Cytel

Unblinded Sample Size Re-Estimation in Bioequivalence Trials with Small Samples

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Goal

- Describe simple adjustment to CHW method (Cui, Hung, Wang 1999) for 2-stage adaptive designs in bioequivalence setting with small samples
  - Control type I error
  - Compatible confidence intervals with guaranteed coverage
- Hypothetical example, motivated by trial design explorations
- Focus is on methodology, not optimality

Example study

- Demonstrate average bioequivalence, treatment vs reference product
- BE limit on geometric mean ratio 0.8 < GMR < 1.25
- Parallel two-stage design, unblinded sample size re-estimation
- Interim at $n_1 = 50$, plan $n = 100$, maximum $n_{max} = 150$ after SSR
- Overall type I error control at 5% with two one-sided tests
- Success if 90% confidence interval for GMR is completely in [0.8, 1.25]
- Cui-Hung-Wang (CHW, 1999) inferential framework, log transformed data

CHW method

- Pre-specify weights

$$w_1 = \sqrt{\frac{n_1}{n}}, \quad w_2 = \sqrt{1 - \frac{n_1}{n}}$$

- Combine independent incremental Wald statistics

$$Z_{CHW} = w_1 Z_1 \ + w_2 \, Z_2$$

- Critical value $b = z_\alpha = 1.645$
- Compatible 90% confidence interval for GMR takes the form

$$\widetilde{\delta} \pm \boldsymbol{b} * \widetilde{SE}$$

Formulas for $\widetilde{\delta}$ and $\widetilde{SE}$ involve weighted precision (omitted)

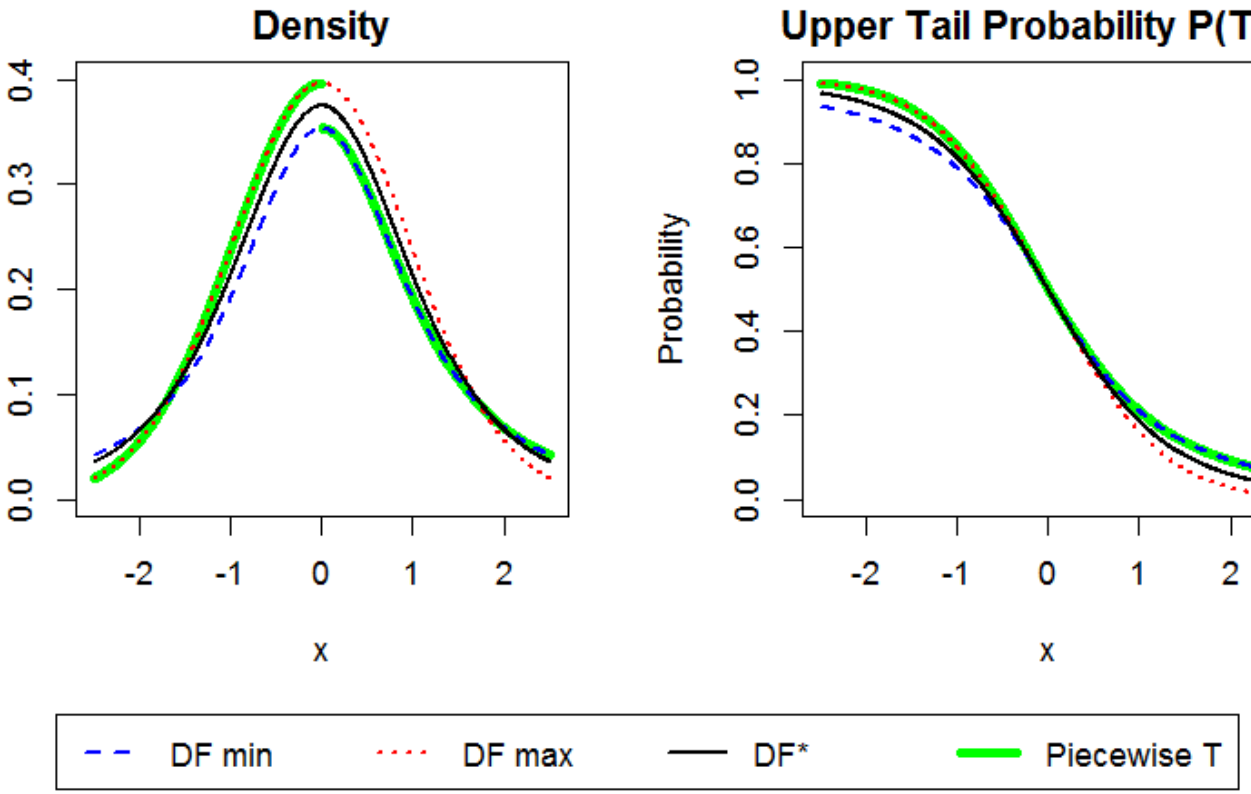
Type I error inflation in CHW method due to small sample sizes

GMR	CV	Empirical Type I Error 1,000,000 simulations
1.25	0.3	0.0533
	0.4	0.0530
	0.5	0.0523

- Incremental Wald statistics have t-distribution, yet a normal critical value $b = z_\alpha$ was used
- Need more conservative efficacy boundary. Complications:
  - Linear combination of t-distributions is not t-distribution
  - Degrees of freedom for stage 2 depends on stage 1 data, SSR rule
  - Exact distribution of CHW statistic depends on true variance

Proposal: Inflate critical value using conservative degrees of freedom

- Pre-specify lower and upper bounds on stage 2 sample size
- Replace Z_2 with "**piecewise T-distribution"** that dominates Z_2



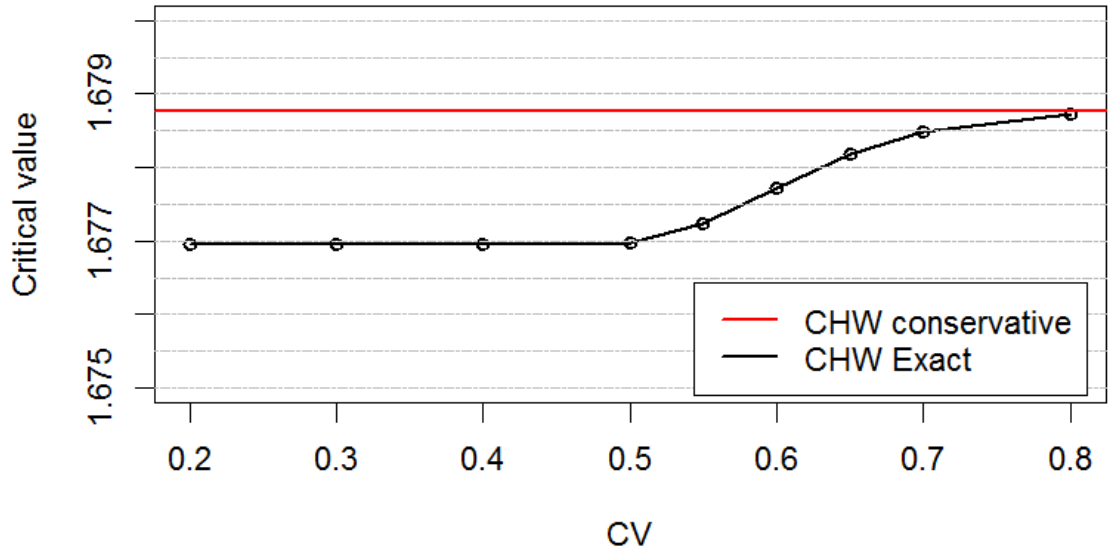
Proposal: Inflate critical value using conservative degrees of freedom

- Numerical integration to solve $Pr_0(w_1 Z_1 + w_2 T > b) = 0.05$
- Use b for two-sided testing and to construct confidence interval

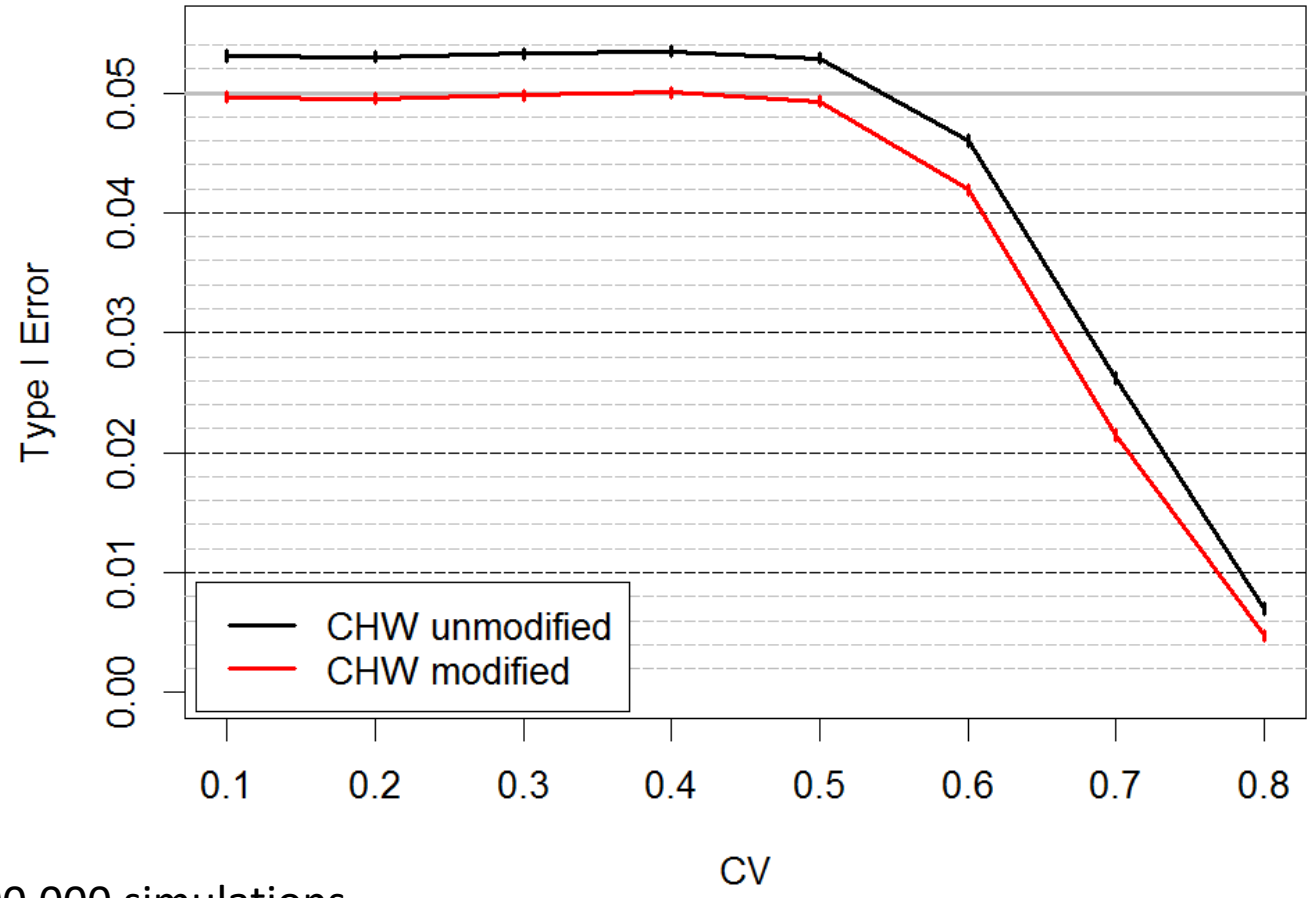
n_1	n_{min}	n_{max}	CHW critical value b	
			Unmodified (Normal z_α)	Conservative (Piecewise T)
50	100	120	1.645	**1.67879**
		150	1.645	**1.67881**
		200	1.645	**1.67883**
		300	1.645	**1.67884**

Modified CHW method

- Use inflated critical value for efficacy testing and confidence interval construction
- Use any sample size re-estimation algorithm (e.g., promising zone), provided final sample size is within pre-specified range
- Not exact, but close

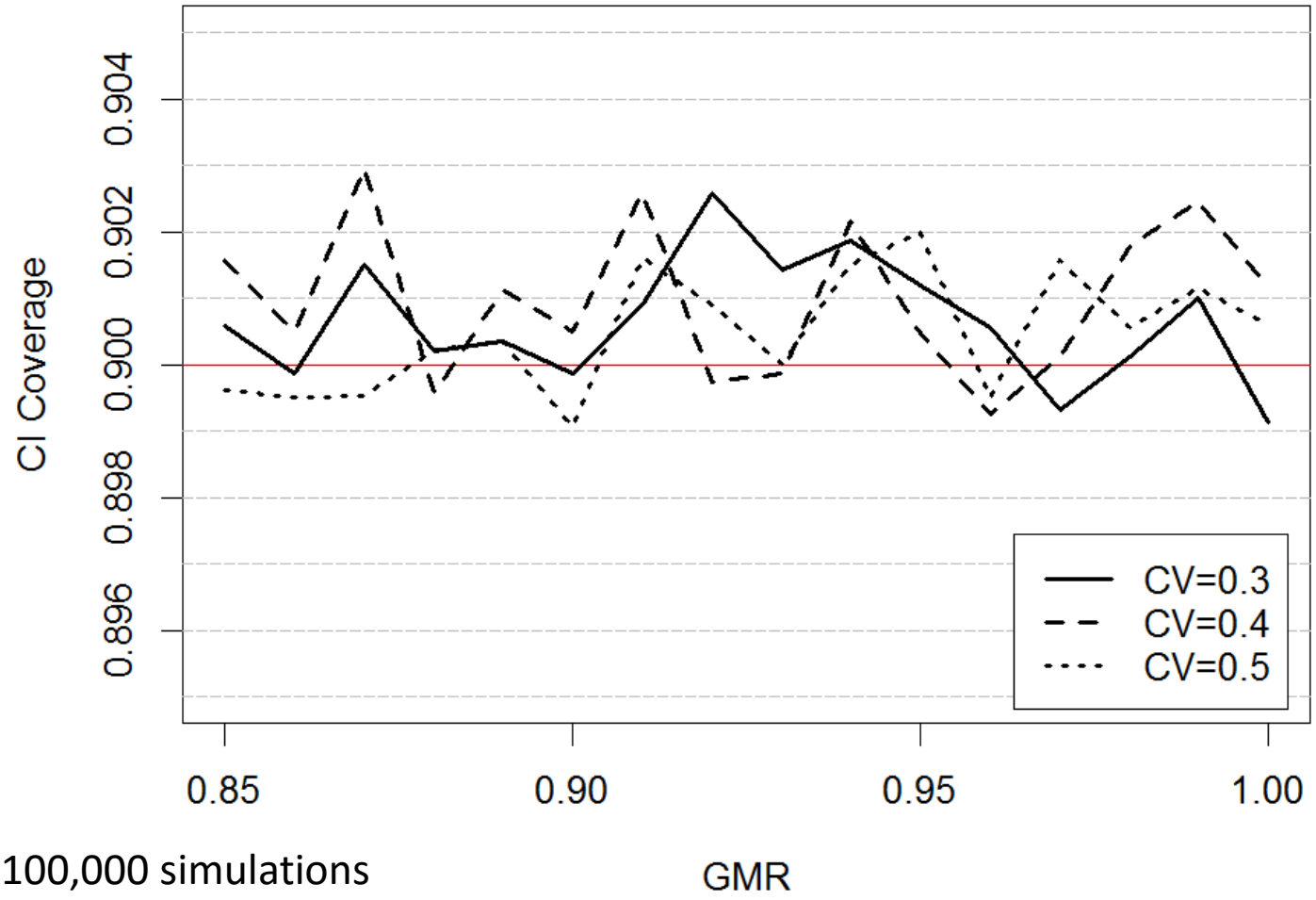


Simulation results 1: empirical type 1 error



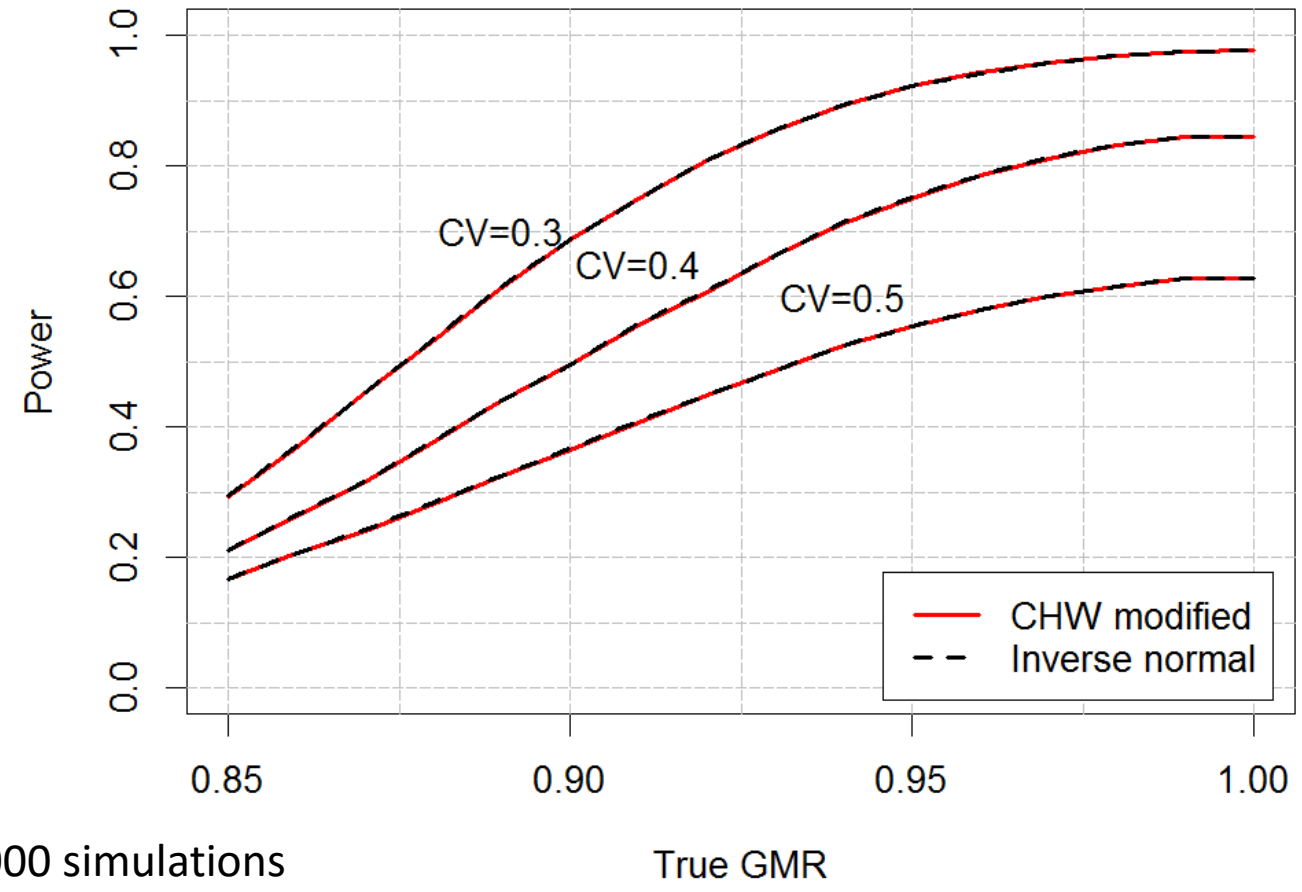
1,000,000 simulations

Simulation results 2: confidence interval coverage



100,000 simulations

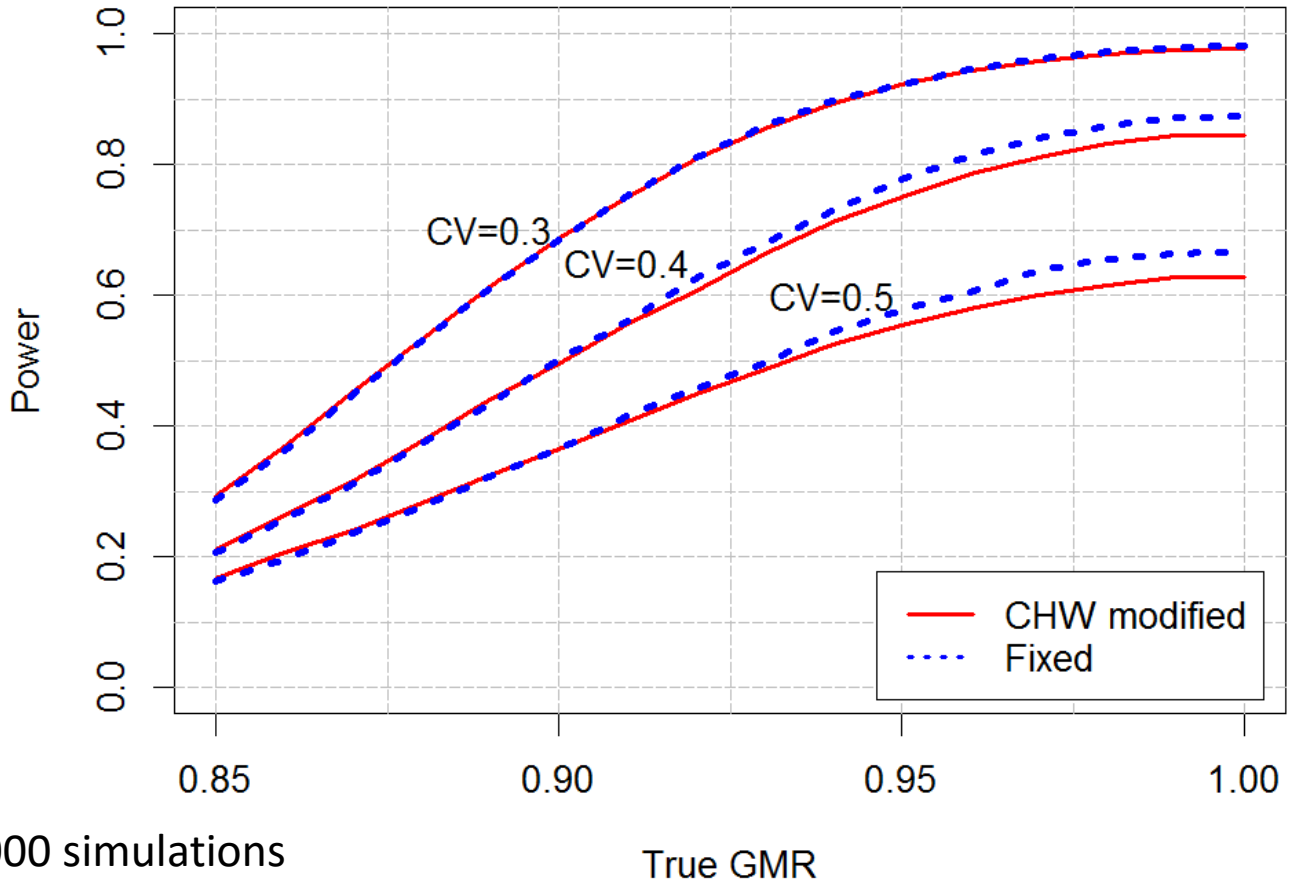
Simulation results 3: modified CHW vs inverse normal



100,000 simulations

Simulation results 4: modified CHW vs fixed design

Fixed design sample size equals average sample size of CHW for each GMR value



100,000 simulations

Summary

- Simple modification of CHW inferential framework for 2-stage parallel design with small sample sizes
- **Valid confidence interval for GMR**, type I error control
- Final sample size must fall within pre-specified range, otherwise no restrictions
- Conservative in theory, but power matches standard inverse normal method, conservative boundaries close to exact CHW

Summary

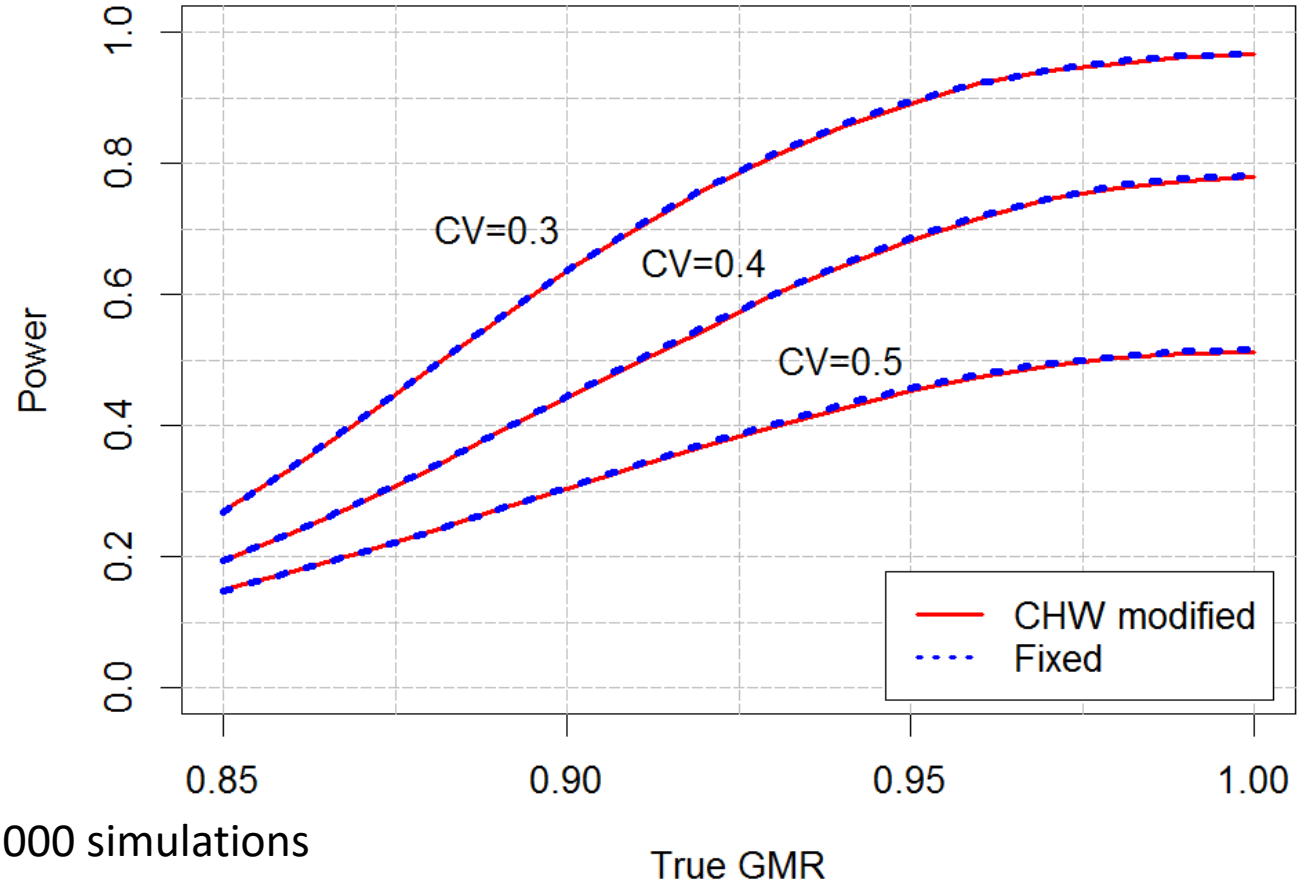
- Method generalizes to allow early stopping, repeated confidence intervals
- Basic idea of **piecewise T-distribution with conservative degrees of freedom** applicable in other small sample situations with pre-specified bounds on DF

Thank you

Simulation results 5: efficiency of modified CHW compared with fixed design with same average N

$n_1 = 50, n = 100, n_{max} = 100$, promising zone 30% < CP < 90%

Fixed design sample size equals average sample size of CHW for each GMR value



100,000 simulations