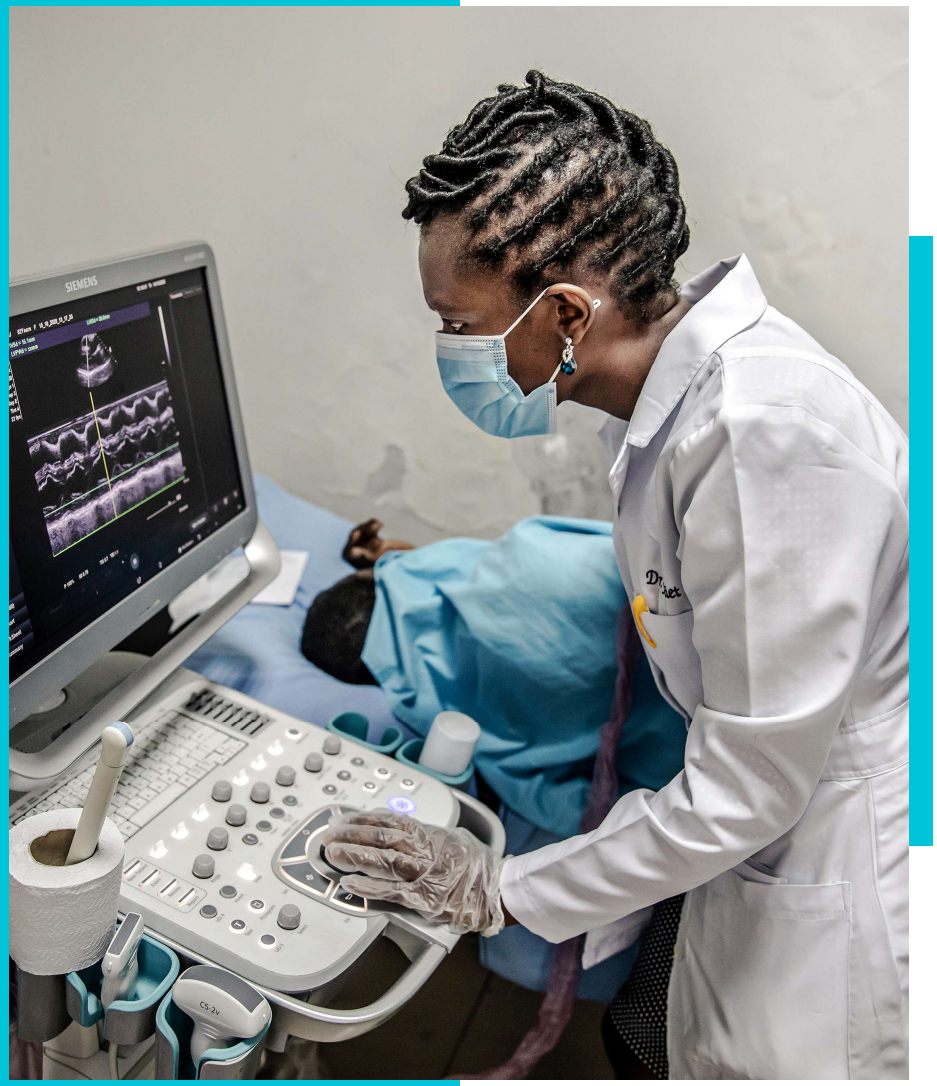

EFSPI EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

Transforming RWD into RWE Overview

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Outline

- Real-world evidence: regulatory and beyond
- Evidence workflow and bias considerations
- Illustrating evidence generation with three examples

Real World Evidence: EMA

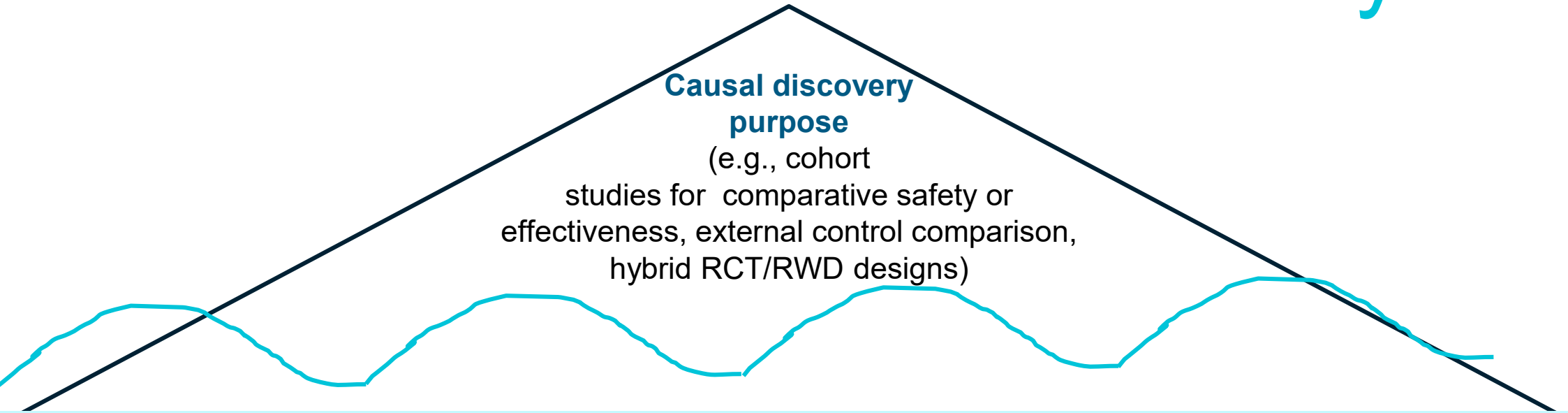
Real world evidence (RWE)

"the information derived from the analysis of routinely collected data (referred to as real-world data, RWD) relating to a patient's health status or the delivery of health care from a variety of sources other than traditional clinical trials."

Source: Arlett (2016)

- Regulatory definitions of RWE are relatively similar across the globe *(e.g.,* Izem, Rima, et al. (2023))
- Some refinements over time (see "Reflection paper of use of RWD in non-interventional studies to generate real-world evidence: Scientific guideline" (EMA 2024)

Real-world evidence: broadly



Descriptive purpose
including the following

- Strategy e.g., definition of indication, description of treatment landscape to inform probability of success or prioritize development
- Benchmarking e.g., understanding of natural history and patient experience
- Clinical study design planning aid e.g., validation of novel endpoints/biomarkers, selection of clinical sites

Examples illustrating RWE

An additional example in causal discovery will be discussed by the next speaker in the session

Causal discovery purpose

Evidence from a study leveraging a compassionate use program for registration of Alpelisib (Example 2)

Evidence from a study leveraging a national transplant registry to support a registration dossier for tacrolimus (Example 3)

Descriptive purpose

Evidence from a rare disease **natural history study and** the consortium **infrastructure** supports RCT planning and launch (Example 1)

Descriptive purpose (Example 1)

Workflow transforming RWD into RWE

1

Clarify purpose

What is the scientific question?

2

Identify fit-for-purpose data

What RWD are sufficiently relevant and reliable?

3

Plan and implement fit-for-purpose methods

What are potential sources of bias? what cohort selection and analyses can eliminate, minimize, or mitigate sources of bias?

Example 1

- Urea Cycle Disorder (UCD)
  - Rare disorder due to genetic mutations affecting the urea cycle
  - Heterogeneity in mutation, diagnosis, and disease progression
  - Treatments include: medical management (nitrogen scavenger therapies, low protein diet), liver transplant

- UCD Consortium Natural History Epidemiologic Database Multicenter, multinational, longitudinal study*
  - >13 years of data, on >800 subjects, 5-16 sites, 4 countries
  - Longitudinality: pre-enrollment medical records, extensive baseline visit, and set visit schedule post-enrollment
  - Funding support for main study includes grants from US-NIH, and foundations

Source: https://ucdc.rarediseasesnetwork.org (study 5101)

UCD consortium : Supporting Evidence Generation (Example 1)

- Building the UCD consortium was an investment in translational medicine
  - Its infrastructure facilitated planning, advertising, recruitment, and medical history data collection of epidemiological studies and interventional studies in UCD or related indications
  - Example: studies supporting the registration, the label expansion, and post-market safety assessments of for N-Carbamylglutamate

Sources: Ah-Mew et al (2019), Ah-Mew et al (2020)

Example 1 (continued)

1

Clarify purpose

Inform clinical trial planning (e.g., What is the expected prevalence rate (person*time) of hospitalization?)

2

Identify fit for purpose data

UCDC natural history study

3

Plan and carry out fit-for-purpose methods

Estimate prevalence rates within the UCDC eligible cohort

Causal discovery purpose (Workflow and Examples 2 and 3)

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

Workflow transforming RWD into RWE

1 — **Clarify purpose**

What is the Scientific question?

What is the target causal estimand?

2 — **Identify fit-for-purpose data**

What RWD are relevant and reliable?

3 — **Plan and carry out fit-for-purpose methods**

What is the design?

What are the analyses?

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

What are the target trial and the estimand?

Estimand attributes
Population
Treatment
Variable/Outcome
Follow-up
Intercurrent event & handling strategy
Summary measure/ Causal contrast

- The target trial is a thought experiment, this is the hypothetical randomized trial that would investigate the causal association between drug and outcome.
- The estimand per the ICH-E9 addendum has five attributes: Population, Treatment, Variable, intercurrent event, summary measure and associated analytical strategies for handling intercurrent events.

Robins-I: Tool to identify sources of bias

The Robins-I tool, sources of bias with observational studies

1	Confounding
2	Selection of participants into the study
3	Classification of interventions
4	Deviations from intended interventions
5	Missing outcome data
6	Measurement of the outcome
7	Selection of the reported result

Distinct from an RCT

Similar to an RCT

Robins'I: Sterne et al (2016)

- The Robins-I tool is a guide for eliciting and prioritizing potential sources of bias from experts
- Design can minimize bias (e.g., pre-specification, choice of validated exposure/outcome, target trial emulation)
- Causal inference analyses can minimize bias (e.g., control for measured confounding) or quantify its impact

Example 2

Clarify purpose

Identify fit-for-purpose data

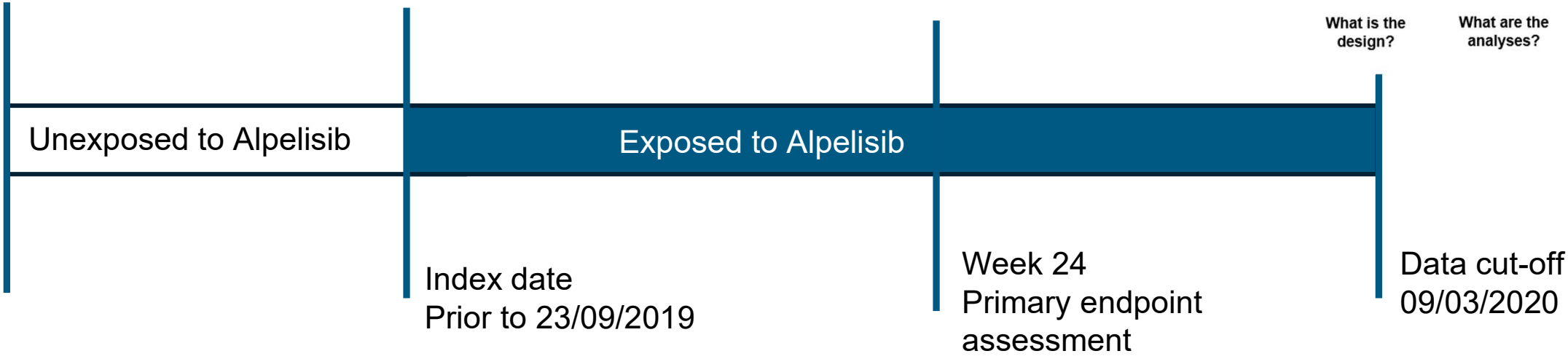
1 2

Purpose: Expand the indication of Alpelisib to treat PIK3CA-related overgrowth syndrome (PRO), a group of rare genetic disorders affecting children and adults

Background: Alpelisib (in combination with fulvestrant) was originally approved for PIK3CA-mutated advanced or metastatic breast cancer

(Source) data: Compassionate use program for severe PRO Venot et al (2018) reported promising data on 19 patients in France with severe PROS treated with Alpelisib under an expanded access program for compassionate use

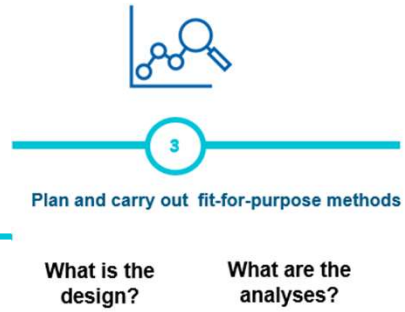
EPIK-P1 Study Design (Example 2)



Select results: By week 24, 37% responders (≥ 20% reduction from baseline in the sum of target lesion volume) for a median length of exposure of 18.1 months

Sources: Canaud, G., et al (2021); O'Connell P et al (2023); Singh, Sonia, et al. (2024)

Some bias mitigation strategies adopted in EPIK-P1 (Example 2)

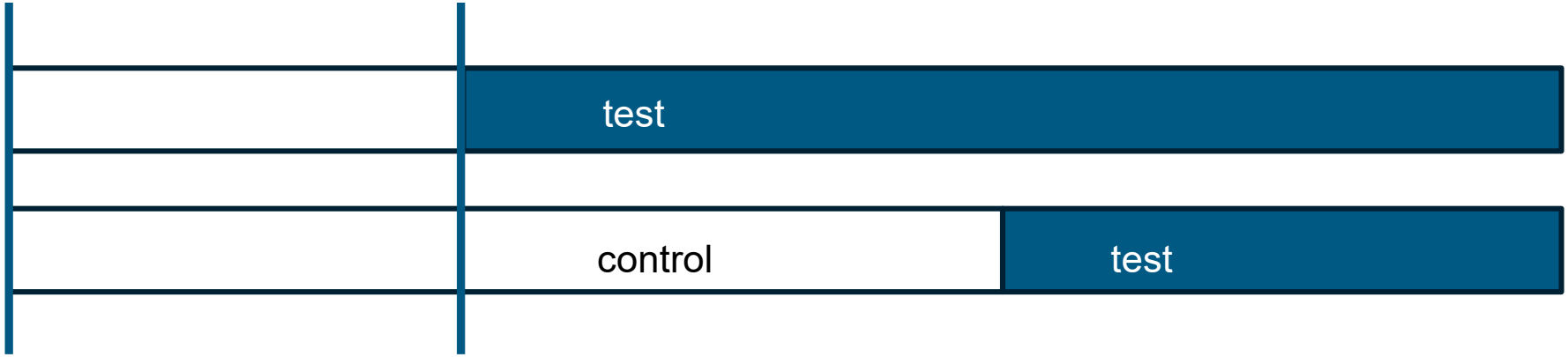


- Protocol and SAP were finalized before abstraction of data from patient medical records
- Primary endpoint assessment was specified to emulate how information would flow into a target clinical trial:
  - Target lesions were selected by an independent central committee based only on scans taken during the 'pre-index' period
  - Response assessed by independent central committee using pre-specified criteria
- Response was a between period, within-subject comparison thereby controlling for (non-time varying) confounding

Sources: Canaud, G., et al (2021); O'Connell P et al (2023); Singh, Sonia, et al. (2024)

What (could have been) a target trial design? (Example 2)

A potential target trial would have been to randomize when patients receive treatment or standard of care (e.g., delayed therapy randomization)



See Izem et al (2021) for other potential designs exploiting within-subject comparisons

Example 3

Purpose: To expand indication of tacrolimus to include prophylaxis of organ rejection in patients receiving allogeneic lung transplant

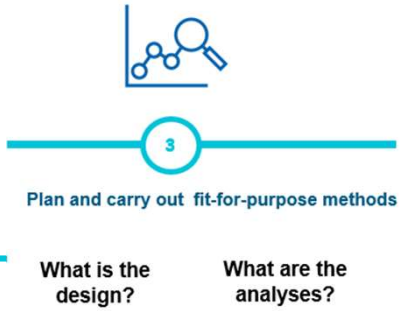
Background: Existing evidence from RCTs in this indication, and other approved indications (kidney, heart transplantation), existing off-label use

(Source) Data: US Scientific Registry of Transplant Recipients (Source: https://srtr.transplant.hrsa.gov/)

Potential target trial (Example 3)

Estimand attributes	Target trial (In theory)
Population	*Subjects undergoing lung transplant surgery*
Treatment	*Regimen with tacrolimus versus regimen without tacrolimus **(post-surgery)***
Variable/Endpoint	*Time to graft rejection, up to one year **after surgery***
Intercurrent event	*Treatment discontinuation or switching* *Adverse events (related or unrelated to endpoint)*
Summary measure/ Causal contrast	*Difference in cumulative incidence proportion at one year*

Some bias mitigation strategies



- Potential immortal time bias (varying duration of time from surgery to discharge) addressed in sensitivity analyses, with different definitions of time-0
- Confounding by calendar time addressed by
  - Assessing effectiveness in each time-period
  - Assessing each drug regimen separately

- Each intercurrent event was handled with either
  - Composite or treatment policy strategies for events that may be related to primary outcome
  - Censoring or competing event strategies (Aalen Johanssen estimation) for events that may not be related with primary outcome

Source: Erdman et al (2022)

In summary

- This presentation illustrates how leveraging real-world data (infrastructure) can accelerate evidence generation for internal decision making or external stakeholders, for descriptive goals or causal discovery
- For descriptive and causal discovery goals, the scientific purpose precedes identification and evaluation of data and methods that are fit for purpose
- In causal discovery, the target trial and estimand framework can help refine the scientific goals, and the Robins'I tool can guide how to address biases in design and analysis

A look forward

- Leveraging academic registries, and distributed networks as source of real-world-data
- Hybrid (RCT/RWD) designs, pre and post-market

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- UCDC – Investigators

References

- Arlett, P. (2016). Use of registries to support real world evidence. European Medicines Agency. Presentation given on April 7th, 2016.
- EMA. (2024) Reflection paper of use of RWD in non-interventional studies to generate real-world evidence Scientific guideline (link)
- Izem et al (2023) "Overview of the Current Real-World Evidence Regulatory Landscape." *Real-World Evidence in Medical Product Development* (2023): 17-28.
- Sterne, J.A. et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919 (2016).
- Ah Mew N, McCarter R, Izem R, et al. (2020). Comparing Treatment Options for Urea Cycle Disorders. Patient-Centered Outcomes Research Institute (PCORI).
- Ah Mew, Nicholas et al. 'Conducting an Investigator-initiated Randomized Double-blinded Intervention Trial in Acute Decompensation of Inborn Errors of Metabolism: Lessons from the N-Carbamylglutamate Consortium'. 1 Jan. 2018 : 157 – 170.
- Venot, Q., Blanc, T., Rabia, S.H. *et al.* Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature* **558**, 540–546 (2018). https://doi.org/10.1038/s41586-018-0217-9
- O'Connell P, Ridolfi A, Fretault N (2023) Case study using RWD in the context of a pivotal trial for regulatory approval in a rare disease, Journal of Biopharmaceutical Statistics
- Canaud, G., et al (2021). LBA23 EPIK-P1: Retrospective Chart Review Study of Patients (Pts) with PIK3CA-Related Overgrowth Spectrum (PROS) Who Have Received Alpelisib (ALP) as Part of a Compassionate Use Programme. *Annals of Oncology* 32:S1297.
- Izem, R., McCarter, R. (2021) Randomized and non-randomized designs for causal inference with longitudinal data in rare disorders. Orphanet J Rare Dis 16, 491 (2021)
- Singh, Sonia, et al. "FDA Approval Summary: Alpelisib for PIK3CA-Related Overgrowth Spectrum." *Clinical Cancer Research* 30.1 (2024): 23-28.
- Erdman, Jay MS[1]; Wolfram, Josephine MA, et al Lung Transplant Outcomes in Adults in the United States: Retrospective Cohort Study Using Real-world Evidence from the SRTR. Transplantation 106(6):p 1233-1242, June 2022.

Thank you!

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