SCIENTIFIC REGISTRY OF TRANSPLANT RECIPIENTS

SRC Analytical Methods Subcommittee Meeting Minutes

Analytical Methods Subcommittee Teleconference

June 29, 2021 1:00 PM – 3:30 PM CDT

Voting Members:	**HRSA:**	**SRTR Staff:**
Brent Logan, PhD (Chair)	Shannon Dunne, JD	Ryutaro Hirose, MD
Andrew Schaefer, PhD	Adriana Martinez	Ajay Israni, MD, MS
David Vock, PhD		Nicholas Salkowski, PhD
Not in Attendance:		Jon Snyder, PhD, MS
Shu-Xia Li, PhD		Andrew Wey, PhD
Katherine Panageas, PhD		Josh Pyke, PhD
		Donnie Musgrove, PhD
		Sommer Gentry, PhD

Welcome and introductions

Dr. Andrew Wey called the Analytical Methods Subcommittee meeting to order. The first agenda item was selecting risk factors for model adjustments used on program- and organ-specific reports (PSRs and OSRs). The second item was how to implement offer acceptance models in simulated allocation models (SAMs) and whether SRTR should use SAMs for organ discard rates. Dr. Wey said he would also give an update on the SRTR Review Committee's (SRC's) handling of COVID-19. He reminded members of conflict-of-interest management and proceeded with the agenda.

Risk-adjustment model building: Selection of appropriate risk factors

Dr. Wey reviewed how SRTR selects variables with posttransplant models (the process also affects pretransplant models.) Posttransplant models currently have a build-and-fit model cycle for selecting predictors. During the build cycle, SRTR gathers information on a transplant (eg, recipient and donor risk factors.) SRTR selects predictive factors and penalties for coefficients. Dr. Wey noted that all risk-adjustment models are run with LASSO. The build cycle output creates a fit build every six months, corresponding to each PSR cycle. SRTR uses these structures to update cohorts for given PSR cycles.

Dr. Wey displayed a chart illustrating the build cycle, which includes selection of variables to include in the PSRs and appropriate penalty terms. Within cohort/data development is a period of two and a half years for posttransplant outcomes. If more than nine events occur during that time, SRTR tries to build a risk-adjustment model. SRTR then runs LASSO on each of the 10 multiple imputed data sets for missing data. If nine-plus models have greater-than -zero covariates, SRTR uses the penalty determined in the fit cycle. Dr. Nicholas Salkowski said the models then find the penalty that

minimizes the point-wise median of the cross-validation error curves. Dr. Wey added that predictors with a non-zero effect at median cross-validation error curves are included in subsequent fit cycles.

Dr. David Vock asked if specific linear splines were selected in the build process and which variables were allowed to have a nonlinear association. Dr. Salkowski explained that for every continuous variable, SRTR generates about 10 knots with an algorithm. LASSO's penalized regression decides which spline basis functions or linear terms are predictive. Those that are predictive move on to the fit stage, in which SRTR offers the model a range of basic functions and linear terms to view the functional form that fits best. The exact location of knots can change with each cycle, so SRTR uses a flexible format between continuous variables and outcomes to fit the data.

Dr. Brent Logan asked if they used a group LASSO for categorical predictors. Dr. Salkowski said they didn't; if a categorical predictor has only two levels, SRTR selects the most frequent level as the reference. If there are three or more levels, indicators at each level determine what is predictive.

Dr. Wey explained the fitting process. If predictors are identified in the build stage, SRTR imputes missing data and the covariates. Cross-validation isn't done for LASSOs; only the previously selected penalty term is used. Covariate effects are averaged. Dr. Logan asked whether variables were restricted for LASSO fits. Dr. Wey said they were and that the build models regularly consider nearly 100 risk factors, not including all splines, while the fit stage includes 15 or 20 risk factors. Dr. Logan asked if the penalty from the 100 risk factors was still good to use for the LASSO with the reduced risk factors. Dr. Wey said the penalty term was not optimal. Dr. Vock didn't think it would have a negative effect, citing the one-to-one correspondence between penalty term, LASSO, and total magnitude of coefficients in the model.

Dr. Wey summarized this entire process with a hypothetical timeline. SRTR would update the build process during the PSR spring 2021 cycle, using the fit results for each fall until 2023. An advantage for the build stage is that risk-adjustment models can consider a large number of predictors, including most donor and recipient risk factors. It also avoids subjectivity in variable inclusion. At the fit stage, transplant centers would have a low data burden, minimizing variables for review.

A disadvantage is suboptimal predictive performance. The fit cycle uses the penalty parameter from the build cycle, and many predictors in the risk-adjustment models are highly correlated or weakly predictive of posttransplant outcomes. Another shortcoming is difficulty updating the models. Adding variables or changing their parameterization requires rerunning the build cycle. Dr. Andrew Schaefer questioned the length of the updating process. Dr. Salkowski said that computing time for the build process takes a few days. Dr. Logan asked how much turnover SRTR has in variables from build to build, and Dr. Salkowski said there is little.

Dr. Vock mentioned the importance of keeping in mind the goal of variable selection and matching the approach to the goal. He said that the goal wasn't to build the most predictive model of outcomes but to adjust for imbalances among different centers in appropriate prognostic covariance. He suggested including variables that were imbalanced among centers and had predictive performance. For precision, variables highly predictive of outcome that might be well balanced among centers should be selected. However, a variable selection approach that relies on predictive performance may lead to the omission of data associated with graft or patient survival.

Dr. Vock asked for the main objectives for this two-step process. Dr. Salkowski explained that it aims to limit the number of data elements programs need to review. The process was also created to lessen time constraints for producing reports; however, since this decision was made, SRTR was able to allot more time for report creation. Dr. Vock asked if there would be two years of overlap between the build and fit models on the hypothetical timeline. Dr. Wey said that fall 2021 would have two years of the same data as spring 2021 and six months of different data.

Dr. Wey proposed an alternative approach to the two-step process consisting of a single step to estimate the risk-adjustment models. For every PSR cycle, SRTR would define the list of covariates for the model to consider. The list would likely be smaller than that in the build cycle. Then SRTR would estimate the model with the LASSO and use cross-validation to select the penalty parameter.

SRTR would estimate using risk factors defined in fall 2021, while in fall 2023 it would estimate using risk factors defined that quarter. The models would be easier to update and have better predictive performance because of re-estimation of penalty parameters and consideration of fewer covariates. However, the model would consider fewer risk factors and lead to an arbitrary selection of risk factors and could increase programs' data review burdens.

Dr. Ryutaro Hirose asked how risk factors would be selected with a more parsimonious variable set. He added that a process that increased the efficiency of adding variables was advantageous. Dr. Vock said that it was appropriate to think about variables currently under consideration at the build stage. He suggested that SRTR consider all the variables for each PSR cycle, select the ones that would have an effect using the LASSO, and re-estimate with a nonpenalized model. Dr. Logan agreed with including too many rather than not enough variables.

Dr. Wey said that the group seemed to favor including more risk factors but wanted to clarify if it would make sense to take all the variables currently under consideration at the build stage and ask clinicians to remove variables they would never consider in terms of transplant outcomes. Dr. Logan suggested including a group of variables in the second step of re-estimation with the nonpenalized model as a face validity, regardless of whether an effect was chosen in the first step. Dr. Salkowski asked how, in the event clinicians want to include a predictor in the model that isn't selected in the LASSO step, the functional form should be defined if the predictor doesn't appear to have any relationship with the outcome. Dr. Logan suggested a default parameterization. Dr. Hirose said that regular feedback with transplant centers would be helpful. Dr. Wey asked if there was a way to adjudicate the most important clinical variables to include in a model. Dr. Logan said included variables should be well supported in terms of evidence and historical data.

SAMs and organ discard

Dr. Wey overviewed SAMs: historical data SRTR uses to predict events occurring under different allocation systems. SAMS are a primary tool for helping OPTN committees understand the effects of policy proposals. The subcommittee will review underlying SAMs issues and solutions. Current SAMs are legacy SAMs underlying software built a little more than 20 years ago.

From Dr. Wey's perspective, SAMs consist of patient trajectories on the waiting list, offer acceptance rates, and posttransplant outcomes. Offer acceptance rate is important because it helps determine

the number and distribution of transplants under different allocation schemes. Dr. Wey explained that because SAMs create match runs for each recovered organ, more organs are recovered for transplant than are transplanted. There must be a process behind how the offer acceptance model determines which organs are discarded in the SAMs. One limitation is that when there is a discard, SRTR does not know when in the match run the organ stopped being offered to a program.

Under these constraints, SAMs implement an ad hoc discard process. All SAMs truncate match runs after a certain number of offers. Any organs not accepted by that offer number are discarded. The truncation is tuned when underlying cohorts are created by adjusting the cutoff number or the baseline acceptance rate. Ad hoc tuning of the acceptance model and its implementation is done so that the baseline scenario is somewhat calibrated. However, this process doesn't align with how discard actually occurs, because organs are sometimes accepted and transplanted after these cutoffs. The process also introduces an inappropriate property to SAMs, in which the number and distribution of transplants under alternative allocation policies depend on discard process implementation rather than allocation policy.

Essentially, how donors are defined for match runs distorts implementation of the offer acceptance process in the last step. Dr. Wey mentioned the simulation study done with kidney-pancreas (KPSAM) that varied factors within the offer acceptance model, discard cutoff numbers, and allocation policies. The results for number of transplants (donor and candidate) showed that the difference between allocation schemes changed depending on the cutoff number. An additional illustration for transplant rate across dialysis at listing showed that transplant distribution changed under different allocation scenarios, depending on discard process implemention.

Dr. Wey said that SRTR decided that legacy SAMs should not model the discard process because of a lack of good data to credibly model the outcome. Also, the ad hoc approach could create differences across alternative allocation policies caused by arbitrary and non-clinical decisions in the SAM. An alternative process was to create match runs for each transplanted organ and never truncate them, which wouldn't depend on arbitrary design decisions. Disadvantages include fewer transplants under allocation systems because of more exhausted match runs, increased simulation run times, and difficulty comparing future and past SAMs studies.

Dr. Josh Pyke went over a future SAM model (OASim), which differs from legacy SAMs in that it is more flexible about simulator organ placement modeling. Additional data analysis or collection might enable better modeling of the actual discard process. The project also focuses on whether more information is available in the current data and how to encourage data collection. Dr. Andrew Schaefer inquired about using SAMs in a way that researchers could integrate patient perspective-based models into a simulation to better understand patient behavior. Dr. Pyke affirmed that from a technical perspective, SRTR would like to enable this inquiry. Dr. Sommer Gentry referred to Dr. Schaefer's suggestion as strategic organ acceptance models, in which acceptance and decline rates change under a different allocation system. Dr. Gentry was enthusiastic about the long-term possibilities of this proposed research. Dr. Hirose suggested integrating past center-specific behavior patterns to make accurate predictions with no behavioral change.

Dr. Wey asked the subcommittee if it agreed that SAMs should not attempt to model organ discard or truncate match runs and should include transplanted organs. Dr. Vock asked if these decisions

would result in a well-calibrated model. Dr. Wey answered that it is well calibrated for thoracic (TSAM). Dr. Pyke said he hoped that with OASim, users would be able to design models suited for their specific research goals. Dr. Wey asked for recommendations on communicating this change to the transplant community and Dr. Vock suggested two potential audiences: SAMs and SAMs outcome users. Dr. Pyke added practitioners, policy makers, and the general public to those suggestions.

COVID-19 update

Dr. Wey informed the subcommittee of the SRC's decision to "carve-out" the period of the pandemic's most significant disruption to clinical practice. Most COVID-19 changes related to clinical practice had stabilized by June 2020. The approach to OSRs and PSRs was to carve out the period of March 13 to June 12, 2020.

Closing business

Hearing no other business, the meeting concluded. The next meeting, which will be held via teleconference, is slated for September or October 2021.