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

Community members

ineligible?

randomly assigned to be screened for AF

AF positive base - 2%

AF detected 100%

start on anticoagulant base - 80%

stroke hope for RRR 0.65

AF negative base - 98%

not started base - 20%

not started base - 4%

randomly assigned to not be screened for AF

AF positive base 2%

AF detected base 0.5%

start on anticoagulant base 80%

stroke base RRR 0.65

AF not detected base 99.5%

not started base 20%

not started base 4%

AF negative base 98%

AF not detected base 100%

followed

followed

stroke base 1%

stroke base 4%

stroke base 1%

Risk of stroke in each arm

0.010376

← 0.010598
Study design flow diagram

- So the risk of stroke in each arm under these assumptions is
  
  0.010376
  0.010598

*RR expected = 0.98*  
*Meaningful?*

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

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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
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 \( \rightarrow \) multilevel meta-regression
Additional slides
Meta analysis - methodology

- Assumes all studies share a common effect-size $\mu$
- Studies differ in their results due to sampling error $\varepsilon$
  \[ G_i = \mu + \varepsilon_i \]

- Each study has its own effect-size that differs from $\mu$ by the ‘study effect’ $\zeta$
- A study’s result is also subject to sampling error $\varepsilon$
  \[ G_i = \mu + \zeta_i + \varepsilon_i \]
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:
    \[ G_i = \mu + \zeta_i + e_i \]
    \[ \text{var}(\zeta) = \tau^2 \]
    \[ \text{var}(G_i) = \tau^2 + V_{G_i} \]

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 \( \tau^2 \) is big

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
  - $Q \sim \chi^2$ 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
  - $I^2 = 100\% \times (Q-df)/Q$
  - Does not inherently depend upon the number of studies considered

- **$\tau^2$** - variance component due to variation among studies
Meta analysis & meta regression

- Dealing with ‘heterogeneity’ among the studies - $\tau^2$
  - Decompose the total variance into: among and within components $\rightarrow$ 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 $\rightarrow$ meta regression
Meta regression

\[ G_i = \mu + \zeta_i + e_i \]

- Overall mean effect
- Random error
- Random effect of the study
- \( X_1 \) study variable – e.g. average income per capita
- \( X_2 \) study variable – e.g. population size
Multi-level meta regression

- Incorporating individual-level variables into the meta-regression – for the $j^{th}$ subject of the $i^{th}$ study

$$G_{ij} = \mu + \beta_j + \zeta_i + e_{ij}$$

- Overall mean effect
- $X_1$ study variable – e.g. average income per capita
- $X_2$ study variable – e.g. population size
- $X_3$ subject variable – e.g. sex
- Random effect of the study
- Random error