# Harnessing Simulations to Inform Endpoint Selection in Cardiovascular Trials

- Clinically meaningful, statistically efficient, and aligned with regulatory expectations

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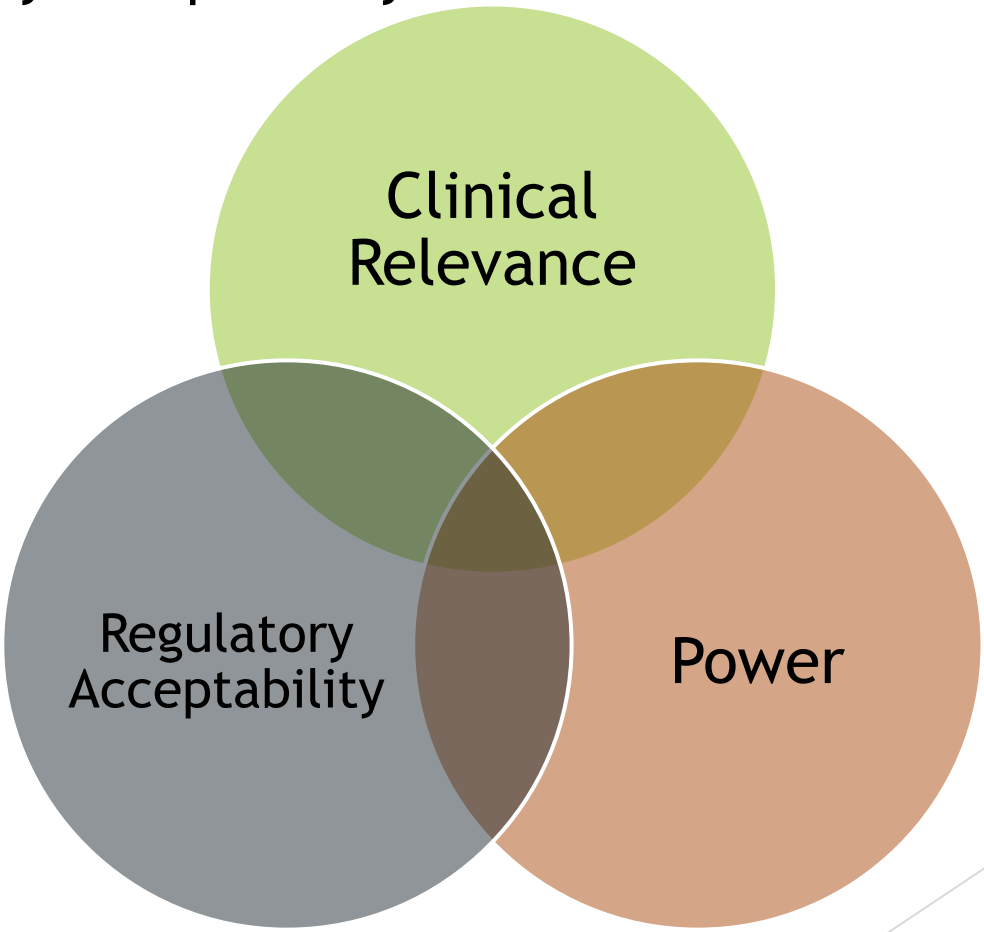
- Conference: BASS

# Introduction

Clinical relevance, statistical power, and regulatory acceptability



# Motivation

- Composite endpoints are common but vary in informativeness
- First event vs. all events? Narrow vs. broad?
- Aim: Use simulation to inform this decision quantitatively

# Simulation Framework Overview

- R-based platform built for recurrent event simulations
- Reflects realistic cardiovascular events: death, stroke, hospitalization, etc.
- Parameters informed by clinical data and literature

# Design of Simulated Trials

- Control vs. Experimental (Treatment) groups
- Pre-specified relative risk reductions by event type
- Follow-up time: 365 days
- Event probabilities and timing rules built in

# Statistical Methods

- Andersen-Gill models with robust sandwich variance
- Poisson analysis for incidence rate ratio and rate difference
- CI and hypothesis tests for:
- - Non-inferiority (e.g., HR UCL < 1.33)
- - Superiority (e.g., HR UCL < 1.0)

# Output Metrics

- Hazard Ratios and 95% CIs
- Power calculations for NI and Superiority
- Rate differences and incidence rate ratios
- Cumulative hazard plots
- Event rates by type and group

- Together, these metrics describe the statistical “personality” of each candidate endpoint.

# Endpoint Variants Compared

- All Events vs. First Occurrence
- Narrow Composite (e.g., death + stroke)
- Broad Composite (all 7 outcomes)
- Effects on power and interpretability

- The comparison shows how adding or removing components affects both power and interpretability.

# Case Study Example

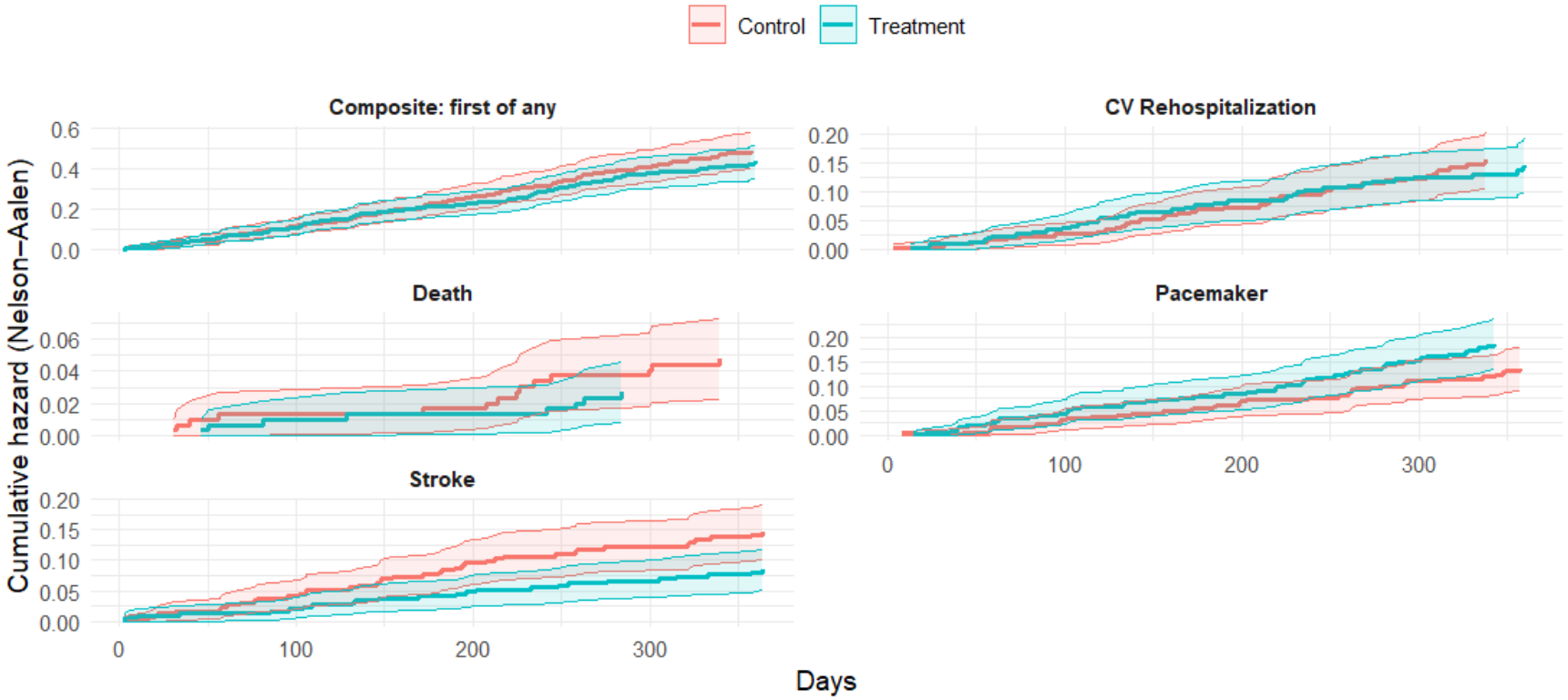
- Show simulated data summary comparing endpoint variants
- Event rates, HRs, power for each definition
- Recommend endpoint with highest informativeness and feasibility

- The next slide visualizes cumulative hazard trajectories for each treatment group.
  The curves demonstrate how risk accumulates over time and illustrate the relative treatment effect.
  They also confirm that the simulated data behave realistically — with divergence patterns similar to observed cardiovascular trials.

# Published first of any event rate for the Control (KM 1 year)

| Trial | | death | stroke | CV hospitalization | new PPI | Composite |
|---|---|---|---|---|---|---|
| Sapien Low Risk (PARTNER 3) | | 0.010 | 0.012 | 0.146 | 0.073 | 0.241 |
| Evolut Low Risk | | 0.022 | 0.043 | 0.066 | 0.191 | 0.322 |
| Sapien Intermediate Risk (PARTNER 2) | | 0.074 | 0.046 | 0.370 | 0.101 | 0.591 |
| Evolut Intermediate Risk | | 0.068 | 0.053 | 0.210 | 0.313 | 0.644 |
| SMART Trial - All Risk | | 0.055 | 0.047 | 0.162 | 0.117 | 0.381 |
| Acurate IDE - All Risk | | 0.039 | 0.034 | 0.105 | 0.128 | 0.306 |
| Trial | Weights | death | stroke | CV hospitalization | new PPI | Composite |
| Sapien Low Risk (PARTNER 3) | 10% | 0.001 | 0.001 | 0.015 | 0.007 | 0.024 |
| Evolut Low Risk | 10% | 0.002 | 0.004 | 0.007 | 0.019 | 0.032 |
| Sapien Intermediate Risk (PARTNER 2) | 5% | 0.004 | 0.002 | 0.019 | 0.005 | 0.030 |
| Evolut Intermediate Risk | 5% | 0.003 | 0.003 | 0.011 | 0.016 | 0.032 |
| SMART Trial - All Risk | 35% | 0.019 | 0.016 | 0.057 | 0.041 | 0.133 |
| Acurate IDE - All Risk | 35% | 0.014 | 0.012 | 0.037 | 0.045 | 0.107 |
| | | death | stroke | CV hospitalization | new PPI | Composite |
| Primary Endpoint Event Rate | | 0.043 | 0.039 | 0.144 | 0.133 | 0.359 |

# Cumulative Hazard Curves




Based on 1,000 simulation runs, roughly 950 evaluable patients yield robust power across plausible control event rates and effect sizes.

Allowing for 5 % attrition, we target about 1,000 total enrolled.

# A-G Sample Size & Power Calculations

| sample size | Death | | Stroke | | CV rehospitalization | | pacemaker | | HR | Power for NI |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | Tx Effect | Control | Tx Effect | Control | Tx Effect | Control | Tx Effect | | |
| 950 | 0.043 | 0% | 0.039 | 0% | 0.144 | 0% | 0.133 | 0% | 0.715 | 79% |
| 950 | 0.043 | 0% | 0.039 | 0% | 0.144 | 0% | 0.133 | 5% | 0.715 | 81% |
| 950 | 0.043 | 0% | 0.039 | 0% | 0.144 | 0% | 0.133 | 10% | 0.715 | 83% |
| 950 | 0.043 | 0% | 0.039 | 0% | 0.144 | 0% | 0.133 | 15% | 0.715 | 85% |
| 950 | 0.043 | 0% | 0.039 | 0% | 0.144 | 5% | 0.133 | 15% | 0.715 | 88% |

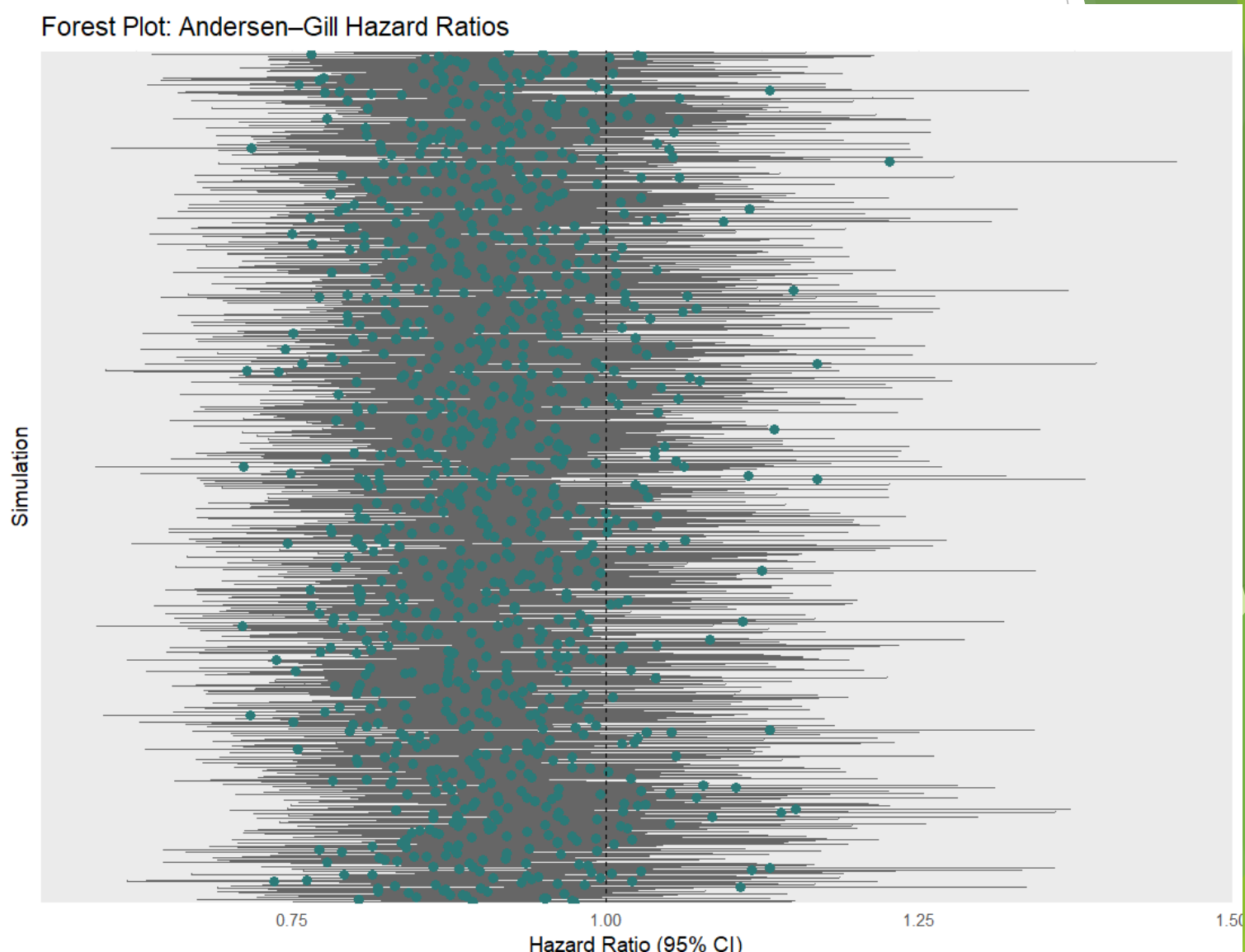
950 patients provide adequate study power under a variety of realistic control event rates and treatment effect simulations.

# Sample simulation output (N=1000 simulations)

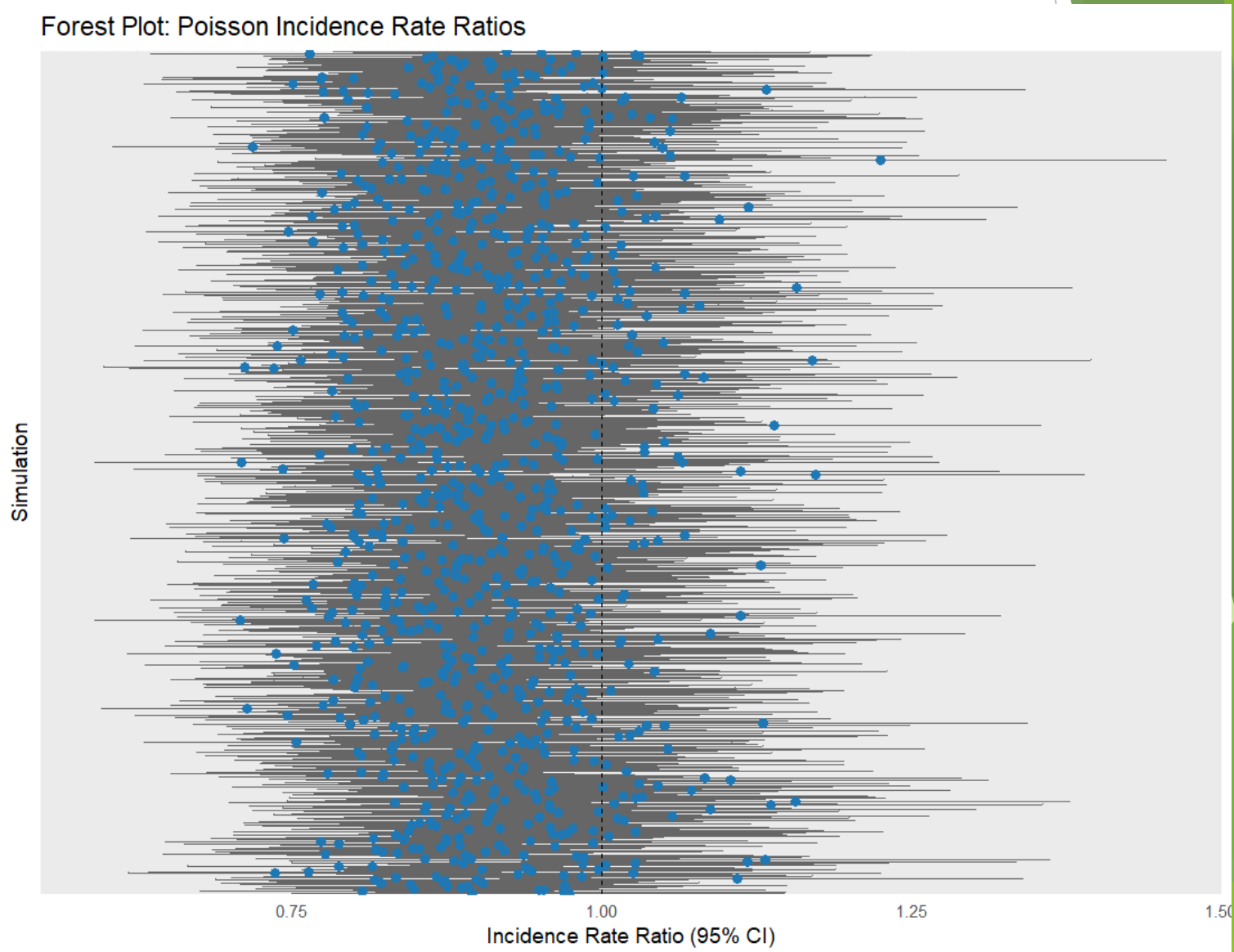
| Sim | Control_Total_Events | Control_Total_Years | Control_Event_Rate | Treatment_Total_Events | Treatment_Total_Years | Treatment_Event_Rate | HR | LCL | UCL | AG_pvalue | Poisson_IRR | Poisson_LCL | Poisson_UCL | Poisson_pvalue | Rate_Diff |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 213 | 491.109589 | 0.4337 | 208 | 492.4520548 | 0.4224 | 0.975 | 0.828 | 1.149 | 0.7643 | 0.9739 | 0.8258 | 1.1484 | 0.75287 | -0.0113 |
| 2 | 209 | 487.2328767 | 0.429 | 187 | 487.0356164 | 0.384 | 0.894 | 0.751 | 1.065 | 0.20949 | 0.8951 | 0.75 | 1.0682 | 0.21933 | -0.045 |
| 3 | 199 | 491.0356164 | 0.4053 | 195 | 496.339726 | 0.3929 | 0.973 | 0.821 | 1.152 | 0.74957 | 0.9694 | 0.8178 | 1.1492 | 0.72054 | -0.0124 |
| 4 | 215 | 492.890411 | 0.4362 | 172 | 489.1616438 | 0.3516 | 0.803 | 0.674 | 0.956 | 0.01392 | 0.8061 | 0.6758 | 0.9616 | 0.01659 | -0.0846 |
| 5 | 209 | 489.4273973 | 0.427 | 200 | 493.4876712 | 0.4053 | 0.951 | 0.802 | 1.128 | 0.56725 | 0.9491 | 0.7996 | 1.1265 | 0.54993 | -0.0218 |
| 6 | 205 | 494.8328767 | 0.4143 | 195 | 493.8191781 | 0.3949 | 0.953 | 0.802 | 1.132 | 0.58119 | 0.9532 | 0.8017 | 1.1333 | 0.58708 | -0.0194 |
| 7 | 228 | 488.8684932 | 0.4664 | 194 | 490.3890411 | 0.3956 | 0.849 | 0.722 | 0.998 | 0.0468 | 0.8482 | 0.7206 | 0.9984 | 0.04781 | -0.0708 |
| 8 | 223 | 488.7671233 | 0.4563 | 199 | 491.6054795 | 0.4048 | 0.889 | 0.755 | 1.046 | 0.15492 | 0.8872 | 0.7532 | 1.0451 | 0.15219 | -0.0515 |
| 9 | 196 | 491.8164384 | 0.3985 | 172 | 493.3205479 | 0.3487 | 0.876 | 0.728 | 1.055 | 0.16194 | 0.8749 | 0.7259 | 1.0544 | 0.1605 | -0.0499 |
| 10 | 205 | 490.5671233 | 0.4179 | 181 | 486.0931507 | 0.3724 | 0.886 | 0.742 | 1.058 | 0.18049 | 0.8911 | 0.745 | 1.0657 | 0.20656 | -0.0455 |
| 11 | 198 | 491.0438356 | 0.4032 | 191 | 488.4136986 | 0.3911 | 0.967 | 0.817 | 1.146 | 0.70184 | 0.9698 | 0.8179 | 1.1501 | 0.72474 | -0.0122 |
| 12 | 206 | 488.7452055 | 0.4215 | 174 | 488.3589041 | 0.3563 | 0.843 | 0.707 | 1.006 | 0.05759 | 0.8453 | 0.7076 | 1.0098 | 0.064 | -0.0652 |
| 13 | 232 | 490.4657534 | 0.473 | 190 | 488.890411 | 0.3886 | 0.818 | 0.69 | 0.969 | 0.02015 | 0.8216 | 0.6923 | 0.975 | 0.02449 | -0.0844 |
| 14 | 197 | 489.7589041 | 0.4022 | 179 | 492.3890411 | 0.3635 | 0.906 | 0.76 | 1.08 | 0.27258 | 0.9038 | 0.7572 | 1.0788 | 0.26252 | -0.0387 |
| 15 | 217 | 489.2849315 | 0.4435 | 189 | 489.0164384 | 0.3865 | 0.871 | 0.738 | 1.027 | 0.09986 | 0.8714 | 0.7374 | 1.0298 | 0.10633 | -0.057 |
| 982 | 195 | 489.9863014 | 0.398 | 190 | 489.9506849 | 0.3878 | 0.973 | 0.816 | 1.162 | 0.76438 | 0.9744 | 0.8153 | 1.1646 | 0.77583 | -0.0102 |
| 983 | 211 | 491.0465753 | 0.4297 | 187 | 491.5013699 | 0.3805 | 0.887 | 0.744 | 1.057 | 0.18062 | 0.8854 | 0.7419 | 1.0567 | 0.17752 | -0.0492 |
| 984 | 214 | 490.9123288 | 0.4359 | 195 | 490.769863 | 0.3973 | 0.91 | 0.774 | 1.071 | 0.2555 | 0.9115 | 0.7739 | 1.0735 | 0.26697 | -0.0386 |
| 985 | 214 | 490.6027397 | 0.4362 | 186 | 490.5917808 | 0.3791 | 0.871 | 0.733 | 1.034 | 0.11475 | 0.8692 | 0.7309 | 1.0336 | 0.11273 | -0.0571 |
| 986 | 214 | 491.4410959 | 0.4355 | 190 | 491.1643836 | 0.3868 | 0.888 | 0.747 | 1.055 | 0.17518 | 0.8884 | 0.7469 | 1.0566 | 0.18091 | -0.0486 |
| 987 | 196 | 491.0712329 | 0.3991 | 178 | 489.890411 | 0.3633 | 0.91 | 0.758 | 1.092 | 0.30965 | 0.9104 | 0.7577 | 1.0938 | 0.31588 | -0.0358 |
| 988 | 202 | 485.9287671 | 0.4157 | 185 | 490.460274 | 0.3772 | 0.911 | 0.764 | 1.087 | 0.30015 | 0.9074 | 0.7596 | 1.0839 | 0.28384 | -0.0385 |
| 989 | 226 | 486.9972603 | 0.4641 | 199 | 486.8767123 | 0.4087 | 0.881 | 0.748 | 1.038 | 0.12924 | 0.8807 | 0.7463 | 1.0394 | 0.13284 | -0.0553 |
| 990 | 209 | 491.4986301 | 0.4252 | 183 | 490.0219178 | 0.3735 | 0.876 | 0.731 | 1.051 | 0.15406 | 0.8782 | 0.7315 | 1.0544 | 0.16387 | -0.0518 |
| 991 | 204 | 491.1232877 | 0.4154 | 194 | 487.4191781 | 0.398 | 0.955 | 0.807 | 1.13 | 0.59105 | 0.9582 | 0.8082 | 1.136 | 0.623 | -0.0174 |
| 992 | 230 | 493.3643836 | 0.4662 | 197 | 492.6191781 | 0.3999 | 0.856 | 0.732 | 1.001 | 0.05146 | 0.8578 | 0.7329 | 1.0041 | 0.0562 | -0.0663 |
| 993 | 209 | 487.9342466 | 0.4283 | 211 | 492.2821918 | 0.4286 | 1.003 | 0.849 | 1.183 | 0.97544 | 1.0007 | 0.8468 | 1.1825 | 0.99389 | 0.0003 |
| 994 | 197 | 492.0876712 | 0.4003 | 202 | 489.4356164 | 0.4127 | 1.029 | 0.873 | 1.212 | 0.7373 | 1.0309 | 0.8734 | 1.2168 | 0.7187 | 0.0124 |
| 995 | 214 | 487.3561644 | 0.4391 | 186 | 490.6164384 | 0.3791 | 0.867 | 0.731 | 1.027 | 0.09881 | 0.8634 | 0.7273 | 1.0249 | 0.09317 | -0.06 |
| 996 | 200 | 488.3232877 | 0.4096 | 205 | 487.2575342 | 0.4207 | 1.026 | 0.866 | 1.215 | 0.76856 | 1.0272 | 0.8659 | 1.2186 | 0.75783 | 0.0112 |
| 997 | 210 | 489.1260274 | 0.4293 | 161 | 490.8520548 | 0.328 | 0.765 | 0.638 | 0.918 | 0.00391 | 0.764 | 0.636 | 0.9177 | 0.00401 | -0.1013 |
| 998 | 197 | 494.0931507 | 0.3987 | 186 | 490.6465753 | 0.3791 | 0.95 | 0.799 | 1.129 | 0.5578 | 0.9508 | 0.7992 | 1.1312 | 0.56922 | -0.0196 |
| 999 | 198 | 492.5753425 | 0.402 | 192 | 487.8356164 | 0.3936 | 0.974 | 0.817 | 1.16 | 0.7639 | 0.9791 | 0.8205 | 1.1683 | 0.8149 | -0.0084 |
| 1000 | 225 | 491.1616438 | 0.4581 | 207 | 489.5369863 | 0.4228 | 0.923 | 0.784 | 1.087 | 0.33702 | 0.9231 | 0.7827 | 1.0886 | 0.34135 | -0.0352 |

This output represents one scenario from 1000 simulations, with the results saved as an Excel file. This allowed different levels of data exploration and graphical analysis.

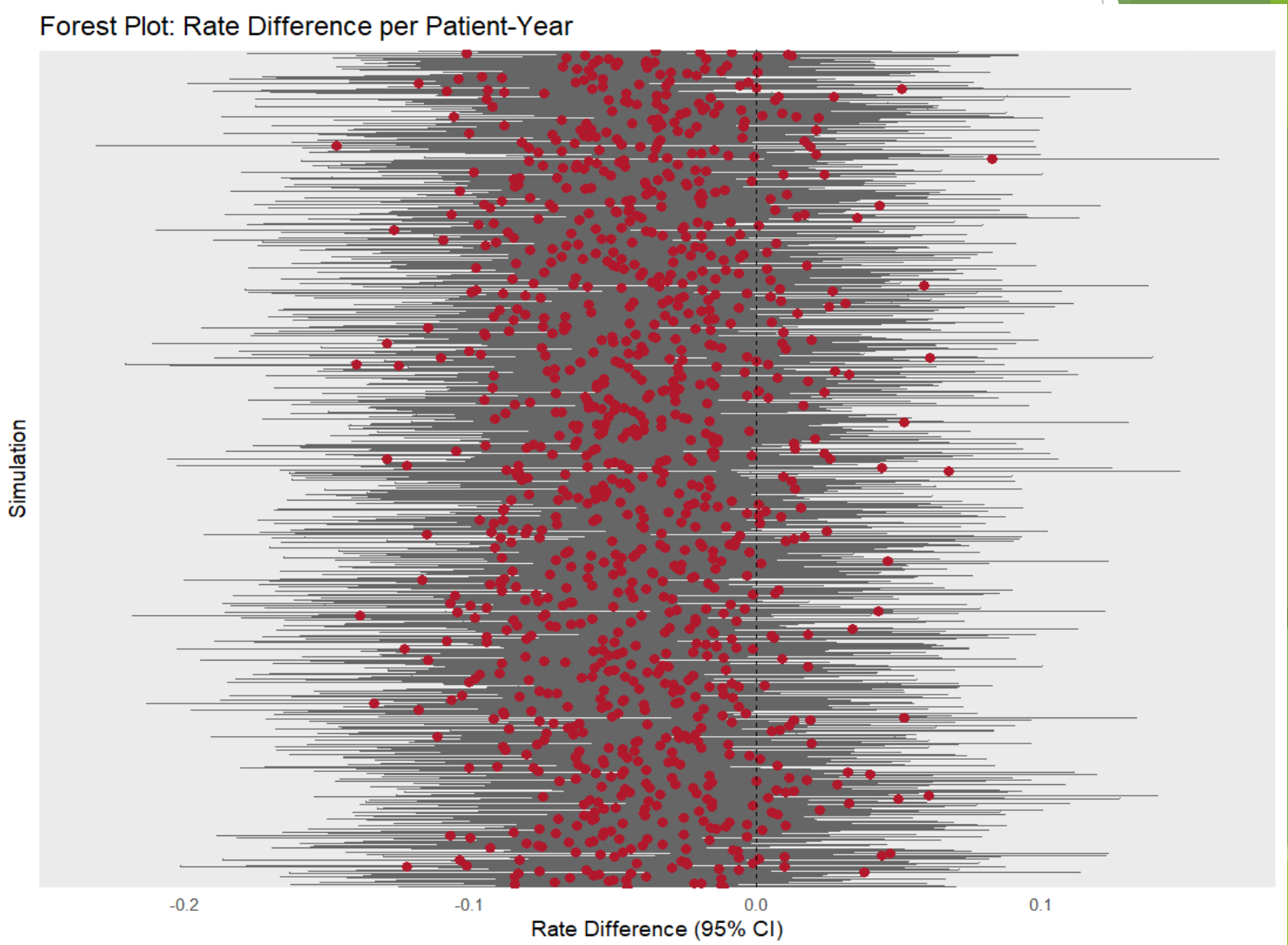
# Forest plot: A-G Hazard Ratios



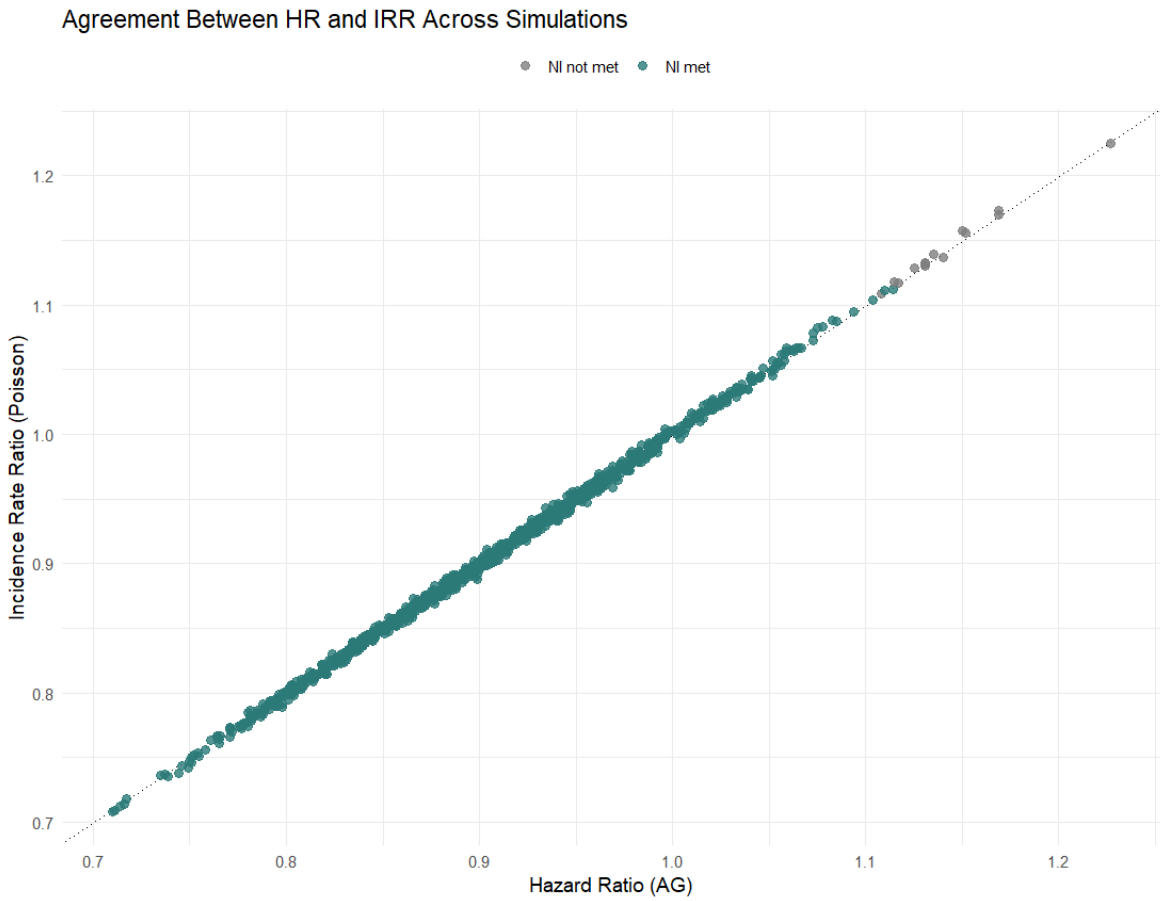
# Forest plot: poison IRR



# Forest plot: rate diff per PT-year

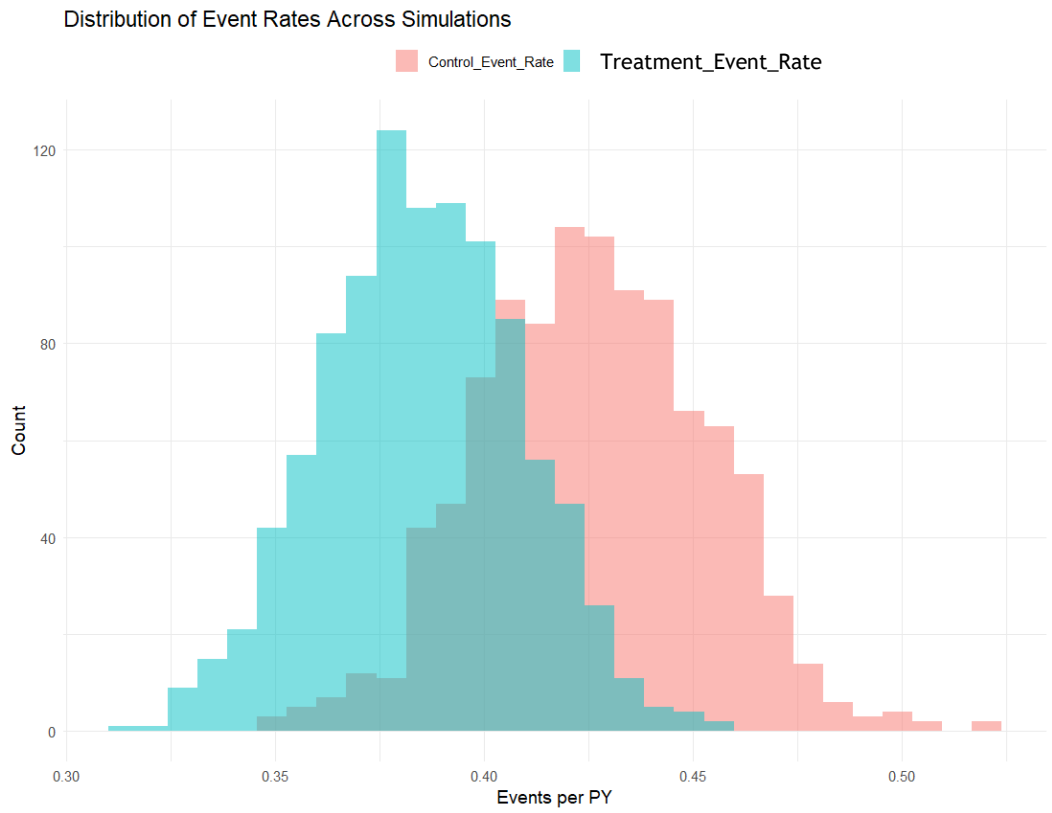


# AG vs IRR



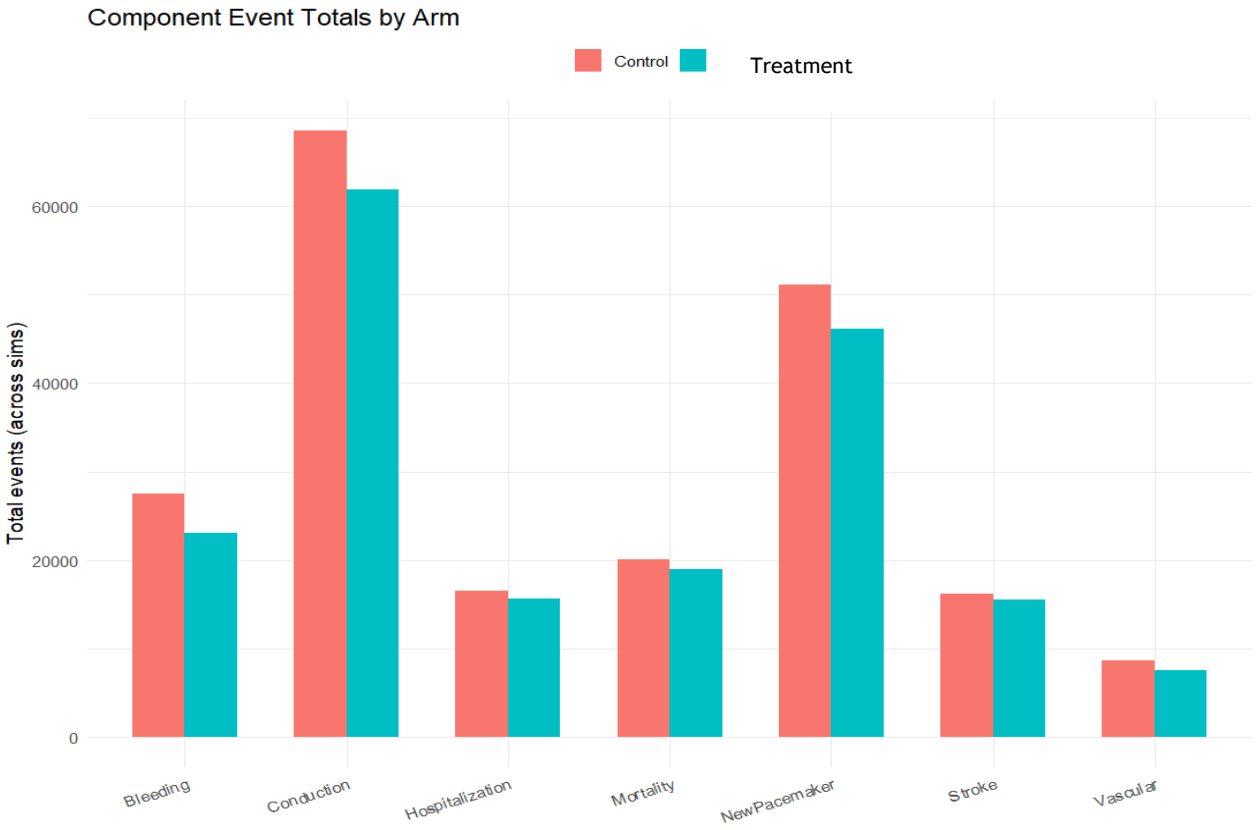

Here, we directly compare the hazard-ratio and incidence-rate-ratio estimates. The alignment between the two confirms the agreement of the findings, while minor deviations reveal sensitivity to recurrent-event handling.

# Distribution of event rates



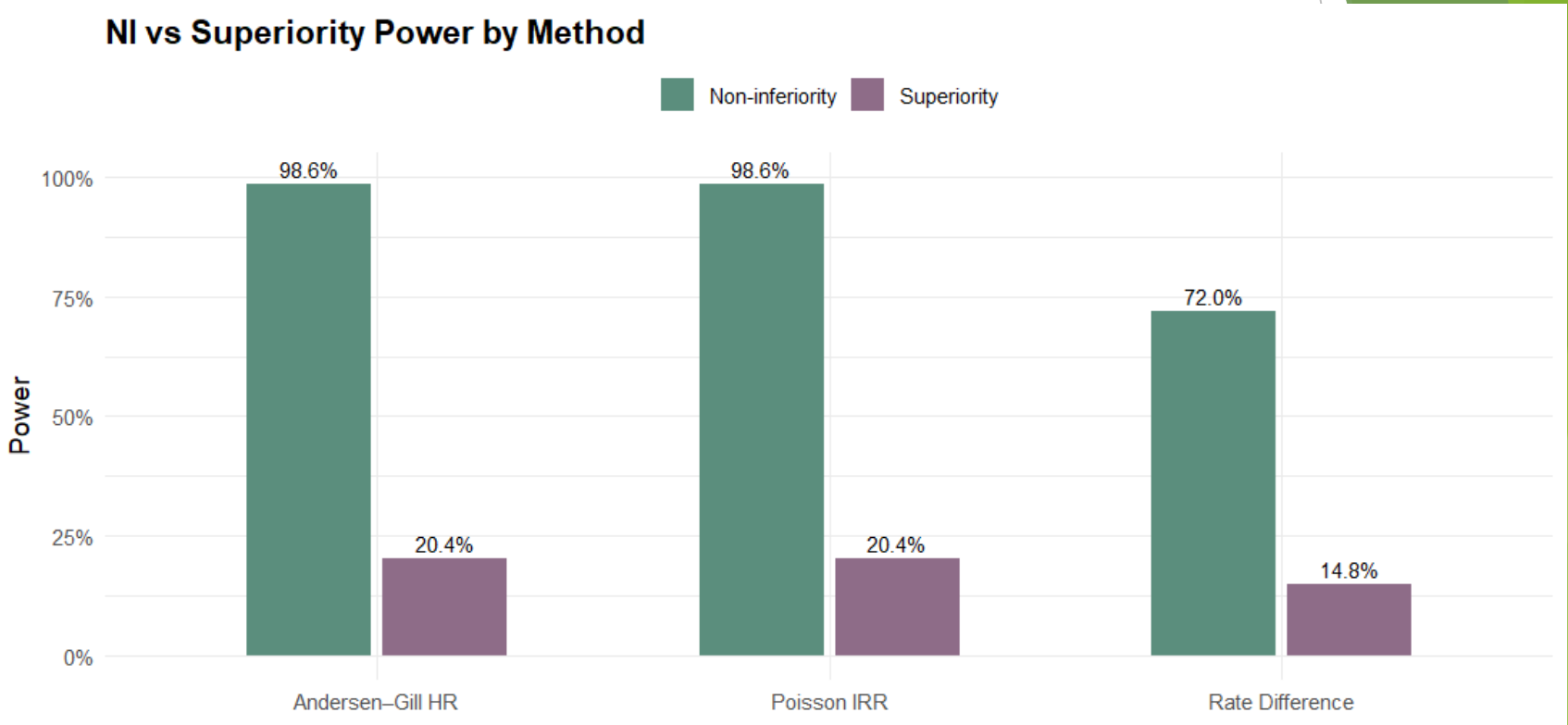

This histogram shows the variability of control and treatment event rates across all simulations.
The spread reflects inherent uncertainty in real-world event incidence and reinforces why simulation-based planning is critical.

# total events by component and arm




Here we break down total events by component endpoint — mortality, stroke, hospitalization, and others — for both Control and Treatment.
This view clarifies which components dominate the composite and contribute most to statistical power.

# Power by Metric




These slides summarize the achieved power for each analysis method. Andersen–Gill and Poisson IRR methods both reached about 99 % power for non-inferiority and 20 % for superiority, while the rate-difference approach achieved 72 % and 15 %, respectively. This underscores that method selection substantially influences sensitivity and study size requirements.

# Regulatory and Clinical Implications

- Aligning simulation with FDA expectations for estimand clarity
- Selecting endpoints that can support Accelerated Approval or Confirmatory Evidence

# Conclusions

- Simulation is a powerful tool for endpoint selection, instead of an analytical approach.
- Enables proactive, data-driven decisions
- Supports defensible trial design with statistical and clinical rigor

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# Acknowledgments and Contact


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- THANK YOU!
- Questions?