Statistical considerations AF-SCREEN Internationally

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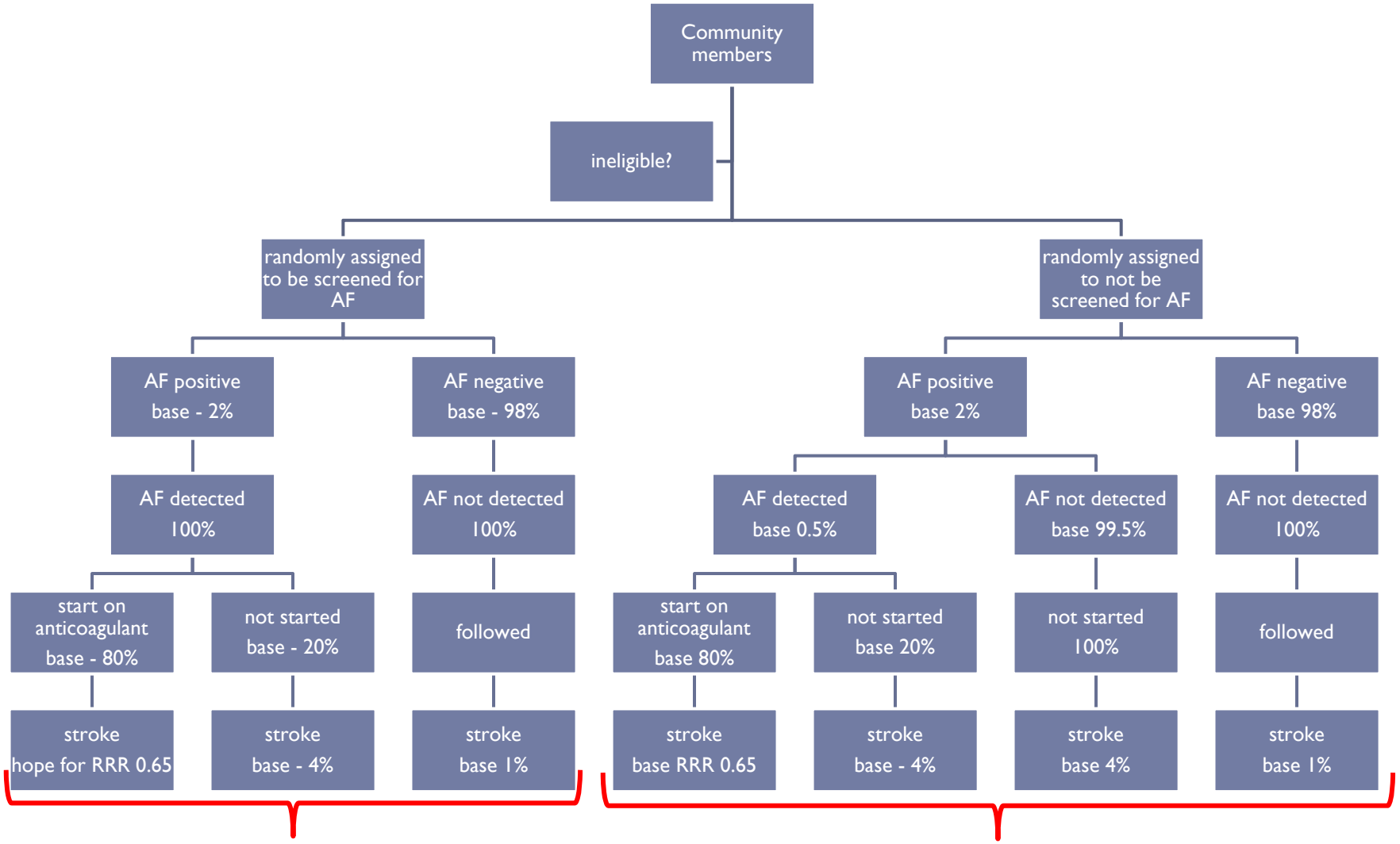
Research question & hypotheses

- Does screening for Atrial Fibrillation (AF) prevent ischemic strokes?
  - Screening for AF → detection of asymptomatic AF
  - Detection of asymptomatic AF → initiation of appropriate effective therapy (oral anticoagulants)
  - Initiation of appropriate effective therapy (oral anticoagulants)
    → increase risk-factor modifications to reduce complications from AF progression
    → reduce stroke and death

Study design flow diagram



0.010376 ← Risk of stroke in each arm→ 0.010598

Study design flow diagram

- So the risk of stroke in each arm under these assumptions is

- Consider translating outcome to # strokes prevented & quantity of $$ saved
- Varying paramters

Feasibility of a single-site RCT

- To test whether randomization to AF screening or not leads to fewer folks getting strokes
- For 80% power, need ~60,000 per arm

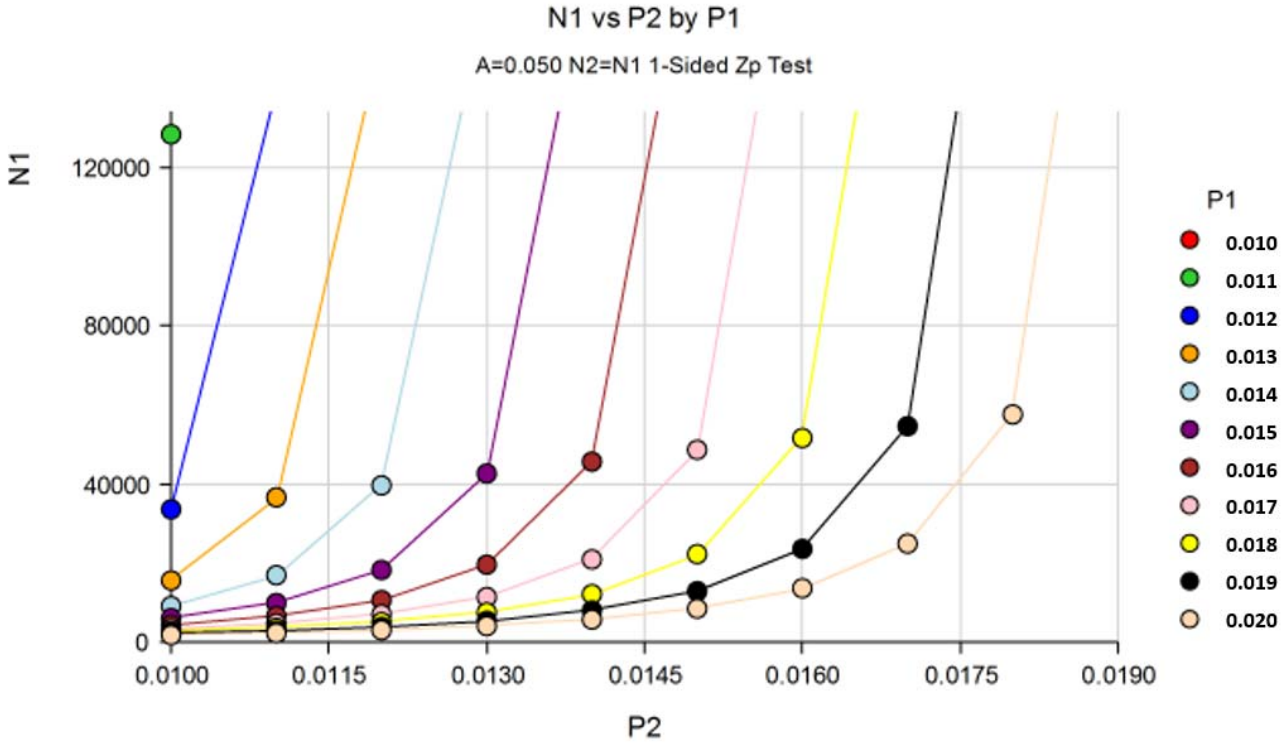
Numeric Results of Tests Based on the Difference: P1 - P2
H0: P1 - P2 ≤ 0. H1: P1 - P2 = D1 > 0. Test Statistic: Z test with pooled variance

Target Power	Actual Power	N1	N2	N	Trt|H1 P1	Cntrl P2	Diff D1	Target Alpha	Actual Alpha
0.80	0.80000			0	0.0104	0.0106	-0.0002	0.0500	

Effect Size

P1 (Treatment Group Proportion|H1): .010376

P2 (Control Group Proportion): .010598

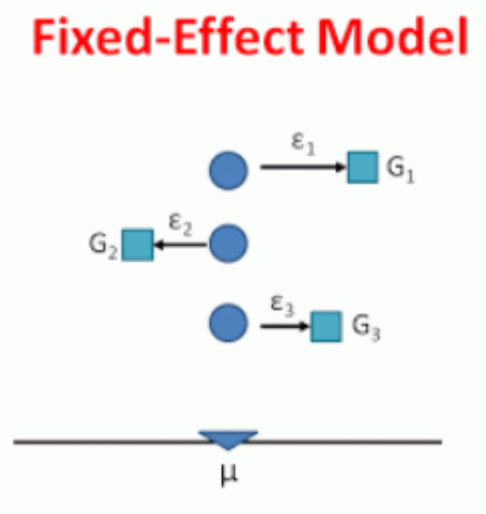


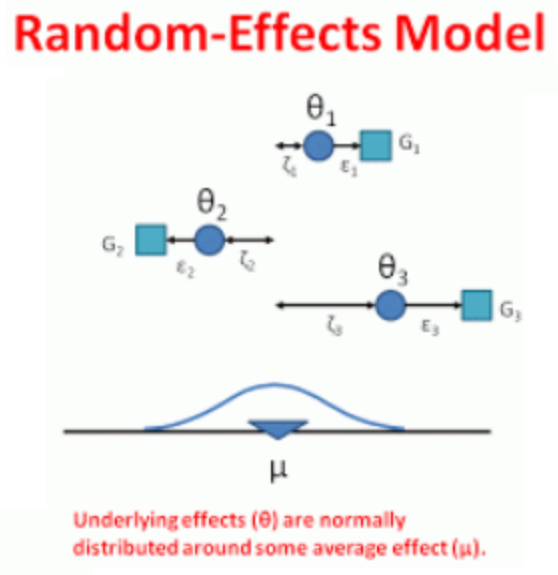
Analytic methodology

- Calculate
  - Individual studies' intervention effect
    - Odds ratio, risk difference or risk ratio, mean difference, etc., standard error of estimate, 95% CI
  - Overall combined studies' intervention effect,
    - Standard error of estimate, 95% CI
    - Account for study-level characteristics, quality and differences
- Use random-effects meta analysis, enhanced with study-level characteristics & individual patient data → multilevel meta-regression

Additional slides

Meta analysis - methodology





- Assumes all studies share a common effect-size μ
- Studies differ in their results due to sampling error ε

  → $G_i = \mu + \varepsilon_i$

- Each study has its own effect-size that differs from μ by the 'study effect' ζ
- A study's result is also subject to sampling error ε

→ $G_i = \mu + \zeta_i + \varepsilon_i$

Meta analysis – estimation of overall effect

- The estimate is a weighted average, where the weight for a study is the reciprocal of its variance (as a measure of 'quality')
- The variance can be calculated using the fixed effects model or the random effects model:
  - The fixed effects model does not use information from the other studies:

$$G_i = \mu + e_i$$

$$\text{var}(G_i) = \text{var}(e_i) = V_{G_i}$$

  - The random effects model considers the variation among studies and within studies →

$$G_i = \mu + \varsigma_i + e_i$$

$$\text{var}(\varsigma) = \tau^2$$

$$\text{var}(G_i) = \tau^2 + V_{G_i}$$

Borenstein et al (2009) Introduction to Meta Analysis

Meta analysis – estimation of overall effect

- Weights with fixed effects

$$w_i = \frac{1}{V_{G_i}}$$

- Weights with random effects

$$w_i^* = \frac{1}{V_{G_i} + \hat{\tau}^2}$$

- Impact: 'attenuation' of weights if τ^2 is big

Borenstein et al (2009) Introduction to Meta Analysis

Random *versus* Fixed Effects

- If the study results are homogeneous, random and fixed effects will be almost identical
- If the study results are heterogeneous, the confidence interval for the random effects model will be wider than that for the fixed effects model

Assessing heterogeneity among studies

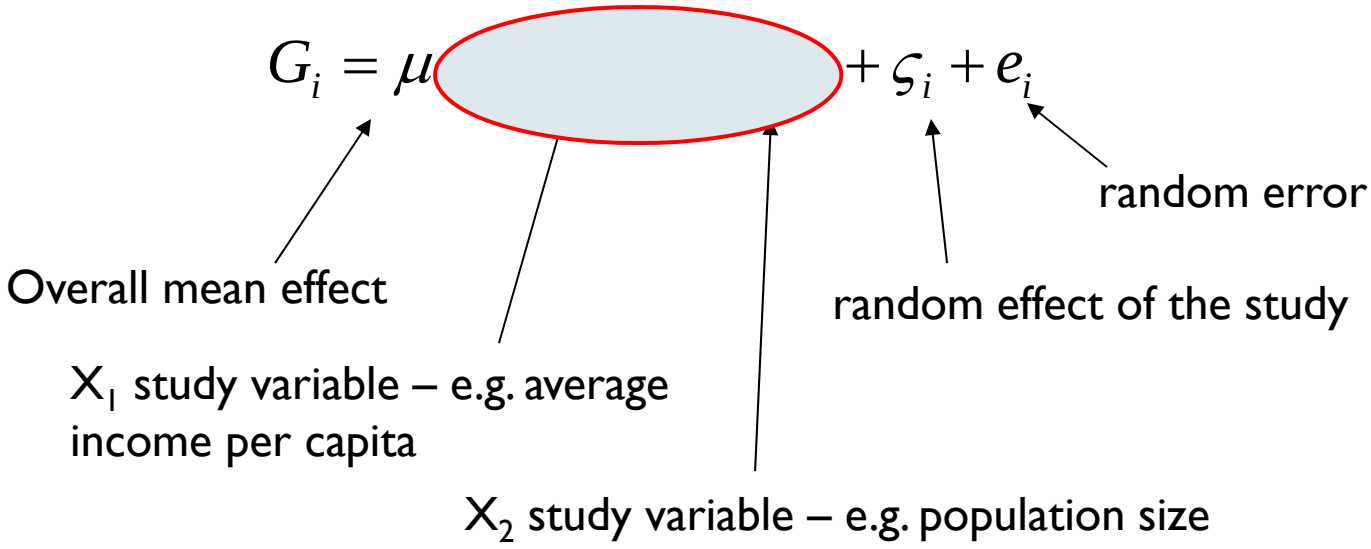
- Cochran's Q - the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method
  - Q ~ χ^2 with k-1 df (k = number of studies)
- I^2 statistic - the percentage of variation across studies that is due to heterogeneity rather than chance
  - I^2 = 100% x (Q-df)/Q
  - Does not inherently depend upon the number of studies considered
- τ^2 - variance component due to variation among studies

Meta analysis & meta regression

- Dealing with 'heterogeneity' among the studies - τ^2
  - Decompose the total variance into: among and within components → using mixed effects models for getting a more precise estimate of the intervention effect
- If there is still residual heterogeneity
  - Expand the mixed effects model to include study-level covariates that may explain some of the residual variability among studies → meta regression

Meta regression

- e.g.



Multi-level meta regression

- Incorporating individual-level variables into the meta-regression – for the j[th] subject of the i[th] study