Adaptive Group Sequential Designs that Balance the Benefits and Risks of Expanding Inclusion Criteria.
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Adaptive, Group Sequential Algorithm for testing H_{0C}, H_{01}

At each interim analysis k:

1. Compute cumulative z-statistics: $Z_{C,k}$ for Combined population; $Z_{1,k}$ for subpopulation 1; $Z_{2,k}$ for subpopulation 2.

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1. Compute cumulative z-statistics: $Z_{C,k}$ for Combined population; $Z_{1,k}$ for subpopulation 1; $Z_{2,k}$ for subpopulation 2.

2. **Assess Efficacy for Combined Population and for Subpopulation 1:** If $Z_{C,k} > u_{C,k}$ reject H_{0C}; if $Z_{1,k} > u_{1,k}$ reject H_{01}. If any rejected, stop all enrollment.

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3. **Assess Futility:** If $Z_{1,k} \leq l_{1,k}$, stop all enrollment;

4. **Decide on Stopping Subpopulation 2 Enrollment:** If $Z_{2,k} \leq l_{2,k}$, stop subpopulation 2 enrollment; at each future analysis:
   - If $Z_{1,k} > u_{1,k}$, reject H_{01} and stop all enrollment.
   - If $Z_{1,k} \leq l_{1,k}$, stop all enrollment and do not reject any null hypothesis.

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   - If $Z_{1,k} > u_{1,k}$, reject H_{01} and stop all enrollment.
   - If $Z_{1,k} \leq l_{1,k}$, stop all enrollment and do not reject any null hypothesis.
5. Else, continue enrolling from the combined population.

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We optimize efficacy and futility boundaries to minimize expected sample size over scenarios of interest, over subclass of above designs.

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Table: Adaptive design (at $\pi_1 = 1/3$). Boundaries on z-statistic scale.

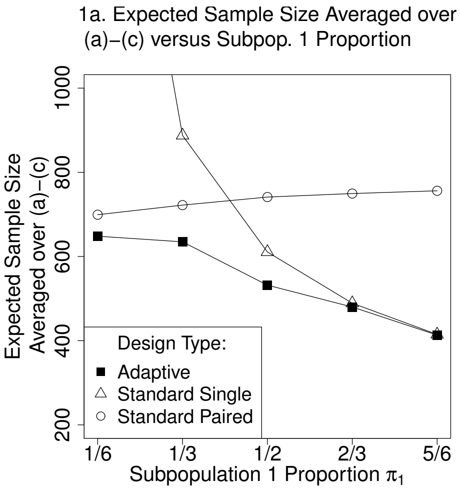
Interim Analysis (k)	1	2	3	4	5
Cum. Sample Size Subpop. 1	93	187	280	428	576
Cum. Sample Size Subpop. 2	187	373	560	560	560
Cum. Sample Size Comb. Pop.	280	560	840	988	1136
H_{0C} Efficacy Boundary ($u_{C,k}$)	4.93	3.49	2.85		
Bndry to Stop Subpop. 2 ($l_{2,k}$)	0	0	∞		
H_{01} Efficacy Boundary ($u_{1,k}$)	5.09	3.60	2.94	2.38	2.05
H_{01} Futility Boundary ($l_{1,k}$)	0	0	0	0	2.05

Comparison to Standard Group Sequential Designs Achieving Goals (i)-(iii)

Table: Comparison of expected sample size (at $\pi_1 = 1/3$).

	Expected Sample Size		
	ADAPT	STD. SINGLE	STD. PAIRED
Scenario:			
a. $\Delta_1 = \Delta_2 = \delta_{\text{min}} > 0$	674	856	823
b. $\Delta_1 = \delta_{\text{min}}, \Delta_2 = 0$	716	1075	795
c. $\Delta_1 = \Delta_2 = 0$	517	723	549
Average over a-c:	**635**	**885**	**722**

Comparison of Expected Sample Size vs. Subpop. 1 Proportion π_1



Summary:

- Substantial Gains in Expected Sample Size vs. Standard Designs
- Adaptive Designs Provide Strong Control of Familywise Type I Error Rate Even if Stop Enrollment Early for Subpop. 2 (e.g. if Higher Adverse Event Rate)
- Limitation: Need Outcomes Observed Soon After Enrollment; Working Now on Extension to Outcomes with Delay

References:

Rosenblum, Michael; Thompson, Richard E.; Luber, Brandon S.; and Hanley, Daniel F., Adaptive, Group Sequential Designs that Balance the Benefits and Risks of Wider Inclusion Criteria (May 2013). Johns Hopkins University, Dept. of Biostatistics Working Papers. Working Paper 250.
http://biostats.bepress.com/jhubiostat/paper250

Later version of the above manuscript (with modifications to data generating distributions and design space considered) here:
Rosenblum, M., Thompson, R., Luber, B., Hanley, D. (In Press) Group Sequential Designs with Prospectively Planned Rules for Subpopulation Enrichment. Statistics in Medicine.
http://goo.gl/7nHAVn

See also: Fisher, Aaron and Rosenblum, Michael, "STOCHASTIC OPTIMIZATION OF ADAPTIVE ENRICHMENT DESIGNS FOR TWO SUBPOPULATIONS" (April 2016). JHU, Dept. of Biostatistics Working Papers. http://goo.gl/OvRELx