SRTR Simulation Study Process Overview

Date:
May 1, 2024
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1 Executive Summary

This document describes the software, team, process, and quality assurance techniques used at the Scientific Registry of Transplant Recipients (SRTR) when responding to simulation inferential data requests from committees of the Organ Procurement and Transplant Network (OPTN). Both organizations work under contractual structures specified by the Health Resources and Services Administration (HRSA) which include obligations for how requests are made by OPTN, reviewed by HRSA, and responded to by SRTR.

SRTR runs simulations using the OASim simulator software. Simulation studies are performed by a collaborative team, including:

- project managers
- biostatistical analysts
- software developers
- SRTR senior staff and leadership

The process of running a simulation study involves multiple phases, including:

- defining the data request and analysis plan
- preparing simulator inputs (configuration files, input data, and submodels) as required by the data request and analysis plan
- running the simulation and analyzing the results
- reviewing, summarizing, and presenting the results

Each simulation study is specific to the data request that initiated it and may take several weeks to several months. Quality assurance steps are included at multiple points in the process in order to identify and correct errors before a final report is provided to the requesting committee.

2 Software

SRTR has developed in-house software tools to perform simulation studies.

Simulator SRTR uses software called OASim to perform simulations of the organ allocation system. OASim uses policy implementations, input datasets, and statistical submodels created by SRTR analysts to simulate the behavior over time of different versions of the organ allocation system. OASim also includes a tool called MRCalc which calculates individual match runs. It uses the same input datasets and policy implementations as OASim to calculate specific individual match runs, which can be used to verify that policy implementations are functioning as expected.

Analysis SRTR uses the R statistical computing platform to prepare input datasets and statistical models, analyze simulation results, and prepare summary reports.

3 Team

The simulation team at SRTR includes members from multiple groups at the organization.

Project Managers SRTR Project Managers are the first line of support for OPTN committees, attending all committee calls and coordinating collaborative OPTN/SRTR projects. For simulation studies, project managers arrange background presentations for the committee, draft request documents and analysis plans, manage the planning and completion of the simulation study work, coordinate with senior staff, and oversee the completion and delivery of the final report to the requesting committee.

Biostatistical Analysts SRTR Biostatistical Analysts provide analytic support to OPTN committees while also leading ongoing methodological, modeling, and study efforts related to policy development and simulation analysis. For simulation studies, analysts contribute to the drafting of request documents and analysis plans, perform the study, and work with senior staff to review and present the results.

Software Developers SRTR Software Developers design, implement, and maintain in-house software tools used in simulation studies.

Senior Staff SRTR Senior Staff are clinicians and academics with significant experience in transplantation. Senior staff assist with simulation study design, review results, and present findings back to requesting OPTN committees.

Leadership SRTR Leadership, including managers in the information technology, project management, and biostatistics teams as well as the overall leadership of the organization, participate in study planning, review, and presentation of results.

4 Process

The simulation study process can be divided into 4 main phases: defining the data request and analysis plan; preparing simulator inputs (configuration files, input data, and submodels) as required by the data request and analysis plan; running the simulation and analyzing the results; reviewing, summarizing, and presenting the results

4.1 I. Data Request and Analysis Plan

1. **Request is made** The simulation study process begins when an OPTN committee approves a request for inferential statistical analysis that will require simulation. OPTN staff communicates the results of this vote and the basic parameters of the request to the SRTR.
2. **Request documents prepared** SRTR staff write a formal document describing the analysis being requested by the OPTN committee. This includes the major analytical questions that the committee would like answered, the allocation policies the committee is proposing, and any particular additional metrics that the committee would like to have reported. This request document is reviewed and approved by OPTN staff as well as HRSA. This process can take up to 2 weeks.
3. **Analysis plan prepared** After the request documents are approved, SRTR staff write a formal analysis plan describing the simulation study that SRTR will undertake to respond to the request. This includes the ways the simulation study will be designed to allow it to address the committee's core analytical questions, the way the simulated results will be presented, how the proposed policies will be compared to a baseline policy, the cohorts for use in generating input datasets and training statistical submodels, methodological background for any new or experimental techniques the analysis team plans to use, and a target date for the delivery of the results. This process can take up to 2 weeks.

4.2 II. Simulator Inputs

After the analysis plan is finalized, the analytic team takes on multiple tasks in parallel to prepare for running the study simulations. Together these processes can take anywhere from several weeks to several months depending on the complexity of the simulation study and the amount of new work required.

1. **Simulation components** A simulation study requires the design and implementation of multiple components used by the simulator OASim. The simulation team

undertakes multiple efforts in parallel during this step:

- **Policy implementation** OASim requires policy definition files, which are translations of the human-readable descriptions of allocation policy from the OPTN Policy Documents or request documents into a structured machine-readable format. Analysts review the source policy documents, implement the policy definition files in the OASim format, test the operation of the files in MRCalc, and review the work with senior staff to ensure that the policy definition files accurately reflect the intent of the policies they model.
- **Input data preparation** OASim also requires data files giving information on the candidates and donors that will be used as input for the study simulations. Analysts prepare these files, starting from historical records of candidates and donors in the OPTN system and using statistical techniques to fill in missing information and provide more variability for the simulation study.
- **Submodel development** OASim may use multiple statistical submodels to represent different features/processes in the allocation system. The specific submodels required for a study depend on the organ system and analytical goals for that study, but often include models of donor arrival, candidate history, and organ placement. Analysts determine which submodels are required by the study and for each of these submodels define the design(s) and corresponding evaluation techniques. Following this they then implement, train, and evaluate potential submodels through non-simulation methods. At this stage each submodel may have a range of potential options.

2. **Operational validation** In the operational validation (OV) stage, analysts evaluate how the simulation components developed in the above steps perform as a whole using simulation. The OV simulations use a "target" cohort (often a specific observed historic period) and are used to evaluate across the range of potential submodels to select the best collection of submodels to address the analytical questions of the study. The OV simulation results include analysis similar to what will be in the final reports; at least, there may be additional analysis as required by the study design. The OV results are not expected to reproduce the target exactly since the simulation process includes random variation. Careful evaluation for each submodel in isolation and as a whole through OV is meant to provide confidence in the final selected collection of submodels and provide credibility

for simulated results for (counterfactual) proposed policies.

4.3 III. Simulation and Analysis

1. **Run study simulations** The simulation team runs the simulations specified by the analysis plan using the components developed and validated during the simulation inputs phase. The exact simulation structure is specific to each individual study but standard parameters include 1 simulation for each proposed policy plus a simulation of a historic period to provide a baseline for comparison. Each simulation typically includes 10 separate iterations to help characterize variability across a range of possible conditions and at least one year of simulated allocations. This generally takes 1-2 weeks.
2. **Analyze simulation results** OASim produces output files giving the outcome of each simulated allocation during the study period. Analysts assemble these files into a single dataset for the study and run standard statistical analysis routines to characterize the performance of each policy against the analytical goals and supplemental metrics specified in the analysis plan. This generally takes 3-4 weeks.
3. **Prepare summary report** Analysts use a standard reporting system in R to generate an initial report document with summary tables and plots for each metric of interest.

4.4 IV. Review, Summary and Presentation

1. **Review results** Internal and senior staff review the initial report. If any results suggest a problem with the simulation components or operation, analysts can investigate the issue and potentially return to Phase II or Phase III to correct it. This generally takes 1-2 weeks.
2. **Add summary narrative** Project managers, analysts, and senior staff collaborate on writing narrative summaries of the study results which are added to the report. This generally takes 1-2 weeks.
3. **Report submitted** The written report is submitted to the OPTN committee that requested the analysis.
4. **Present results** Senior staff lead a presentation of the results highlighting key outcomes for the requesting committee.

5 Quality Assurance

Quality assurance steps are included at multiple points in the process. This section provides additional detail on some of these steps.

- **Software support** OASim provides several features designed to support avoidance, identification, and correction of errors:
  - MRCalc generates individual match runs to help with verifying implementation performance.
  - OASim separates responsibility for different allocation policy components, including screening and sorting, into separate configuration files that can be verified individually.
  - OASim validates agreement between input data and policy implementation, and will not run simulations when required input fields are missing or malformed.
- **Structured code review** All configuration and analytic code files are reviewed by at least one other member of the simulation team before being used.
- **Policy implementation report** A standard report is run for all new policy implementations giving summary statistics for policy areas of potential concern including screening rates, blood type compatibility handling, and sensitivity.
- **Operational validation** Operational validation helps to establish credibility of the simulated results as configured for the study and rule out major problems with input data and statistical submodels.
- **Senior staff review** Senior staff have deep experience and strong intuition about the historical performance of the allocation system. They are consulted at multiple points during the process, including study design, policy implementation, and results review, and internal staff investigate any concerns raised at those times.
- **Complementary analysis** While simulation analysis remains a useful and standard technique for characterizing the performance of proposed allocation systems, empirical (non-simulated) analysis is preferred when available. SRTR uses other techniques whenever possible, including match run analysis, to look at proposed policies from other angles. Discrepancies between simulation and match run analysis can help highlight potential limitations in the simulation study.
- **Challenges specific to continuous distribution** There are particular potential pitfalls in moving from classification-based allocation to continuous distribution, including the potential conflation of screening and tier inclusion criteria. SRTR

and OPTN staff analyze the policy implementation and simulation results in these areas with extra care to try to identify any errors.