SRC Analytical Methods Subcommittee Meeting Minutes

Analytical Methods Subcommittee Teleconference

January 21, 2022, 11:30 AM – 2:00 PM CST

Voting Members:	**HRSA:**	**SRTR Staff:**
David Vock, PhD (Co-Chair)	Adriana Martinez	Ryutaro Hirose, MD
Shu-Xia Li, PhD		Ajay Israni, MD, MS
Katherine Panageas, PhD	**Not in attendance:**	Jon Miller, PhD
	Shannon Dunne, JD	Josh Pyke, PhD
Not in attendance:		David Zaun, MS
Andrew Schaefer, PhD		Grace Lyden, PhD
Brent Logan, PhD		Larry Hunsicker, MD
		Nicholas Wood, PhD
Ex-Officio Members:		
Jon Snyder, PhD (SRTR Co-Chair)		

Welcome and opening remarks

Dr. Jon Snyder called the Analytical Methods Subcommittee (AMS) meeting to order. Dr. David Vock reviewed the agenda, and Dr. Snyder went over conflict of interest management.

Brief updates

Dr. Snyder updated the subcommittee on two topics discussed at the last meeting. The first was rebuilding risk adjustment models under the new period-prevalent framework, and how to do variable selection in the context of least absolute shrinkage and selection operator (LASSO) analysis. There are no current updates, and the work will resume soon. The second topic was the Scientific Registry of Transplant Recipients (SRTR) position on adjustment for sociodemographic factors, which will be worked into manuscripts.

COVID-19 update: Assessment of COVID deaths and the approved carve-out

Dr. Jon Miller reviewed that the carve-out of the first 3 months of the pandemic was first introduced in the July 2021 program-specific report (PSR) release. Transplants happening before March 13, 2020, had follow-up censored on March 12, 2020, and follow-up for these patients will not resume after the carve-out. Transplants from March 13, 2020, through June 12, 2020 (the “carve-out period”) were excluded from the PSR evaluations. Patients who underwent transplant after June 12, 2020, are included and followed up per normal PSR methodology. The SRTR Review Committee (SRC) previously approved the carve-out because 1) there was significant disruption to the nation’s transplant system during the first 3 months of the pandemic and 2) early evaluations would be affected by geographic variation in the pandemic. Dr. Miller then presented analyses of how the

carve-out affects the January 2022 posttransplant outcomes evaluations, exploring alternate scenarios that 1) removed the carve-out and 2) censored at a COVID-reported death.

Dr. Miller said that, since April 2020, the Organ Procurement Transplantation Network (OPTN) has COVID-19 as an available cause of death that can be entered for transplant recipients. In addition to specific codes for "Infection: Viral - COVID-19" as a cause of death, programs can also choose "Viral - Other Specify" with an associated text field in which the program can specify COVID-19. One primary and two secondary causes of death can be entered for transplant recipients. After these three fields were searched for either COVID-19 cause of death or COVID in the text field, 4318 COVID-19 deaths were identified in the entire dataset of heart, kidney, liver, and lung transplant recipients. Of those, 4047 had COVID-19 indicated as primary cause of death and 256 as a secondary cause of death; for 15, COVID was found in the text field.

Dr. Miller analyzed the PSR released on January 6, 2022, which included 2.5 years of transplants with an additional 6 months of follow-up. The number of COVID-19 deaths and nondeaths are relatively predictable, increasing as proportion of total deaths during the first COVID-19 wave. More deaths occurred mid-April to mid-May 2020, followed by a surge in winter 2020-2021. Dr. Miller then presented the proportion of first-year posttransplant COVID-19 deaths to total deaths by center, with 349 (9.3%) COVID-19 deaths of the 3742 deaths in the evaluation; 130 (51%) of 257 centers in the evaluation having at least one COVID-19 death. Of 349 COVID-19 deaths identified during this period, 191 are carved out of the public evaluations—meaning a little more than half of the COVID-19 deaths are already censored and removed due to the carve-out.

Dr. Miller then presented the effect of censoring COVID-19 deaths in addition to the current carve-out. There was a high correlation between the results from the current carve-out and the method of censoring at COVID-19 deaths when comparing the resulting hazard ratios (HRs) (r=0.98, R^2=0.96, ß=1). Members had a few questions to clarify the analysis. Dr. Miller noted that the HRs are calculated as observed to expected (expected derived from the risk adjustment models) with the Bayesian shrinkage parameter applied based on the gamma (2,2) prior distribution per standard SRTR methodology. OPTN region is not adjusted for in the model; however, Dr. Miller presented results by OPTN region. Dr. Miller added that regional differential effects were difficult to identify. Dr. Ryutaro Hirose observed that some centers had larger effects of censoring than others, but no systematic biases by region were apparent. Dr. Miller said that centers would be affected either to their benefit or detriment for any analysis that would differ from current practice, but the results of the current analysis demonstrate that the current carve-out does not impart a regional bias. Dr. Hirose added that the data would improve as we move farther away from the March 2020 date.

Dr. Miller then compared removing the carve-out to the current carve-out. He said there was a larger spread observed on the scatter plot when the carve-out was removed (r=0.91, R^2=0.82, ß=0.89). He noted that some programs have speculated that the carve-out as currently applied has imparted regional biases in the evaluations. Dr. Miller presented the data by OPTN region, which showed no biases within most regions, with only a small effect in Region 6 (northwest, Alaska, and Hawaii). Dr. Miller presented the effect of the carve-out on which programs would be identified for review by the Membership and Professional Standards Committee (MPSC). Of 1608 program evaluations, 21 programs (1%) would have their MPSC evaluation status change; 8 programs would

have their flags removed if COVID-19 deaths were censored, and 13 would have flags added if censored. Looking at the effects on tier evaluations under the same scenario, 22 evaluations would drop below tier 4 if censoring were applied, but 33 evaluations would rise into tier 4 or 5 if censored.

Dr. Miller then explained how the initial argument that there was differential effect of COVID-19 by geography applied to the January 2021 PSR cohort, where the bulk of cases were seen in the northeast region. As the PSR cohorts advance, waves of COVID-19 have now affected all regions of the country. The most recent PSR demonstrates that most regions had peaks in winter 2020-2021 and in spring 2021.

Dr. Shu-Xia Li and Dr. Katherine Panageas asked if there would be further analysis of COVID-19's effect by region, and a revaluation of the available COVID-19 data as data matured. Dr. Miller noted that the available data on COVID-19 incidence were not granular enough to analyze the effect of COVID-19 at the program level, and the SRC and AMS had previously recommended not to adjust for regional incidence due to differential effects even within regions. However, SRTR will continue to evaluate datasets and possible ways to address COVID-19's impact on centers. Dr. Snyder added that the "finest grain" datasets were at county level, however, the effect of COVID-19 often differed in the same areas, as well as by different hospitals. Dr. Vock said there may be factors more prominent than geography that contribute to these variances. Dr. Larry Hunsicker said in accounting for hospital specifics and the effect of COVID-19, it was important to consider the type of hospital and its location. However, he thought it was best to avoid over adjusting for an identifiable hospital-specific issue, which is exactly the effect the PSRs are intended to elucidate. Dr. Hirose agreed, and Dr. Hunsicker added that it was important to be clear if the purpose was to evaluate center performance or inform the public where they can get the best outcomes for their transplant.

Dr. Vock asked if the only focus was on the 1-year patient and graft survival, or if there were other metrics that centers focused on. Dr. Snyder said that, to date, concern was mostly on first-year outcomes largely because they are used by MPSC to review center performance and by insurance providers to designate preferred centers. However, this may change as MPSC has decided to look at waitlist mortality starting midyear 2022.

Review of SRTR decision aids and proposed kidney-pancreas tool

In this discussion, Dr. Grace Lyden emphasized the opportunity to present more patient-centric information in an accessible format. She also noted the Health Resources and Services Administration's (HRSA's) interest in SRTR expanding online tools for patient decision making. Dr. Lyden gave background information on the current SRTR decision aid tools. One is the kidney waitlist calculator, which through a statistical modelling approach, allows users to input their medical information to calculate risk and outcomes from 0-5 years postlisting. The liver waitlist calculator uses sampling of historical data to present the likelihood of various waitlist outcomes. Unlike many survival analyses, this method samples patients at any time on the waiting list and is interpretable at any time postlisting.

While possible future decision aids include heart and lung waitlist calculators, a decision tool would be particularly helpful for patients needing a kidney-pancreas (KP) transplant, since the organs could be transplanted in various ways. KP transplants can be accomplished following either a

simultaneous pancreas-kidney (SPK) transplant or pancreas after living donor kidney (PALK) strategy. With the numerous options of varying wait times and the potential living donor factor, Dr. Lyden said it can be difficult for patients to compare options and choose an ideal transplant strategy.

To answer which strategy is best for patient survival, Drs. Vock and Lyden used a framework of dynamic treatment regimens (DTRs). Also called adaptive treatment strategy, DTRs are essentially a subfield of causal inference and personalized medicine. DTRs assign treatment over time as a function of evolving patient information (eg, starting a patient on drug A, and if patient doesn't respond, switching to drug B). Once a strategy is codified as a DTR, causal inference methods can be applied to estimate survival under the DTR. One method is running simulations to generate outcomes under a DTR (requires a large number of correct models). Another approach is inverse probability weighting (IPW), which is possibly nonparametric.

Dr. Lyden described what IPW does for DTRs, and then showed results. For SPK, they analyzed what survival for patients waiting for a deceased donor transplant under their allocation policy would look like. Survival was estimated using IPW with censoring when an action is not compliant with the strategy (eg, getting kidney transplant alone before SPK). Weights are used to account for selection bias. The IPW up-weights those who are uncensored by their probability of having complied through listing until end of follow-up. This creates a pseudo-population, where compliance with the strategy does not differ by confounders or risk adjustment factors.

With the weighted dataset, standard survival methods like a Kaplan-Meier analysis can be applied to estimate survival under the DTR. Conditional inference can be done with marginal structural models, or fitting a Cox regression to the weighted dataset. Dr. Lyden showed an example through a sample of 8000 people from 2001-2014, through 5 years of follow-up. PALK-6 represents the strategy of getting a living donor kidney within 6 months, then joining the waiting list for a pancreas transplant. PALK-12 is the same strategy but seeks living donor kidney within 12 months. Survival under PALK-6 strategy was optimal, probably because people are guaranteed to get a kidney transplant within 6 months; the second-best option being PALK-12, and the lowest survival being the wait-for-SPK strategy.

However, the problem in applying existing methods for DTRs in this scenario is that the transplant rates and distributions of accepted-organ kidney/pancreas donor risk index (KDRI/PDRI) have changed since 2014 and vary by center. And so, if these existing methods are applied naively, that would mean averaging over rates and organ qualities that might not be applicable to current patients. Dr. Lyden proposed the solution of defining a different target parameter, and adapted the method to estimate that parameter. This solution compared survival under the versions of treatment available to patients, by defining dynamic treatment regimens that assign treatment probabilistically with the transplant probabilities of similar patients in the target population (eg, patients today at a specific center). The methods used for estimations are still IPW, with a numerator of estimated treatment probability for patients in the target population.

Dr. Lyden reviewed weighted Kaplan-Meier curves for an average or typical KP patient. The figure showed postlisting patient survival under different strategies, and specified by different listing years that determine distribution of transplant rates and organ quality. The black survival curve illustrates that the strategy of joining the SPK waiting list in 2017 is an estimated improvement over previous

years as a result of patients undergoing transplant faster. This is comparable to the PALK-12 strategy, where patients are receiving a living donor kidney transplant in a year, then waiting for pancreas. This method can also be applied to look at survival under these strategies by centers.

Dr. Lyden went over weighted Cox regression, showing figures conditioned on a score that represents a combination of factors indicating how quickly a patient will get SPK in practice. The greater the score, the more likely the patient will get SPK. If a patient inputs information indicating the patient is very likely to get a transplant quickly, they may be shown conditional survival curves that might indicate that SPK is preferable to PALK. The conditional models also provide HRs for comparing three strategies. An additional figure demonstrated that to incorporate risk to the living donor, SPK might be preferred unless PALK has a significantly greater survival benefit.

Dr. Lyden discussed how this new method of analysis could be applicable for patients. Instead of conditioning on a score, she suggested conditioning on a slate of patient factors. Survival probability over time could also be shown. In terms of extensions, it may be helpful to look at graft survival and patient survival, and incorporate more uncertainty as to whether a living donor can be found. Limitations of the analyses included COVID-19 and postlisting analysis being restricted to patients who list for KP.

Dr. Hunsicker said it was important to bear in mind that perhaps getting a kidney quickly was the biggest benefit, as opposed to focusing on SPK. Dr. Nicholas Wood suggested looking into a full year of data on a national level, as opposed to center-specific. Dr. Hunsicker suggested applying a multiplier to the probability of getting a transplant this year nationwide and applying it to each of the preceding local probabilities, assuming that they will not have changed other than proportionally to the national level. Dr. Panageas said she had trouble with the practical interpretations for patient decision making and that the framing for how much control a patient had over certain decisions had to be communicated clearly.

Dr. Josh Pyke added SRTR has made progress prototyping these kinds of tools and having them available for initial evaluative research to address the best way to frame core statistical findings that communicate implications clearly to a target audience. Dr. Wood expressed interest in creating decision tools regarding suboptimal liver and split liver for pediatric candidates. Members briefly discussed the possibility of using simulated allocation models (SAMs) for offer acceptance modeling with decision aids in the future.

Closing business

With no other business being heard, the meeting concluded. The next meeting date is to be determined.