STATISTICAL PLAN
Evaluating Alternative Medical Therapies in Primary Hyperparathyroidism
NCT02525796
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Statistical Plan

Analytic Plan, Sample Size and Power: A sample size of 20 subjects per intervention arm (n=60 total) has been chosen using *conservative* calculations. The **primary outcome**, ΔPTH in response to randomized drug therapy, will be analyzed using a 2-arm ANOVA analysis evaluating the difference between EPL and placebo. A 3-arm ANOVA including the amiloride arm will also be conducted. Sample size calculations are presented in **Figure** using preliminary data from the RAAS-PARC study where the ΔPTH= -13 pg/mL was seen with RAAS inhibition in participants with P-HPTH, but also using a more conservative estimate (-9.0 pg/mL) that is 25% lower. It is expected that ΔPTH with placebo will range from 0 to +4.57pg/mL, and calculations have been made to anticipate that amiloride may serve as either a negative control (like placebo) or positive control (like EPL). With these conservative estimates, a sample size of 20 subjects/arm will be sufficient to demonstrate a ΔPTH with a type I error of <0.05 and power=80%.

The **secondary outcomes**, change in calcium, will be analyzed in the same fashion as PTH. For calcium, sample size calculations are based on decreases in *total calcium* seen in the RAAS-PARC study (ΔCa= -0.32 mg/dL); treatment with EPL is expected to result in a <u>much greater</u> effect estimate. Thus, using *conservative* estimates of ΔCa= -0.20 to -0.32 mg/dL, a sample size of 20 subjects per intervention arm will be sufficient to achieve 80% power.

Figure: Sample size calculations based on ΔPTH.

	ΔPTH Placebo	ΔPTH Amiloride	ΔPTH SPIRO	SD	Sample Size per Arm PWR=0.8	PWR=0.9
2-arms	0 pg/mL	-	**-9.0 pg/mL**	9.4	19	24
	0 pg/mL	-	**-13.0 pg/mL**	9.4	10	13
3-arms	0 pg/mL	0 pg/mL	**-9.0 pg/mL**	9.4	17	22
	0 pg/mL	0 pg/mL	**-13.0 pg/mL**	9.4	9	11
	0 pg/mL	-6.5 pg/mL	**-13.0 pg/mL**	9.4	12	15
	0 pg/mL	-9.0 pg/mL	**-13.0 pg/mL**	9.4	11	14
	0 pg/mL	-13.0 pg/mL	**-13.0 pg/mL**	9.4	9	11

Figure: Sample size calculation based on ΔCa.

ΔCa Placebo	ΔCa Amiloride	ΔCa SPIRO	SD	Sample Size per Arm PWR=0.8	PWR=0.9
0 mg/dL	0 mg/dL	**-0.20 mg/dL**	0.21	17	22
0 mg/dL	0 mg/dL	**-0.32 mg/dL**	0.21	8	10