



At a glance

Title: Data Collection on Uterus Transplant Recipient Outcomes

Sponsoring Committee: Vascularized Composite Allograft Transplantation

What is current practice and why address it?

Uterus transplantation in the U.S. is rapidly growing. As such, the health of the recipient and post-transplant outcomes is a key concern to the OPTN and the transplant community. Currently, very little data about children born to women who have had a uterus transplant is reported to the OPTN, and only on a voluntary basis. In order to monitor post-transplant outcomes and the health of the recipient, feedback is requested to inform a future project about what data to report on children born to uterus transplant recipients.

What's the concept?

- To consider what, if any, additional, appropriate data that could be reported about children born to uterus transplant recipients
 - At birth
 - As follow-up
- Consider how long after birth should information be reported
- Identify any challenges a requirement to report additional information could present

What this feedback could accomplish

- Could help develop future data reporting requirements

What this concept wouldn't do

- Collect unnecessary data on children born to uterus transplant recipients
- Mandate data collection at this time

Terms you need to know

- **Vascularized Composite Allograft (VCA):** Transplant of multiple structures, which may include connective tissue, skin, bone, muscles, blood vessels, and nerves. For example, face and hand transplants are two of the most well-known types of VCA transplants
- [Click here to search the OPTN glossary](#)

Request for Feedback

Measuring Transplant Outcomes by Collecting Data on Children Born to Uterus Recipients

OPTN Vascularized Composite Allograft Transplantation Committee

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Measuring Transplant Outcomes by Collecting Data on Children Born to Uterus Recipients

Sponsoring Committee: Vascularized Composite Allograft
Public Comment Period: January 22, 2020 – March 24, 2020

Executive Summary

For women with absolute uterine factor infertility, uterine transplantation restores reproductive anatomy by allowing them to conceive, experience gestation, and become mothers.¹ Because of this, the OPTN Vascularized Composite Allograft (VCA) Transplantation Committee (Committee) recognizes that the sole purpose of a uterus transplant is to enable pregnancy and birth. Furthermore, the Committee recognizes the need to collect data at birth and the subsequent development of a child in order to measure post-transplant outcomes and to monitor the health of the recipient.

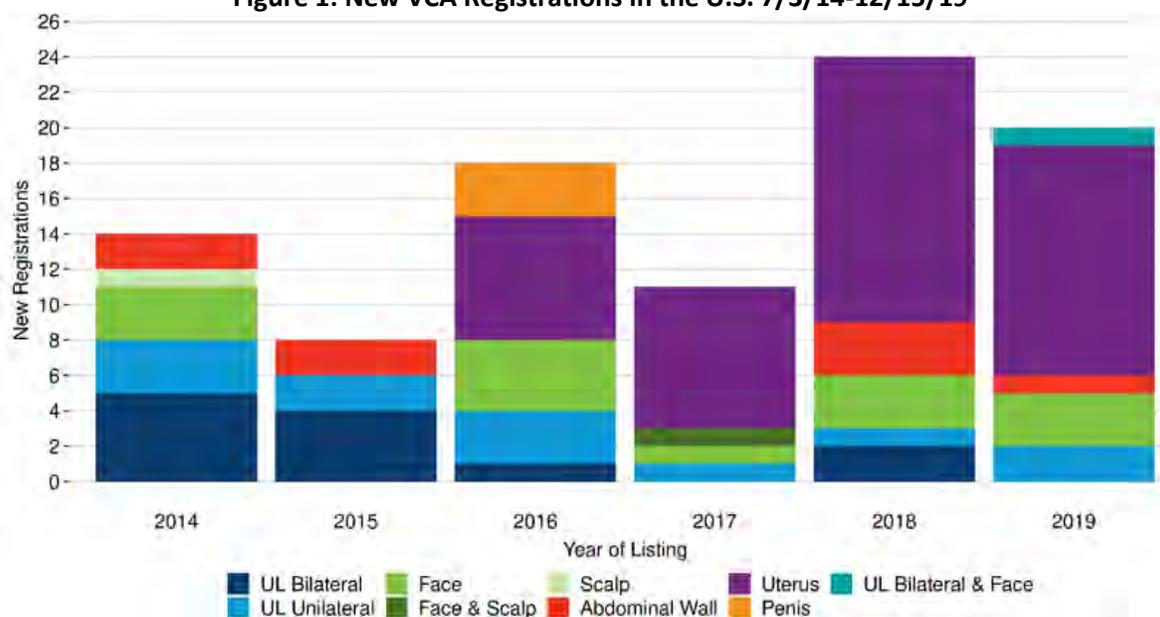
Currently, the OPTN is aware of four children that have been born from uterus transplant recipients in the U.S. However, the data collected on these children are limited and voluntarily submitted to the OPTN by transplant programs. In order to ensure both safety and efficacy, the Committee is requesting community feedback to consider for a future data collection proposal on children born from uterus transplant recipients. This document is not a proposal, but instead is a request for discussion, feedback, and suggestions on potential data elements and the timing of data collection that should be considered. This request for feedback aligns with the OPTN Strategic Goal for improving transplant recipient outcomes, by supporting the development of data submission requirements that monitor transplant recipient safety and post-transplant outcomes of uterus transplantation.

¹ Benjamin P. Jones, Srdjan Saso, Isabel Quiroga, Joseph Yazbek, and J. Richard Smith, "UK criteria for uterus transplantation: a review", *British Journal of Obstetrics and Gynecology*, 126, 12, (2019): 1507-1508. doi.org/10.1111/1471-0528.15844

Purpose

For the past three years, over half of the candidates added to the OPTN VCA waiting list were uterus candidates. (Figure 1) Thus far, uterus recipients have given birth to eight children in the U.S. However, the data collected on these children is limited and voluntarily submitted to the OPTN by transplant programs. The Committee agrees that with an increasing number of uterus transplants being performed, along with limited and non-compulsory data collection on children born from uterus recipients, challenges may arise in determining transplant outcomes and monitoring the health of the recipient. Moreover, it is important that the OPTN monitors the data of these children, because it is not known what the post-transplant outcomes are from having a fetus develop within a transplanted uterus. This document presents the transplant community with an opportunity to discuss and provide feedback that should be considered for a future data collection proposal.

Figure 1: New VCA Registrations in the U.S. 7/3/14-12/15/19²



Background

Uterus transplantation and the data surrounding its outcomes is an emerging and developing area in transplantation. The desired outcome, gestation and birth, is different than any other transplant type. Monitoring the safety, risks, and outcomes associated with this type of transplant is necessary and is done for all organ transplants as part of OPTN responsibilities. This type of data collection does present some unique questions as there are medical outcomes not typically considered by the OPTN.

Following uterus transplantation, the main issues for uterus transplant recipients are successful embryo implantation as well as issues related to immunosuppressive medications and the avoidance of rejection, and infection prevention.³ When a recipient undergoes a uterus transplant,

² Based on OPTN data as of December 15, 2019.

³ Flyckt, Rebecca, et al. "Uterine Transplantation: Surgical Innovation in the Treatment of Uterine Factor Infertility." *Journal of Obstetrics and Gynaecology Canada* 40, no. 1 (2018): 86-93 doi: 10.1016/j.jogc.2017.06.018

immunosuppression medications are needed to maintain the transplant, typically for several years in order to carry a fetus to delivery, and longer if the recipient decides to have more children.⁴ The major adverse effects of immunosuppressive medications for a developing fetus in recipients of non-uterus transplants have been shown to be prematurity, low birth weight, and birth defects.⁵ However, such risks may be similar or different for a child born from a transplanted uterus versus a child that has been born from a non-transplanted uterus.⁶

Experts in the field of uterus transplantation have recognized the potential unknown risks to the recipient and fetus, along with the lack of transplant outcome data. Uterus transplant is a surgically complex operation with special considerations regarding vasculature. Ensuring adequate blood flow to the organ is critical both for graft survival as well as the ability to host a viable future pregnancy. Compromised blood supply can contribute to placental insufficiency which in turn can have negative effects on development of a fetus as well as potential health implications or complications for the pregnant mother such as preeclampsia.⁷ These risks are noted by Flyckt et al (2018) who “recommended uterine transplant protocols provide for frequent assessments of fetal wellbeing, especially to monitor for the development of pregnancy induced hypertension and preeclampsia in the mother as well as potential growth restriction in the fetus.”⁸

These examples highlight the need to develop data collection requirements that will adequately address the unique needs in evaluating uterus transplantation and allow transplant programs the opportunity to have evidence-based discussions on post-transplant outcomes and the overall safety of uterus transplantation.

Earlier in 2019, the Committee began discussing the data collected on VCA transplant recipients, specifically uterus recipients. During these preliminary discussions, Committee members identified a need to develop a set of data that transplant programs would be required to report to the OPTN at birth. These data would specifically focus on collecting data on both the uterus recipient and the newborn infant.

This request for feedback focuses on data related to the offspring resulting from uterus transplant. In addition, the Committee has a separate proposal titled “VCA Data Collection” on proposed modifications to the data collected on the uterus recipient through required OPTN VCA recipient registration (TRR) and transplant recipient follow-up (TRF).

In order to solicit feedback from experts, the Committee developed the OPTN Uterus Workgroup (Workgroup). The Workgroup was comprised of VCA Committee members and stakeholders from uterus transplant programs. Invited obstetric and gynecological experts provided consultation to these efforts. Members of the workgroup noted challenges of collecting data on children born from uterus recipients, primarily how the OPTN would collect data beyond birth. The Workgroup also reviewed and discussed

³ John A. Robertson. “Other women’s wombs: uterus transplants and gestational surrogacy.” *Journal of Law and the Biosciences* vol. 3,1 (2016): 68-86. doi:10.1093/jlb/lsw011

⁴ *ibid.*

⁶ Mats Brännström, et al. “First clinical uterus transplantation trial: a six-month report.” *Fertility and Sterility* Vol. 101, No. 5 (2014): 1228-36. doi: 10.1016/j.fertnstert.2014.02.024

⁷ Laura Donovan. “Pushing the boundaries: Uterine transplantation and the limits of reproductive autonomy.” *Bioethics* (2018): 32: 489–498. doi.org/10.1111/bioe.12531. Judith Daar, and Sigal Klepstein. “Refocusing the ethical choices in womb transplantation.” *Journal of Law and the Biosciences* (2016): 383-388. doi:10.1093/jlb/lsw031. Dionne Tannetta, and Ian Sargent. “Placental Disease and the Maternal Syndrome of Preeclampsia: Missing Links?” *Current Hypertension Rep* (2013): 15:590–599. DOI 10.1007/s11906-013-0395-7. Colin Sibley. “Treating the dysfunctional placenta”. *Journal of Endocrinology* (2017) 234, R81–R97. https://doi.org/10.1530/JOE-17-0185.

¹⁰ Rebecca Flyckt, et al. “Uterine Transplantation: Surgical Innovation in the Treatment of Uterine Factor Infertility.”

the data elements currently collected from uterus transplant programs on a voluntary basis. The Workgroup suggested collecting two additional data elements at birth, including length of stay (LOS) in the hospital and the physical length of the infant. The Workgroup considered both LOS and length of the infant to be measures of post-transplant outcomes, because LOS is indicative of whether the neonate required admission to the intensive care unit (such as for prematurity), and length of the infant helps indicate whether the neonate was born with a growth restriction.

Next, the Committee reconvened to discuss the Workgroup's feedback. During this discussion, the Committee members agreed that data should be collected on children at birth in order to monitor post-transplant outcomes as well as overall safety for the transplant recipient, the mother. The Committee members had varied opinions as to the timeframes for post-natal data collection (e.g.: from 2-18 years of age), the possible impact of confounding environmental factors on data collected, concerns regarding low sample sizes and logistical challenges to collecting this data. In terms of confounding environmental factors, the Committee discussed how certain factors, such as a child's education, could impact long-term data collection. However, the Committee also acknowledged that if there were negative effects on these children as a result from having developed in a transplanted uterus, then such post-transplant outcomes may not be seen for many years. Committee members also pointed out that the recording of most of the current standard of care developmental milestones can be collected by the child's mother and the data be submitted directly to the transplant centers. Based on the discussion, the Committee concluded that further community and stakeholder outreach was necessary in order to determine how other external organizations may be conducting data collection on children and for how long after birth.

Also during their discussions, Committee members considered the ethics of long term data collection. Members of the OPTN Ethics Committee were consulted in order to understand any potential ethical issues. The feedback from this discussion focused on ensuring the consent of both the mother (from birth to 17 years of age) and child (after 18 years of age), along with how transplant programs would ensure proper follow-up. VCA Committee leadership considered these issues while developing a request for community feedback.

The Committee reached out to numerous stakeholder and community organizations, including the American Academy of Pediatrics (AAP), Transplant Pregnancy Registry International, Society for Assisted Reproductive Technology (SART), and the Society for Reproductive Surgeons (SRS). Overall, there was general support from these organizations in requiring data collection on children born from uterus recipients. The Transplant Pregnancy Registry International provided the Committee with an annual report detailing data voluntarily reported on children born from all organ transplant recipients. Though their annual report did not contain data collection on children born from uterus recipients, the report did draw some conclusions from data collected from recipients having undergone the use of assisted reproductive technologies.

Further discussions with SART indicated that the SRS may be pursuing a similar initiative to collect data on children born from uterus recipients. Similarly, the International Society of Uterus Transplantation (ISUTx) has sought to develop an international registry that would collect data on uterus transplant patients, children and donors.⁹ However, it was noted that the SRS initiative may still be in preliminary discussions and would need to secure funding. Furthermore, though all of the above organizations may support registry development, such registries would not have the authority to require data collection or data reporting from U.S. transplant programs. Because of this, transplant programs could choose not to

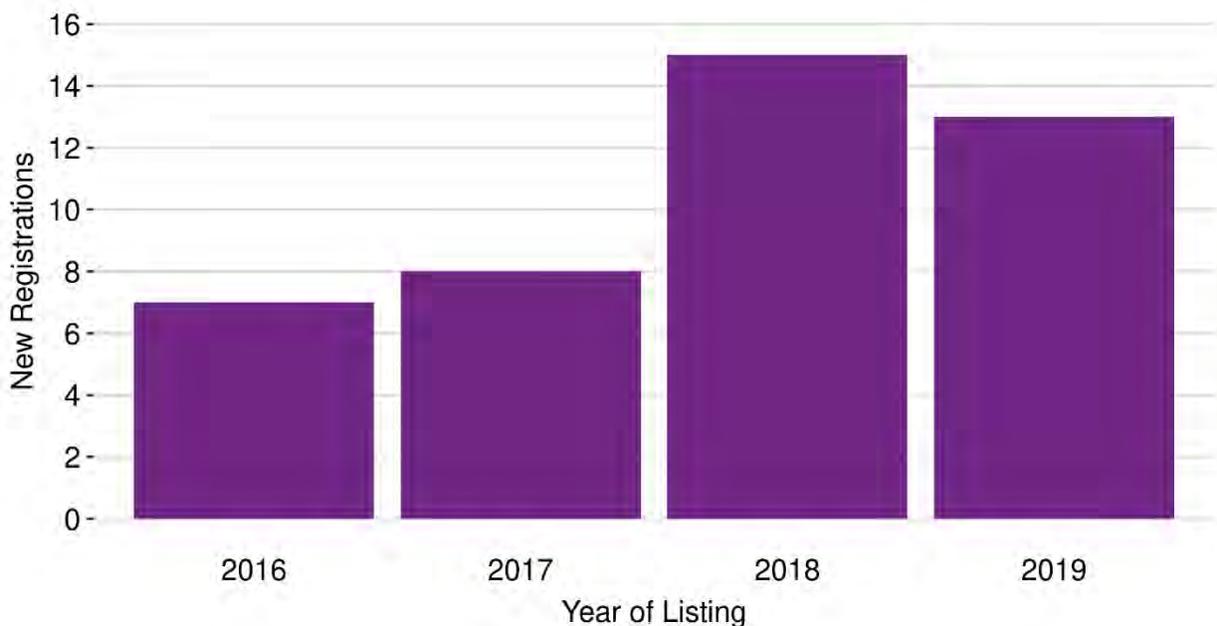
⁹ International Society of Uterus Transplantation. Accessed January 2, 2020. <http://www.isutx.org/about/#history-row>.

submit data about complicated births or other poor outcomes to a registry, and neither the registry, nor the transplant community would be aware. Voluntary exclusion of such data would skew understanding of post-transplant outcomes, and hinder the transplant community from properly assessing the transplant outcomes and health of the recipient.

The American Society for Reproductive Medicine (ASRM) issued a position statement on uterus transplantation in 2018. In their position paper, they acknowledge that as uterus transplantation has become more common therapeutic procedure that neonatal and long term pediatric outcomes need to be collected. The OPTN is acknowledged as the organization authorized to collect data on uterus VCA transplants. It is also stated that “The breadth of the data mandated should be extensive enough to allow the needed analysis of the effectiveness, risks, and overall utility of this emerging and rapidly proliferating organ transplant”.¹⁰ The need for standardized reporting and data evaluation on uterus recipients as well as their offspring is noted in other recent published articles on the state of uterus transplant.¹¹

The OPTN has collected data that is not required by OPTN policy on children born from uterus recipients since the first resulting birth in 2017. Such data collection is projected to increase in the future, since more candidates are being registered on the uterus transplant waiting list.

Figure 2: VCA Uterus Candidates added to Waiting List in the U.S. 1/1/2016 - 11/15/2019¹²



As such, it will be important that data collection is required in order to ensure transplant programs continue to report necessary data on transplant outcomes and safety. Moreover, both OPTN members and non-members may request this data on children born to uterus recipients. In conclusion, the

¹⁰ “American Society for Reproductive Medicine position statement on uterus transplantation: a committee opinion.” *Fertility and Sterility*, Volume 110, Issue 4 (2018): 605-610. doi.org/10.1016/j.fertnstert.2018.06.017.

¹¹ S. Zaami, A. Di Luca, and E. Marinelli. “Advancements in uterus transplant: new scenarios and future implications.” Mats Brännström et al. “Uterus Transplantation: A Rapidly Expanding Field.” *Transplantation*, 102 no. 4, (2018). DOI: 10.1097/TP.0000000000002035.

¹² Based on OPTN data as of December 15, 2019.

Committee determined that the following were supportive reasons for having the OPTN collect data on children born to uterus recipients:

- The OPTN has a responsibility to monitor post-transplant outcomes
- The OPTN has already been collecting this data on a voluntary basis
- The OPTN would have the authority to require transplant programs to report data at birth and beyond birth
- The data collected may be requested by OPTN and non-OPTN members for certain authorized purposes (such as de-identified, aggregate data for research)

The Committee concluded that the information gathered from their work and outreach revealed a need to collect data on children born from uterus recipients. The Committee agreed that additional discussion and feedback were needed from the transplant community to further assess the data elements and timeframes to collect data on children born from uterus recipients. This feedback will be considered for a data collection proposal in the future.

Potential data collection

In terms of regulatory alignment, the OPTN Final Rule¹³ requires OPTN members to submit to the OPTN information that the Secretary deems appropriate and HHS has determined that the OPTN should collect information on children born from mothers who had uterus transplants. Such data collection would require the submission of official OPTN data that are not presently collected by the OPTN. The OPTN Board of Directors approved the OPTN Principles of Data Collection in 2006.¹⁴ The Principles state that institutional members must provide sufficient data to enable the OPTN to:

- a) Develop transplant, donation and allocation policies
- b) Determine if Institutional Members are complying with policy
- c) Determine Member-specific performance
- d) Ensure patient safety when no alternative sources of data exist
- e) Fulfill the requirements of the OPTN Final Rule

The feedback requested in this paper aligns with the principles outlined above because there are no alternative sources of data that exist. From outreach conducted thus far, the Committee identified that the OPTN is the only entity that currently collects data on all the children born from uterus recipients in the U.S. Furthermore, the OPTN could require data collection on these children, which would ensure that the transplant community monitors the safety of the uterus transplant recipient. Requiring this data collection will inform the OPTN and transplant community about the transplant outcomes and risks from having a uterus transplant. This will also support public trust.

Based on previous discussions, current voluntarily reported data, and consultation with stakeholders, the Committee is seeking feedback on the following data elements that could potentially be collected on children born to uterus recipients. **Table 1** outlines the data elements that are currently reported to the OPTN voluntarily and the data elements the Committee proposes requiring data collection in the future:

¹³ OPTN Final Rule 42 C.F.R §121.8, Accessed January 2, 2020. <https://www.govinfo.gov/content/pkg/CFR-2018-title42-vol1/xml/CFR-2018-title42-vol1-part121.xml>.

¹⁴ OPTN, Principles of Data Collection. Accessed January 2, 2020. <https://optn.transplant.hrsa.gov/members/committees/data-advisory-committee/>

Table 1: Comparison of Data Elements

Current Data Elements Collected Voluntarily at Birth	Proposed Data Elements to be Required at Birth
Neonate status (alive/deceased)	Neonate status (alive/deceased)
Neonate status date (last time infant was seen by the program)	Neonate status date (last time infant was seen by the program)
Neonate gestational age(week or weeks/days)	Obstetric estimate of gestation (week or weeks/days)
Neonate APGAR scores (one and five minute)	Neonate APGAR scores (one and five minute)
Neonate delivery weight	Birthweight
Neonatal complications at birth (yes/no)	Neonatal complications at birth (yes/no); If yes, an open text field would be provided
	Neonate delivery length
	Neonate length of stay

The data elements proposed in **Table 1** were based on Committee and Workgroup feedback, discussion and other standardized data collection instruments, such as the U.S. Standard Certificate of Live Birth.¹⁵ Also, these proposed data elements would allow the OPTN to properly assess the outcomes and efficacy of a uterus transplant, including the well-being of the child. For example, if a trend was seen whereby children born from uterus transplant recipients were born with birth defects, or required extended hospital stays, then this would be an important outcome for the OPTN to measure, as it relates to the effectiveness of the transplant.

Additional data elements collected post-birth may allow the OPTN to identify any patterns or trends, which could help inform the transplant community about any possible impacts of uterus transplants. The effects of a child having been born in a non-native uterus are not known, and such possible effects may not be seen until years after birth. Additional data collection past birth would allow the OPTN to identify short and long term outcomes associated with uterus transplant, thereby informing recipient safety and future OPTN policies. The Committee briefly discussed the inclusion of developmental milestones for evaluating a child past birth. For example, the Centers for Disease Control and Prevention (CDC) has established developmental milestones for assessing the well-being of a child, starting at two months of age and progressing to five years old.¹⁶ The Committee suggests requiring developmental information on children born from uterus recipients past birth, and is requesting feedback as to which data elements to collect and for how long to collect the data.

The Committee requested feedback from multiple OPTN Committees, including the Data Advisory and Pediatric Committees, regarding the data elements and timeframes for data collection. All of these OPTN Committees agreed that additional feedback and input from the transplant community was necessary. There were concerns regarding the logistical challenges of collecting data on these children past birth. The Committee discussed these challenges, such as transplant programs obtaining data from pediatricians. It was mentioned that some of these providers may not be affiliated with the transplant hospital or that they may be located a great distance away. There was also concern regarding the administrative burden associated with additional data collection, and it was suggested that mitigating

¹⁶ U.S. Standard Certificate of Live Birth. Accessed January 2, 2020. <https://www.cdc.gov/nchs/data/dvs/birth11-03final-ACC.pdf>

¹⁷ "CDC's Developmental Milestones:" Centers for Disease Control and Prevention. Accessed January 2, 2020. <https://www.cdc.gov/ncbddd/actearly/milestones/index.html>

this burden would entail allowing programs to report a child as “lost to follow-up” for data collection past birth.¹⁷ Importantly, the Committee noted that the child’s caregiver completes most data collection instruments and thus, the caregiver could submit the data directly to the transplant program, which could submit the necessary information to the OPTN. Based on these discussions, there was overall support from these OPTN Committees to pursue this data collection.

Conclusion

Unlike other solid organ transplants, the sole purpose of a uterus transplant is to enable pregnancy and birth. Therefore, it is necessary to monitor data on children born from uterus transplant recipients in order to measure post-transplant outcomes and to monitor the health of the recipient. Moreover, as the number of uterus transplant candidates registered with the OPTN increases, it is necessary to require data collection on children born from uterus recipients in order to analyze post-transplant outcomes of uterus transplantation. The intent of this request for input is to solicit feedback from the community on the outlined set of data questions. This feedback will be taken into consideration for a future data collection proposal to further assess the outcomes and safety of uterus transplantation.

The Committee is requesting feedback on the content and ideas in this paper in general, and specifically on the following questions:

- What data, if any, should transplant programs be required to report at birth on children born to uterus recipients?
- What data, if any, should transplant programs be required to submit as follow-up on children born to uterus recipients?
- How long after birth should the OPTN require transplant programs to report data on the child?
- What would be the challenges that this type of data requirement would present?
- Are there additional consent, Health Insurance Portability and Accountability Act (HIPAA), Institutional Review Board (IRB) or other regulatory challenges specific to collecting data on pediatric patients that should be considered?

¹⁸ The “lost to follow-up” designation is currently allowed on OPTN data collection instruments. Transplant programs may designate recipients as “lost to follow-up” on OPTN data collection instruments when they encounter difficulty contacting a recipient for periodic wellness exams, or obtaining a recipient’s health information from another provider. The result of this designation is the transplant program no longer receives automated data collection instruments from the OPTN for a given recipient. The effect of this designation to the OPTN is incomplete recipient data.