Sample Size Calculation for Active-Arm Trial with Counterfactual Incidence Based on Recency Assay

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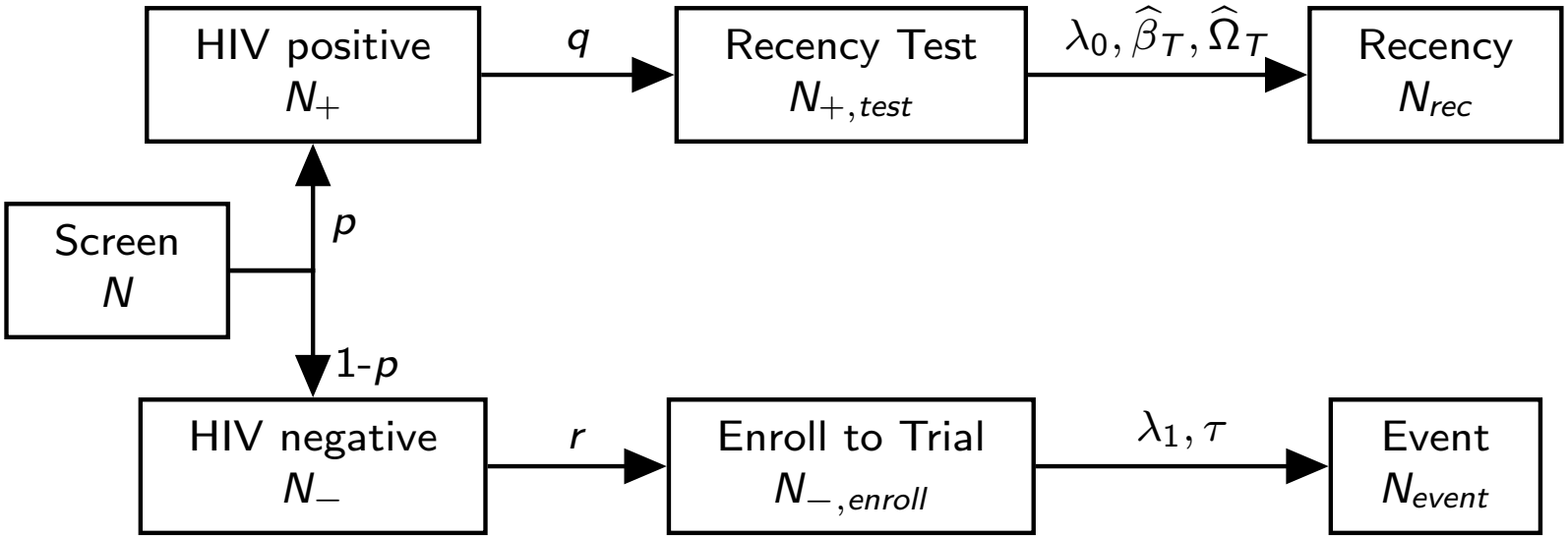
Joint work with Drs. Deborah Donnell, Dave Glidden, Jim Hughes

Hypothetical One-Arm Trial with Recency Assay Counterfactual Placebo



T: cutoff time ($\sim$ 2 years)
$\widehat{\beta}_T$: False recency rate (FRR).
$\widehat{\Omega}_T$: Mean duration of recent infection (MDRI).
τ: follow-up time.

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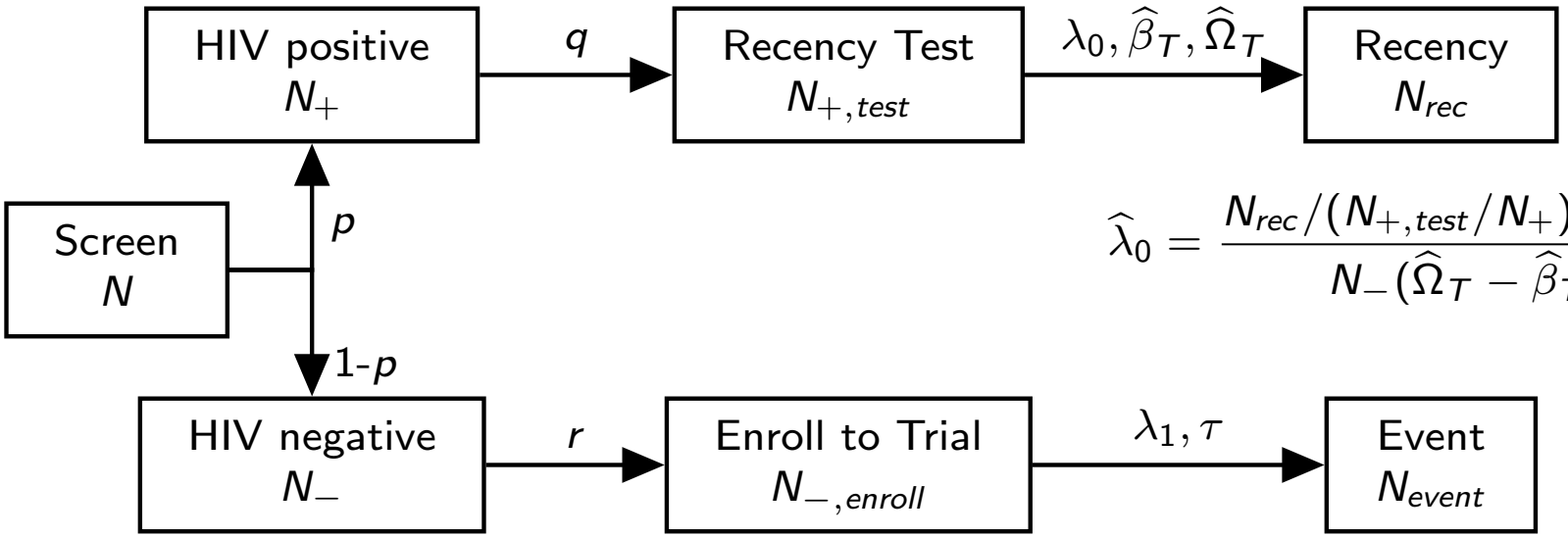

$$\widehat{\lambda}_0 = \frac{N_{rec}/(N_{+,test}/N_+) - \widehat{\beta}_T N_+}{N_-(\widehat{\Omega}_T - \widehat{\beta}_T T)}$$

$$\widehat{\lambda}_1 = \frac{N_{event}}{N_{-,enroll}\tau}$$

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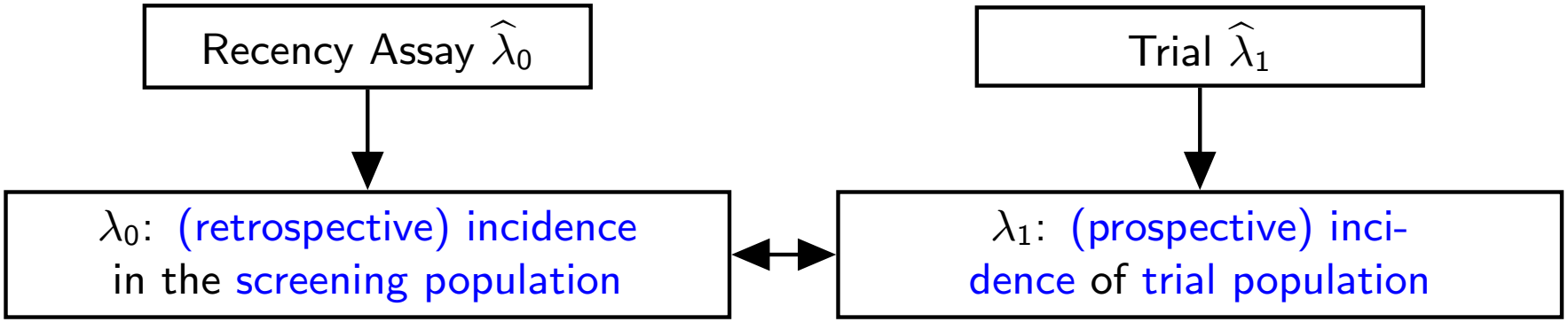
$\widehat{\lambda}_0$ adapted from Kassanjee et al. (2012).

Assumptions



Hypothesis and Test Statistic

- $H_0 : \lambda_1 = \lambda_0$ vs. $H_1 : \lambda_1 = R_1 \lambda_0$ for some $R_1 < 1$.
  - H_1: risk ratio R_1, or equivalently $(1 - R_1)$ reduction in incidence.
- We would like to construct a test with significance level $\alpha = 0.05$, power $\beta = 0.8$ (against H_1).

Hypothesis and Test Statistic

- Two Test Statistics

$$Z = \frac{\log \widehat{\lambda}_1 - \log \widehat{\lambda}_0}{\sqrt{\hat{var}(\log \widehat{\lambda}_1 - \log \widehat{\lambda}_0)}}, \qquad \widetilde{Z} = \frac{\widehat{\lambda}_1 - \widehat{\lambda}_0}{\sqrt{\hat{var}(\widehat{\lambda}_1 - \widehat{\lambda}_0)}}$$ †

† https://github.com/SACEMA/inctools/tree/master/shiny-inctools/sample_size_baseline_and_cohort

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- Under H_0, both are asymptotically $N(0, 1)$.
  - Z is based on normal approximation of $\log \widehat{\lambda}_1$ and $\log \widehat{\lambda}_0$.
    - $\log \widehat{\lambda}_l \sim N(\log \lambda_l, var(\log \widehat{\lambda}_l))$.
  - $\widetilde{Z}$ is based on normal approximation of $\widehat{\lambda}_1$ and $\widehat{\lambda}_0$.
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  - $\widehat{\lambda}_l \sim N(\lambda_l, var(\widehat{\lambda}_l))$.
  - Confidence interval (CI) for λ_l

$$\left(\widehat{\lambda}_l - 1.96\hat{var}(\widehat{\lambda}_l)^{1/2}, \widehat{\lambda}_l + 1.96\hat{var}(\widehat{\lambda}_l)^{1/2}\right)$$

  - Symmetric, may cross 0 in some cases.

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    - Not symmetric, never cross 0 (for non-zero $\widehat{\lambda}_l$).
  - Log hazard ratio, i.e., $\log \widehat{\lambda}_1 - \log \widehat{\lambda}_0$, is commonly used in describing treatment effect (or covariate effect).

- $\widetilde{Z}$ is based on normal approximation of $\widehat{\lambda}_1$ and $\widehat{\lambda}_0$.
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Sample Size Calculation: Settings

Setting	1	2	3	4
Location	Mozambique	South Africa	South Africa	USA
Population	adults	AGYW 14-17	MSM	MSM
Incidence(λ_0)	1.01%	4.70%	12.50%	3.42%
Prevalence(p)	12.6%	27.6%	32.4%	14.5%
Subtype	C	C	C	B
MDRI (days)	118	118	118	142
MDRI RSE	7%	7%	7%	10%
FRR	1.5%	1.5%	1.5%	1.0%
FRR RSE	25%	25%	25%	25%
Cutoff Time T (years)	2	2	2	2
RA coverage (q)	90%	90%	90%	70%
Recruitment (r)	90%	90%	90%	90%
Yrs f/u (τ)	2	2	2	2

Sample Size Calculation

$\alpha = 0.05$, $\beta = 0.8$, $R_0 = 1$

		Mozambique Adults		South Africa AGYW 14-17		South Africa MSM		USA MSM	
R_1	%Red.	Z	$\widetilde{Z}$	Z	$\widetilde{Z}$	Z	$\widetilde{Z}$	Z	$\widetilde{Z}$
0.5	50	44,304	614,668	4,747	8,219	1,423	2,226	4,396	7,624
0.35	65	11,860	32,224	2,006	3,838	647	1,174	1,873	3,599
0.2	80	4,920	14,504	950	2,273	316	728	892	2,135

- The calculated sample size based on Z is much smaller than that based on $\widetilde{Z}$ (7% - 64%).

Sample Size Calculation: A Hypothetical MSM Trial

Proportion	40%	30%	10%	10%	10%
Subtype	B	C	A	D	A/E
Population	US/LA, EU	South Africa +East Africa	East Africa	East Africa	Thailand
Incidence(λ_0)	3%	12%	5%	5%	5%
Prevalence(p)	15%	25%	15%	15%	15%
MDRI (days)	142	118	159	182	NA
MDRI RSE	10%	7%	13%	19%	NA
FRR	1.5%	1.0%	0.3%	3.9%	NA

- Incidence 6.3%, prevalence 18%.
- We use a weighted MDRI = 140 days with RSE 12%, weighted FRR = 1.5%.
- Cutoff Time $T = 2$ years, FRR RSE = 25%.
- RA coverage: $q = 1$.
- Recruitment percentage: $r = 80\%$.
- Years of follow-up: $\tau = 1, 2$.
- Effectiveness of the product compared to no PrEP: 85%. ($R_1 = 0.15$)

Sample Size Calculation

Hypothetical MSM Trial ($\alpha = 0.05$, $\beta = 0.8$)

- $H_0 : \lambda_1 = \lambda_0$ vs. $H_1 : \lambda_1 = 0.15\lambda_0$.

τ	Screening	Recency Test		Active-Arm Trial	
	N	$E(N_{+,test})$	$E(N_{rec})$	$E(N_{-,enroll})$	$E(N_{event})$
1	424	76.2	8.9	278.1	2.6
2	327	58.9	6.9	214.5	4.1

- Example: screen $N = 424$ subjects in total
  - 76 HIV-positive subjects receive recency test, with 9 positive.
  - 278 HIV-negative subjects are enrolled to active-arm trial, followed for 1 year, with 3 events.

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- Example: screen $N = 424$ subjects in total
  - 76 HIV-positive subjects receive recency test, with 9 positive.
    - $\widehat{\lambda}_0 = 6.39\%$, $CI_Z = (2.91\%, 14.1\%)$, $CI_{\widetilde{Z}} = (1.36\%, 11.43\%)$.
  - 278 HIV-negative subjects are enrolled to active-arm trial, followed for 1 year, with 3 events.
    - $\widehat{\lambda}_1 = 1.08\%$, $CI_Z = (0.35\%, 3.35\%)$, $CI_{\widetilde{Z}} = (-0.14\%, 2.30\%)$.

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  - $Z = -2.53$ vs. $\widetilde{Z} = -2.01$.

Sample Size Calculation

Hypothetical MSM Trial ($\alpha = 0.05$, $\beta = 0.8$)

- $H_0 : \lambda_1 = 0.7\lambda_0$ vs. $H_1 : \lambda_1 = 0.15\lambda_0$.

Yrs f/u	Screening	Recency Test		Active-Arm Trial	
τ	N	$E(N_{+,test})$	$E(N_{rec})$	$E(N_{-,enroll})$	$E(N_{event})$
1	665	119.7	13.9	436.2	4.1
2	499	89.8	10.5	327.3	6.2

Sample Size Calculation

Summary

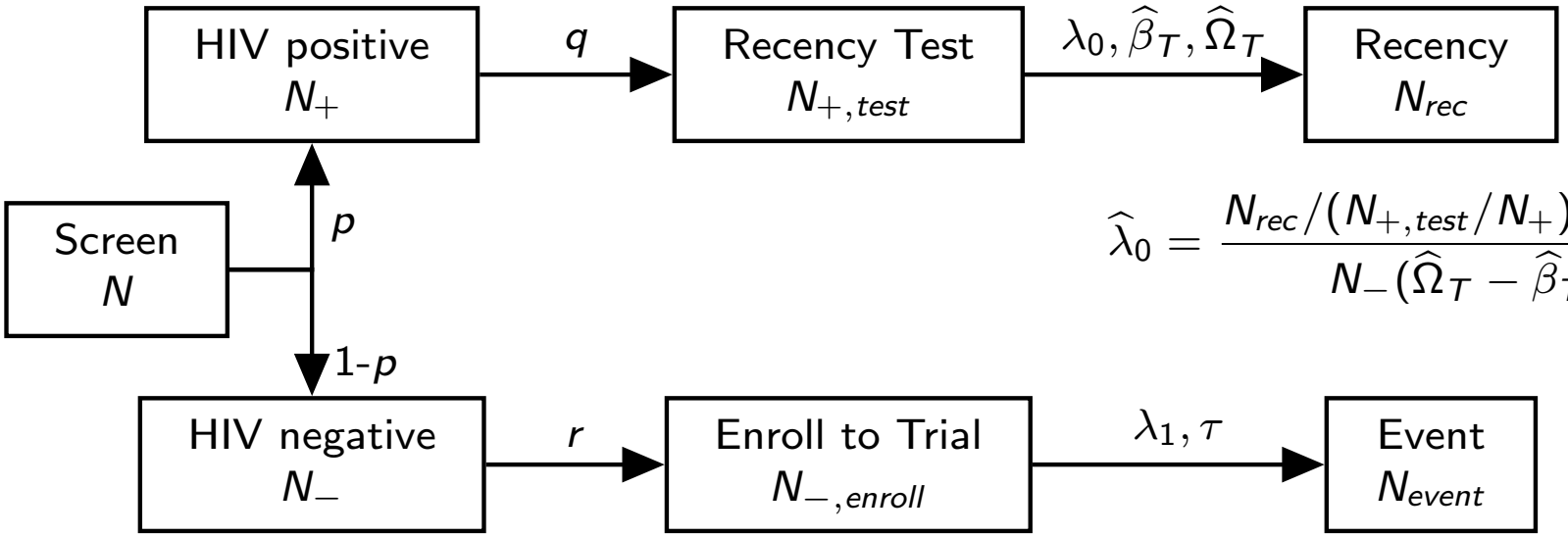
- Two test statistics Z and $\widetilde{Z}$ based on normal approximations of incidence and log incidence, respectively.
  - Both are valid testing procedure.
  - The test statistic Z is more powerful given the same set of data, such that the required total screening sample size N is smaller.

Sample Size Calculation

Summary

- Two test statistics Z and $\widetilde{Z}$ based on normal approximations of incidence and log incidence, respectively.
  - Both are valid testing procedure.
  - The test statistic Z is more powerful given the same set of data, such that the required total screening sample size N is smaller.
- Small expected number of events (recent infections) when sample size is small.
  - The sample size calculation is based on normal approximation, which may not be accurate in small samples $\Rightarrow$ We need simulations to verify the sample sizes.

Simulation Procedure



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$\widehat{\lambda}_0$ adapted from Kassanjee et al. (2012).

Type-I Error and Power Calculation

$\alpha = 0.05$, β=0.8, $R_0 = 1$

Setting	R_1	N	Z		$\widetilde{Z}$	
			Type-1 Err.	Power	Type-1 Err.	Power
Mozambique	0.5	44,304	0.037	0.776	0.046	0.642
Adults	0.35	11,860	0.042	0.769	0.050	0.562
	0.2	4,920	0.047	0.772	0.049	0.456
South Africa	0.5	4,747	0.041	0.796	0.053	0.664
AGYW 14-17	0.35	2,006	0.038	0.786	0.054	0.575
	0.2	950	0.040	0.767	0.057	0.448
South Africa	0.5	1,423	0.044	0.802	0.053	0.670
MSM	0.35	647	0.038	0.795	0.056	0.591
	0.2	316	0.032	0.780	0.067	0.438
USA	0.5	4,396	0.042	0.819	0.051	0.680
MSM	0.35	1,873	0.043	0.799	0.056	0.586
	0.2	892	0.030	0.793	0.064	0.445

Percentage of Simulations with Issue

$\alpha = 0.05$, β=0.8, $R_0 = 1$

Setting	R_1	N	% Neg. $\widehat{\lambda}_0$	% Zero $\widehat{\lambda}_1$
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Adults	0.35	11,860	0.0	0.0
	0.2	4,920	0.7	0.0
	0.05	1,868	5.1	22.8
South Africa	0.5	4,747	0.0	0.0
AGYW 14-17	0.35	2,006	0.0	0.0
	0.2	950	0.3	0.0
	0.05	403	4.1	29.5
South Africa	0.5	1,423	0.0	0.0
MSM	0.35	647	0.0	0.0
	0.2	316	0.1	0.0
	0.05	143	2.2	33.1
USA	0.5	4,396	0.0	0.0
MSM	0.35	1,873	0.0	0.0
	0.2	892	0.2	0.0
	0.05	403	3.1	35.5

Type-I Error and Power Calculation

Hypothetical MSM Trial, $\alpha = 0.05$, β=0.8, $R_0 = 0.7, R_1 = 0.15$

Yrs f/u τ	N	Z		$\widetilde{Z}$		% Neg. $\widehat{\lambda}_0$	% Zero $\widehat{\lambda}_1$
		Type-1 Err.	Power	Type-1 Err.	Power		
1	665	0.041	0.764	0.045	0.654	0.0	1.8
2	499	0.030	0.776	0.055	0.530	0.02	0.2

- Possibility of negative $\widehat{\lambda}_0$ when λ_0 is small, N is small, and FRR is not zero.
- Possibility of zero $\widehat{\lambda}_1$ when R_1 is small and N is small.

Remarks and Some Issues

- Current calculation gives reasonable screening sample size for testing risk ratio (or equivalently, incidence reduction) based on recency assay counterfactual placebo.

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  - Possibility of negative $\widehat{\lambda}_0$ when λ_0 is small, N is small, and FRR is not zero.
  - Possibility of zero $\widehat{\lambda}_1$ when R_1 is small and N is small.
- Justification of assumptions.
- One-arm trial versus active-control trial.

Thank you

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Variance Formula for $\log \widehat{R}$

$$\log \widehat{R} \sim N\left(\log R, V_0(\lambda_0) + V_1(\lambda_1)\right)$$

- $V_0(\lambda_0) = \gamma_{00}(\lambda_0)/N + \gamma_{01}(\lambda_0)$

$$\gamma_{00}(\lambda_0) = \frac{1}{p}\left\{\frac{P_R\left(1-P_R\right)}{q\left(P_R-\beta_T\right)^2} + \frac{1}{(1-p)} + \frac{(1-pq)\sigma^2_{\widehat{\beta}_T}}{q\left(P_R-\beta_T\right)^2}\right\}$$

$$\gamma_{01}(\lambda_0) = \frac{\sigma^2_{\widehat{\Omega}_T}}{\left(\Omega_T-\beta_T T\right)^2} + \sigma^2_{\widehat{\beta}_T}\left\{\frac{\left(\Omega_T-P_R T\right)^2}{\left(P_R-\beta_T\right)^2\left(\Omega_T-\beta_T T\right)^2}\right\}$$

$$P_R = \beta_T + \frac{\lambda_0(1-p)}{p}\left(\Omega_T-\beta_T T\right)$$

- $V_1(\lambda_1) = \gamma_1(\lambda_1)/N$

$$\gamma_1(\lambda_1) = \frac{1}{\lambda_1(1-p)r\tau}$$

Sample Size Formula based on Z

$$Z = \frac{\log \widehat{R} - \log R_0}{\sqrt{\hat{var}(\log \widehat{R})}}$$

- significance level α: rejection region $|Z| > z_{1-\alpha/2}$
- power β

$$\Pr\left(W_{R_1} + \frac{\log R_1 - \log R_0}{\sqrt{(\gamma_{00}(\lambda_0) + \gamma_1(\lambda_0 R_1))/N + \gamma_{01}(\lambda_0)}} > z_{1-\alpha/2} \right) \geq \beta,$$

  - $W_{R_1} \sim N(0, V_{R_1})$.

- Total screening sample size

$$N = \frac{\gamma_{00}(\lambda_0) + \gamma_1(\lambda_0 R_1)}{\left(\frac{\log R_1 - \log R_0}{z_{1-\alpha/2} + \sqrt{V_{R_1}} z_\beta} \right)^2 - \gamma_{01}(\lambda_0)}$$

Simulation Procedure

- Simulation data under risk ratio R, total screening sample size N, $\lambda_1 = \lambda_0 R$
  1. $N_+ \sim Bin(N, p)$, $N_- = N - N_+$
  2. $N_{+,test} \sim Bin(N_+, q)$, $N_{rec} \sim Bin(N_{+,test}, P_R)$
     - $P_R = \beta_T + \frac{\lambda_0(1-p)}{p}(\Omega_T - \beta_T T)$
     - $\widehat{\beta}_T \sim N(\beta_T, \sigma^2_{\widehat{\beta}_T})$, $\widehat{\Omega}_T \sim N(\Omega_T, \sigma^2_{\widehat{\Omega}_T})$,
  3. $N_{-,enroll} \sim Bin(N_-, r)$, $N_{event} \sim Poisson(\tau \lambda_1 N_{-,enroll})$.
  4. Estimate λ_0, λ_1, and R, calculate Z statistic.
- Calculate empirical type-1 error and power
  - $Pr(|Z| > z_{1-\alpha/2})$ evaluated under $R = R_0$ and $R = R_1$.

Type-I Error and Power Calculation

$\alpha = 0.05$, β=0.8, $R_0 = 0.7$

Setting	R_1	N	Z		$\widetilde{Z}$		% Neg.	% Zero
			Type-1 Err.	Power	Type-1 Err.	Power	$\widehat{\lambda}_0$	$\widehat{\lambda}_1$
Mozambique	0.35	44,279	0.037	0.770	0.045	0.630	0.0	0.0
Adults	0.2	8,218	0.039	0.759	0.047	0.532	0.1	0.0
	0.05	2,356	0.041	0.741	0.034	0.300	3.6	15.0
South Africa	0.35	4,935	0.041	0.786	0.047	0.655	0.0	0.0
AGYW 14-17	0.2	1,525	0.032	0.776	0.055	0.539	0.1	0.0
	0.05	509	0.035	0.755	0.048	0.298	2.3	20.9
South Africa	0.35	1,499	0.047	0.802	0.053	0.681	0.0	0.0
MSM	0.2	507	0.036	0.784	0.057	0.555	0.0	0.0
	0.05	180	0.035	0.762	0.064	0.298	1.1	25.2
USA	0.35	4,628	0.046	0.811	0.050	0.686	0.0	0.0
MSM	0.2	1,450	0.036	0.790	0.053	0.563	0.0	0.0
	0.05	510	0.032	0.772	0.069	0.293	1.2	26.0