RMSTSS Presentation – Synced Full Speaker Script

The Fundamental Goal: Planning Better Clinical Trials

Every trial begins with two critical design questions: how many participants do we need, and what chance do we have of detecting a true effect? These correspond to sample size and statistical power. Getting them right is not just a mathematical exercise—it's an ethical obligation to avoid underpowered studies, a financial necessity because trials are costly, and a scientific requirement to ensure valid conclusions.

The Standard Approach: Survival Models

In time■to■event trials, outcomes are measured as time until progression, recurrence, or death. We define true event time T, censoring time C, and observe Y = min(T,C) with event indicator δ. The survival function S(t) and hazard function h(t) are central quantities. This notation is standard, but it sets the stage for why hazard■based approaches can be problematic.

Proportional Hazards (PH) and Hazard Ratio Issues

The proportional hazards assumption says that treatment hazard is a constant multiple of control hazard, h1(t) = θ h0(t). When it holds, the hazard ratio θ is simple and interpretable. But in reality, this assumption often fails. Many modern therapies have delayed effects, some treatments wear off over time, and survival curves may cross. In such cases, the hazard ratio becomes a vague, time■averaged number without a clear causal meaning.

The Solution: Restricted Mean Survival Time (RMST)

The Restricted Mean Survival Time, or RMST, is defined as the area under the survival curve up to a cutoff time L. It has several advantages: it is directly interpretable in time units, such as months of additional event■free survival; it requires no proportional hazards assumption, making it robust when survival curves cross; and it is clinically meaningful because it quantifies absolute time gained or lost.

Causal Interpretation of RMST Difference

The treatment effect can be expressed as the difference in RMST between arms, Δ(L) = μ_treat(L) – μ_control(L). This is the average gain in event■free time due to treatment, over the study horizon L. Graphically, it is the difference in area under the two survival curves. Whether hazards are proportional or not, this difference remains a valid causal estimand.

Bridging Gap: Theory and Implementation

Our contribution is to bridge statistical theory and practical trial planning. We provide a unified RMST framework for power and sample size calculation, implemented in an open■source R package, RMSTSS, and exposed through a Shiny web app for non■programmers. Together, these tools make RMST■based design accessible and reproducible.

Notation and Linear RMST Model

We assume a linear model for the conditional mean RMST: E[min(T,L)|A,Z] = β0 + βA A + βZ■Z. Here, βA represents the adjusted difference in RMST between treatment groups. However, censoring prevents direct regression, so we must use techniques like IPCW or pseudo■observations.

Simple Linear IPCW Model

Inverse Probability of Censoring Weights, or IPCW, adjust for the bias introduced by censoring. We estimate the censoring survival function G(t), assign each subject a weight wi = δi / ■(Yi), and then fit a weighted regression. This recovers unbiased estimates of treatment effects under random censoring.

Generalized Additive Model

Pseudo■observations provide an alternative route. For each subject, we calculate a jackknife■like contribution to the overall RMST estimate, which is unbiased for E[min(T,L)]. These pseudo■values can then be treated as uncensored outcomes. By fitting a Generalized Additive Model (GAM) to them, we retain interpretability of βA while capturing nonlinear effects of covariates with smooth splines. This combines Andersen and Parner's pseudo■observation framework with Hastie and Tibshirani's GAM methodology.

Stratified Models

In stratified designs, we can model treatment effects additively or multiplicatively across strata. The additive model assumes a constant survival gain across all strata, while the multiplicative model assumes a constant RMST ratio across strata. The choice depends on the scientific question—whether clinicians view effects as added months or as a ratio of survival times.

Dependent Censoring

If censoring depends on covariates, using a single G(t) is biased. Instead, we estimate cause■specific censoring hazards and combine them into G(t|Z). This leads to valid IPCW

weights under dependent censoring, ensuring unbiased estimates even when dropout patterns are informative.

Core Computational Approaches for Power and Sample Size

To calculate power and sample size, RMSTSS offers two approaches. The analytical approach uses asymptotic variance of β■A to compute power quickly, suitable for grid searches. The bootstrap approach resamples pilot data, allowing flexible validation of power under complex models at the cost of computation. Analytical is fast; bootstrap is robust.

Example 1: Linear IPCW RMST Model

As a first example, we analyze the veteran dataset. We target 40% power at L = 365 days, adjusting for Karnofsky score. Starting from 1000 per arm and stepping by 250, we search up to 5000. The simulation shows steadily increasing power, reaching ~40% at 4500 per arm. This illustrates analytic sample size search under a linear IPCW model.

Example 2: Multiplicative Stratified RMST Model

Our second example uses colon cancer survival data with strata. We run bootstrap power estimation with 100 replicates, cutoff L = 1825, and step size 50. The output reports a mean RMST ratio of 1.0065 with a 95% CI of 0.968 to 1.057. This demonstrates bootstrap■based power analysis for a multiplicative stratified RMST model.

Application Interface: RMSTSS Web Application

For those who do not code in R, we provide a Shiny app interface. Users upload pilot data in CSV, map columns, select models and goals, and see interactive outputs. The interface ensures accessibility and reproducibility.

Application Feature: RMSTSS Web App

The app workflow is straightforward: Input → Configure → Export. Users can optionally visualize survival and power curves and customize fonts and themes. The app is fully web■based, requiring no R installation, and it produces ready■to■share PDF reports.

Conclusion & Future Aims

To conclude: RMSTSS provides rigorous, interpretable tools for clinical trial design. It supports linear, GAM, stratified, and dependent censoring models, with treatment effects that are causally interpretable. Practically, it is available as an R package and a Shiny app. Future aims include support for time■varying treatments, pilot■free design through data generation,

and modules for multi■arm and platform trials.

Access & Acknowledgments

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