have demonstrated the successful use of intended incompatible blood type hearts in pediatric transplants at ages and isohemagglutinin titer ratios greater than those in current OPTN heart policy. The changes in this policy proposal comprise another incremental step based on accepted medical practice to expand pediatric access to donor hearts. After consideration, the Committee chose not to revise the isohemagglutinin titer values.

³⁴ 42 C.F.R. §121.8(a)(7).

Expanding eligibility to pediatric candidates who are registered prior to turning 18 years old, and pediatric status 2 candidates is expected to increase the number of pediatric heart and pediatric heart-lungs transplants. Consequently, as more pediatric candidates are transplanted, their waiting list mortality rates are expected to decrease. In addition, expanding eligibility is also expected to reduce the number of donor hearts that are discarded due to the unavailability of an appropriate compatible blood type match candidate. Moreover, the data collected about ABO-Incompatible transplants of pediatric candidates older than two years old will help inform future clinical practices, limitations, and monitoring approaches, all of which can be used to revise the proposed policy changes.³⁵

The Heart Committee and the Pediatric Committee seek feedback on the following questions:

- What factors or considerations are preventing transplant programs and/or candidates and candidate support teams from indicating a willingness to accept an intended incompatible blood type donor heart or heart-lungs?
- What steps can be taken to improve the use of this policy, even if no changes are made?
- Are candidates who are registered on the heart waiting list put at unnecessary risk by the proposed changes to the eligibility criteria for receiving a heart from an intended blood group incompatible deceased donor?
- To what extent might adult heart candidates be impacted by increasing pediatric candidates' access to intended incompatible blood type donor hearts and heart-lungs?
- Are pediatric candidates who are registered on the lung waiting list put at unnecessary risk by the proposed changes to the eligibility criteria for receiving a heart-lung from an intended blood group incompatible deceased donor?
- The proposal will expand eligibility to receive a heart from an intended blood group incompatible deceased donor to pediatric heart status 2 candidates. Is that appropriate? Should only the pediatric heart status 1A and status 2A candidates continue to be eligible? Why or why not? Should a pediatric candidate be hospitalized at the time of listing to qualify for eligibility?
- *Policy 6.6.B: Eligibility for Intended Blood Group Incompatible Offers for Deceased Donor Hearts* currently states that a “candidate must not have received treatments that may have reduced isohemagglutinin titers to 1:16 or less within 30 days of when this blood sample was collected.” The proposal maintains the timeframe of 30 days from when the blood sample was collected for candidates with titers of 1:16 or less. Is 30 days the appropriate timeframe? Why or why not? If not, what is the appropriate timeframe?
- Are there opportunities to make pediatric candidates, their families, and their caregivers aware of the opportunity to accept ABOi donor hearts and lungs?

³⁵ Urschel and West, “ABO-incompatible Heart Transplantation,” p. 616.

Policy Language

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

1 **5.3.E Pediatric Heart Acceptance Criteria to Receive Intended Incompatible Blood**
 2 **Group Incompatible Type Hearts**

3 A transplant hospital may specify whether a candidate registered before ~~two~~ 18 years of age is
 4 willing to accept a heart or heart-lungs from an intended incompatible blood group
 5 ~~incompatible type~~ deceased donor.

7 **6.6 Heart Allocation Classifications and Rankings**

8 **6.6.A ~~Allocation of Hearts by Blood Type~~ Matching Priority for Heart Offers**

9 ~~Within each classification, hearts are first allocated to primary blood type candidates then to~~
 10 ~~secondary blood type candidates according to the blood type matching requirements in Table 6-4~~
 11 ~~below. Hearts are prioritized according to the blood type matching requirements in Table 6-4:~~
 12 ~~Blood Type Matching Prioritization for Heart Allocation. Pediatric candidates who are eligible for~~
 13 ~~intended incompatible blood type offers are prioritized according to Policy 6.6.B.ii: Blood Type~~
 14 ~~Prioritization for Intended Incompatible Offers.~~

16 **Table 6-4: Blood Type Matching Prioritization for Heart Allocation**

Hearts from Deceased Donors with:	Are Allocated to Primary Candidates defined as:	Then to Secondary Candidates, defined as:
Blood Type O	Blood type O or <u>or</u> blood type B	Blood type A or blood type AB
Blood Type A	Blood type A or blood type AB	Not applicable
Blood Type B	Blood type B or blood type AB	Not applicable
Blood Type AB	Blood type AB	Not applicable

17
 18 ~~Pediatric candidates that are less than one year old at the time of the match run, including~~
 19 ~~candidates eligible to receive a heart from an intended blood group incompatible deceased~~
 20 ~~donor, will be classified as a primary blood type match candidate.~~

21
 22 ~~Pediatric candidates that are at least one year of age at the time of the match run but registered~~
 23 ~~before their second birthday and are eligible to receive a heart from an intended blood group~~
 24 ~~incompatible deceased donor will be classified as a secondary blood type match candidate,~~
 25 ~~unless they are a primary blood type match candidate according to Table 6-4.~~

26

6.6.B — Eligibility for Intended Blood Group Incompatible Offers for Deceased Donor Hearts

The candidate will be eligible for intended blood group incompatible heart offers if the candidate meets at least *one* of the following conditions:

1. Candidate is less than one year old at the time of the match run, and meets *both* of the following:
 - a. Is registered as status 1A or 1B.
 - b. Has reported isohemagglutinin titer information for A or B blood type antigens to the OPTN within the last 30 days.
2. Candidate is at least one year old at the time of the match run, and meets all of the following:
 - a. Is registered prior to turning two years old.
 - b. Is registered as status 1A or 1B.
 - c. Has reported to the OPTN isohemagglutinin titers less than or equal to 1:16 for A or B blood type antigens from a blood sample collected within the last 30 days. The candidate must not have received treatments that may have reduced isohemagglutinin titers to 1:16 or less within 30 days of when this blood sample was collected.

Accurate isohemagglutinin titers must be reported for candidates eligible to accept an intended blood group incompatible heart according to *Table 6-5* below, at all of the following times:

1. Upon initially reporting that a candidate is willing to accept an intended blood group incompatible heart.
2. Every 30 days after initially reporting that a candidate is willing to accept an intended blood group incompatible heart.

6.6.B Intended Incompatible Blood Type Heart Offers Eligibility and Prioritization

6.6.B.i Eligibility for Intended Incompatible Blood Type Heart Offers

Pediatric heart and pediatric heart-lung candidates are eligible for an intended incompatible blood type heart offer if *all* of the following conditions are met:

- The transplant program specifies the candidate is willing to accept an intended incompatible blood type heart according to *Policy 5.3.E: Pediatric Heart Acceptance Criteria to Receive Intended Incompatible Blood Type Heart*, and reports isohemagglutinin titer(s) information according to *Table 6-5: Isohemagglutinin Titer(s) Reporting Requirements for Pediatric Candidates Willing to Receive an Intended Incompatible Blood Type Heart*
- The transplant program reports updated isohemagglutinin titer information every 30 days
- And the candidates meets one of the following conditions:
 - Is less than one year old at the time of the match run
 - Is at least one year old at the time of the match run, and has titers

69 less than or equal to 1:16, and has not received treatments that
 70 may have reduced isohemagglutinin titers to 1:16 or less within 30
 71 days of when this blood sample was collected.

72
 73 **Table 6-5: Isohemagglutinin Titer Reporting Requirements for a Candidate Who is Willing to Receive**
 74 **an Intended Incompatible Blood Group Incompatible Type Heart**

If the candidate's blood type is:	Then the transplant program must report the following isohemagglutinin titers to the OPTN:
A	Anti-B
B	Anti-A
O	Anti-A and Anti-B

75
 76 **6.6.B.ii Blood Type Matching Priority for Intended Incompatible Blood**
 77 **Type Heart Offers**

78 An eligible pediatric candidate who is less than one year old at the time of the
 79 match run is classified as a primary blood type match candidate.

80
 81 An eligible pediatric candidate who is at least one year old at the time of the match
 82 run is classified as a secondary blood type match candidate, unless they are a
 83 primary blood type match candidate according to Table 6-4.

84
 85 **6.6.B.iii Reporting Requirements for Recipients of Intended Incompatible**
 86 **Blood Type Hearts**

87 Accurate isohemagglutinin titers must be reported for recipients of an intended
 88 incompatible blood type heart, according to Table 6-6, as follows:

- 89
 90
 91
 92
 93
 94
 95
1. At transplant from a blood sample taken within 24 hours prior to transplant.
 2. If graft loss occurs within one year after transplant from the most recent blood sample, if available.
 3. If recipient death occurs within one year after transplant from the most recent blood sample, if available.

96 **Table 6-6: Isohemagglutinin Titer Reporting Requirements for a Recipient of an Intended Incompatible**
 97 **Blood Group Incompatible Type Heart**

Deceased donor's blood type:	Recipient's blood type:	Isohemagglutinin titer reporting requirement:
A	B or O	Anti-A
B	A or O	Anti-B
AB	A	Anti-B
AB	B	Anti-A
AB	O	Anti-A and Anti-B

98

99 If a laboratory provides more than one isohemagglutinin titer value for a tested
 100 blood sample, the transplant program must report to the OPTN the highest titer
 101 value.
 102

103 **10.4.A Eligibility for Intended Incompatible Blood Group Incompatible Type Offers**
 104 **for Deceased Donor Lungs**

105 Incompatible blood types are defined in *Table 10-2: Incompatible Blood Groups Types for*
 106 *Deceased Donor Lungs*.

107 **Table 10-2: Incompatible Offers Blood Groups Types for**
 108 **Deceased Donor Lungs**

Deceased Donor's Blood Type	Candidate's Blood Type
A	O and B
B	O and A
AB	O, A, and B

109 Candidates with incompatible blood types will be screened from lung match runs unless the
 110 candidate meets the criteria for eligibility in *Table 10-3: Eligibility for Intended Incompatible*
 111 *Blood Group Incompatible Type Offers for Deceased Donor Lungs* below.
 112

113 **Table 10-3: Eligibility for Intended Incompatible Blood Group Incompatible Type Offers for**
 114 **Deceased Donor Lungs**
 115

If the candidate is <u>registered prior to turning 18 years old and is:</u>	And meets <i>all</i> of the following:
Less than one year old at the time of the match run	<ol style="list-style-type: none"> 1. Has a waiting list survival score of at least 1.9073 Has reported isohemagglutinin titer information for A or B blood type antigens to the OPTN within the last 30 days
At least one year old at the time of the match run	<ol style="list-style-type: none"> 1. Is registered prior to turning two years old 2. Has a waiting list survival score of at least 1.9073 Has reported to the OPTN isohemagglutinin titers less than or equal to 1:16 for A or B blood type antigens from a blood sample collected within the last 30 days. The candidate must not have received treatments that may have reduced isohemagglutinin titers to 1:16 or less within 30 days of when this blood sample was collected

#