

Public Comment Proposal

Report Primary Graft Dysfunction in Heart Transplant Recipients

OPTN Heart Transplantation Committee

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Report primary graft dysfunction in heart transplant recipients

Affected Instrument: Heart Transplant Recipient Registration (TRR)
Sponsoring Committee: Heart Transplantation
Public Comment Period: August 3, 2021 – September 30, 2021

Executive Summary

Primary Graft Dysfunction (PGD) is the leading cause of 30-day mortality post-heart transplantation.¹ However, the Organ Procurement and Transplantation Network (OPTN) does not collect post-transplant information that could identify recipients who develop primary graft dysfunction. This proposal intends to add relevant data elements to the Heart Transplant Recipient Registration form (TRR) to identify PGD in heart transplant recipients and better assess the impact PGD has on recipient outcomes post-transplant.

An initial list of proposed data elements was shared with the community as a request for feedback during the Winter 2021 public comment period. Public feedback was largely supportive of the new post-transplant data elements identified and offered several ideas about the collection timeframes. The Committee incorporated these considerations in the recommended data elements included in this proposal.

This data collection proposal supports the OPTN strategic goal of improving waitlisted patient, living donor, and transplant recipient outcomes. The information collected will allow the Committee to monitor outcomes for recipients with PGD and the data collected will support evidence-based policy development in the future, including the development of a continuous distribution heart allocation framework.

¹ Singh, Sanjeet, Singh Avtaar, Dalzell, Jonathan R, Berry, Colin, and Al-Attar, Nawwar. "Primary Graft Dysfunction after Heart Transplantation: A Thorn amongst the Roses." *Heart Failure Reviews* 24, no. 5 (2019): 805-20.

Background

PGD is a leading cause of early mortality post-heart transplantation² and several single-center studies show the incidence of PGD varies from 2.3 percent to 28.2 percent.³ PGD presents as ventricular dysfunction occurring within 24 hours post-transplant⁴ where there is no identifiable secondary cause such as hyperacute rejection, pulmonary hypertension, or known surgical complications.⁵ The 2013 International Society of Heart and Lung Transplantation (ISHLT) consensus conference established a classification system with a severity scale to enable a more valid and reproducible diagnosis of PGD and improve transplant program comparisons for incidence and treatment options.⁶ **Appendix A** contains the ISHLT consensus statement and severity scale.

Following the conference, the community has sought to further clarify PGD's reach and impact on recipient mortality. For instance, a study applying the 2013 ISHLT consensus classification showed that severe PGD (i.e. need for mechanical circulatory support following transplantation) is associated with poor outcomes.⁷ This two-center study described a 518 patient cohort with a 14 percent prevalence of PGD and a mortality of 54 percent in patients with severe PGD.⁸ Another study evaluating the outcomes of a different cohort of 195 patients found worse 30-day and one-year mortality in patients transplanted who developed moderate and severe PGD, as defined by ISHLT criteria, compared to those diagnosed with mild PGD or no PGD.⁹ The patients also experienced increased intensive care unit (ICU) length of stays, postoperative bleeding, and infections. A consortium of Virginia cardiac transplant programs also examined outcomes and resource utilization following the development of PGD using the ISHLT definition.¹⁰ Of the 718 patients studied, 15.3 percent developed PGD and these patients had longer ICU length of stays, longer duration of intubation, more multi-organ failure, and higher mortality.

Two recent studies from Canada and the United Kingdom also applied the use of the ISHLT PGD criteria to outcomes. In 2019, a study of a 412 patient cohort at the University of Toronto reported significantly elevated hazard ratios of 7.0 and 15.9 for one-year mortality for patients with moderate and severe

² Singh, Sanjeet, et al. "Primary Graft Dysfunction." 805-20.

³ Kobashigawa, Jon, Zuckermann, Andreas, Macdonald, Peter, Leprince, Pascal, Esmailian, Fardad, Luu, Minh, Mancini, Donna, Patel, Jignesh, Razi, Rabia, Reichenspurner, Hermann, Russell, Stuart, Segovia, Javier, Smedira, Nicolas, Stehlik, Josef, and Wagner, Florian. "Report from a Consensus Conference on Primary Graft Dysfunction after Cardiac Transplantation." *The Journal of Heart and Lung Transplantation* 33, no. 4 (2014): 327-40.

⁴ Kobashigawa, Jon, et al. "Report." 337.

⁵ Kobashigawa, Jon, et al. "Report."

⁶ Kobashigawa, Jon, et al. "Report." 327-40.

⁷ Sabatino, Mario, Vitale, Giuseppe, Manfredini, Valentina, Masetti, Marco, Borgese, Laura, Maria Raffa, Giuseppe, Loforte, Antonio, Martin Suarez, Sofia, Falletta, Calogero, Marinelli, Giuseppe, Clemenza, Francesco, Grigioni, Francesco, and Potena, Luciano. "Clinical Relevance of the International Society for Heart and Lung Transplantation Consensus Classification of Primary Graft Dysfunction after Heart Transplantation: Epidemiology, Risk Factors, and Outcomes." *The Journal of Heart and Lung Transplantation* 36, no. 11 (2017): 1217-225.

⁸ Ibid.

⁹ Squiers, John J, Saracino, Giovanna, Chamogeorgakis, Themistokles, MacHannaford, Juan C, Rafael, Aldo E, Gonzalez-Stawinski, Gonzalo V, Hall, Shelley A, DiMaio, J Michael, and Lima, Brian. "Application of the International Society for Heart and Lung Transplantation (ISHLT) Criteria for Primary Graft Dysfunction after Cardiac Transplantation: Outcomes from a High-volume Centre." *European Journal of Cardio-thoracic Surgery* 51, no. 2 (2017): 263-70.

¹⁰ Quader, Mohammed, Hawkins, Robert B, Mehaffey, J. Hunter, Mazimba, Sula, Ailawadi, Gorav, Yarbboro, Leora, Rich, Jeffrey, Speir, Alan, Fonner, Clifford, Wolfe, Luke, and Kasirajan, Vigneshwar. "Primary Graft Dysfunction after Heart Transplantation: Outcomes and Resource Utilization." *Journal of Cardiac Surgery* 34, no. 12 (2019): 1519-525.

PGD, respectively.¹¹ Similarly, a 2019 study examined the incidence, risk factors and outcomes following PGD in all adult heart transplant patients in the United Kingdom from October 2012 to October 2015 using the ISHLT consensus definition¹². For the 450 adults included in this study, the incidence of PGD was 36.2 percent with an increased one-month mortality that was highest in the severe PGD group.

Many donor, recipient, and procedural risk factors have been found to be associated with the development of PGD.¹³ These include donor age, recipient age, recipient inotropic support, and pre-transplant mechanical support.¹⁴ Ischemia time is also considered an independent risk factor.¹⁵ Nonetheless, it is difficult to definitively establish the risk factors, according to researchers, because of the variability in the studies that have been performed. When the OPTN Thoracic Committee first considered a PGD project in 2014, there were concerns that there might be a rising incidence of PGD at that time. However, research studies suggest that it is difficult to determine whether there has been an increase or decrease.^{16,17} Furthermore, it is difficult to know whether future allocation changes, such as the continuous distribution of hearts, may impact the rate of PGD. An understanding of the gravity of this problem is needed to inform future policy making.

Presently, transplant programs are reviewed and compared primarily by 30-day, one- and three-year mortality rates. However, PGD adds considerable morbidity in addition to mortality to transplant recipients' outcomes, especially within the first year following transplant.¹⁸ It is important for a patient to be aware of what the chances are that mechanical support post-transplant will be required, which usually means longer ICU stays, more complications, slower recovery, longer hospitalizations, more need for rehabilitation, or additional prolonged care. Because the OPTN does not collect post-transplant data specific to PGD, it is not possible to make program-level comparisons. This proposal would help in addressing this knowledge gap.

Currently, analysis of PGD is limited due to the lack of available data. In August 2020, the Committee identified PGD as a high priority project and sought to identify the most important parameters needed to identify PGD. They acknowledged that current data collection efforts were inadequate to actually define PGD based on the 2013 ISHLT consensus definition. Data collection that accurately captures the incidence of PGD will enable the heart transplant community to better assess the impact PGD has on the morbidity and mortality of heart transplant recipients. Information collected as part of this initiative will be used to develop future policy options. Furthermore, PGD-specific data may be beneficial to the

¹¹ Foroutan, Farid, and Ross, Heather J. "Primary Graft Dysfunction: The Devil Is in the Details." *Transplantation* 103, no. 2 (2019): 229-30.

¹² Avtaar Singh, Sanjeet Singh, Banner, Nicholas R, Rushton, Sally, Simon, Andre R, Berry, Colin, and Al-Attar, Nawwar. "ISHLT Primary Graft Dysfunction Incidence, Risk Factors, and Outcome: A UK National Study." *Transplantation* 103, no. 2 (2019): 336-43.

¹³ Nicoara, Alina, Ruffin, David, Cooter, Mary, Patel, Chetan B, Thompson, Annemarie, Schroder, Jacob N, Daneshmand, Mani A, Hernandez, Adrian F, Rogers, Joseph G, Podgoreanu, Mihai V, Swaminathan, Madhav, Kretzer, Adam, Stafford-Smith, Mark, Milano, Carmelo A, and Bartz, Raquel R. "Primary Graft Dysfunction after Heart Transplantation: Incidence, Trends, and Associated Risk Factors." *American Journal of Transplantation* 18, no. 6 (2018): 1466.

¹⁴ Nicoara, Alina, et al. "Primary Graft Dysfunction after Heart Transplantation: Incidence, Trends, and Associated Risk Factors." 1466.

¹⁵ Nicoara, Alina, et al. "Primary Graft Dysfunction after Heart Transplantation: Incidence, Trends, and Associated Risk Factors." 1466.

¹⁶ Kobashigawa, Jon, et al. "Report." 328.

¹⁷ Quader, Mohammed, et al. "Primary Graft Dysfunction after Heart Transplantation." 1520.

¹⁸ Kobashigawa, Jon, et al. "Report." 328.

Committee as it develops a continuous distribution allocation framework, which is expected to begin in 2023.

A Subcommittee was created to address the majority of the work, and tasked with defining the project's scope and identifying potential data elements. It was determined that obtaining community feedback would help identify the best data elements to consider and better gauge what data collection would be feasible. As a result, the members developed a Request for Feedback document as a way to gather such information during the January-March 2021 public comment cycle.

Throughout the development of the proposed list of data elements, the Committee requested input and guidance from the OPTN Data Advisory Committee (DAC), which is responsible for monitoring and maintaining all OPTN data to ensure its accuracy, completeness, timeliness, and relevance. The DAC reviewed this data collection proposal to ensure that the data elements proposed for addition were aligned with the OPTN Principles for Data Collection, specifically to allow the OPTN to “develop transplant, donation, and allocation policies.”¹⁹ The DAC endorsed this project in September 2020.

Purpose

Primary graft dysfunction is considered to be fairly common after heart transplantation.²⁰ However, the OPTN does not currently collect post-transplant data that could help identify PGD. The lack of data limits the community's ability to identify the incidence of primary graft dysfunction among recipients as well as associated post-transplant outcomes. This proposal intends to address this limitation by modifying the Heart TRR instrument to collect additional data elements relevant to identifying PGD in heart transplant recipients. This proposal also intends to remove the data element “Airway Dehiscence” from the Post-Transplant section of the TRR as this information is not relevant to heart recipients.

Summary of Request for Feedback Responses

A request for feedback document was submitted for community review during the January-March, 2021 public comment cycle to collect feedback on potential data elements and data collection timeframes.²¹ The data elements proposed went beyond those identified in the ISHLT consensus statement in order to have a more comprehensive dataset to evaluate and the community was asked to provide comment on both the usefulness of the data elements as well as the potential for burden associated with collecting and reporting.

Four general themes arose during public comment. First, public comment feedback indicated overall support for the proposed data collection effort. A second theme involved the mixed responses concerning when the new data elements should be collected. The third theme centered on the community's suggestions for the collection of additional data elements. A fourth public comment theme encouraged the Committee to consider the potential impact on transplant programs associated with any new data collection requirements.

¹⁹ OPTN, *Principles of Data Collection*, <https://optn.transplant.hrsa.gov/members/committees/data-advisory-committee/> (accessed June 29, 2019).

²⁰ Kobashigawa, Jon, et al. "Report."

²¹ OPTN, *Develop Measures for Heart Primary Graft Dysfunction*, <https://optn.transplant.hrsa.gov/media/4340/develop-measures-for-heart-primary-graft-dysfunction.pdf/> (accessed June 29, 2021).

Support for Proposed Post-Transplant Data Elements

Respondents largely supported collection of the post-transplant data elements identified in the Request for Feedback document. Many respondents acknowledged the value of collecting the proposed data elements given the importance of addressing PGD and the current lack of useful data. Several respondents strongly supported the inclusion of device support as a new data element, along with the associated data elements that provide additional details as proposed. Community feedback strongly supported the removal of airway dehiscence from the TRR as it is not applicable to heart transplantation.

Some commenters, including the Data Advisory Committee, expressed concerns about the challenges associated with collecting inotropic support data.²² Respondents pointed out that the level of inotropic support immediately following transplant varies by program.²³ Furthermore, there are multiple, accepted methods for delivering inotropic support to recipients. The feedback received largely supported collecting inotrope information in pre-determined ranges, rather than discrete values to reduce data entry burden. The Committee incorporated this feedback into the proposed data elements outlined in **Table 1** below.

No Clear Consensus for When Data Collection Should Occur

The Request for Feedback document asked the community to indicate how many hours following transplant the data should be collected. Commenters felt strongly that 24 hours was an important data collection time point, in keeping with the ISHLT Consensus Statement which states that PGD be diagnosed within 24 hours post-transplant. Multiple responses recommended collection at 24 hours and at different timeframes beyond 24 hours. Other post-transplant timeframes suggested during public comment included 72 hours, 96 hours, and even seven days. In addition to several post-transplant timeframes, ISHLT's response suggested data should be collected 24 hours prior to transplantation. The most common suggestions were 24 hours and 72 hours after transplantation. The Committee agreed with this recommendation and is proposing that the data be collected at 24 and 72 hours plus or minus 4 hours following the patient's arrival to the ICU. The 4-hour window is being recommended to allow some flexibility around when measurements are taken and reduce the potential need to adapt existing workflows.

Additional Data Elements for Consideration

In addition to the new post-transplant data elements proposed for collection on the TRR form, commenters identified other data elements that they believed would further the community's understanding of PGD. These included consideration of procurement factors and donor factors. Donor information recommended by public comment included specifics about donation after cardiac death (DCD) donors, perfusion device types, and predicted heart mass. Some commenters recommended collecting donor information about the prior use of temporary mechanical cardiac support and

²² OPTN, Public Comment webpage, *Develop Measures for Primary Graft Dysfunction in Hearts*, OPTN Data Advisory Committee comments submitted March 9, 2021, <https://optn.transplant.hrsa.gov/governance/public-comment/develop-measures-for-primary-graft-dysfunction-in-hearts/>, (accessed June 18, 2021).

²³ OPTN, Public Comment webpage, *Develop Measures for Primary Graft Dysfunction in Hearts*, OPTN Transplant Coordinators Committee comments submitted March 19, 2021, <https://optn.transplant.hrsa.gov/governance/public-comment/develop-measures-for-primary-graft-dysfunction-in-hearts/>, (accessed June 18, 2021).

ventricular assist devices (VAD). Several commenters identified collecting information about the presence of amiodarone in the donor as another potentially important data element for determining PGD risk factors. Other donor-related information included sensitization, transfusions, and preoperative hemodynamics.

The Committee acknowledged that the existing data elements currently implemented for collecting DCD, perfusion, and troponin donor information in DonorNet® are adequate for this project's purpose. Other donor-related data elements were determined to add too much complexity to this project as this would modify other data collection instruments and some of the recommendations such as transfusion volumes may be too difficult to collect. The Committee decided to focus the effort on adding relevant data elements to the TRR only.

Proposed Data Collection Effort Should Be Appropriate to Transplant Program Resources

As mentioned, almost all commenters supported collection of the proposed new data elements. Many commenters also recommended the inclusion of donor-specific information as part of this project in order to identify potential risk factors. While respondents were largely in favor of additional data collection, many cautioned against overburdening transplant programs with more data collection and reporting requirements. Organizations including American Society of Transplant Surgeons and the Organization for Donation and Transplant Professionals (NATCO) recommended the Committee propose the least amount of data elements necessary to achieve the desired result in light of the data challenges transplant programs already face.²⁴ Others commented on the need to ensure that all of the proposed data elements have clear definitions so transplant program staff can quickly and consistently identify the appropriate values. The Committee members discussed the associated burden for each data element by evaluating the accessibility and ease of reporting when finalizing the list included in this proposal.

Overview of Proposal

This proposal intends to modify the current Heart TRR by adding the following data elements outlined in **Table 1**. These data will be collected by transplant programs on all heart transplant recipients at 24 and 72 hours (plus/minus 4 hours) after candidate arrives in the ICU. The table below also outlines the values or ranges associated with the data elements as well as the rationale for inclusion. **Table 2** provides additional detail into the inotrope and vasopressor dosing ranges proposed for collection.

²⁴ OPTN, Public Comment webpage, *Develop Measures for Primary Graft Dysfunction in Hearts*, American Society of Transplant Surgeons comments submitted March 23, 2021 and NATCO comments submitted March 22, 2021, <https://optn.transplant.hrsa.gov/governance/public-comment/develop-measures-for-primary-graft-dysfunction-in-hearts/> (accessed June 17, 2021).

Table 1: Proposed Data Elements for Addition to the Transplant Recipient Registration Form (TRR) Associated with Primary Graft Dysfunction (PGD)

Data Element	Value	Description / Rationale
Primary Graft Dysfunction (PGD)	Yes or No	PGD refers to graft dysfunction occurring immediately after transplant, requiring greater than typical medical support, or mechanical support. PGD is graft dysfunction not attributable to hyperacute rejection, acute rejection, antibody mediated rejection, surgical implant issues, or acute infarction. Data collection may help identify and understand post-transplant morbidity and mortality impact.
Left Ventricular Dysfunction (LVD)	Yes or No	LVD is defined by common society standards, and the presence of LVD can be determined using imaging and/or hemodynamics (e.g.: low ejection fraction (EF), cardiac index < 2.2). LVD is considered the most important aspect of graft performance following transplant (other than gross graft failure).
Right Ventricular Dysfunction (RVD)	Yes or No	RVD is determined using imaging and/or hemodynamics (e.g.: dilated hypokinetic right ventricle (RV) on echo, low EF, central venous pressure (CVP)>15, CVP/pulmonary capillary wedge (PCW)>0.63, pulmonary artery pulsatility index (PAPi)<1.85, cardiac index (CI) under 2.2.) RVD is considered important for identifying whether PGD involves the left, right, or both ventricles.
Left Ventricular Ejection Fraction (LVEF)	Percentage	The following definition is associated with LVEF in other OPTN data collection forms: The ratio of the volume of blood the heart empties during systole to the volume of blood in the heart at the end of diastole expressed as a percentage (typically normal is over 50% and abnormal below 50%). LVEF is the major component when determining LVD, and considered important for determining whether PGD involves the left, right, or both ventricles.
Right Atrial Pressure (RAP)	mm Hg	RAP is defined by common society standards. RAP is available from hemodynamic data.
Pulmonary Capillary Wedge Pressure (PWCP)	mm Hg	PWCP is defined by common society standards and is available from hemodynamic data. PWCP is an important element for determining presence of PGD because it measures left ventricular filling pressure, which is elevated when LVD is present.
Pulmonary Artery (PA) Systolic Pressure Pulmonary Artery Diastolic Pressure	mm Hg	PA systolic and diastolic pressures are defined by common society standards. PA systolic and diastolic pressures are routinely and continuously measured after heart transplantation by use of a pulmonary artery catheter. PA systolic and diastolic pressures are elevated when LVD or other causes of pulmonary hypertension are present.

Data Element	Value	Description / Rationale
Cardiac Output ²⁵ (CO)	Liters / minute	The following definition is associated with CO in other OPTN data collection forms: “The volume of blood pumped out of the heart. Cardiac output is expressed as volume of blood per unit time or liters per minute. Cardiac output can be calculated using the Fick method (oxygen consumption divided by arteriovenous oxygen difference) or by the thermodilution technique, using a Swan-Ganz catheter.” CO is a standard measurement used when defining heart failure. CO is elevated when LVD or other causes of pulmonary hypertension are present.
Support device	Yes or No	Support device information is currently collected on OPTN’s TCR and TRR forms as “Patient on life support?” and/or “Patient on ventricular assist device?,” where responses are yes or no for both. Obtaining presence of a support device is important because device use reflects sicker candidates and would confirm the suspicion that the need for a support device is associated with increased risk of PGD.
If yes, to support device	Right, Left, or Biventricular	PGD can occur in either ventricle, or both ventricles. Knowing the ventricle is important as the type of PGD based on the affected ventricle carries different treatment options and different prognoses. Obtaining this information will help identify the incidence of PGD and also risk factors for each type of PGD and risks of the different support devices used.
Type of support device ²⁶	Drop down list of devices	Device type can reflect severity of PGD and each device type has unique management and complication profiles that could differently impact outcomes.
Inotrope support	Drop down list of medications (Select all that apply) Dosings ²⁷	There is wide variety among transplant programs on the type and amount of inotrope support used routinely post-transplant and when PGD ensues. Data collection is necessary because such program-specific decisions can have a strong effect on patient outcomes. All heart transplant recipients are on inotropes following transplant. Comprehensively understanding the use of inotropes, along with the presence of PGD, may help with analyses of risk factors and patient outcomes.
Nitric Oxide following transplant	Yes or No	Nitric Oxide is not always administered to treat PGD, but to treat a patient’s pulmonary hypertension to prevent PGD or graft dysfunction and thereby may indicate PGD
Flolan following transplant	Yes or No	Flolan is not always administered to treat PGD, but to treat a patient’s pulmonary hypertension to prevent PGD or graft dysfunction and thereby may indicate PGD

²⁵ Reported cardiac output will be used to calculate cardiac index in UNetSM.

²⁶ See **Appendix B** for the list of support devices

²⁷ See Table 2: List of Inotropes and Vasopressors Ranges To Be Collected for Inotrope Support

Table 2: List of Inotropes and Vasopressors Ranges To Be Collected for Inotrope Support

Inotrope	Dose (mcg/kg/min)	Dose (mcg/min)
Epinephrine	<ul style="list-style-type: none"> • None • >0 – ≤0.05 • >0.05 – ≤1.0 • >1 	--
Milrinone	<ul style="list-style-type: none"> • None • >0 – ≤0.3 • >0.3 – ≤0.5 • >0.5 	--
Dobutamine	<ul style="list-style-type: none"> • None • >0 – ≤3 • >3 – ≤7.5 • >7.5 	--
Dopamine	<ul style="list-style-type: none"> • None • >0 – ≤3 • >3 – ≤7.5 • >7.5 	--
Vasopressors	Dose (mcg/kg/min)	Dose (mcg/min)
Levo (Norepinephrine – Levophed)	<ul style="list-style-type: none"> • None • >0 – ≤0.05 • >0.05 – ≤0.1 • >0.1 	<ul style="list-style-type: none"> • None • <5 • 5 – <12 • ≥12
Vaso (Vasopressin – Pitressin)	--	<ul style="list-style-type: none"> • None • >0 – <0.05 • 0.05 – <0.08 • ≥0.08
Neo (Phenylephrine – Neosynephrine)	--	<ul style="list-style-type: none"> • None • >0 – <100 • 100 – <200 • ≥200

The Committee acknowledged that inotropes are most commonly administered in micrograms per kilograms per minute (mcg/kg/min) while vasopressors are commonly administered in micrograms per minute (mcg/min). Levo is commonly administered in both units and the data collection instrument will allow the entry in the user’s preferred unit.

As supported by the community, the Committee is proposing ranges for inotrope and vasopressor dosing to allow easier reporting. The ranges are intended to indicate a high, medium, and low dose of each therapy. The Committee determined these ranges by referencing how high dose inotropes are described in existing OPTN policy.²⁸ Other ranges were based on dosing recommendations provided in clinical reference handbooks.

²⁸ OPTN, *Policy 6.1.C.ii Multiple Inotropes or a Single High Dose Inotrope and Hemodynamic Monitoring*, https://optn.transplant.hrsa.gov/media/4190/bp_202012_guidance_addressing_use_ped_heart_exceptions.pdf (Accessed June 29, 2019)

Proposed removal from the Heart TRR

When reviewing existing data elements on the Heart TRR, the Committee identified "Airway Dehiscence" for potential removal because it is not relevant to heart transplants. Community feedback received in response to the Request for Feedback supported removing this data element.

NOTA and Final Rule Analysis

The Committee submits this proposal for consideration under the authority of the OPTN Final Rule, which states, "An organ procurement organization or transplant hospital shall, as specified from time to time by the Secretary, submit to the OPTN...information regarding transplantation candidates, transplant recipients, [and] donors of organs..."²⁹ Additionally, the OPTN shall "[m]aintain records of all transplant candidates, all organ donors and all transplant recipients[.]"³⁰ As authorized by NOTA, the OPTN is required to "collect, analyze, and publish data concerning organ donation and transplants."³¹ This proposal intends to add collection of PGD-related data elements on heart transplant recipients on Office of Management and Budget (OMB)-approved OPTN data collection instruments.

Implementation Considerations

Member and OPTN Operations

Operations affecting Histocompatibility Laboratories

This proposal is not anticipated to affect the operations of histocompatibility laboratories.

Operations affecting Organ Procurement Organizations

This proposal is not anticipated to affect the operations of organ procurement organizations.

Operations affecting Transplant Hospitals

This proposal will require transplant program staff to become familiar with the changes to the Heart TRR and data definitions. The additional data collection may require adjustments to existing workflows and require additional staff time for data entry.

Operations affecting the OPTN

This proposal will require programming in UNetSM to update the existing Heart TRR form within Transplant Information Electronic Data Interchange[®] (TIEDI), an OPTN data entry system for transplant centers, OPOs, and histocompatibility laboratories across the country.

The OPTN Contractor has agreed that data collected pursuant to the OPTN's regulatory requirements in §121.11 of the OPTN Final Rule will be collected through OMB approved data collection forms. Therefore, after OPTN Board approval, the forms will be submitted for OMB approval under the

²⁹ 42 CFR §121.11(b)(2).

³⁰ 42 CFR §121.11(a)(1)(ii).

³¹ 42 U.S.C. § 274(b)(2)(I).

Paperwork Reduction Act of 1995. This will require a revision of the OMB-approved data collection instruments, which may impact the implementation timeline.

Projected Fiscal Impact

This proposal is projected to have a fiscal impact on the OPTN and a minimal impact on transplant hospitals, but it is not anticipated to have any fiscal impact on organ procurement organizations or histocompatibility laboratories.

Projected Impact on the OPTN

This proposal will require programming in UNetSM to update the existing Heart TRR within TIEDI.

Projected Impact on OPOs

There is no expected impact for OPOs.

Projected Impact on Transplant Hospitals

There is an expected minimal impact on transplant hospitals. Additional staff time will be required for training prior to implementation and additional staff time will be required for completing the transplant recipient registration form with the proposed data elements. Training is expected to require 1 to 2 hours and the additional data entry is estimated to require an additional 30 to 60 minutes per form. Collecting and reporting on the proposed data elements is not expected to significantly alter existing processes or workflows.

Projected Impact on Histocompatibility Laboratories

There is no expected impact for histocompatibility laboratories.

Post-implementation Monitoring

Member Compliance

This proposal will not change the current routine monitoring of OPTN members. Any data entered into UNetSM may be reviewed by the OPTN, and members are required to provide documentation as requested.

Policy Evaluation

The OPTN will analyze PGD-related metrics and outcomes as data become available, no more frequently than annually for two years after implementation. Timeline is subject to change based on the results. Data will be presented in tabular and graphical form as appropriate.

The following metrics, and any others subsequently requested by the Committee, will be evaluated as data become available:

- PGD data elements will be summarized using counts and percentages for categorical data elements and mean, median, interquartile range (IQR), minimum and maximum for continuous data elements.

- Incidence of PGD will be summarized overall and by de-identified center, OPTN region and Donor Service Area.
- Six-month patient and graft survival by PGD (left, right and overall) are subject to sample size.
- Distribution of donor characteristics (including DCD/non-DCD and machine perfusion) among recipients with and without PGD

Conclusion

Primary Graft Dysfunction has a substantial effect on the morbidity and mortality of heart transplant recipients. The new data elements the Committee is proposing for addition to the Heart TRR form are not currently collected by the OPTN and will provide valuable insights into the occurrence of PGD in heart recipients. The Committee understands that several years of data collection may be necessary before there will be enough data for an appropriate analysis to identify PGD in heart transplant recipients and assess the impact PGD has on recipient outcomes post-transplant. However, this data will allow the opportunity to have informed, evidence-based discussions when developing future policies.

The Committee is requesting feedback about the following:

Data elements

- Are there additional data elements that should be considered for inclusion? Exclusion?
- Do any of the proposed data elements create unreasonable burden to collect and report?
- Would any modification reduce the level of effort required?
 - Could any modifications allow better alignment with patient data currently reported in a program's electronic medical records (EMR)?

Timing of data collection

- Does offering a window of plus or minus 4 hours at 24 and 72 hours from arrival at ICU reduce the need to modify existing workflows?
 - Will this window significantly impact the ability to compare patient outcomes?
- Is arrival at ICU an appropriate starting point?
- Should additional time points be considered in addition to 24 and 72 hours (plus or minus 4 hours)?

Inotrope and Vasopressor Reporting

- Are the proposed ranges of inotrope and vasopressor dosing applicable to pediatric patients?
- Are the proposed ranges appropriately stratified to indicate high, medium, and low dosages?
- Is collecting vasopressor dosing in mcg/kg/mins with the option of also reporting in mcg/mins reasonable or is there another preferred unit of measure that would allow easier reporting or alignment with what is reported in a program's EMR?

Other

- What challenges would this request present for transplant programs responsible for collecting the additional data?
- Is the data requested readily accessible?

- Should the data collection be part of the “Clinical Information: POST TRANSPLANT” section of the TRR, or is there a more appropriate section?
- Are there differences and/or similarities between adult and pediatric PGD the Heart Committee should consider as part of its future reviews?
- How can the Committee ensure the data collection is reported consistently by all transplant programs?

Appendix A: ISHLT Consensus Statements on Primary Graft Dysfunction (PGD) and Definition of Severity Scale for PGD

Consensus Statements

1. Graft dysfunction is to be classified into PGD or secondary graft dysfunction where there is a discernible cause such as hyperacute rejection, pulmonary hypertension, or known surgical complications (e.g., uncontrolled bleeding).
2. The diagnosis of PGD is to be made within 24 hours after completion of the cardiac transplant surgery.
3. PGD is to be categorized into PGD-LV or PGD-RV.
4. A severity scale for PGD-LV will include mild, moderate or severe grades based on specified criteria.
5. Risk factors are categorized in terms of donor, recipient, or surgical procedural factors. Optimization of risk factors and improved allocation and matching of donors and recipients may result in decreased incidence of PGD.
6. Medical management with inotropic support should initially be instituted for PGD. The use of levosimendan may also be helpful. For PGD-RV, nitric oxide and phosphodiesterase inhibitors may be helpful.
7. Mechanical circulatory support of PGD such as ECMO is indicated when medical management is not sufficient to support the newly transplanted graft.
8. Retransplantation for severe PGD may be indicated in select patients if risk factors are minimal.
9. All patients in whom mechanical circulatory support is placed directly into the heart should have a biopsy performed at that time.
10. It was recommended that an autopsy should be performed in all patients who are diagnosed with PGD and subsequently expire.
11. Potential future studies include creation of a PGD registry, impact of preservation solutions on PGD, mechanistic studies to understand pathophysiology of PGD, and study of donor management to minimize PGD, among others.

Definition of Severity Scale for Primary Graft Dysfunction (PGD)

1. PGD Left ventricle (PGD-LV):	<i>Mild PGD-LV: One of the following criteria must be met:</i>	LVEF \leq 40% by echocardiography, <i>or</i> Hemodynamics with RAP > 15 mm Hg, PWCP > 20 mm Hg, CI < 2.0 L/min/m ² (lasting more than 1 hour) requiring low-dose inotropes
	<i>Moderate PGD-LV: Must meet one criterion from I and another criterion from II:</i>	I. <i>One</i> criteria from the following: Left ventricular ejection fraction \leq 40%, <i>or</i> Hemodynamic compromise with RAP > 15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m ² , hypotension with MAP < 70 mm Hg (lasting more than 1 hour) II. <i>One</i> criteria from the following: i. High-dose inotropes—Inotrope score > 10 ^a <i>or</i> ii. Newly placed IABP (regardless of inotropes)
	<i>Severe PGD-LV</i>	Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP.
2. PGD-right ventricle (PGD-RV):	Diagnosis requires either both i and ii, or iii alone:	i. Hemodynamics with RAP > 15 mm Hg, PCWP < 15 mm Hg, CI < 2.0 L/min/m ² ii. TPG < 15 mm Hg and/or pulmonary artery systolic pressure < 50 mm Hg, <i>or</i> iii. Need for RVAD

BiVAD, biventricular assist device; CI, cardiac index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVAD, right ventricular assist device; TPG, transpulmonary pressure gradient.

^a Inotrope score = dopamine (x1) + dobutamine (x1) + amrinone (x1) + milrinone (x15) + epinephrine (x100) + norepinephrine (x100) with each drug dosed in $\mu\text{g}/\text{kg}/\text{min}$.

Source: Kobashigawa, Jon, Zuckermann, Andreas, Macdonald, Peter, LePrince, Pascal, Esmailian, Fardad, Luu, Minh, Mancini, Donna, Patel, Jignesh, Razi, Rabia, Reichenspurner, Hermann, Russell, Stuart, Segovia, Javier, Smedira, Nicolas, Stehlik, Josef, and Wagner, Florian. "Report from a Consensus Conference on Primary Graft Dysfunction after Cardiac Transplantation." *The Journal of Heart and Lung Transplantation* 33, no. 4 (2014): 337-38.

Appendix B: List of Mechanical Circulatory Support Devices Associated with Certain Adult Heart Statuses

Dischargeable VADs	Non-Dischargeable VADs	Percutaneous Devices	Total Artificial Hearts
Evaheart	Abiomed AB5000	Biomedicus	AbioCor
Heartmate II	Abiomed BVS 5000	Cardiac Assist Tandem Heart	SynCardia CardioWest
Heartmate III	Berlin Heart EXCOR	Cardiac Assist Protek Duo	Other Specify
Heartsaver VAD	Biomedicus	CentriMag (Thoratec/Levitronix)	—
Heartware HVAD	CentriMag (Thoratec/Levitronix)	Impella Recover 2.5	—
Jarvik 2000	Maquet Jostra Rotaflow	Impella Recover 5.0	—
ReliantHeartAssist 5	Medos	Impella CP	—
ReliantHeart aVAD	PediMag (Thoratec/Levitronix)	Impella RP	—
Worldheart Levacor	Terumo Duraheart	Maquet Jostra Rotaflow	—
Other Specify	Thoratec IVAD	PediMag (Thoratec/Levitronix)	—
—	Thoratec PVAD	Other Specify	—
—	Toyobo	—	—
—	Ventricor VentrAssist	—	—
—	Other Specify	—	—

Notes: There are no device brands for Venoarterial Extracorporeal Membrane Oxygenation (VA ECMO) or Intra-aortic Balloon Pump (IABP). The “Other Specify” category is included for instances where a candidate’s device brand is not identified.

Source: OPTN website (accessed on June 29, 2021):

https://optn.transplant.hrsa.gov/media/2457/heart_device_brand_background.pdf