Should phase II cancer screening trials include a control arm?

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Objective

To evaluate the assets and drawbacks of including a control arm into Phase II cancer screening trials.

Methods

Recent literature, discussion with physicians and statisticians, simulations studies.
Results I

Assets:

- Avoid uncertainty of historical controls and bias due to selection criteria.
- Reduce the risk of false positive results.
- Higher qualification of evidence and thus easier to be published.
- Possibly more appropriate to test combination therapies, cytostatic drugs and 'biologics' in particular.
- Appropriate if the patient population is heterogenous.
Results II

Downside:

- Less feasible and more expensive.
- Not feasible for rare diseases.
- Compromise on power and significance to keep the sample size low.
- Sometimes appear merely as underpowered phase III trials and are mis-interpreted by physicians.
Information is costly

Phase II trials Schuller 2009
Twilight zone in Simon’s design

\[
p_0 = 0.4, p_1 = 0.6, \alpha = 0.05, 1 - \beta = 0.8
\]
Model of the 3 buckets

Phase II trials

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"Enrichment" of effective compounds (aka model of the 3 buckets)

- After Phase I
- After Phase II
- After Phase III

Phase II trials

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Simulation of the first bucket (after Phase I)

a. Poor

Draw 10000 normally distributed numbers \( i \in R, \mu = 0, \sigma = 1 \)

Calculate \( i = |\left( -\frac{\log_2 i}{10} \right) | \)

If \( i > 1 \): \( i = i/2 \)

b. Medium

Pick a random sample of \( n = 100 \) and replace them with uniformly distributed numbers \( 0 < i < 1, i \in R \)

c. Rich

Pick a random sample of \( n = 1000 \) and replace them with uniformly distributed numbers \( 0 < i < 1, i \in R \)
Simulation of the second bucket (after Phase II)

Draw a sample of 10000 with replacement.

a. Blunt:

\[ p = \begin{cases} \alpha & p_t \leq p_1 \\ 1 - \beta & p_t > p_1 \end{cases} \]  

(1)

b. Simon’s two stage design:

\[ p = 1 - (B(r_1, p_t, n_1) + \sum_{x=r_1+1}^{\min(n_1,r)} b(x, p_t, n)B(r - x, p_t, n_2)) \]  

(2)

\[ \alpha = 0.05, \beta = 0.2, p_1 = 0.6, p_0 = 0.4 \]
After Phase I (aka 1st bucket)

Phase II trials

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After Phase II (aka 2nd bucket)

Phase II trials

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After Phase II, Simon’s \((n_1 = 21, n_2 = 20, r_1 = 9, r = 21)\)
Dirk observed:

"It is a convolution of Simon's function and the prior distribution of treatments"
Perspective I: Prior distribution determines the search algorithm — learn from the treasure seekers!
Perspective II: Beware of local maxima!

Phase II trials

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