**Power Analysis – Cerebros**

**Sample For Objective 1 of the proposal:**

Comparison of CCAA natural history and treatment with either FDS, coiling, or other invasive methods to improve symptoms.

**Estimation of Effect Sizes for the Objective**

Estimated effect sizes are based on findings of Zanaty et al., and the meta-analysis on CCAA natural history by Shahbandi et al.

Due to an absence of symptom relief following cavernous segment treatment specific meta-analyses the single cohort of Zanaty et al., is used although this is a large limitation when calculating effect size. Thus, I will provide different effect size scenarios to help inform how many patients would be needed within treatment groups to achieve sufficient power (80%).

Because the reported symptom improvement outline in Shahbandi et al., is reported in incidence per 100 patient-years and the Zanaty paper is in percentages, both will be converted to an annual probability of symptom improvement with calculations below:

**Natural History (from Shahbandi et al.):**

* Non-cerebrovascular symptoms: 2.51 per 100 person-years = 0.0251 annual rate
* Annual probability: 1 - exp(-0.0251) = 0.0248 = 2.48%
* The rate of spontaneous cerebrovascular symptom resolution is even lower in the study, however because this will be compared against the single cohort, I will use a larger estimate of 5% recovery to ‘play it safe’.

**Treatment outcomes (from Zanaty et al.):**

For a mean of 14.5 months (1.21 years) follow-up:

1. **PED (Flow Diversion)**:
	* 92.16% improvement over 1.21 years
	* Annual rate: -ln(1-0.9216)/1.21 = 2.12
	* Annual probability: 1 - exp(-2.12) = 0.880 = 88.0%
2. **SAC**:
	* 50.84% improvement over 1.21 years
	* Annual rate: -ln(1-0.5084)/1.21 = 0.58
	* Annual probability: 1 - exp(-0.58) = 0.440 = 44.0%
3. **Coiling**:
	* 50.00% improvement over 1.21 years
	* Annual rate: -ln(1-0.5000)/1.21 = 0.57
	* Annual probability: 1 - exp(-0.57) = 0.435 = 43.5%
4. **CVD**:
	* 78.57% improvement over 1.21 years
	* Annual rate: -ln(1-0.7857)/1.21 = 1.27
	* Annual probability: 1 - exp(-1.27) = 0.719 = 71.9%

**Sensitivity Analysis:**

Using G\*Power to perform basic sensitivity analysis with 80% power and 800 patients we get the following output:

**χ² tests -**  Goodness-of-fit tests: Contingency tables

**Analysis:** Sensitivity: Compute required effect size

**Input:** α err prob = 0.05

Power (1-β err prob) = 0.80

Total sample size = 800

Df = 4

**Output:** Noncentrality parameter λ = 11.9352858

Critical χ² = 9.4877290

Effect size w = 0.1221438

**Sample Size Estimate Calculation:**

Using the following scenarios for effect size (Cohen's h), the best-case scenario, moderate, and conservative calculations are based on annual symptom improvement probabilities. These probabilities are adjusted by 0%, 20%, and 40% respectively from the original estimates. Cohen's h is calculated as 2×arcsin(√p₁) - 2×arcsin(√p₂), where p₁ and p₂ are the proportions of patients showing improvement in each treatment group.

The effect sizes below represent the standardized difference between treatment outcomes after this arcsine transformation:

| **Comparison** | **Best Case (h)** | **Moderate (h)** | **Conservative (h)** |
| --- | --- | --- | --- |
| NH vs. FDS | 2.37 | 1.89 | 1.42 |
| NH vs. SAC | 1.09 | 0.87 | 0.65 |
| NH vs. Coiling | 1.08 | 0.86 | 0.65 |
| NH vs. CVD | 1.81 | 1.45 | 1.09 |
| FDS vs. SAC | 1.28 | 1.02 | 0.77 |
| FDS vs. Coiling | 1.29 | 1.03 | 0.77 |
| FDS vs. CVD | 0.56 | 0.45 | 0.34 |
| CVD vs. SAC | 0.72 | 0.58 | 0.43 |
| CVD vs. Coiling | 0.73 | 0.58 | 0.44 |
| SAC vs. Coiling\* | 0.01 | 0.01 | 0.01 |

Next is an example summary of how many patients would need to be in each category to attain sufficient power.

For a 5×2 contingency table (5 treatment groups × 2 outcomes: improved/not improved), the effect size w can be approximated by dividing the average Cohen's h by √2. We can use this w to then provide the minimum sample size required to achieve our benchmark of 80% power.

The G\*Power calculation determined we can detect an effect size of w = 0.1221438 with 800 patients. The required sample sizes for each scenario would be calculated by multiplying 800 by the square of the ratio of the minimum detectable effect size (0.1221438) to the actual effect size (w) for each scenario: Sample size = 800 × (0.1221438/w)².

Sample sizes are summarized below for different treatment comparisons. SAC vs Coiling was not summarized as the effect size difference was miniscule – therefore the minimum sample size would likely be in excess of 10,000 patients even in the best-case scenario.

**1. FDS vs. SAC comparison**

| **Scenario** | **Cohen's h** | **Required sample size per group (α=0.05, power=0.80)** |
| --- | --- | --- |
| Best Case | 1.28 | 13 patients per group (26 total) |
| Moderate | 1.02 | 20 patients per group (40 total) |
| Conservative | 0.77 | 34 patients per group (68 total) |

**2. FDS vs. Coiling comparison**

| **Scenario** | **Cohen's h** | **Required sample size per group (α=0.05, power=0.80)** |
| --- | --- | --- |
| Best Case | 1.29 | 13 patients per group (26 total) |
| Moderate | 1.03 | 19 patients per group (38 total) |
| Conservative | 0.77 | 34 patients per group (68 total) |

**3. FDS vs. CVD comparison**

| **Scenario** | **Cohen's h** | **Required sample size per group (α=0.05, power=0.80)** |
| --- | --- | --- |
| Best Case | 0.56 | 63 patients per group (126 total) |
| Moderate | 0.45 | 97 patients per group (194 total) |
| Conservative | 0.34 | 171 patients per group (342 total) |

**4. Treatment vs. Natural History comparisons**

| **Comparison** | **Scenario** | **Cohen's h** | **Required sample size per group** |
| --- | --- | --- | --- |
| NH vs. FDS | Best Case | 2.37 | 4 patients per group (8 total) |
|  | Moderate | 1.89 | 6 patients per group (12 total) |
|  | Conservative | 1.42 | 10 patients per group (20 total) |
| NH vs. SAC | Best Case | 1.09 | 18 patients per group (36 total) |
|  | Moderate | 0.87 | 28 patients per group (56 total) |
|  | Conservative | 0.65 | 50 patients per group (100 total) |
| NH vs. Coiling | Best Case | 1.08 | 18 patients per group (36 total) |
|  | Moderate | 0.86 | 28 patients per group (56 total) |
|  | Conservative | 0.65 | 50 patients per group (100 total) |
| NH vs. CVD | Best Case | 1.81 | 7 patients per group (14 total) |
|  | Moderate | 1.45 | 10 patients per group (20 total) |
|  | Conservative | 1.09 | 18 patients per group (36 total) |

**Conclusion**

Although this is a very rough overview of the statistics that would be subject to change depending on the specific characteristics of the LHSC data, this is meant to be an estimation of the required sample sizes to assess symptom resolution across the natural history and common treatments such as FDS, Coiling, SAC, and CVD in this example.

Major highlights include that the sample likely has enough power to compare NH with other treatments in all scenarios. Treatment comparisons may struggle, for instance, SAC vs coiling and FDS and CVD (or other treatments routinely used at UH) may need larger sample sizes that are not likely to be present within the LHSC data.