Interim Analysis

clinical trials are longitudinal and takes lots of time to complete
impossible to enroll all patients at the same time
interim analysis at primary endpoint data prior to all patients being enrolled or completing treatment to reevaluate or for adaptive design

- early efficacy = convincing evidence of benefit of the new product
- safety concerns = evidence of harm of the new product
- futility = change of conditional power of significant beneficial effect by the end of the study is small given the observed data
- re-estimate final sample size required to yield adequate power to obtain significant result

Group Sequential Design

data is analyzed at regular intervals
k = # of total planned analysis
after every $n = \frac{N}{k}$ patients are enrolled and followed for 30 days, perform an interim analysis on all patients followed cumulatively
if there is significant treatment difference at any point, stop the trial early for superior/inferior efficacy of new drug

<u>Issues with Multiple Testing</u>
inflated Type I error if use $\alpha = 0.05$ at each interim
interim analysis shouldn't be performed using the family-wise error rate $\alpha = 0.05$
compare to preset efficacy significant levels at each interim
data at each interim analysis contains data from previous interims, so aren't independent

Pocock Tests

constant Z critical values across all stages to maintain overall $\alpha = 0.05$

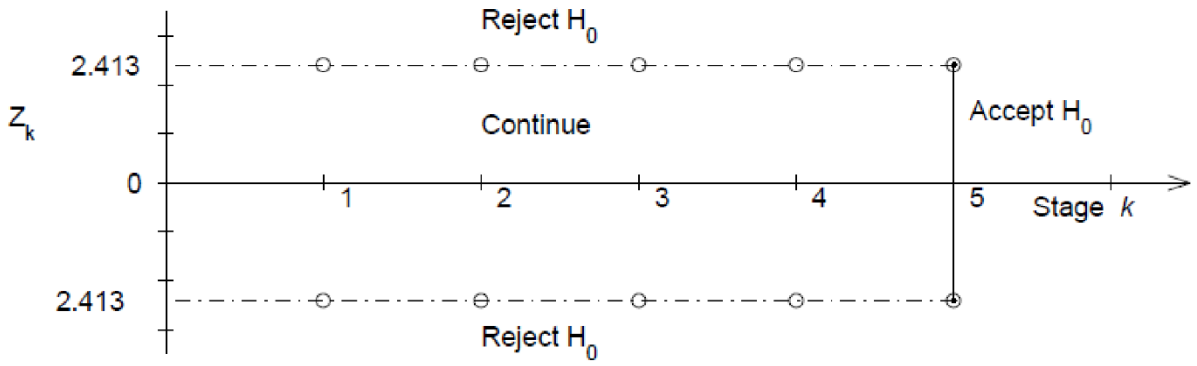
compare two proportions using chi-squared test

critical value depends on number of interim analysis, but is the same for each interim look

after group $k = 1,2,3 \ldots k-1$, if $|Z_k| \geq C_P(k,\alpha)$, stop the trial and reject H_0

if $|Z_k| < C_P(k,\alpha)$ otherwise, continue to group $k+1$

after group K, if $|Z_k| \geq C_P(k,\alpha)$, reject H_0, otherwise accept H_0



Pocock Z critical values $C_P(k,\alpha)$	
k	$\alpha = 0.05$
1	1.960
2	2.178
3	2.289
4	2.361
5	2.413
6	2.453
7	2.485
8	2.512
9	2.535
10	2.555
15	2.626
20	2.672

O'Brien-Fleming Approach

sequential testing procedure where critical values decrease over the stages

chi-squared critical values depend on total number of interim analysis and the stage of the interim analysis

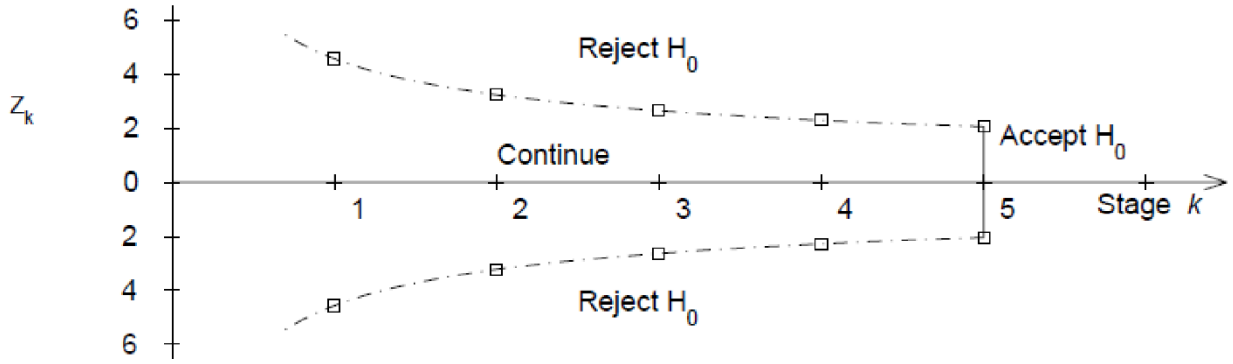
after group $k = 1,2,3 \ldots k-1$, if $|Z_k| \geq C_B(k,\alpha)\sqrt{\frac{K}{k}}$, stop the trial and reject H_0

if $|Z_k| < C_B(k,\alpha)\sqrt{\frac{K}{k}}$, continue to group $k+1$

after group K, if $|Z_k| \geq C_B(k,\alpha)$, reject H_0, otherwise accept H_0

more difficult to declare superiority at the earlier looks

more conservative than Pocock at earlier stages



O'Brien Fleming Z critical values $C_B(k,\alpha)$	
k	$\alpha = 0.05$
1	1.960
2	1.977
3	2.004
4	2.024
5	2.040
6	2.053
7	2.063
8	2.072
9	2.080
10	2.087
15	2.110
20	2.126

Alpha-Spending (α_s)

s = proportion of sample size accrued

beginning of the study	$s = 0$	0% of information is accrued
	$\alpha(0) = 0$	no α is spent
end of the study	$s = 1$	0% of information is accrued
	$\alpha(1) = 0.05$	amount of α used up after the K analysis

$\alpha(s_k)$ = alpha-spending function, probability of Type I error willing to be spent up to time k
alpha-spending is not the same as significance level

$k = 5$			
s	$\alpha(s)$	Z	Significance Level
0.2	0.000001	4.8769	0.000001
0.4	0.00079	3.3571	0.00078
0.6	0.00762	2.6803	0.00736
0.8	0.02442	2.2898	0.02204
1	0.05	2.0310	0.04226

If the first interim analysis occurs after 20% of information is gathered, reject treatment equality if p-value < 0.000001

If the second interim analysis occurs after 40% of information is gathered, reject treatment equality if p-value < 0.00078

If the third interim analysis occurs after 60% of information is gathered, reject treatment equality if p-value < 0.0074

If the fourth interim analysis occurs after 80% of information is gathered, reject treatment equality if p-value < 0.022