# Appendix

Adaptive Randomization

We use an adaptive randomization algorithm similar to the one proposed in Trippa[8] (2012) and refined in Cellamare[20] et al. (2017). Randomization to treatment arm *k* is proportional to a power function of the probability that the median QoR15 of arm *k* is greater than the control divided by the sum of all similar terms for all treatment arms:

$$p_i(k) \propto \frac{P(QoR_{median}\ arm\ k > QoR_{median}\ control \mid data)^{h(i)}}{\sum_{j=1}^{3} P\ (QoR_{median}\ arm\ j > QoR_{median}\ control \mid data)^{h(i)}}$$

Setting the function *h(i)* equal to 1 leads to a randomization probability directly proportional to the probability of a treatment being more effective than control. We chose a function that ensures equal randomization in the early burn-in stage of the trial (e.g. until data are collected for approximately 20 patients per am, *h(i)*=0) and then, as more data are collected, increases the probability of a patient being randomized to the most promising treatment. Technically, this can be achieved using the function:

$$h(i) = \gamma \left(\frac{n(i)}{N}\right)^{\eta} I(i)$$

where the *I(i)* is an indicator function for patient *i* with *I(i)* = 0 if the trial is in the burn-in period and *I(i)*=1 otherwise; $n(i)$ is the total number of observed patient outcomes prior to the $i^{th}$ enrolment; *N* the total (maximum) number of patients on the trial. The parameter $\eta > 0$ controls the speed at which we favor the most promising treatment(s) and $\gamma$ is the maximum

achieved by this *h(i)* function – see figure below with $\gamma = 3$. The parameters $\gamma$ and $\eta$ were chosen based on simulations.

To ensure enough patients are allocated to the comparator group, we matched their number to the best performing arm. The probability of assignment to control is set high when the number of patients in the best treatment arm exceeds the number of controls. Alternatively, if the number of controls is greater, the probability of assignment to an treatment arm will be high according to:

$$p_i(control) \propto \frac{exp\left(\max_{k=1,2,3}\{n_k\} - n_{control}\right)}{3}$$

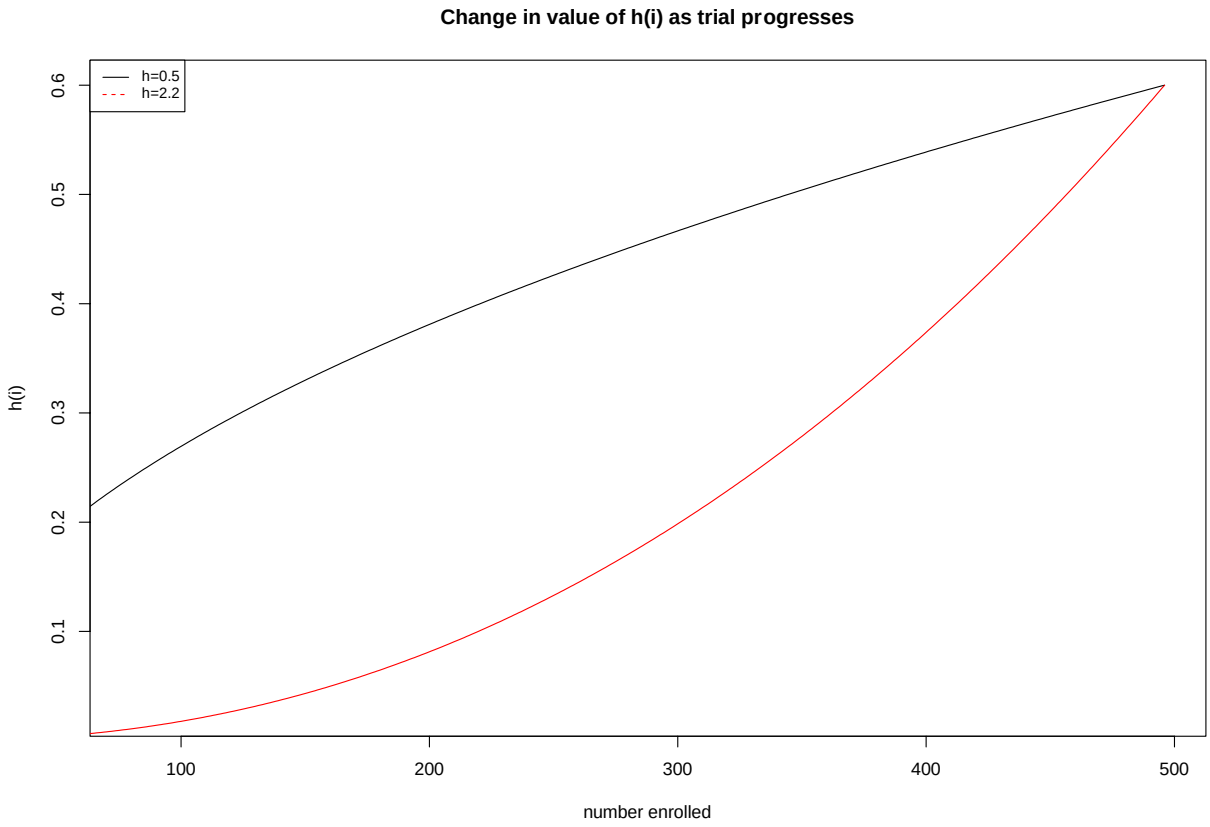
Where $n_k$ is the number of patients in the $k^{th}$ intervention arm and $n_{control}$ is the number in control arm. (See Cellamare[20] et al. (2017)).

Stopping Rules

A trial stops early if all arms meet criteria for early stopping. The arm may stop for futility if the probability that a treatment is superior to control is less than $f_i$ and stops for efficacy if the probability that a treatment is superior to control is greater than $s_i$. The futility and efficacy stopping rules use varying cutoffs at each interim analysis, leading to criteria that are strict at the beginning of the trial and become more liberal as data accumulates. This can be achieved using the following increasing function for $f_i$:

$$f_i = b_{futility}\left(\frac{n(i)}{N}\right)^{p_f}$$

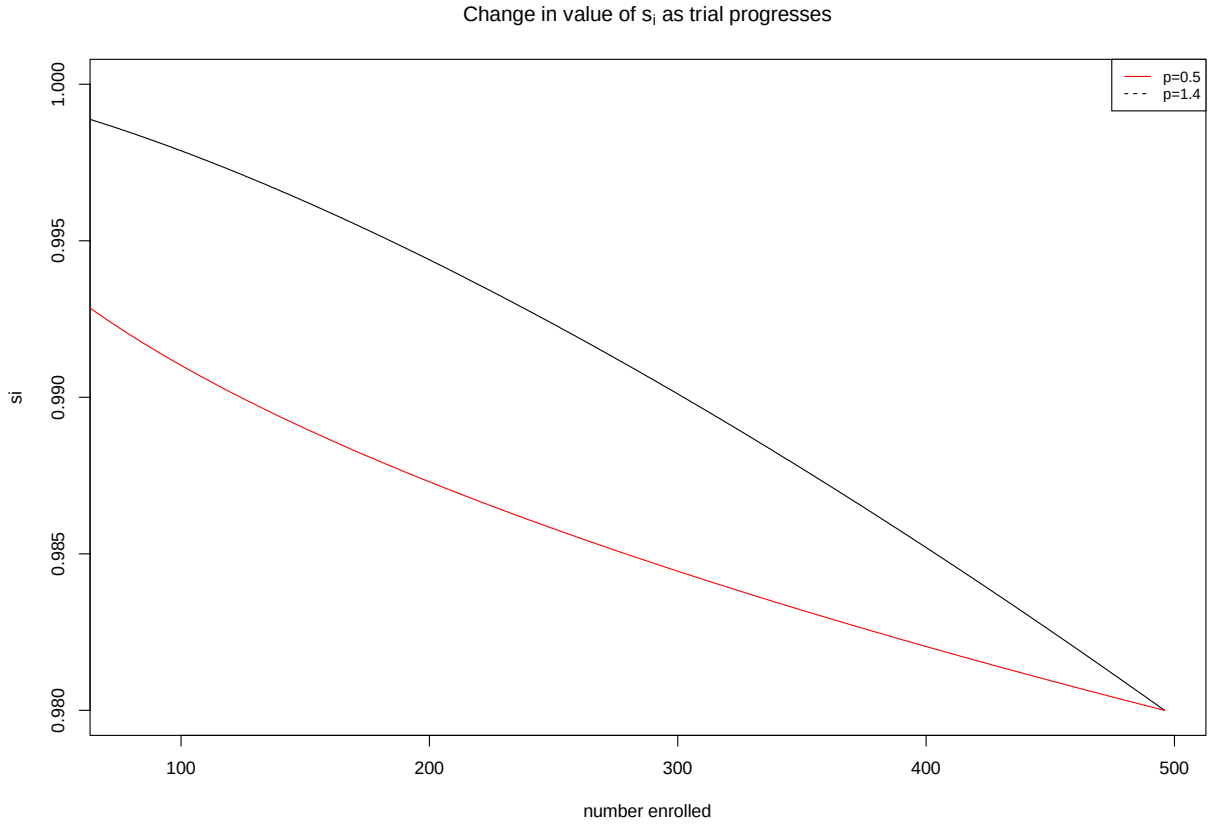
Where $b_{futility}$ is the futility boundary at the end of the trial, $n(i)$ is the number enrolled up to the $i^{th}$ patient and $p_f$ is a tuning parameter that determines the shape of the function. The plot below shows the effect of two different value of $p_f$.




Similarly, the efficacy boundary can be set using the decreasing function $s_i$:

$$s_i = 1 - b_{efficacy}\left(\frac{n(i)}{N}\right)^{p_s}$$

The plot below shows the effect of two different values of $p_s$.




Parameters $b_{futility}, b_{efficacy}, p_f, p_s, \gamma, \eta$ are chosen to achieve a trade-off between learning and adaptation that results in acceptable frequentist characteristics, in this case, a one-sided frequentist false positive rate ≤0.025 when all arms are neutral and true positive rate ≥0.8 when all arms are superior to control by a QoR15 score of 8. Other objectives, in terms of false positive control and power target, may lead to different parameter values.

Parameter summary

$N_{max}$ =500 $\gamma = 3$ $\eta = 1.4$ $p_f = 2.2,$ $p_s = 1.4$ $b_{futility} = 0.6, b_{efficacy} = 0.02$

Model

As discussed earlier, QoR15 has a left skewed distribution. An empirical logit transformation[30],

$f(QoR15) = log\left(\frac{QoR15+c}{150-QoR15+c}\right)$ , where c =0.5 is a constant to avoid division by 0,

was used to remove skewness and achieve approximate normality using the pilot data[15] available for this population. In other populations this transformation may not be appropriate and other more flexible parametric or non-parametric techniques may be required to model the bounded discrete outcome scores[31, 32].

Since f(QoR15) is assumed to be normally distributed with mean ($\mu$) and variance ($\sigma^2$), some assumptions must be made on the parameters of interest $\mu$ and variance $\sigma^2$ that may be different by treatment arm. For simplicity, we assumed a normal-inverse-chi-squared prior distribution with $\mu = 0.92$ , $\sigma^2 = 1$ and $k_0 = v_0 = 1$. This represents a dispersed prior. Such prior distributions are common for normal data.[33] While priors can have an impact on the results, this effect is greatly reduced when enough data have been collected and priors are minimally informative.

Random deviates were drawn from the marginal posterior distribution of the mean for each of the arms and pairwise empirical estimates were made of the probability that mean transformed QoR15 of arm *k* was superior to control.