Estimating the treatment effect in randomized trials with correlated time-to-event outcomes

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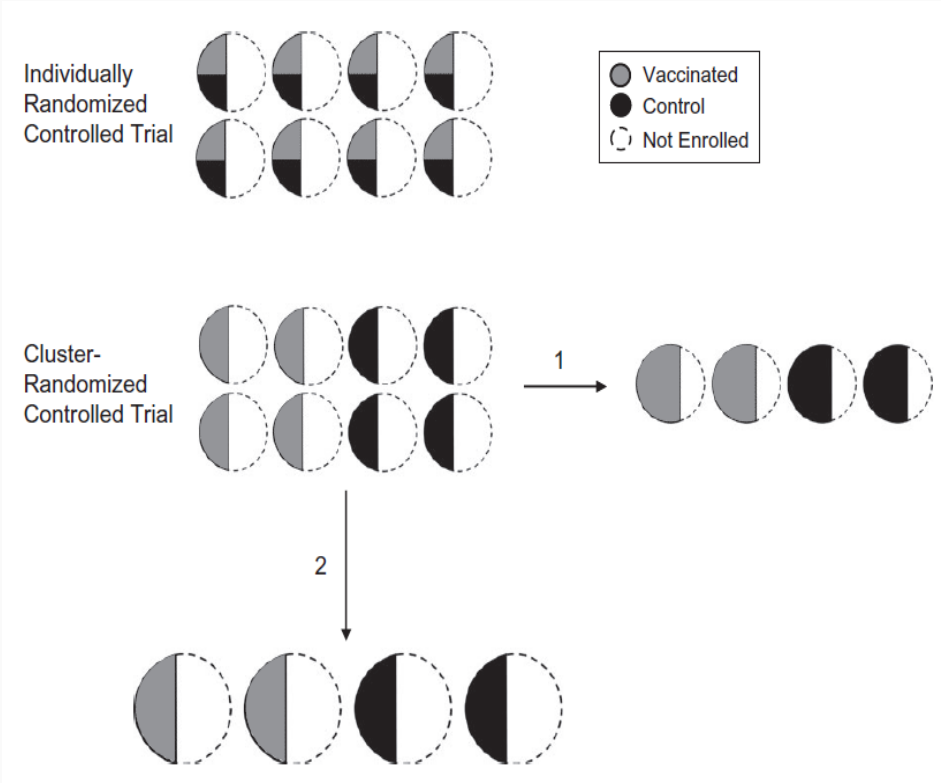
Background

Background: Clinical Trial Randomization Strategies



Individual RCT

- e.g Herceptin vs. Lapatinib

Cluster RCT

- e.g. Cancer screening intervention trials

Background: Clinical Trial Randomization Strategies

Individual RCT regardless of cluster

- Framework that has received less attention
- Example: Vaccine studies (e.g COVID19)

Background: Goal of Project

How to estimate randomized intervention effects for trials with individual randomization and correlated outcomes?

Compare performance of various analysis strategies

- Unstratified model-based
- Unstratified robust sandwich
- Stratified model-based

Methods

Methods: Data Generation Model

Model: Clayton copula model

- Generated from R copula package

Copulas

- Decomposes a joint probability distribution into their marginals, and a function which couples them together
- Kendall's Tau - correlation parameter ranging between -1 and 1

Methods: Data Generation Steps

Data Generation Steps

1. Assign each individual to a cluster
2. Randomly assign treatment indicator X to each person
3. Generate the marginal survival functions s(T|X) using copula model
4. Given s(T|X), generate survival times using Weibull distribution quantiles
5. Generate censor times using exponential distribution
6. Choose minimum of survival time and censor time and record indicators accordingly

Methods: Simulation Parameters

Based off of COVID19 vaccine study:

- Number of people = 30,000
- Hazard ratio (trt vs. ctrl) = 0.4
- Total expected events = 150
- Number of simulations per scenario = 3,000
- Beta (parameter of interest) = log(0.4) = -0.92

Methods: Varying Simulation Parameters

Cluster type/size

- Small - 10,000 clusters of size 3
- Large - 100 clusters of size 300
- Mixed - 5000 clusters of size 3, 50 clusters of size 300

Randomization Type (Individual, cluster, within-cluster)

Kendall's Tau (correlation parameter)

Stratification

Methods: Statistics of Interest

Statistics of Interest

- Average $\hat{\beta}$
- Average estimated standard error
- Coverage probability of a nominal 95% CI
- Width of the CI

Methods: Analysis

Unstratified Cox Regression: $h(t) = h_0(t)exp(\beta X)$

- Model variance
- Robust sandwich variance (Lin and Wei, 89)

Stratified Cox Regression: $h(t) = h_{0g}(t)exp(\beta X)$

- Model variance

Results

Results: Individual Unstratified Generation

Small clusters (10,000 clusters of size 3)

	Stratified Model				
			Model-based		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width
0	-0.958	0.404	0.383	0.952	1.503
0.1	-0.950	0.394	0.383	0.958	1.501
0.2	-0.945	0.402	0.384	0.951	1.504
0.3	-0.951	0.387	0.382	0.960	1.497
0.7	-0.965	0.387	0.385	0.965	1.510

	Unstratified Model							
			Model-based			Robust		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.928	0.170	0.173	0.954	0.677	0.173	0.955	0.677
0.1	-0.920	0.176	0.173	0.944	0.678	0.173	0.945	0.677
0.2	-0.925	0.174	0.173	0.952	0.678	0.173	0.953	0.677
0.3	-0.928	0.173	0.173	0.952	0.678	0.173	0.952	0.677
0.7	-0.923	0.173	0.173	0.948	0.677	0.173	0.948	0.677

Results: Individual Unstratified Generation

Large clusters (100 clusters of size 300)

	Stratified Model				
			Model-based		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width
0	-0.921	0.178	0.178	0.950	0.699
0.1	-0.929	0.185	0.179	0.944	0.701
0.2	-0.926	0.183	0.179	0.949	0.700
0.3	-0.929	0.184	0.179	0.943	0.701
0.7	-0.973	0.185	0.183	0.949	0.716

	Unstratified Model							
			Model-based			Robust		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.920	0.174	0.173	0.950	0.677	0.171	0.949	0.671
0.1	-0.925	0.180	0.173	0.946	0.678	0.171	0.943	0.671
0.2	-0.921	0.176	0.173	0.949	0.677	0.171	0.942	0.669
0.3	-0.918	0.178	0.173	0.946	0.678	0.171	0.938	0.670
0.7	-0.927	0.177	0.176	0.955	0.689	0.170	0.935	0.667

Results: Individual Unstratified Generation

Mixed clusters (5,000 clusters of size 3, 50 clusters of size 300)

	Stratified Model				
			Model-based		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width
0	-0.925	0.236	0.228	0.946	0.895
0.1	-0.928	0.226	0.228	0.956	0.895
0.2	-0.925	0.233	0.229	0.952	0.898
0.3	-0.941	0.233	0.231	0.953	0.904
0.7	-0.974	0.246	0.235	0.943	0.921

	Unstratified Model							
			Model-based			Robust		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.920	0.175	0.173	0.949	0.677	0.172	0.947	0.674
0.1	-0.919	0.170	0.172	0.952	0.676	0.172	0.952	0.673
0.2	-0.919	0.174	0.173	0.951	0.678	0.172	0.951	0.674
0.3	-0.930	0.179	0.174	0.946	0.681	0.172	0.945	0.674
0.7	-0.923	0.176	0.174	0.950	0.682	0.172	0.943	0.673

Results: Individual Unstratified Generation

Main takeaways

- Lose efficiency if data is generated from an unstratified model and a stratified model is fit.
- This effect is more substantial for small cluster sizes.

Results: Individual Stratified Generation

Small clusters (10,000 clusters of size 3)

	Stratified Model				
			Model-based		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width
0	-0.935	0.307	0.307	0.957	1.203
0.1	-0.943	0.308	0.307	0.958	1.204
0.2	-0.951	0.314	0.309	0.962	1.213
0.3	-0.948	0.310	0.310	0.958	1.215
0.7	-1.011	0.315	0.320	0.962	1.255

	Unstratified Model							
			Model-based			Robust		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.896	0.181	0.182	0.951	0.715	0.182	0.950	0.714
0.1	-0.895	0.181	0.182	0.944	0.715	0.182	0.944	0.714
0.2	-0.895	0.184	0.183	0.947	0.716	0.182	0.945	0.715
0.3	-0.895	0.186	0.183	0.942	0.716	0.182	0.940	0.715
0.7	-0.892	0.181	0.182	0.952	0.715	0.182	0.949	0.715

Results: Individual Stratified Generation

Large clusters (100 clusters of size 300)

	Stratified Model				
			Model-based		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width
0	-0.928	0.197	0.191	0.951	0.747
0.1	-0.929	0.188	0.191	0.957	0.749
0.2	-0.937	0.200	0.193	0.951	0.755
0.3	-0.951	0.192	0.194	0.958	0.761
0.7	-1.061	0.219	0.213	0.887	0.834

	Unstratified Model							
			Model-based			Robust		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.899	0.195	0.188	0.943	0.736	0.177	0.915	0.695
0.1	-0.893	0.186	0.188	0.950	0.737	0.175	0.915	0.684
0.2	-0.895	0.198	0.190	0.941	0.743	0.174	0.895	0.681
0.3	-0.900	0.191	0.191	0.956	0.748	0.173	0.897	0.677
0.7	-0.922	0.229	0.207	0.922	0.813	0.178	0.828	0.692

Results: Individual Stratified Generation

Mixed clusters (5,000 clusters of size 3, 50 clusters of size 300)

	Stratified Model				
			Model-based		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width
0	-0.925	0.232	0.231	0.950	0.904
0.1	-0.934	0.241	0.233	0.944	0.914
0.2	-0.940	0.237	0.236	0.963	0.926
0.3	-0.957	0.244	0.237	0.951	0.930
0.7	-1.049	0.267	0.259	0.923	1.015

	Unstratified Model							
			Model-based			Robust		
Tau	$\hat{\beta}$	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.895	0.189	0.185	0.937	0.724	0.181	0.925	0.709
0.1	-0.895	0.191	0.186	0.943	0.728	0.180	0.927	0.706
0.2	-0.894	0.185	0.187	0.956	0.731	0.181	0.940	0.709
0.3	-0.901	0.189	0.187	0.951	0.732	0.181	0.929	0.708
0.7	-0.911	0.203	0.193	0.944	0.755	0.185	0.913	0.726

Results: Individual Stratified Generation

Main takeaways

- Unstratified model estimating a different parameter
- Variance slightly increases with Tau
- Robust seems to underestimate the true variance

Other Data Generation

Within-cluster data generation

- Results are very similar to the individual generation

Cluster data generation

- Robust provides much better coverage
- Results are more stable for small clusters

Conclusion

Concluding thoughts

Unstratified correlated data

- Unstratified cox model is best

Stratified correlated data

- Unstratified cox model estimates a different parameter
- Robust estimates underestimate the true variance for large/mixed clusters

Future work

- Randomization-based inference
- Use other copula models

Thank You!

Thanks for listening! Questions?

Special thanks to Rui Wang and Dongdong Li for their support and guidance throughout this project.

Appendix

Results: Cluster Unstratified Generation

CLUSTER UNSTRATIFIED DATA GENERATION

Small clusters

			Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.923	0.170	0.173	0.957	0.676	0.172	0.957	0.676
0.1	-0.927	0.174	0.173	0.946	0.677	0.173	0.946	0.677
0.2	-0.923	0.175	0.173	0.949	0.677	0.173	0.949	0.678
0.3	-0.922	0.174	0.173	0.950	0.678	0.173	0.949	0.680
0.7	-0.924	0.176	0.173	0.948	0.677	0.176	0.951	0.689

*0 observations removed (> 5 sd from mean)

Large clusters

			Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.922	0.170	0.173	0.957	0.677	0.171	0.952	0.668
0.1	-0.921	0.200	0.173	0.919	0.677	0.194	0.945	0.759
0.2	-0.917	0.231	0.174	0.858	0.681	0.219	0.935	0.859
0.3	-0.921	0.255	0.174	0.825	0.682	0.247	0.939	0.968
0.7	-0.930	0.461	0.179	0.550	0.703	0.424	0.922	1.661

*0 observations removed (> 5 sd from mean)

Mixed clusters

			Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.921	0.177	0.173	0.947	0.678	0.172	0.949	0.674
0.1	-0.913	0.187	0.173	0.934	0.679	0.183	0.950	0.718
0.2	-0.918	0.200	0.173	0.917	0.679	0.197	0.951	0.772
0.3	-0.924	0.222	0.174	0.880	0.682	0.213	0.938	0.833
0.7	-0.928	0.342	0.176	0.692	0.690	0.310	0.914	1.214

*0 observations removed (> 5 sd from mean)

Results: Cluster Stratified Generation

CLUSTER STRATIFIED DATA GENERATION

Small clusters

			Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.895	0.189	0.183	0.942	0.715	0.187	0.949	0.733
0.1	-0.888	0.190	0.182	0.937	0.715	0.188	0.946	0.737
0.2	-0.897	0.185	0.182	0.942	0.715	0.189	0.954	0.742
0.3	-0.894	0.192	0.183	0.937	0.716	0.191	0.948	0.748
0.7	-0.897	0.201	0.183	0.924	0.716	0.204	0.949	0.798

*0 observations removed (> 5 sd from mean)

Large clusters

			Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.883	0.588	0.195	0.496	0.764	0.563	0.951	2.205
0.1	-0.905	0.660	0.198	0.460	0.777	0.597	0.925	2.340
0.2	-0.897	0.737	0.203	0.413	0.795	0.634	0.908	2.487
0.3	-0.920	0.817	0.208	0.381	0.816	0.676	0.892	2.649
0.7	-0.912	1.341	0.260	0.253	1.020	0.889	0.802	3.490

*35 observations removed (> 5 sd from mean)

Mixed clusters

			Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.895	0.400	0.189	0.645	0.739	0.384	0.924	1.504
0.1	-0.906	0.446	0.189	0.583	0.740	0.402	0.898	1.576
0.2	-0.898	0.482	0.191	0.537	0.747	0.417	0.894	1.633
0.3	-0.917	0.509	0.193	0.529	0.757	0.430	0.882	1.685
0.7	-0.909	0.696	0.202	0.441	0.791	0.502	0.854	1.969

*0 observations removed (> 5 sd from mean)

Results: Within-cluster Unstratified Generation

Within-cluster UNSTRATIFIED DATA GENERATION

Small clusters

	Stratified Model					Unstratified Model							
			Model-based					Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.938	0.335	0.328	0.954	1.287	-0.923	0.171	0.173	0.958	0.677	0.173	0.958	0.676
0.1	-0.937	0.332	0.328	0.960	1.285	-0.927	0.166	0.173	0.960	0.677	0.172	0.961	0.676
0.2	-0.942	0.337	0.329	0.953	1.290	-0.923	0.180	0.173	0.941	0.677	0.172	0.941	0.676
0.3	-0.934	0.333	0.327	0.954	1.284	-0.920	0.174	0.173	0.949	0.677	0.172	0.949	0.675
0.7	-0.961	0.343	0.332	0.955	1.301	-0.926	0.176	0.173	0.954	0.677	0.172	0.951	0.673

*1 observation removed (> 5 sd from mean)

Large clusters

	Stratified Model					Unstratified Model							
			Model-based					Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.923	0.176	0.178	0.952	0.697	-0.923	0.172	0.173	0.951	0.676	0.171	0.947	0.671
0.1	-0.926	0.179	0.179	0.952	0.700	-0.924	0.174	0.173	0.951	0.678	0.172	0.945	0.673
0.2	-0.922	0.176	0.178	0.953	0.699	-0.917	0.169	0.173	0.951	0.677	0.171	0.946	0.669
0.3	-0.927	0.178	0.179	0.949	0.701	-0.919	0.172	0.173	0.952	0.679	0.171	0.945	0.669
0.7	-0.969	0.181	0.182	0.947	0.714	-0.922	0.172	0.175	0.957	0.688	0.168	0.941	0.660

*4 observations removed (> 5 sd from mean)

Mixed clusters

	Stratified Model					Unstratified Model							
			Model-based					Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.931	0.220	0.222	0.953	0.870	-0.928	0.172	0.173	0.953	0.679	0.172	0.951	0.676
0.1	-0.928	0.224	0.221	0.951	0.867	-0.921	0.173	0.172	0.950	0.676	0.172	0.948	0.673
0.2	-0.929	0.220	0.221	0.957	0.867	-0.921	0.171	0.173	0.954	0.676	0.171	0.951	0.672
0.3	-0.934	0.229	0.222	0.952	0.872	-0.924	0.173	0.173	0.954	0.678	0.172	0.954	0.673
0.7	-0.970	0.231	0.227	0.948	0.890	-0.927	0.177	0.174	0.951	0.682	0.170	0.939	0.665

*2 observations removed (> 5 sd from mean)

Results: Within-cluster Stratified Generation

Within-cluster STRATIFIED DATA GENERATION

Small clusters

	Stratified Model					Unstratified Model							
			Model-based					Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.928	0.268	0.265	0.953	1.037	-0.892	0.180	0.182	0.953	0.715	0.181	0.950	0.708
0.1	-0.926	0.263	0.264	0.961	1.035	-0.893	0.180	0.182	0.953	0.714	0.180	0.949	0.706
0.2	-0.945	0.273	0.266	0.954	1.042	-0.891	0.181	0.182	0.952	0.714	0.179	0.946	0.703
0.3	-0.953	0.269	0.267	0.955	1.047	-0.897	0.183	0.183	0.946	0.716	0.180	0.943	0.704
0.7	-1.024	0.282	0.277	0.948	1.086	-0.895	0.174	0.182	0.956	0.715	0.175	0.946	0.686

*0 observations removed (> 5 sd from mean)

Large clusters

	Stratified Model					Unstratified Model							
			Model-based					Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.927	0.197	0.191	0.950	0.748	-0.898	0.192	0.188	0.948	0.738	0.174	0.906	0.683
0.1	-0.929	0.192	0.190	0.955	0.746	-0.896	0.188	0.188	0.950	0.736	0.173	0.911	0.676
0.2	-0.939	0.201	0.192	0.951	0.754	-0.896	0.194	0.189	0.950	0.743	0.172	0.908	0.674
0.3	-0.947	0.199	0.196	0.955	0.767	-0.895	0.193	0.192	0.950	0.754	0.173	0.896	0.676
0.7	-1.066	0.222	0.217	0.899	0.849	-0.928	0.221	0.211	0.943	0.828	0.177	0.846	0.687

*54 observations removed (> 5 sd from mean)

Mixed clusters

	Stratified Model					Unstratified Model							
			Model-based					Model-based			Robust		
Tau	Beta_Hat	SE (empirical)	ESE	CP	Width	Beta_Hat	SE (empirical)	ESE	CP	Width	ESE	CP	Width
0	-0.926	0.223	0.219	0.954	0.858	-0.897	0.187	0.184	0.943	0.723	0.177	0.925	0.695
0.1	-0.928	0.223	0.221	0.954	0.867	-0.892	0.186	0.185	0.950	0.726	0.178	0.932	0.697
0.2	-0.936	0.230	0.222	0.950	0.870	-0.891	0.184	0.185	0.953	0.727	0.177	0.935	0.695
0.3	-0.953	0.232	0.226	0.953	0.884	-0.896	0.189	0.187	0.951	0.733	0.179	0.929	0.701
0.7	-1.050	0.248	0.241	0.919	0.946	-0.909	0.195	0.192	0.941	0.752	0.178	0.906	0.697

*9 observations removed (> 5 sd from mean)