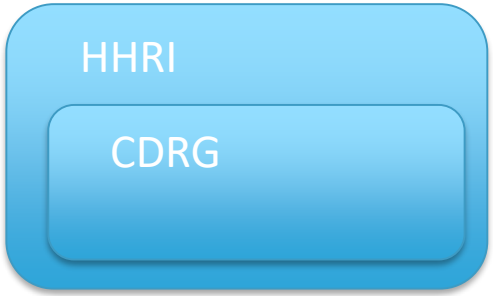
SCIENTIFIC REGISTRY OF TRANSPLANT RECIPIENTS

Real-World Evidence Submission: A Case Study in Lung Transplantation

Tim Weaver, MS

SRTR Background

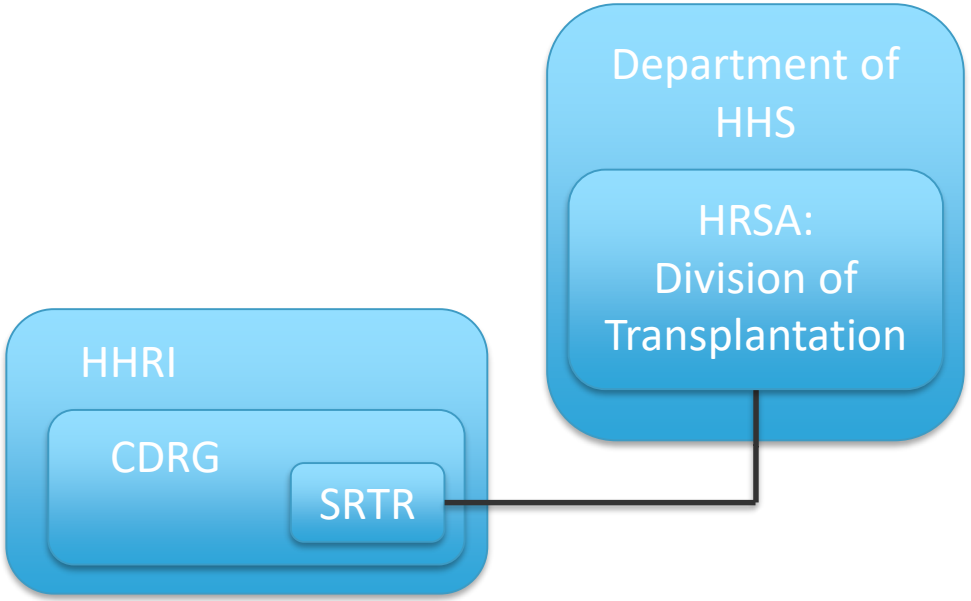
The Chronic Disease Research Group (CDRG) is a division of Hennepin Healthcare Research Institute (HHRI)



SRTR Background

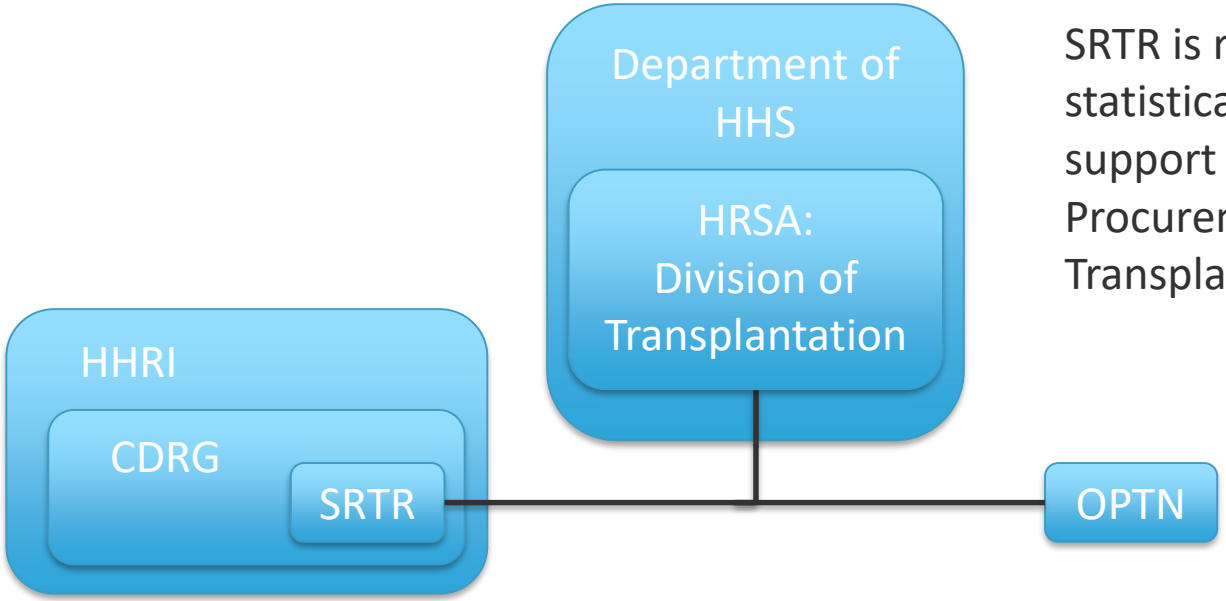
CDRG operates the Scientific Registry of Transplant Recipients (SRTR)

SRTR Background



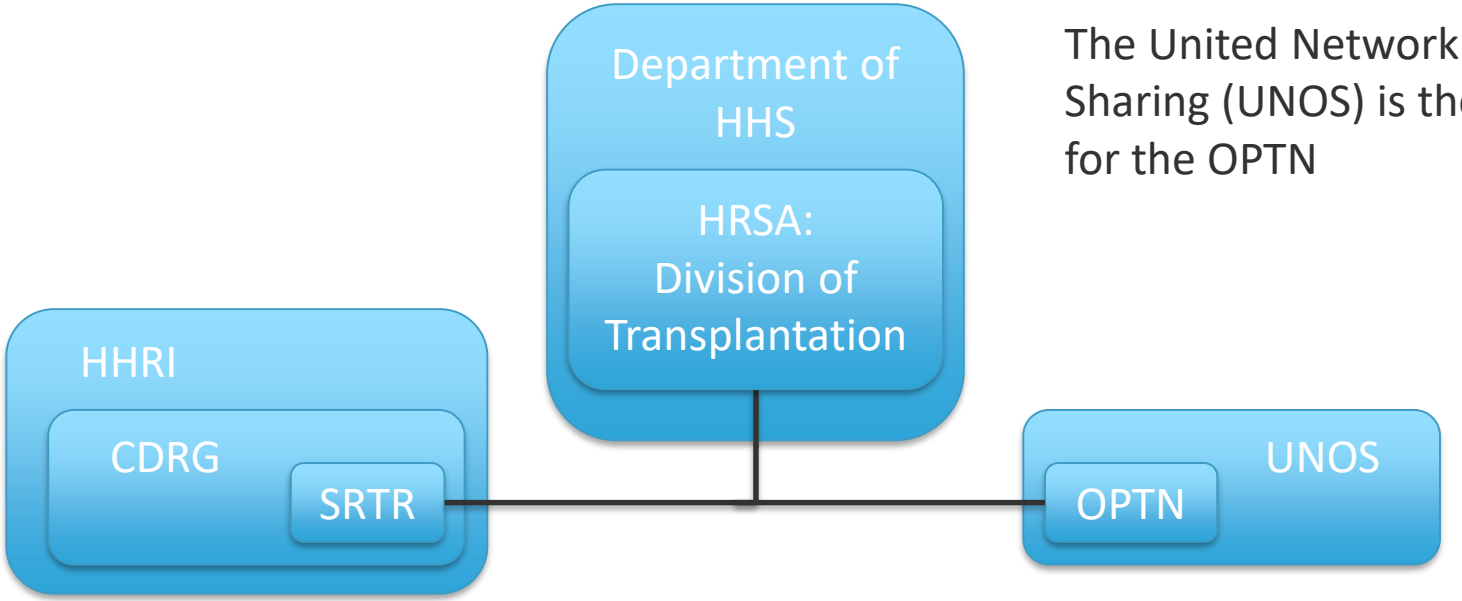
CDRG operates the SRTR under contract from the Division of Transplantation, Healthcare Systems Bureau, Health Resources and Services Administration (HRSA), US Department of Health and Human Services (HHS)

SRTR Background



SRTR is responsible for providing statistical and other analytic support to the Organ Procurement and Transplantation Network (OPTN)

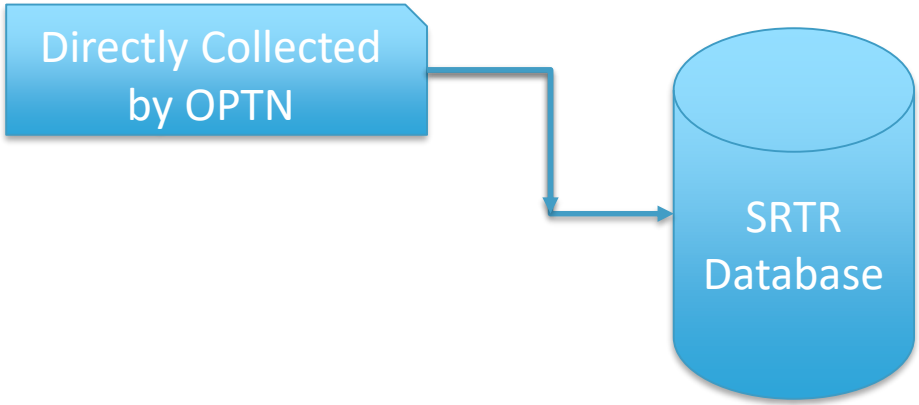
SRTR Background



The United Network for Organ Sharing (UNOS) is the contractor for the OPTN

The SRTR Database

Primary Data Source



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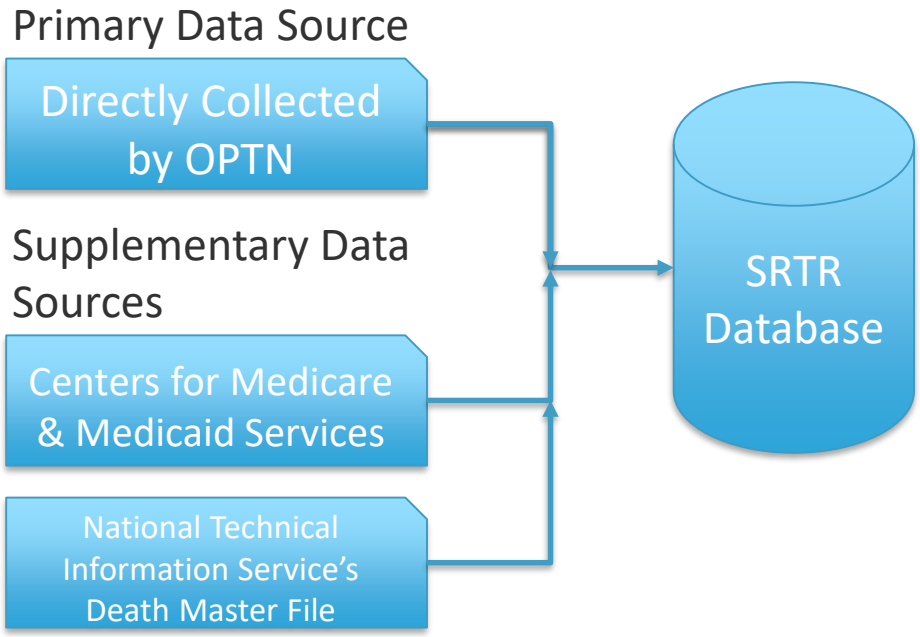

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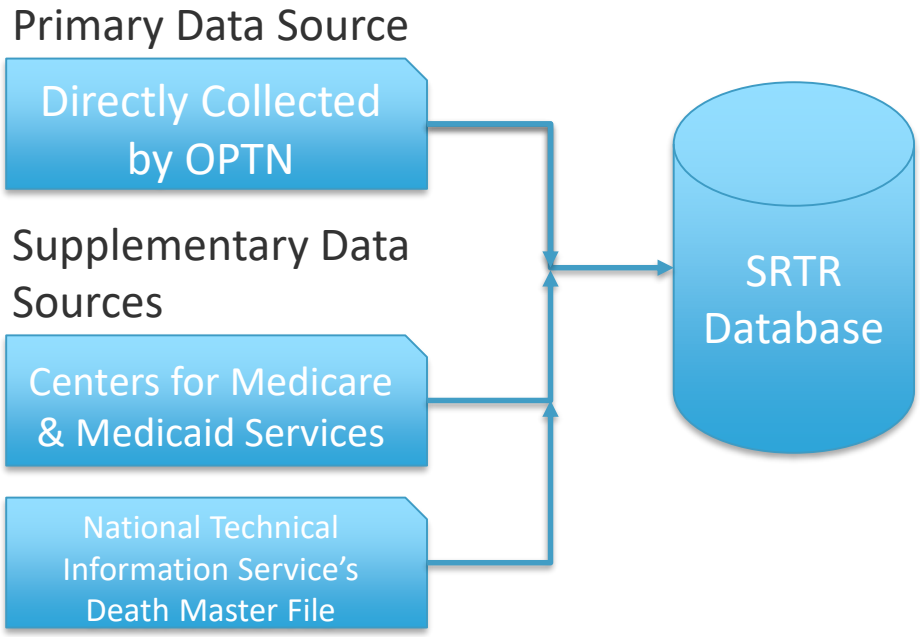
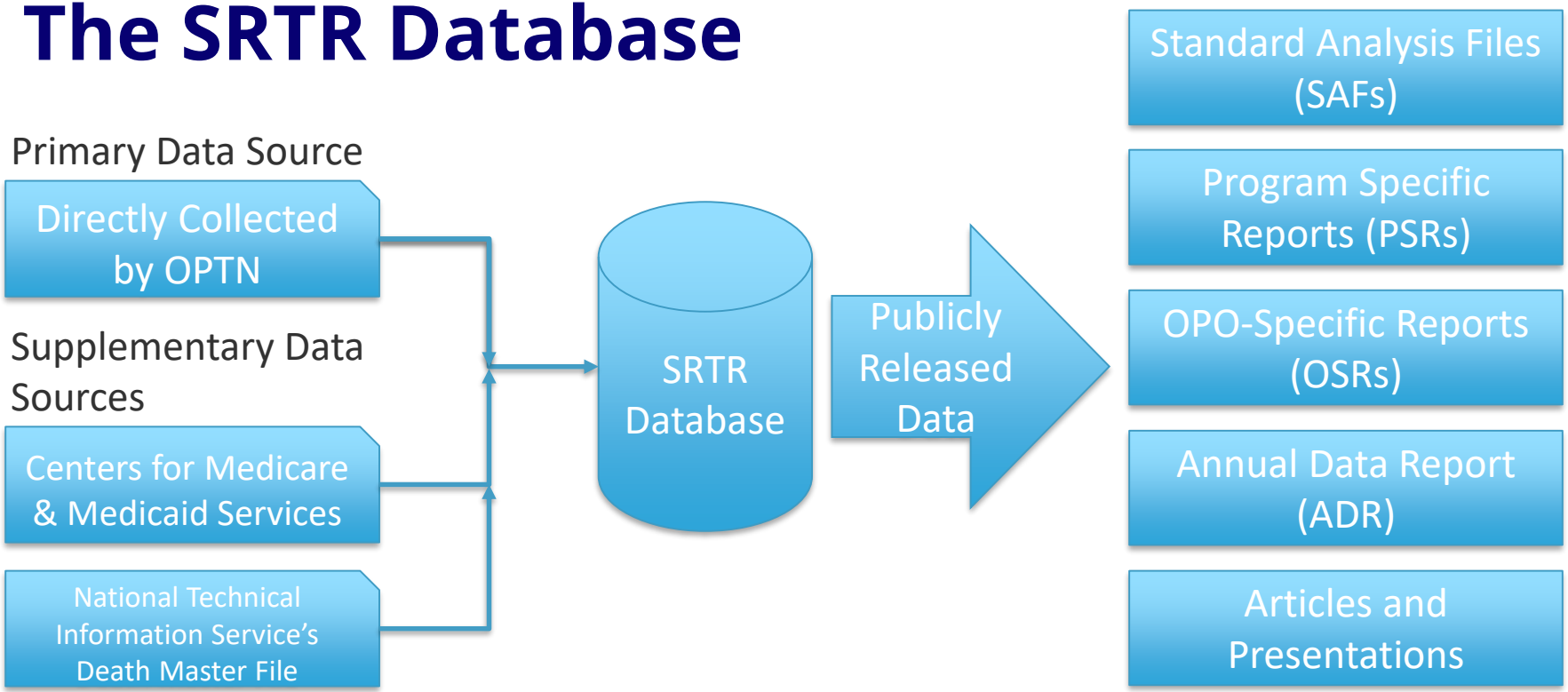


The US Department of Health and Human Services (HHS) Final Rule requires:

- SRTR make all data available to the public while honoring applicable statutes and requirements for patient privacy
- SRTR to respond to requests from the public for data needed for bona fide research or analytic purposes, to assess the performance of HRSA contractors and transplant programs, and for other purposes

The SRTR Database



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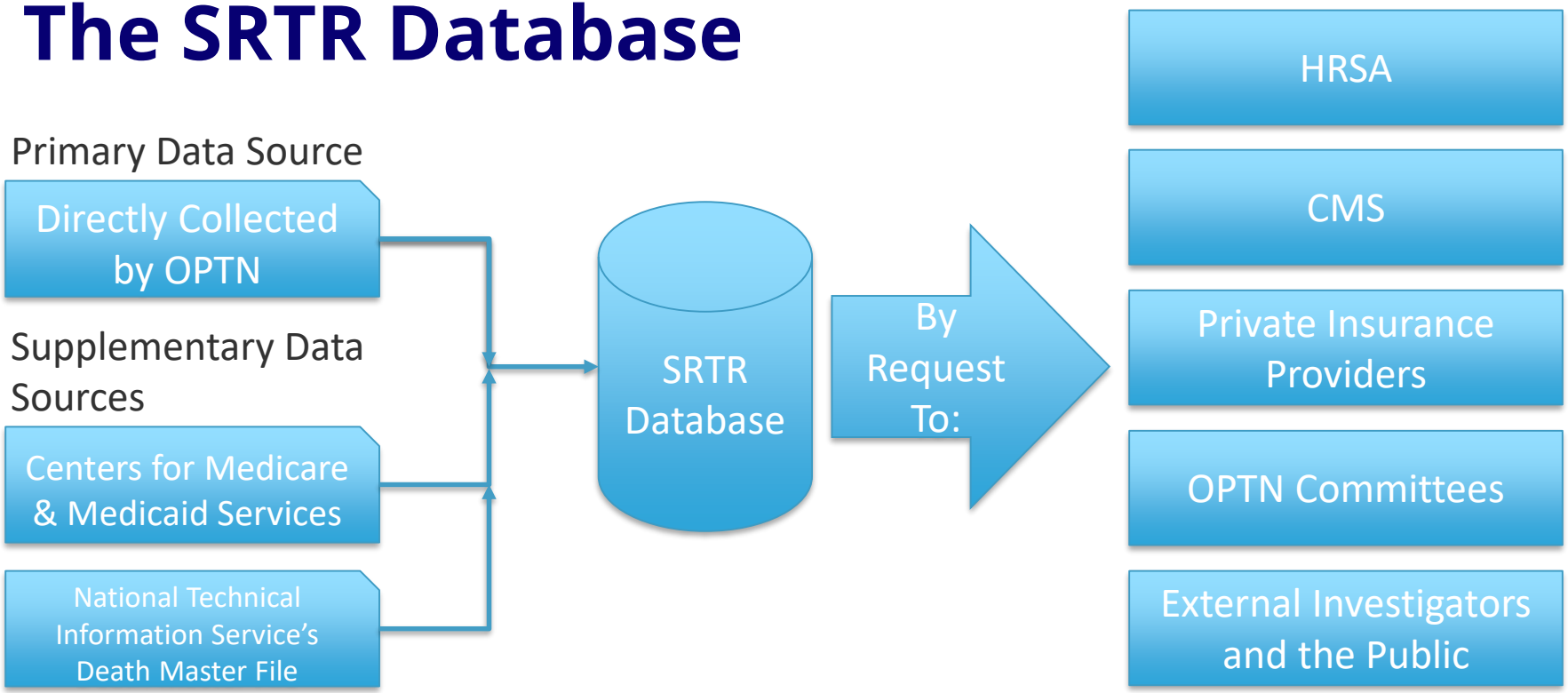


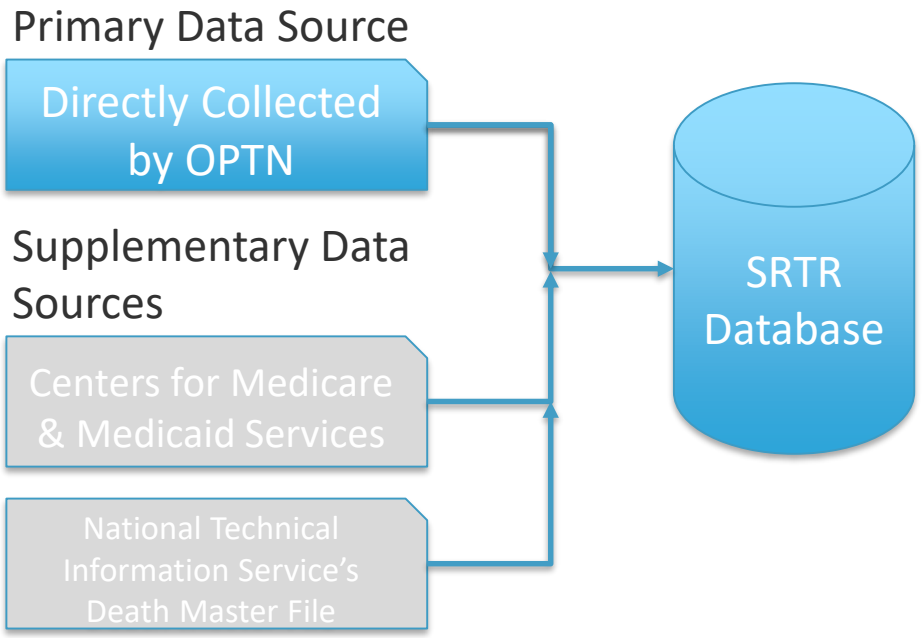
The SRTR Database

OPTN Data Sources:

- Transplant programs
- OPOs
- Histocompatibility laboratories

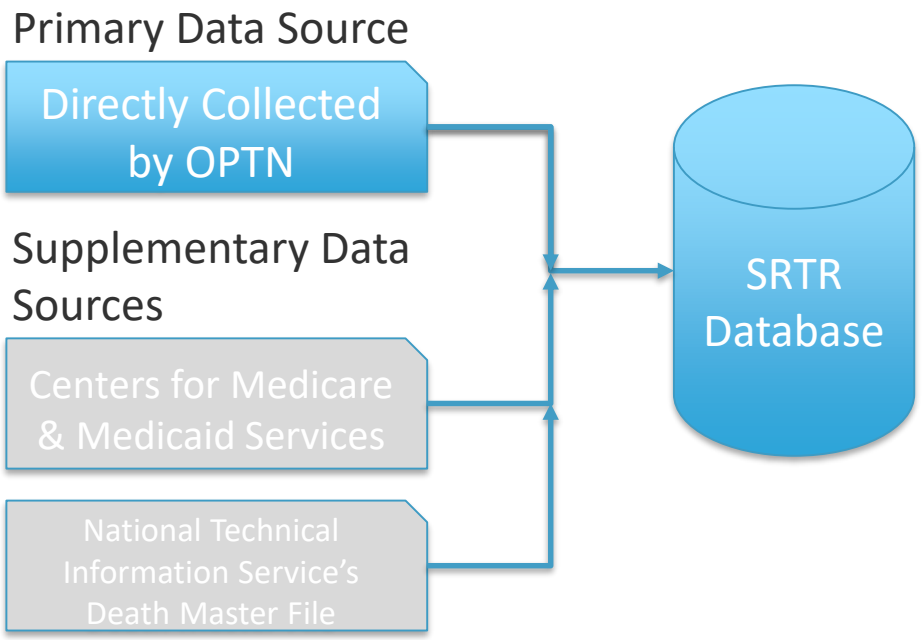
Internet-based System, Unet, allows transplant programs to:

- Register candidates for transplant
- Match donated organs to candidates
- Submit data on donors, candidates, and recipients before and after transplant



The SRTR Database

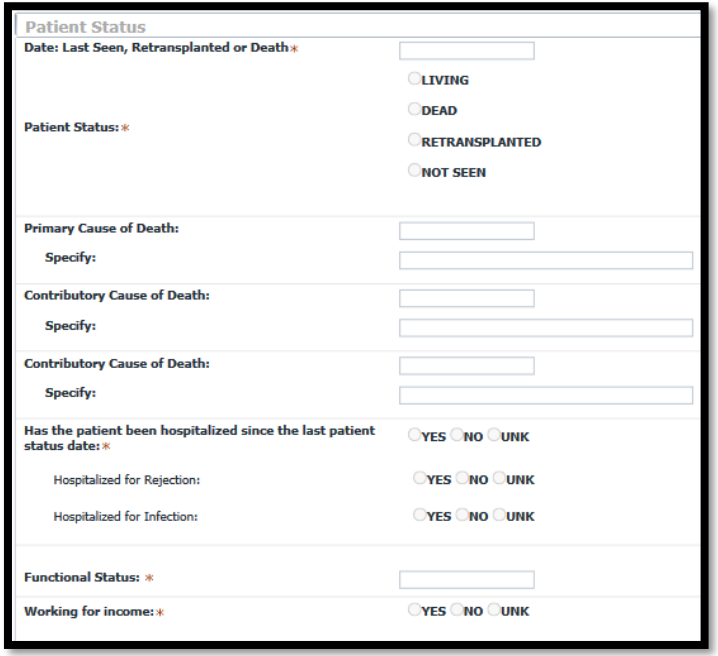
UNet system includes information on every transplant and organ donation that has occurred in the US since October 1, 1987



Observational Data

This study relied on the observational data from the SRTR database

Compared to a clinical trial there is a tradeoff between breadth and depth of the data



Patient Status

Date: Last Seen, Retransplanted or Death *

Patient Status: *
- LIVING
- DEAD
- RETRANSPLANTED
- NOT SEEN

Primary Cause of Death:

Specify:

Contributory Cause of Death:

Specify:

Contributory Cause of Death:

Specify:

Has the patient been hospitalized since the last patient status date: * YES NO UNK

Hospitalized for Rejection: YES NO UNK

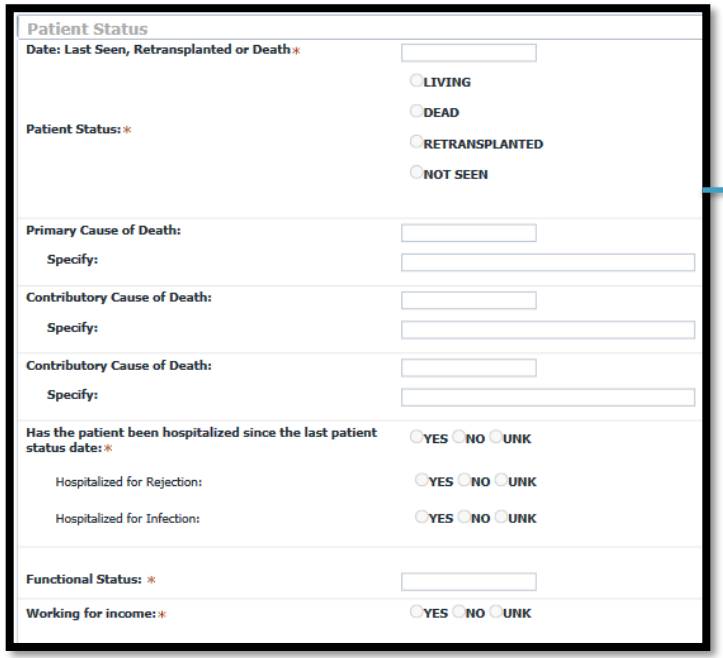
Hospitalized for Infection: YES NO UNK

Functional Status: *

Working for income: * YES NO UNK

Detail of: “Adult Thoracic Transplant Recipient Follow-Up Worksheet”

Observational Data



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Detail of: "Adult Thoracic Transplant Recipient Follow-Up Worksheet"

Primary Data Source

Directly Collected by OPTN

Supplementary Data Sources

Centers for Medicare & Medicaid Services

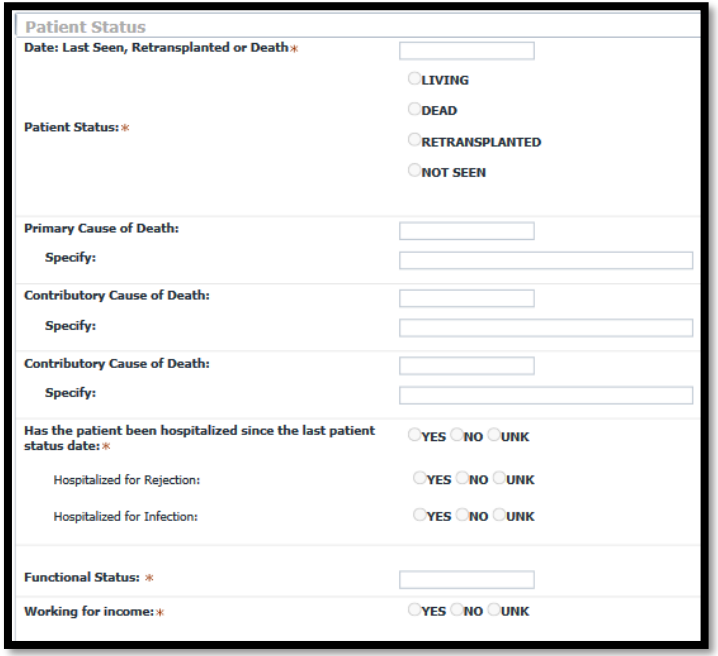
National Technical Information Service's Death Master File

SRTR Database

Observational Data

The SRTR database is broad; recall it includes information on *every* transplant and organ donation that has occurred in the US since October 1, 1987

Information is (mostly) limited to the specific questions (and wording) on the collection forms; thus the database information is not always deep



Patient Status

Date: Last Seen, Retransplanted or Death *	
Patient Status: *	LIVING DEAD RETRANSPLANTED NOT SEEN
Primary Cause of Death:	
Specify:	
Contributory Cause of Death:	
Specify:	
Contributory Cause of Death:	
Specify:	
Has the patient been hospitalized since the last patient status date: *	YES NO UNK
Hospitalized for Rejection:	YES NO UNK
Hospitalized for Infection:	YES NO UNK
Functional Status: *	
Working for income: *	YES NO UNK

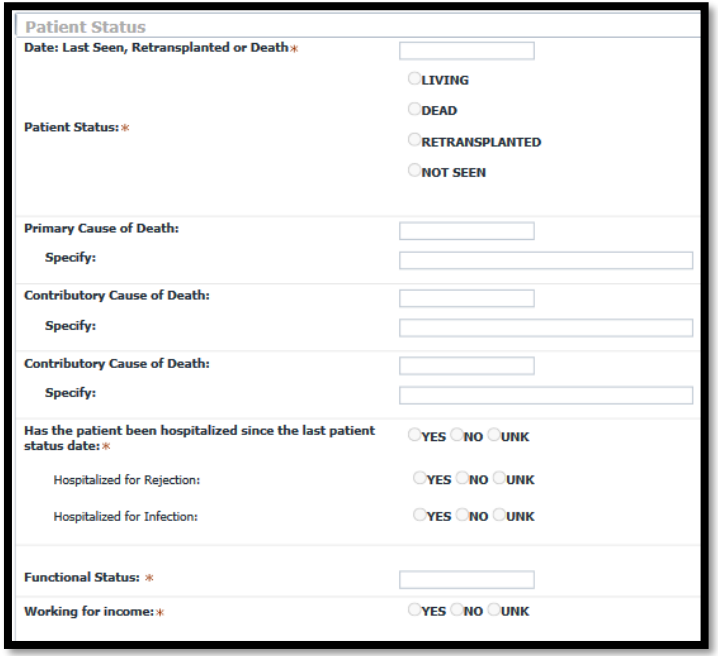
Detail of: “Adult Thoracic Transplant Recipient Follow-Up Worksheet”

Observational Data: Outcomes

The data collection guidelines and wording of questions determined the form the analysis could take

OPTN Policy “18.1 Data Submission Requirements” states: The organ specific transplant recipient follow-up (TRF) must be submitted to the OPTN within either of the following:

- 30 days after the six-month and annual anniversary of the transplant date until the recipient’s death or graft failure
- 14 days from notification of the recipient's death or graft failure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Specify:

Contributory Cause of Death:

Specify:

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Hospitalized for Rejection: YES NO UNK

Hospitalized for Infection: YES NO UNK

Functional Status: *

Working for income: * YES NO UNK

Detail of: “Adult Thoracic Transplant Recipient Follow-Up Worksheet”

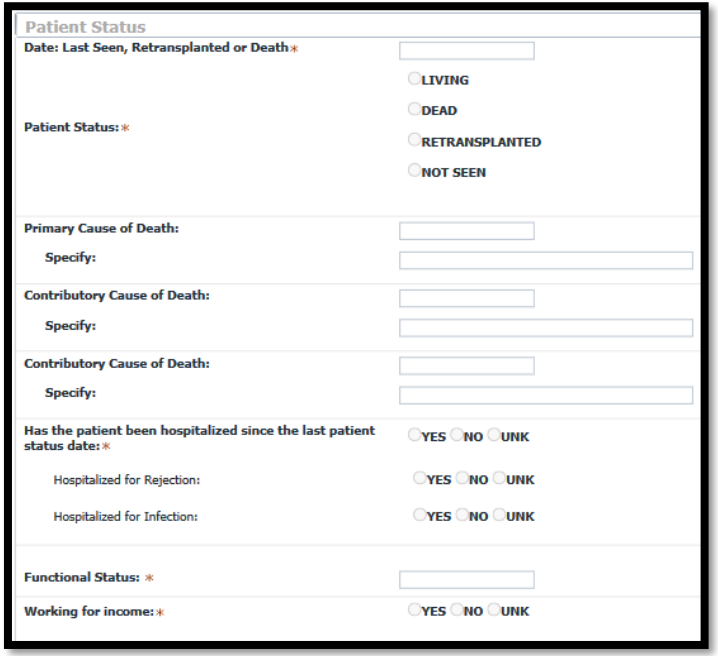
Observational Data: Outcomes

Transplant recipient follow-up (TRF) must be submitted within 14 days of death/GF

The TRF asks for a specific death date and GF date (not shown)

This allowed for time to event analysis for death and GF outcomes:

- Kaplan-Meier survival estimates
- Proportional hazard models

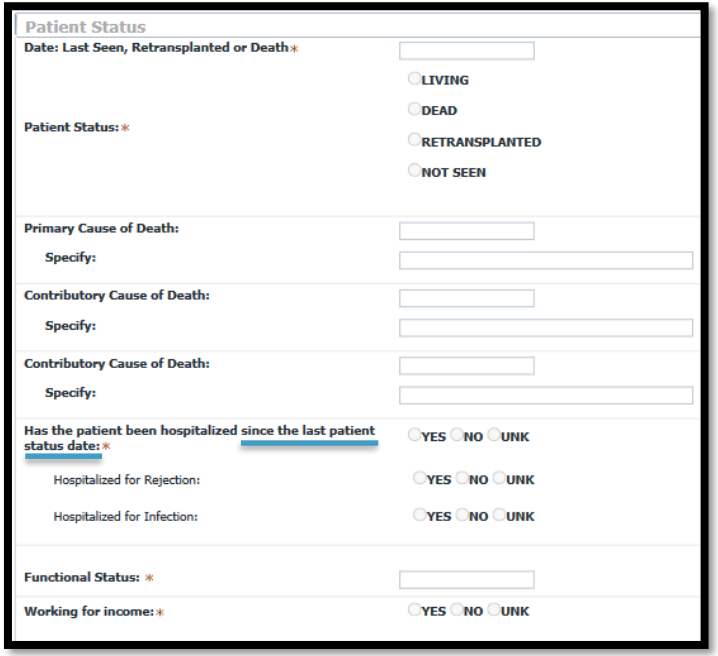


Detail of: “Adult Thoracic Transplant Recipient Follow-Up Worksheet”

Observational Data: Outcomes

Without death or GF the TRF must be submitted within 30 days after the six-month and annual anniversary of the transplant date until the recipient's death or graft failure

The TRF does not ask for specific dates of other outcomes



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Contributory Cause of Death:

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Contributory Cause of Death:

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Hospitalized for Infection: YES NO UNK

Functional Status: *

Working for income: * YES NO UNK

Detail of: "Adult Thoracic Transplant Recipient Follow-Up Worksheet"

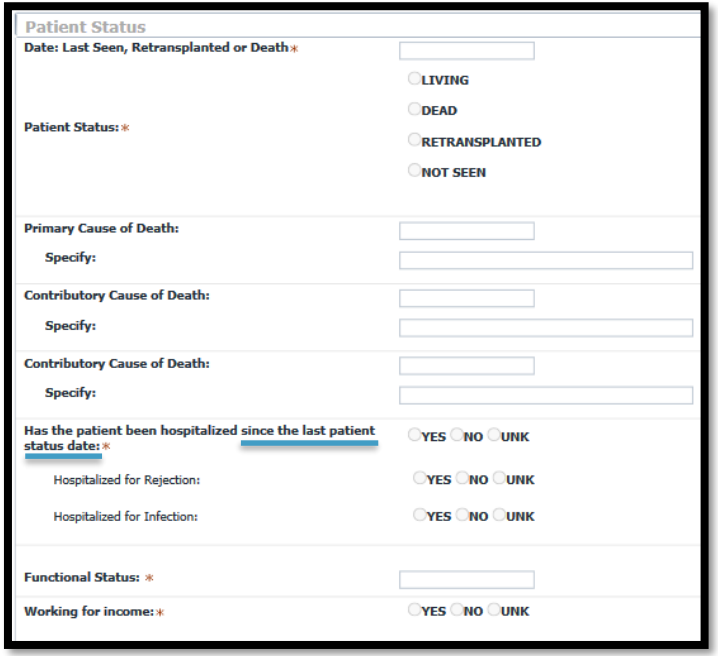
Observational Data: Outcomes

Time-to-event analysis was not possible for other outcomes

The analysis was presented as a “crude cumulative incidence percent”

The number of events in 0-1y, 0-2y, 0-3y post-transplant divided by the total number of recipients

The events from year one are counted in years two and three and likewise for year two



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Detail of: “Adult Thoracic Transplant Recipient Follow-Up Worksheet”

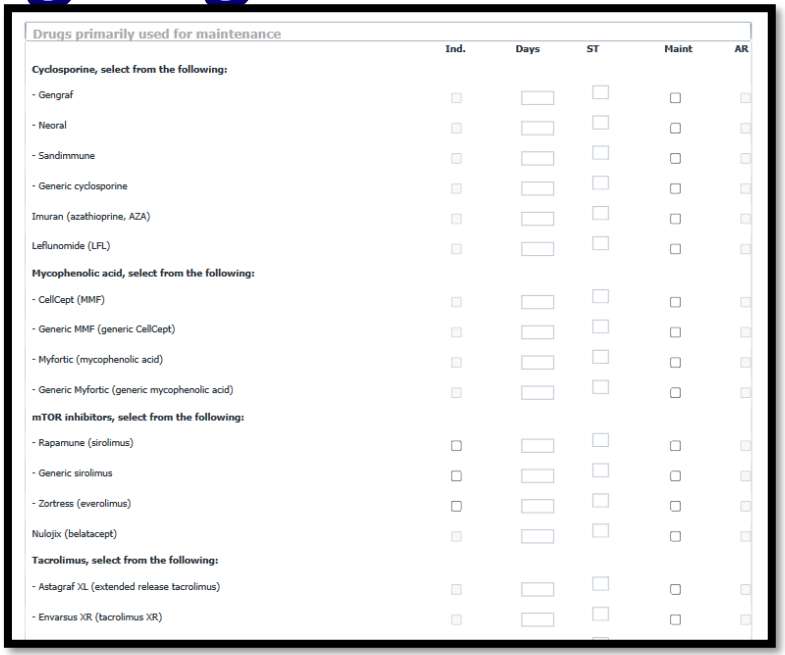
Observational Data: Drug Regimen

The data collection process also influenced the assignment of drug regimen

This is recorded on the transplant recipient registration (TRR) form

OPTN Policy "18.2 Timely Collection of Data" states: the information for the TRR must be collected:

- when the transplant recipient is discharged from the hospital or
- 42 days following the transplant date, whichever is first



Drugs primarily used for maintenance

	Ind.	Days	ST	Maint	AR
Cyclosporine, select from the following:					
- Gengraf	☐		☐	☐	☐
- Neoral	☐		☐	☐	☐
- Sandimmune	☐		☐	☐	☐
- Generic cyclosporine	☐		☐	☐	☐
Imuran (azathioprine, AZA)	☐		☐	☐	☐
Leflunomide (LFL)	☐		☐	☐	☐
Mycophenolic acid, select from the following:					
- CellCept (MMF)	☐		☐	☐	☐
- Generic MMF (generic CellCept)	☐		☐	☐	☐
- Myfortic (mycophenolic acid)	☐		☐	☐	☐
- Generic Myfortic (generic mycophenolic acid)	☐		☐	☐	☐
mTOR inhibitors, select from the following:					
- Rapamune (sirolimus)	☐		☐	☐	☐
- Generic sirolimus	☐		☐	☐	☐
- Zortress (everolimus)	☐		☐	☐	☐
Nulojix (belatacept)	☐		☐	☐	☐
Tacrolimus, select from the following:					
- Astagraf XL (extended release tacrolimus)	☐		☐	☐	☐
- Envarsus XR (tacrolimus XR)	☐		☐	☐	☐

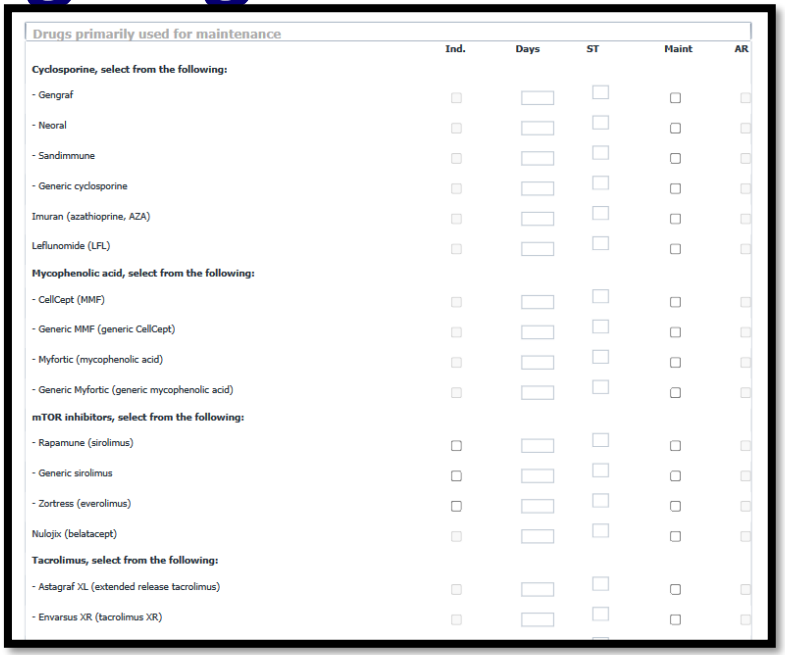
Detail of: "Adult Thoracic - Lung Transplant Recipient Registration Worksheet"

Observational Data: Drug Regimen

Ideally, we would like to know drug regimen from transplant but that is not available

The dataset is left-truncated prior to hospital discharge

This is a standard data condition for the KM estimator and was handled in PH regression models by including length of hospital stay as an adjustment factor



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- Sandimmune	☐	☐	☐	☐	☐
- Generic cyclosporine	☐	☐	☐	☐	☐
Imuran (azathioprine, AZA)	☐	☐	☐	☐	☐
Leflunomide (LFL)	☐	☐	☐	☐	☐
Mycophenolic acid, select from the following:					
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- Generic MMF (generic CellCept)	☐	☐	☐	☐	☐
- Myfortic (mycophenolic acid)	☐	☐	☐	☐	☐
- Generic Myfortic (generic mycophenolic acid)	☐	☐	☐	☐	☐
mTOR inhibitors, select from the following:					
- Rapamune (sirolimus)	☐	☐	☐	☐	☐
- Generic sirolimus	☐	☐	☐	☐	☐
- Zortress (everolimus)	☐	☐	☐	☐	☐
Nulojix (belatacept)	☐	☐	☐	☐	☐
Tacrolimus, select from the following:					
- Astagraf XL (extended release tacrolimus)	☐	☐	☐	☐	☐
- Envarsus XR (tacrolimus XR)	☐	☐	☐	☐	☐

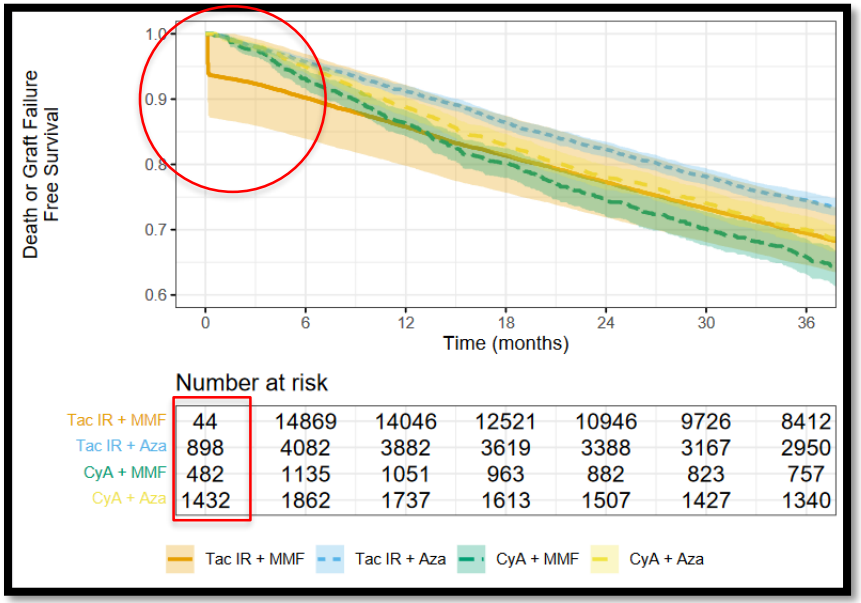
Detail of: “Adult Thoracic - Lung Transplant Recipient Registration Worksheet”

Framing the Analysis Questions

The TRR collection process led to a left-truncated dataset

4 recipients in the Tac IR + MMF group had early discharge and death

This had an outsized impact on the survival estimates



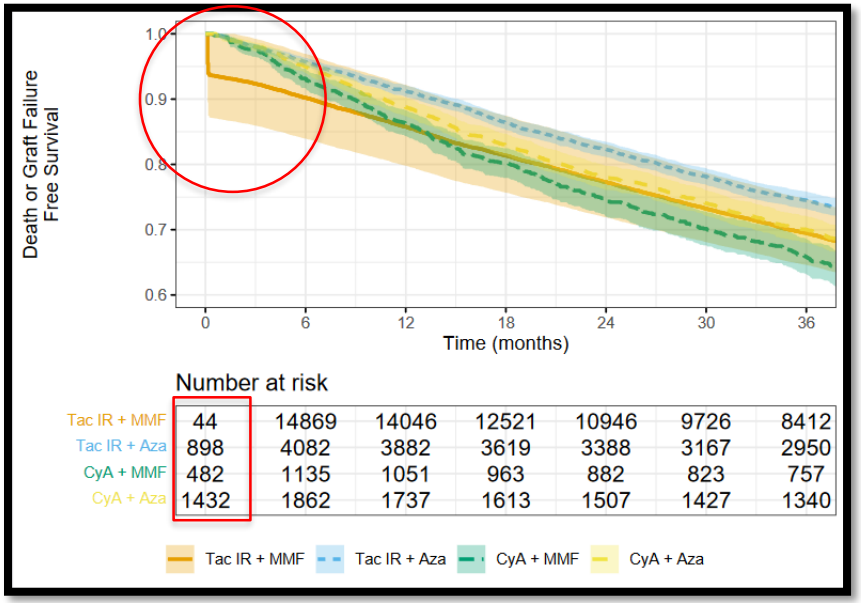
No Adjustment

Framing the Analysis Questions

What is the medical rational for these 4 early events?

- Perhaps they were “discharged” to a different unit at the hospital
- Perhaps it was …

Ultimately, the medical rational cannot be determined from the data available

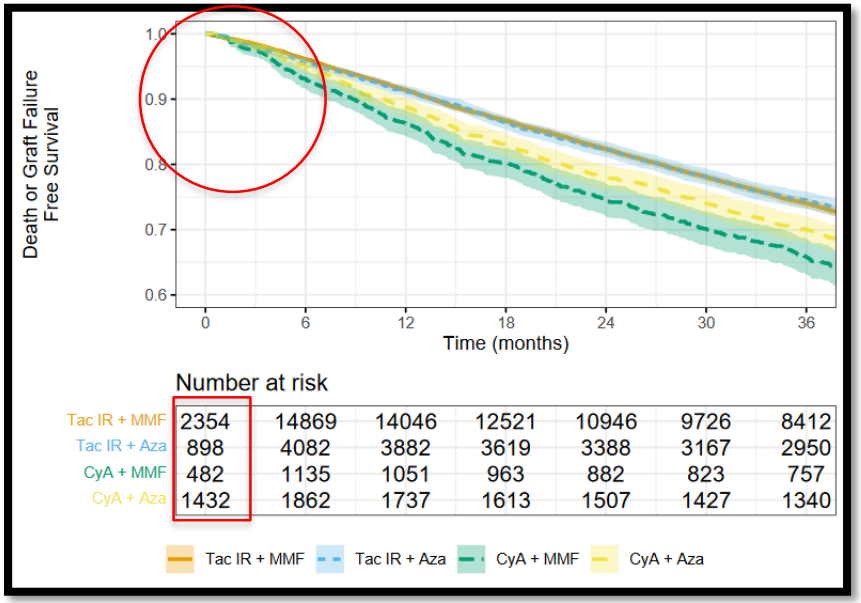


Left Truncation: No Adjustment

Framing the Analysis Questions

Had to reframe to question address the impact of these 4 recipients

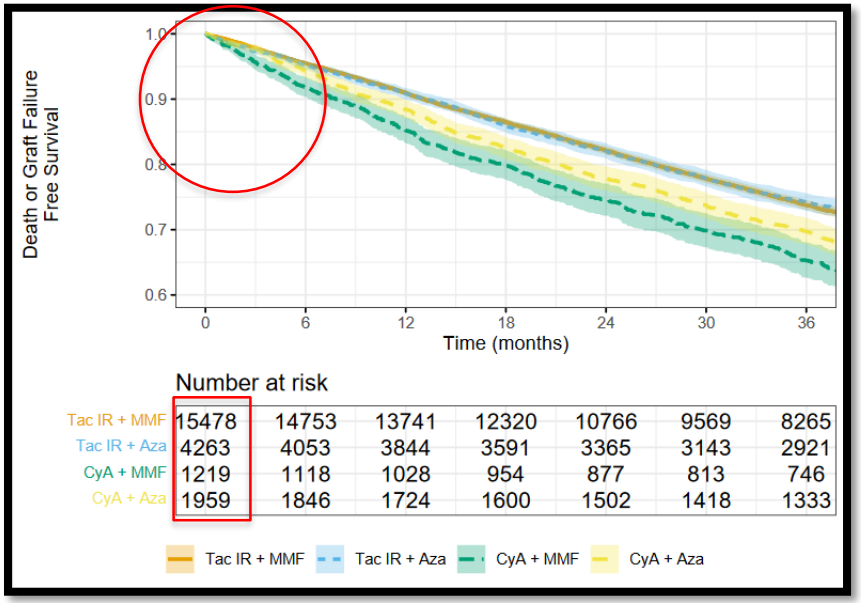
Shifting their event date ahead to the earliest of the other groups (10 days post transplant)



Left Truncation: Shifted Early Events

Framing the Analysis Questions

Treating the discharge date as the start of time at-risk



At-Risk Time Starts at Discharge

Technical Aspects

All analysis performed in markdown, which interweaves code and text and allows:

- One-to-one tie between code and results
- Few(er) intermediary datasets

Utilized software development practices:

- Modularity: common functions were reused throughout the reporting
- `dplyr` paradigm for subgroup calculations allows readability and consistency
- Documented code review via GitLab merge requests

CDRG

Transplantation

Director Jon Snyder, PhD, MS

Investigators Bertram Kasiske, MD FACP
Ajay Israni, MD, MS
Allyson Hart, MD, MS

Program Manager Caitlyn Nystedt, MPH, PMP

Sr. Administrative Assistant Pamela Giles

Medical Editor Mary Van Beusekom, MS, ELS, MWC

Marketing & Comm. Mona Shater, MA
Amy Ketterer
Tonya Eberhart

Project Managers Katherine Audette, MS
Bryn Thompson, MPH

Project Coordinator Chris Folken

Sr. Manager, Biostatistics David Zaun, MS

Biostatisticians David Schladt, MS
Tim Weaver, MS
Yoon Son Ahn, MS
Jon Miller, PhD, MPH

IT, Web, Database, Simulation Ryan Follmer
Carl Fils-Aime
Mark Fredrickson
Patrick Johnson
Joshua Pyke, PhD
Eugene Shteyn, MS
Matthew Tabaka
Greta Knefelkamp

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