

Risk-Stratified Imputation in Informative Censoring

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CREST
Carotid Revascularization
Endarterectomy vs. Stenting Trial

Motivating Study Background

- **The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)**
 - 2502 patients randomized to “traditional” surgery (endarterectomy – CEA) versus “novel” endovascular (carotid stenting – CAS) therapy
 - Primary outcome
 - Stroke, MI or death in periprocedural period
 - Ipsilateral stroke afterward

How the best of intentions can get you into quite a pickle

- **Much higher withdrawal rates in CAS than CEA**
 - Randomization could be on the basis of ultrasound
 - Subsequent angiography in CAS group only could show patient ineligible for treatment
 - Powerful predictors of ineligibility included age and disease severity (both tightly tied to outcomes)
 - Untreated were more likely to withdraw from follow-up
 - Approximately half way through recruitment, policy was instituted where coordinators had to call study PI to discuss each case of dropout
 - Dramatic decline in dropouts

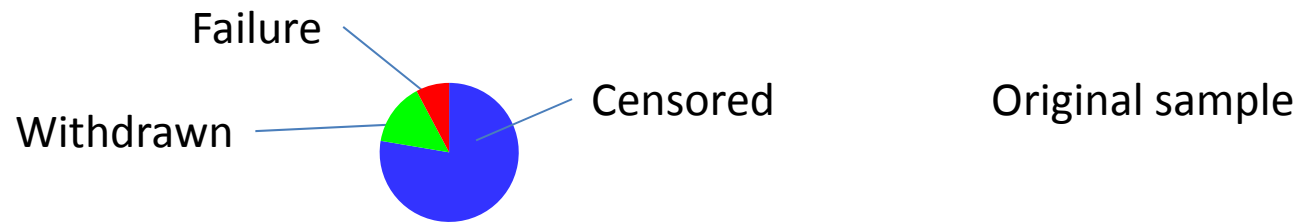
How the best of intentions can get you into quite a pickle

- Also large changes in eligibility over time
 - Eligibility was originally only symptomatic patients
 - Approximately half way through enrollment, opened to asymptomatic patients
 - Asymptomatic patients are at much lower risk of events
- Hence, no real reason to think randomization balanced risk in the study groups
 - High dropout of high risk patients only in CAS group early
 - Inclusion of low risk patients (asymptomatics) relatively uniform later
- → need to institute some kind of adjustment to more truly implement intention to treat

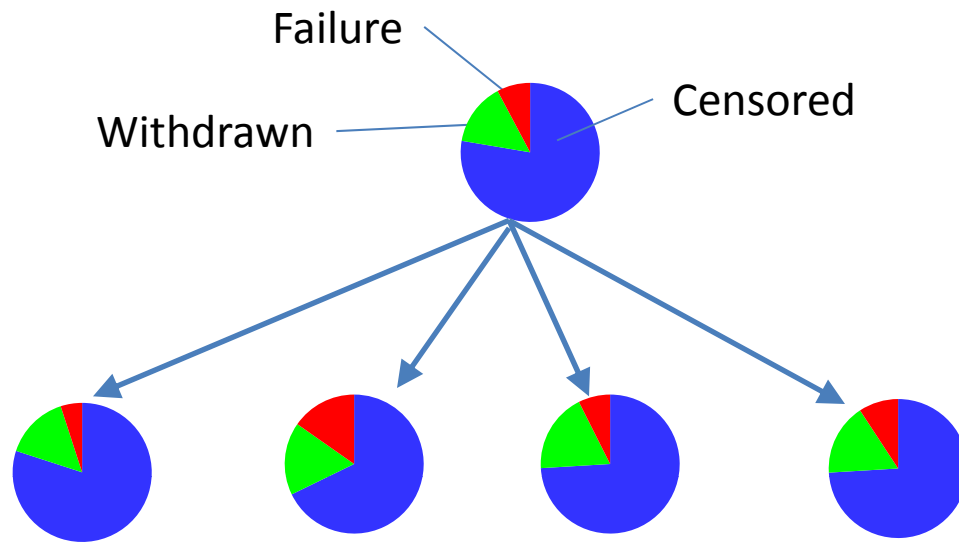
Imputation Aims

- Focus needed to be on treatment difference in withdrawals
- Procedures are well known, as are predictors of outcome events (age, symptomatic status, degree of stenosis, and gender)
- Primary analysis plan included covariate adjustment
- However, withdrawals require secondary analysis accounting for missing data
- Withdrawals are basically only missing data ... and a target for multiple imputation
- Situation where withdrawals (missing data) are associated with both covariates and likelihood of study outcomes

Approach of Taylor



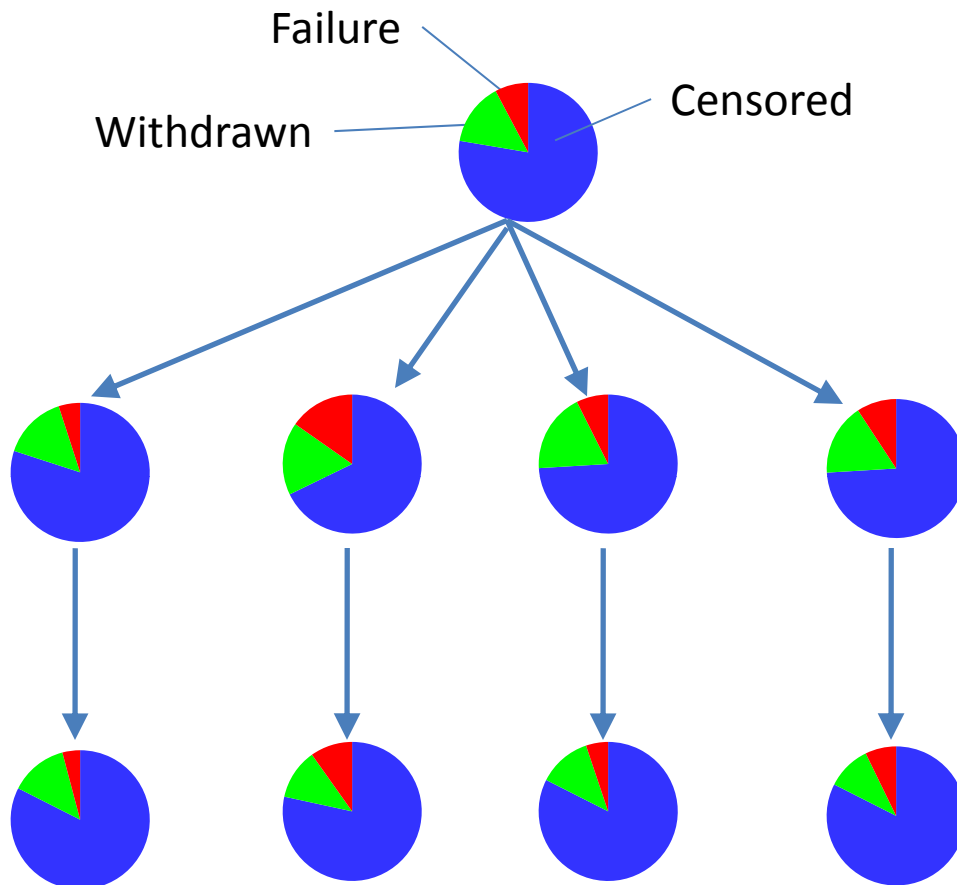
Approach of Taylor



Original sample

Create "m" bootstrap samples of size n

Approach of Taylor

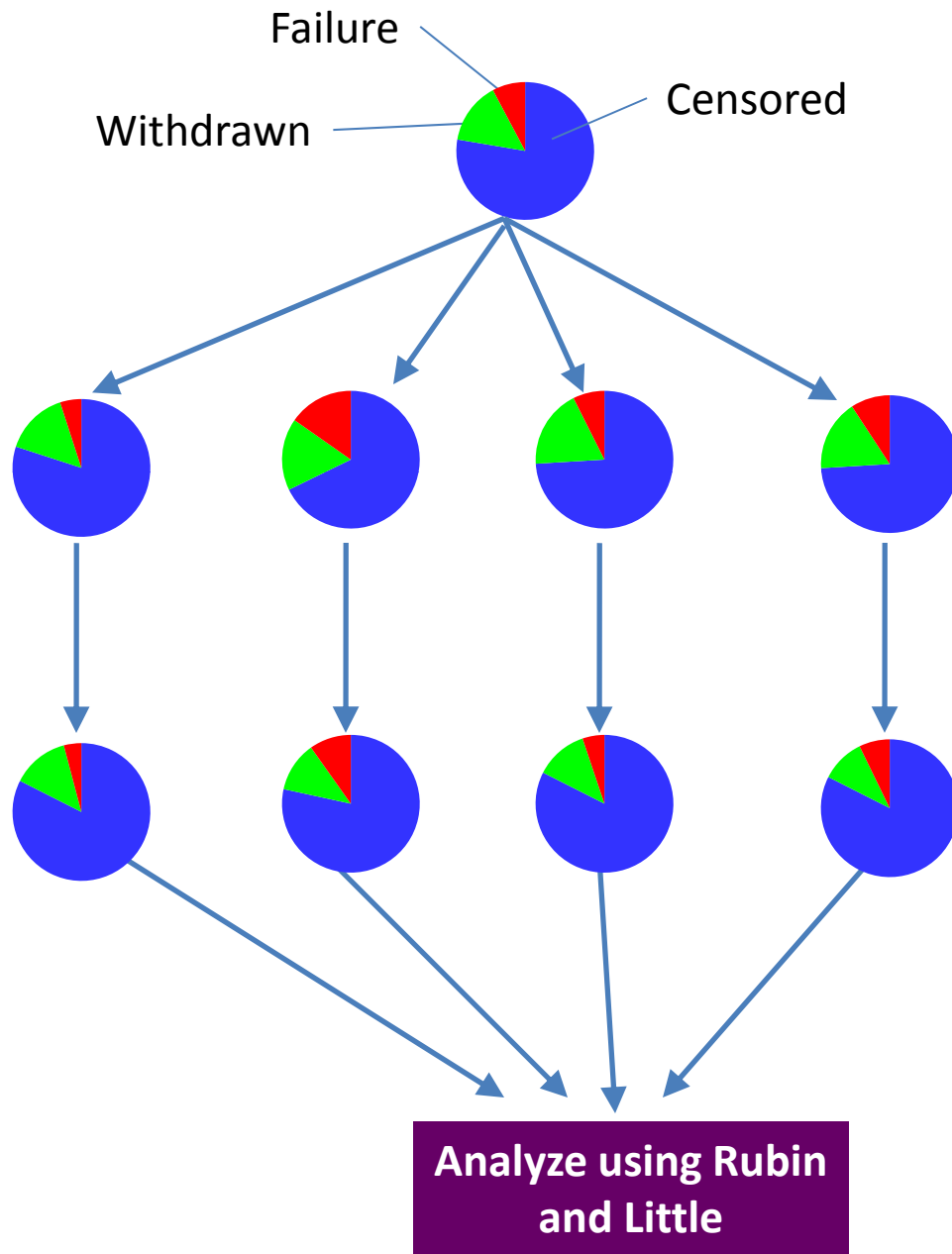


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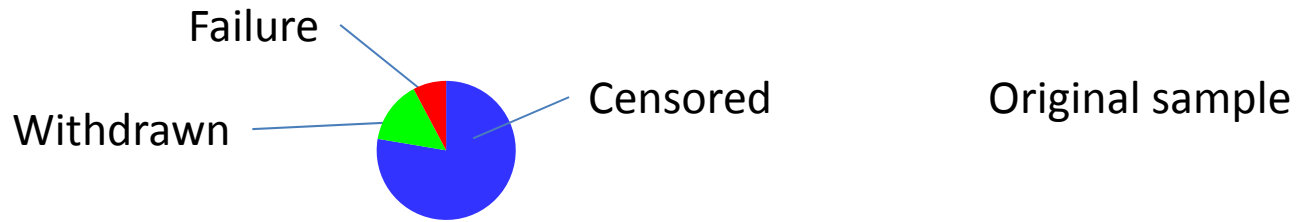
Create "m" bootstrap samples of size n

Impute withdrawals and censored from those remaining in the study at the time of removal for the index case

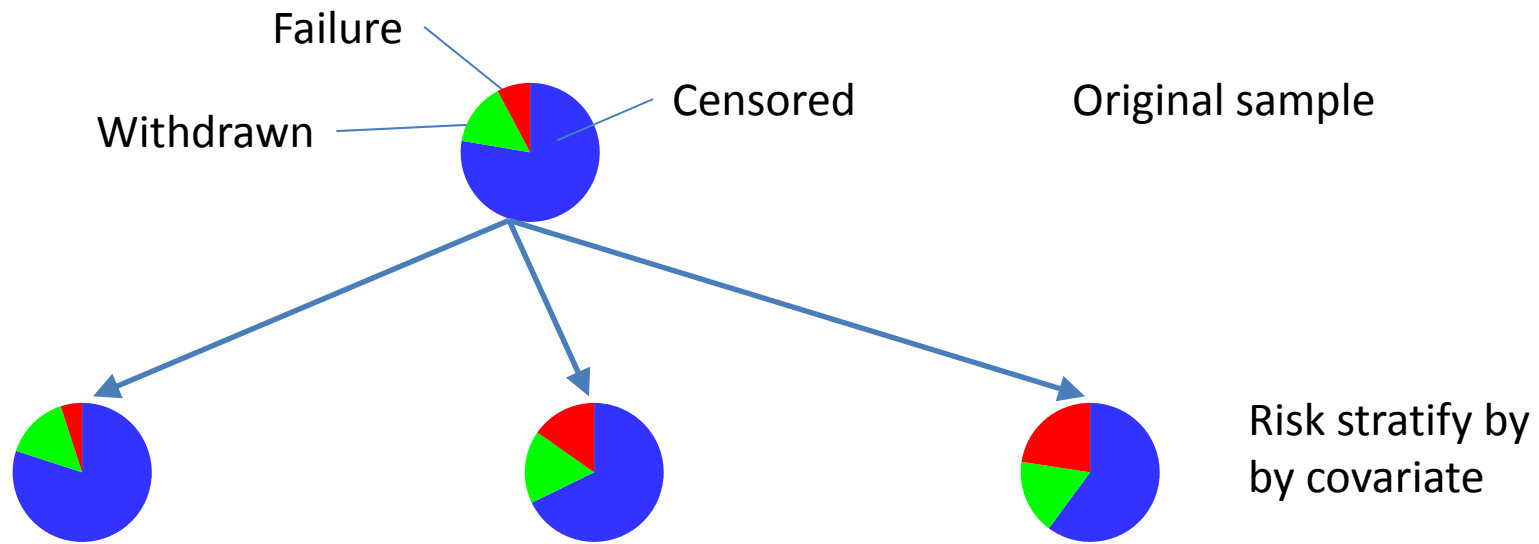
Approach of Taylor



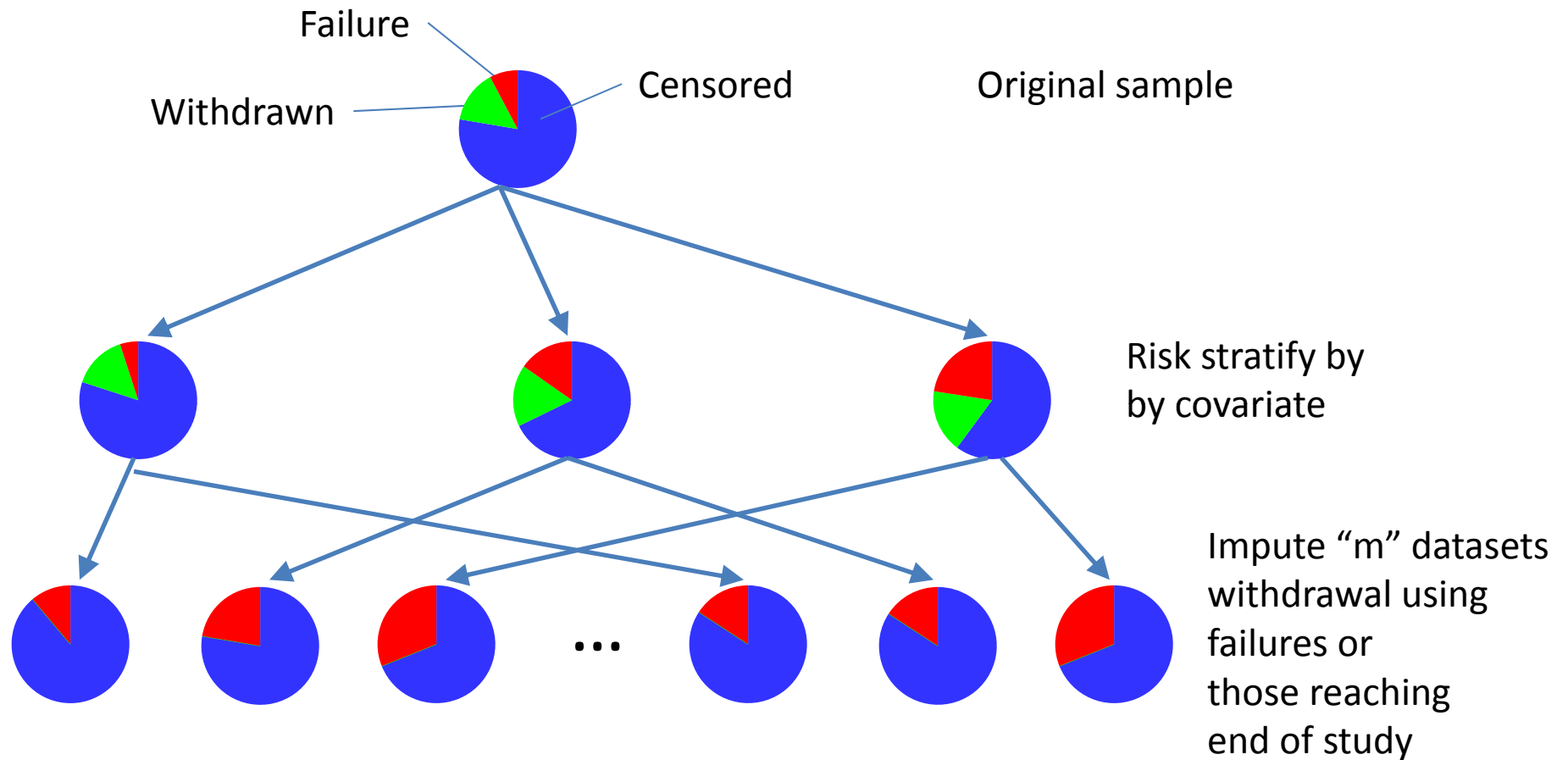
Proposed Risk Stratification Approach



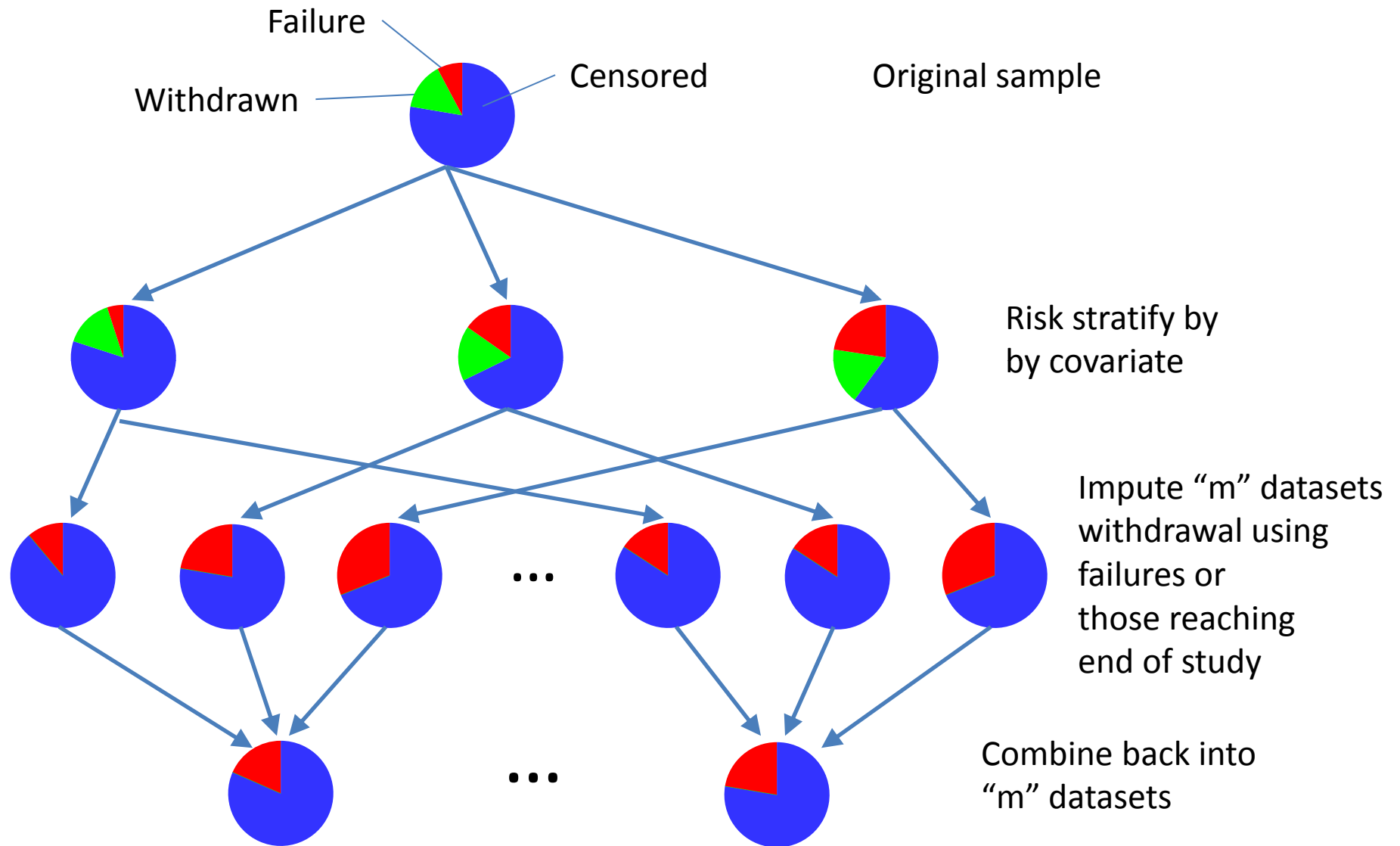
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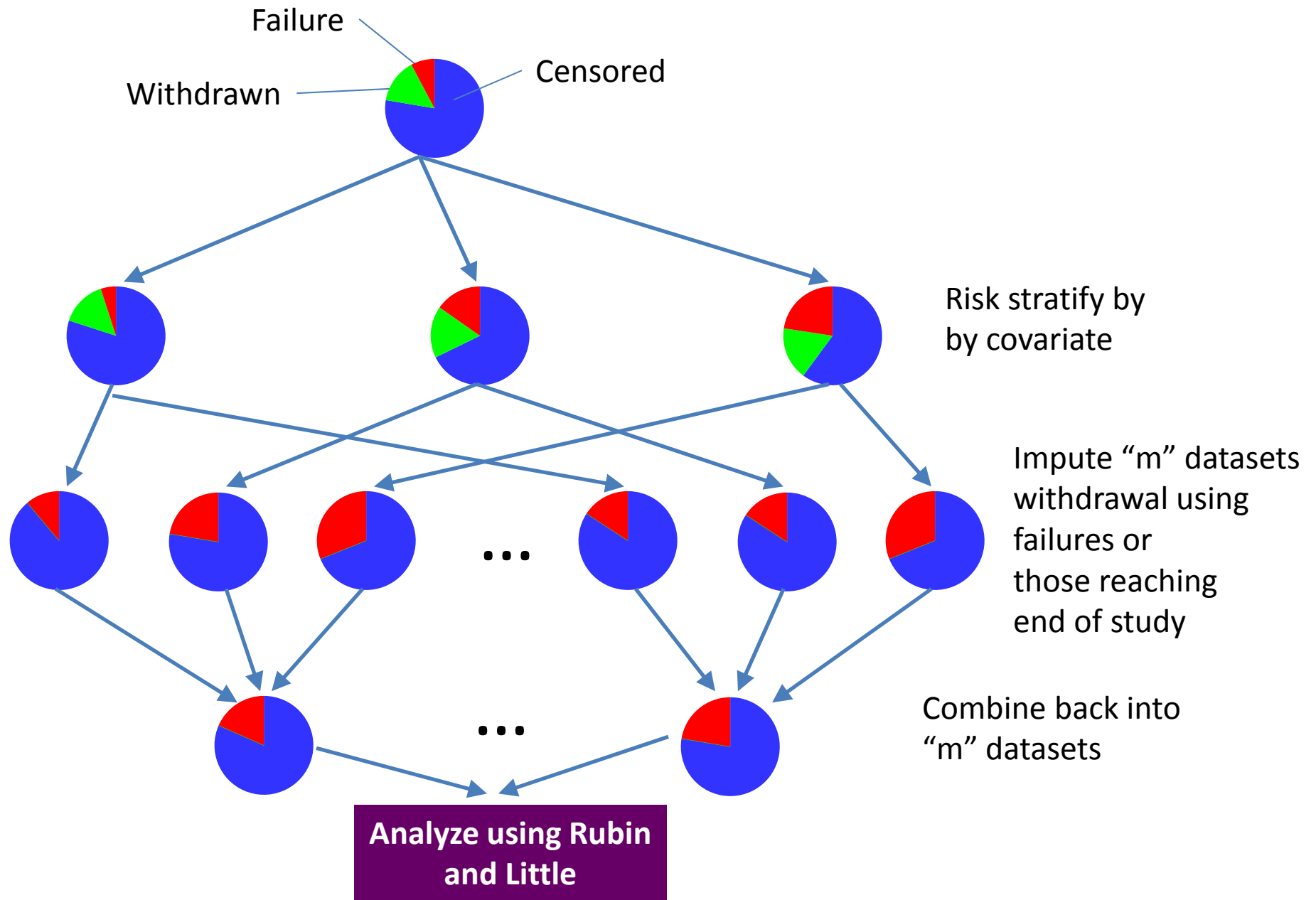
Proposed Risk Stratification Approach



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Proposed Risk Stratification Approach



Simulation Design

- Considered one factor of interest (treatment) and one covariate (measure of risk)
- Considered 5 scenarios
 - Treatment/covariate related to outcome and withdrawal
 - Treatment related to outcome and withdrawal
 - Treatment related to outcome only
 - Treatment related to outcome and withdrawal, covariate related to outcome only
 - Treatment and covariate related to both outcome and withdrawal
- Performance was evaluated by root mean square error (magnitude of bias) and proportional coverage of known parameter



The scenario that we think CREST has

Simulation Outcomes

			Complete Data	Risk-Stratified Imputation	Bootstrap Imputation (Taylor)
Scenario 1 <i>Treatment/covariate related to neither outcome or withdrawals</i>	failure: 19% withdraw: 7% censored: 75%	Mean (SE)	0.00007 (0.00010)	-0.00003 (0.00010)	-0.00003 (0.00010)
		RMSE	0.0952	0.0954	0.0995
		Coverage	95.0	94.9	99.6
Scenario 2 <i>Treatment related to outcome only</i>	failure: 13% withdraw: 7 % censored: 80%	Mean (SE)	1.0023 (0.0013)	1.0042 (0.0013)	1.0078 (0.0013)
		RMSE	0.1256	0.1260	0.1331
		Coverage	95.2	95.3	99.1
Scenario 3 <i>Treatment related to outcome and withdrawal</i>	failure: 17% withdraw: 7% censored: 76%	Mean (SE)	0.9978 (0.0011)	1.0014 (0.0011)	1.0044 (0.0011)
		RMSE	0.1095	0.1099	0.1150
		Coverage	95.4	95.5	99.2
Scenario 4 <i>Treatment related to outcome and withdrawal, covariate related to outcome only</i>	failure: 16% withdraw: 13% censored: 71%	Mean (SE)	0.9242 (0.00113)	0.9978 (0.00113)	1.0005 (0.00119)
		RMSE	0.1358	0.1131	0.1186
		Coverage	89.5	95.3	98.9
Scenario 5 <i>Treatment and covariate related to both outcome and withdrawal</i>	failure: 16% withdraw: 18% censored: 66%	Mean (SE)	0.9386 (0.00113)	0.9921 (0.00114)	0.9944 (0.00119)
		RMSE	0.1288	0.1146	0.1193
		Coverage	91.3	94.6	98.7

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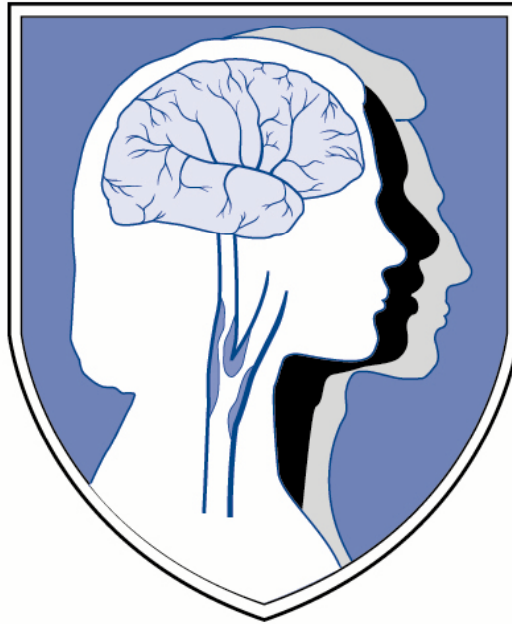
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Conclusions

- **Approach appears to address the difficult issue when treatment and patient characteristics are related to both outcomes and withdrawal**
- **Easy to implement**
- **Secondary analysis in CREST proved to be quite similar to primary analysis (after all this ... in this study it did not matter!!!)**
- **Better safe than sorry!**

**Thanks to the CREST co-authors,
Investigators, and patients!**



CREST

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