

SRC Analytical Subcommittee Meeting Minutes

Analytical Methods Subcommittee Teleconference

March 24, 2021 11:00 AM – 1:30 PM CDT

Voting Members:

Brent Logan, PhD (Chair)
Shu-Xia Li, PhD
Katherine Panageas, PhD
Andrew Schaefer, PhD
David Vock, PhD

HRSA:

Shannon Dunne, JD
Adriana Martinez

SRTR Staff:

Ryutaro Hirose, MD
Ajay Israni, MD, MS
Nicholas Salkowski, PhD
Jon Snyder, PhD, MS
Andrew Wey, PhD
Josh Pyke, PhD
Donnie Musgrove, PhD

Welcome and introductions

Dr. Andrew Wey thanked the subcommittee members for attending and started with introductions.

- Brent Logan, PhD, Subcommittee Chair, Head Statistician, public reporting on bone marrow transplant, Medical College of Wisconsin
- Shu-Xia Li, PhD, Associate Director and Research Scientist, Yale Centers for Outcomes Research and Evaluation (CORE)
- Katherine Panageas, PhD, Epidemiology and Biostatistics Department, Health Outcomes Research Group work, Memorial Sloan Kettering Cancer Center
- Andrew Schaefer, PhD, Professor of Computational Applied Math, Rice University, Advisory Committee on Organ Transplantation (ACOT) member 2011-2017
- David Vock, PhD, Associate Professor of Biostatistics, University of Minnesota
- Andrew Wey, PhD, SRTR Biostatistician, public reporting on pretransplant metrics, lung and liver transplant policy development

Dr. Wey viewed the agenda and reminded members of conflict of interest management.

Background of SRTR

Dr. Wey explained that the Department of Health and Human Services (HHS), specifically the Health Resources and Services Administration (HRSA), oversees the solid organ transplant system. A HRSA division of transplantation manages the SRTR and OPTN contract. The OPTN contract, held by the United Network for Organ Sharing (UNOS), maintains the database of all waitlisted candidates and allocates available organs. It handles policy-making initiatives. In comparison, SRTR uses OPTN data to publish public reports on transplant hospitals and support OPTN policy. Under Hennepin Health Research Institute (HHRI), the Chronic Disease Research Group (CDRG), CDRG Transplantation, and the SRTR contract.

Dr. Wey went on to explain SRTR analytical work, which consists of three categories: public reporting, simulated allocation models (SAMs), and other analytical projects. SRTR is responsible for public reports for transplant programs and organ procurement organizations (OPOs). Public reports are published twice a year in January and July. They begin 4 months before public release and involve a “data review period” for programs to check data for errors. October is the data review period for January, and December is the report preview (final review). However, SRTR begins working on data review a month before the review period. For July, April is for data review, and June is when reports are previewed. Reports contain descriptive characteristics, but the transplant community is most interested in risk-adjusted metrics, which require a statistical model to adjust for differences in candidate and recipient populations.

Dr. Wey discussed SRTR-reported metrics. OPTN and SRTR have sufficient data on what happens to a listed patient. Metrics are separated into three phases of the patient experience after listing. The first, outcomes on the waitlist, are waitlist mortality and transplant rates (how likely a transplant program would perform a transplant on different patients). The second, offer acceptance, measures relative acceptance rates of transplant programs when given an offer through OPTN allocation policy. The metric has high variability in terms of the propensity of different programs to accept or decline offers. The third phrase is posttransplant outcomes. The 1-year posttransplant metric has received the most interest and criticism over the last 20 years. All-cause graft failure reports if the transplanted organ is still functioning, as well as patient mortality, which has similar outcomes for most solid organ transplants.

Another metric is patient morality after listing, which summarizes pretransplant and posttransplant metrics into a single metric. SRTR also reports on OPO metrics, including the eligible donation rate and number of donors per death, given eligibility criteria conducive to donation. The second is donor yield, or the average number of organs transplanted from donors with at least one organ recovered for donation.

Dr. Wey said it is difficult in the donation field to collect data on donor populations of interest. Many data collection issues occur in the OPO field in terms of getting the metric that correspond to good OPO performance. Dr. Wey went over likely public reporting topics the subcommittee would discuss, including how to handle COVID-19 in public reports, transitioning to a period-prevalent approach for posttransplant cohorts, new OPO evaluation metrics, and quality improvement metrics for programs (eg, risk-adjusted length-of-stay metrics).

Dr. Josh Pyke explained the second category of SRTR analytic work, SAMs, or software that internal analysts (SRTR) and outside researchers use to inform allocation policy development. In the SAMs family of software programs, there are three main simulators: liver (LSAM), thoracic (TSAM), and kidney-pancreas (KPSAM). The software simulators take candidate and donor information from the OPTN database and use it to simulate allocation by applying new rules to explore. The software outputs information on modeled results of new allocation rules, including the number of candidates given transplants or who died waiting and posttransplant mortality.

Dr. Pyke explained the SAMs structural process. A rule file describes how to process donors and candidates as they enter the allocation policy simulation. The pool of candidates and donors come from OPTN data. Candidates can be added as they arrive in real life or removed at death or waitlist

removal. Donors are varied with each run to provide variability for makeup of the population might be in a given year.

To reach an offer acceptance decision, the simulator takes a donor with candidates in a current waitlist period and generates a ranked list of candidates in priority order. The simulator moves down the ranked list, making offers to each candidate. An offer acceptance model calculates the probability of acceptance for an organ offer based on candidate and donor characteristics. If a drawn number exceeds the probability of acceptance and the candidate accepts the organ, the simulator moves to the next donor. If the candidate declines the offer, the offer is made to the next candidate. The process is continued until the offer is accepted, taken off the list, or hits a cutoff. With transplants, posttransplant survival modeling is used to report how long the graft survived and find out if the candidate needs to relist.

Dr. Ryutaro Hirose commented that the assumptions made when running LSAMs, especially offer acceptance criteria, could give an output that might result in overinterpretation of accuracy by SAMs consumers. Dr. Pyke replied that the work done with simulators exists in a technical and political context. It is political because the decisions made about allocation policy take place in a committee of clinicians. OPTN works hard to drive an evidence-based decision-making process. Dr. Pyke said that from the SRTR perspective, it is not ideal but not a fatal flaw in the SAMs, and the limitations of these systems are understood.

Dr. Pyke reviewed potential simulation modeling topics. One is offer acceptance modeling in the legacy SAMs, which include data availability and modeling training, how to respond to OPTN committee requests, and the approach to public release versions. The second topic is replacing the 20-year-old legacy SAMs, called the organ allocation simulator (OASim). Dr. Pyke plans to give progress updates and consult the committee on methodological guidelines and documentation of candidate history generation. Dr. Wey added that SRTR may bring questions from other analytical work, like the OPTN revision of its allocation systems.

Framework for assessing impact of COVID-19 on program-specific evaluations (PSRs)

Dr. Wey informed the committee that handling COVID-19 in PSRs and organ-specific reports (OSRs) was first discussed at the January 2021 SRC meeting. Some SRC members and SRTR staff voiced concerns that the decisions on how to manage COVID-19 across different metrics was inconsistent. SRTR wants to develop a general framework to determine the appropriate reporting of SRTR metrics in the COVID-19 era. Dr. Wey said SRTR wants an algorithmic approach less susceptible to subjective decisions.

Dr. Wey proposed two types of frameworks for this approach. One is a philosophical framework not based on the goals of public reporting and the conceptual impact of COVID-19. An option under this framework is public reporting describing outcomes during specific periods. COVID-19 may confound those outcomes, and SRTR wants to describe those outcomes after adjusting for known candidate, donor, and recipient risk factors. Second, past public health disasters did not alter public reporting, and understanding how COVID-19 is different will help in development of the philosophical framework. Third, COVID-19 changed the practice of transplant, which precluded any meaningful public reporting. Dr. Wey said that transplant practices are always in flux, so there is a need to define just how different the changes in response to COVID-19 are. While COVID-19 disrupted

clinical practice, healthcare providers adapted to some degree in a few months, and it may be reasonable to establish a period in which reporting needs to resume.

The second framework is data based. Dr. Wey said that from an analytical perspective, COVID-19 may confound PSRs and OSRs due to a differential impact of COVID throughout the country. If COVID did not differ across the United States, the concern wouldn't be as great. Because COVID-19 was not well measured with testing, it is not possible to accurately assess its geographic variability.

Dr. Wey said the analysis of interest for understanding confounding risks is estimating the difference-in-differences (DID) analyses: the difference between differences from the national expectation before COVID-19 and that after COVID-19. This could be done by estimating hazard ratios in donation service areas (DSAs) before and after COVID-19 and then estimating the difference in differences, or the ratio of those two effects. The lower the relative outcome of a DSA after COVID-19, the better. DID analyses has identified different parts of the nation with relatively worse outcomes after COVID-19 accounting for changes in outcomes. High variability in differences suggested potential confounding from COVID-19. Dr. Wey stressed that the approach can't distinguish between differences caused by COVID-19 and those that would have occurred without it.

At the last SRC meeting, members hadn't formalized this framework and relied on heuristics to identify problematic geographic variability. The first heuristic was whether DSAs with different outcomes aligned with parts of the country with severe outbreaks. The usefulness of this approach rapidly decreased as time went on because the country experienced bigger outbreaks, and it was difficult to create a coherent nonsubjective data narrative. The second heuristic was whether there were meaningful variability in differences before and after COVID-19. This is difficult to discuss because meaningful variability is poorly defined and would exist without COVID-19. Also, the level of variability is likely to change across metrics and organs due to highly variable effective sample sizes.

These heuristics no longer work well, and SRTR wants a formal process to help determine when to resume public reporting. Dr. Wey presented two broad approaches for handling the COVID-19 period. One is model modification. SRTR could have an indicator for post-COVID time or adjust for the incidence of COVID-19 in the county of the transplant hospital. However, neither are a feasible approach for public reporting because the transplant community won't accept the face validity of these types of adjustments.

The second approach, cohort modifications to remove problematic periods of the pandemic, was seen as reasonable. The three modifications include stopping follow-up at March 12, 2020, for some metrics; removing follow-up from March 13 to June, 2020; or resuming normal follow-up for other cohorts. While these modifications will be implemented into the July reports, a formal approach to determine cohort modification for the January report was needed. Dr. Wey said that development of an algorithm to determine a course of action automatically is under consideration.

Dr. David Vock said it might be worthwhile to precisely define the effect the SRTR wants to capture. He claimed it is important to consider the different mechanisms that could affect outcomes and which mechanisms related to center performance the subcommittee wouldn't want to adjust for. Dr. Shu-Xia Li agreed. Dr. Wey declared that creating strict definitions and parsing all outcomes would be incredibly challenging. Dr. Hirose stated, confounding variables were difficult to adjust for with COVID-19. Dr. Vock brought up the possibility of comparing centers that may be penalized because

they wanted to be cautious during COVID-19, versus more aggressive centers. Dr. Nicholas Salkowski replied, it wasn't necessarily about punishing a particular course of action but giving credit for making good decisions. Dr. Hirose cautioned against using language like "good" or "bad" decisions, because a good decision might have been a lucky one. Many decisions made during COVID-19 were due to factors beyond anyone's control. Dr. Vock said that geographical variability could help answer questions about some mechanisms, particularly those related to the incidence of COVID-19 in the general population. Dr. Katherine Panageas added it would be helpful to see more information on how COVID-19 may affect public reporting. Dr. Wey said there is a fair amount of hesitancy about relying on a strictly empirical approach.

Dr. Wey reviewed the DID analysis for the COVID-19 cohort. An approach to capture whether the variability was the same or higher after the emergence of COVID-19 involved using a control cohort that shifted 2 years before the COVID-19 cohort. This analysis could estimate all metrics/organs at the DSA level. Then DSA level effects could be used for the pre-COVID period and the difference effect for the difference between the pre- and post-COVID periods. The Bayesian normal inverse gamma model (Normal-IG) allows estimation of the posterior distribution for the variance parameter difference effects. The result is a posterior distribution for the variance parameter on the difference effect for the COVID-19 and control cohort. Then the probability that the variance was higher for the COVID-19 cohort could be compared with that of the control. The potential issues with this approach are the inverse-gamma in the variance influencing the operating characteristics of the decision rule. Second, effective sample size for these analyses are likely to be different between the COVID and control cohorts.

Closing business

When no other business was raised, the meeting concluded. The next meeting will be planned for June or July 2021 by teleconference.