My Views on Two Papers

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Virtual Journal Club, DIA Statistical Community & PSI
October 29, 2013

Disclaimer

- This presentation reflects only the views of the presenter and should not be construed to represent the views or policies of the U.S. Food and Drug Administration

Two Papers

- Blinded Sample Size Recalculation in Longitudinal Clinical Trials Using Generalized Estimating Equations
  - **Daniel Wachtlin and Meinhard Kieser**, TIRS 2013

- Adaptive Blinded Sample Size Adjustment for Comparing Two Normal Means – A Mostly-Bayesian Approach
  - **Andrew M. Hartley**, PhrmStat 2012

The GEE paper by Drs. Wachtlin and Kieser

- **Blinded SSR in GEE analysis setting for longitudinal data**
  - Compare slopes b/t treatment groups
    - N calculation based on formula by Jung & Ahn
  - Data simulated based on
    - constant risk of dropout
    - damped exponential family for within-subject correlations, i.e., $\rho^{t^{\theta}}$, where θ is "damping" parameter

The GEE paper by Drs. Wachtlin and Kieser

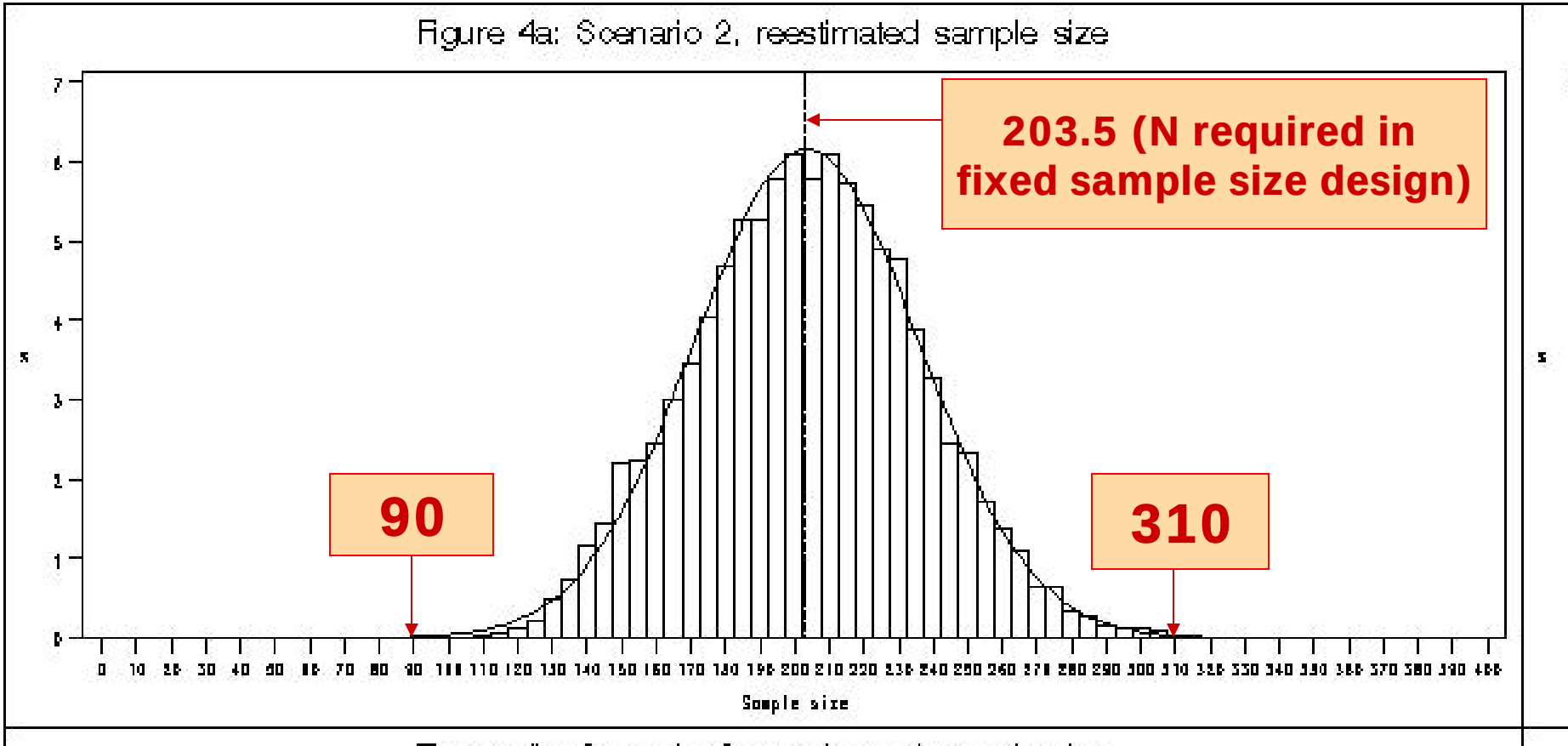
- **Simulation Results:** re-calculated N on average near (slightly above) that from fixed N design
  - **My View:** distributions of re-calculated Ns suggest variability non-negligible, particularly with smaller IPS* (see plots in next 2 slides)
    - **Q1:** impact of N variability on study power, such as in fixed N design?
    - **Q2:** impact of IPS size on N variability?

*IPS: internal pilot study

The GEE paper by Drs. Wachtlin and Kieser

Source: plot copied and enlarged directly from Dr. Wachtlin's slide

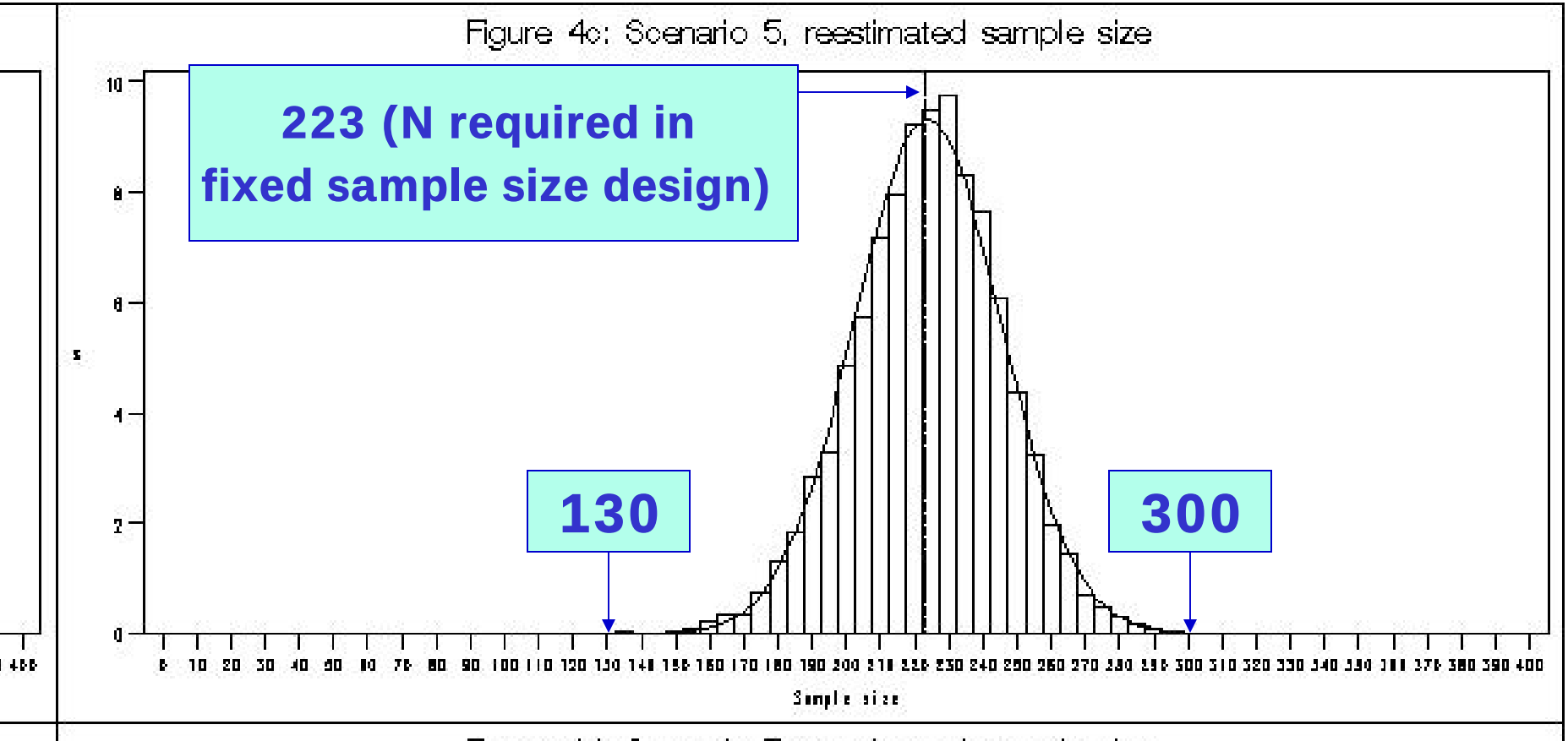
N for IPS = 41 in Scenario 2



The GEE paper by Drs. Wachtlin and Kieser

Source: plot copied and enlarged directly from Dr. Wachtlin's slide

N for IPS = 112 in Scenario 5



The GEE paper by Drs. Wachtlin and Kieser

- **Simulation Results:** estimation of θ ("damping" parameter) associated with high variability and risk bias when parameter value is extreme
  - **Q:** any impact of estimation variability/bias on increasing variability of re-calculated N? If so, how much impact compared with that of IPS size?

The GEE paper by Drs. Wachtlin and Kieser

- **Simulation Results:** Type I error rate mostly very near to nominal value based on 10,000 simulation runs
  - **My View:** type I error rates generally large whether based on adaptive design or fixed sample size design
    - **Q:** feasible to enhance precision by increasing # of simulation runs?

The GEE paper by Drs. Wachtlin and Kieser

- **My View on Parameter Assumptions**
  - Good guesses may be needed for within-subject correlation structure, working covariance matrix, dropout mechanism, and treatment effect (relative to control)
    - unclear impact of wrong guesses on study power
    - challenge in postulating treatment effect
      - **Preliminary finding from depression trials:** negative trials largely due to over-optimistic assumption of treatment effect (rather than variance) at design stage

The Semi-Bayesian Paper by Dr. Hartley

- Blinded sample variance depends on treatment effect (Δ) & within-treatment variance (Σ)
  - $E[S_b^2] \approx \Sigma + (¼)\Delta^2$
- **Frequentist Framework:** SSR based on fixed values of treatment effect & variance
- **Dr. Hartley Proposal (Semi-Bayesian):** uncertainty of treatment effect & variance incorporated in blinded SSR

The Semi-Bayesian Paper by Dr. Hartley

- **Dr. Hartley's blinded SSR**
  - prior beliefs about treatment effect and variance refined based on blinded sample variance estimated at interim look
  - SSR determined based on reaching certain PP
- **My View:** reasonable for N planning
  - **Preliminary finding from depression trials:** for negative trials, observed treatment effects generally smaller than postulated at design stage.

The Semi-Bayesian Paper by Dr. Hartley

- Comparisons with GS method
  - **GS Method:** derived in frequentist framework by reaching certain CP rather than PP
  - **Results:** general superiority of semi-Bayesian method to GS method based on certain loss function
- **My View:** semi-Bayesian method associated with larger N on average
  - **Q:** unclear about the variability of N as well as its impact.

The Semi-Bayesian Paper by Dr. Hartley

- **Investigation of Type I Error Rate with Semi-Bayesian Method**
  - **Dr. Hartley Results:** evidence of small inflation
  - **My View:** inflation possibly due to opportunity of adjusting belief about treatment effect based on blinded estimate of sample variance
  - **Q:** same Type I error definition as in frequentist framework? extent of inflation and scenarios where it most likely occur?

The Semi-Bayesian Paper by Dr. Hartley

- **My View on Loss Function**
  - Another loss function, such as rNPV (risk-adjusted Net Present Value) illustrated in Dr. Hartley's slides, may be worth consideration
    - **Rationale:** to balance b/t study power & sampling cost
- **My View on Prior Beliefs**
  - unclear impact of wrongly assumed priors
  - challenge to adequately quantify priors

Summary on Both Papers

- **My Overall Views**
  - **Interesting approaches to blinded SSR**
    - applicable to respective situations
  - **Suggestions for further explorations**
    - impact of wrong assumptions about parameters
    - Likelihood/impact when re-calculated N falls at the lower end of N distribution
    - enhancing precision in evaluation of type I error rates

Acknowledgements

- Dr. H.M. James Hung
- Dr. Yeh-Fong Chen
- Dr. George Kordzakhia
- Dr. John Lawrence