Disclaimer: The following information is fictional and is only intended for the purpose of illustrating key concepts for results data entry in the Protocol Registration and Results System (PRS).

Cross-Over Study Design Example

(A Phase II, Randomized, Double-Blind Crossover Study of Hypertena and Placebo in Participants with High Blood Pressure)

Methods

Study Design

This is a single-center, randomized, double-blind (subject/investigator), 2-way crossover study design. Enrolled participants had high blood pressure being treated at a specialty clinic associated with a hospital in Springfield, IL. The study consisted of two intervention periods of 2 weeks separated by a washout period of 2 weeks. (Figure 1) The objective of the study is to determine whether Hypertena has an effect on reducing systolic and diastolic blood pressure in participants diagnosed with high blood pressure.

The protocol and informed consent documents were reviewed and approved by a recognized ethics review board at the study facility. The study was performed in accordance with the Declaration of Helsinki.

Participants

Inclusion Criteria

Participants, regardless of gender, at least 18 years of age and diagnosed with high blood pressure based on the average of two or more properly measured, seated, blood pressure readings during two or more office visits were eligible for the trial. Participants were diagnosed with high blood pressure if the classification was Stage 1 or 2 as defined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7, NHLBI; http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf): Systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg. Participants were also required to have a sufficient level of education to understand study procedures and be able to communicate with site personnel.

Exclusion Criteria

Patients were excluded if they had a history of kidney disease; diabetes; acute liver injury (e.g., hepatitis) or severe cirrhosis; pregnancy or breast-feeding; allergy to Hypertena or lactose; history of drug or alcohol abuse; or participation in a study of an investigational medication within the past 30 days.

Participants were randomized in a 1:1 ratio to receive either Hypertena 20 mg tablet or Placebo tablet (matching Hypertena 20 mg) once daily in the morning in a fasting state for 2 weeks. After 2 weeks of washout, participants crossed over to receive the alternative intervention for 2 weeks, Placebo tablet (matching Hypertena 20 mg) or Hypertena 20 mg tablet, respectively, once daily in the morning in a fasting state.

Primary Endpoints

The co-primary endpoints were the change from baseline in mean sitting systolic and diastolic blood pressure at 2 weeks. Blood pressure was assessed after the participant was in a seated position for at least 5 minutes. Blood pressure was measured with an automated measurement device 3 times at 1 to 2 minute intervals and a mean of the 3 measurements was calculated.

Secondary Endpoints

The secondary endpoint was response rate, with response defined as achieving a mean sitting systolic blood pressure < 140 mmHg and a mean sitting diastolic blood pressure < 90 mmHg at 2 weeks.

Statistical Analysis

All participants who received at least one dose of each intervention and completed all study visits were included in the efficacy analysis. A sample size of 125 participants was needed to provide 90% power to detect a 5 mmHg difference in systolic blood pressure. ANCOVA was used to compare the difference between participants receiving Hypertena and Placebo, with the trough blood pressure at baseline, body weight, and age as covariates, and the treatment group and study site as factors. The test was performed with a significance level of 0.05 (two-sided). Statistical analyses were carried out using SAS software version 6.12 (SAS Institute, Inc., Cary, NC, USA).

Adverse Event Assessment

Safety was assessed by the number of participants with adverse events (AEs). AEs were collected by systematic assessment using terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 11.1 in participants who received one or more doses of intervention. Adverse events during washout were not collected.

Results

Of the 200 patients screened for eligibility between May 2008 and October 2008, 65% (N = 130) were randomized to intervention (Figure 1). Of those not randomized, 35 did not meet inclusion criteria and 35 declined to participate. The last participant completed in February 2009. Participant characteristics for the overall study population are shown in Table 1.

The co-primary clinical endpoints are reported in Table 2. With response defined as achieving a sitting blood pressure <140/90 mmHg, response rates were 45% (n = 57) of participants receiving Hypertena as compared to 35% (n = 43) of participants receiving Placebo.

Numbers of participants with adverse events are shown in Table 3. There were no deaths in the study, but one participant receiving Placebo experienced a myocardial infarction requiring hospitalization.

Table 1. Demographic characteristics of all study participants

Characteristic	**All Study Participants** *n = 130*
Age (Years) *Mean (SD)*	40.3 (5.6)
Gender (n) *Male* *Female*	70 60
Weight (kg) *Mean (SD)*	65 (11.2)
Sitting Systolic Blood Pressure (mmHg) *Mean (SD)*	146.9 (19.9)
Sitting Diastolic Blood Pressure (mmHg) *Mean (SD)*	91.8 (9.3)

SD = Standard Deviation

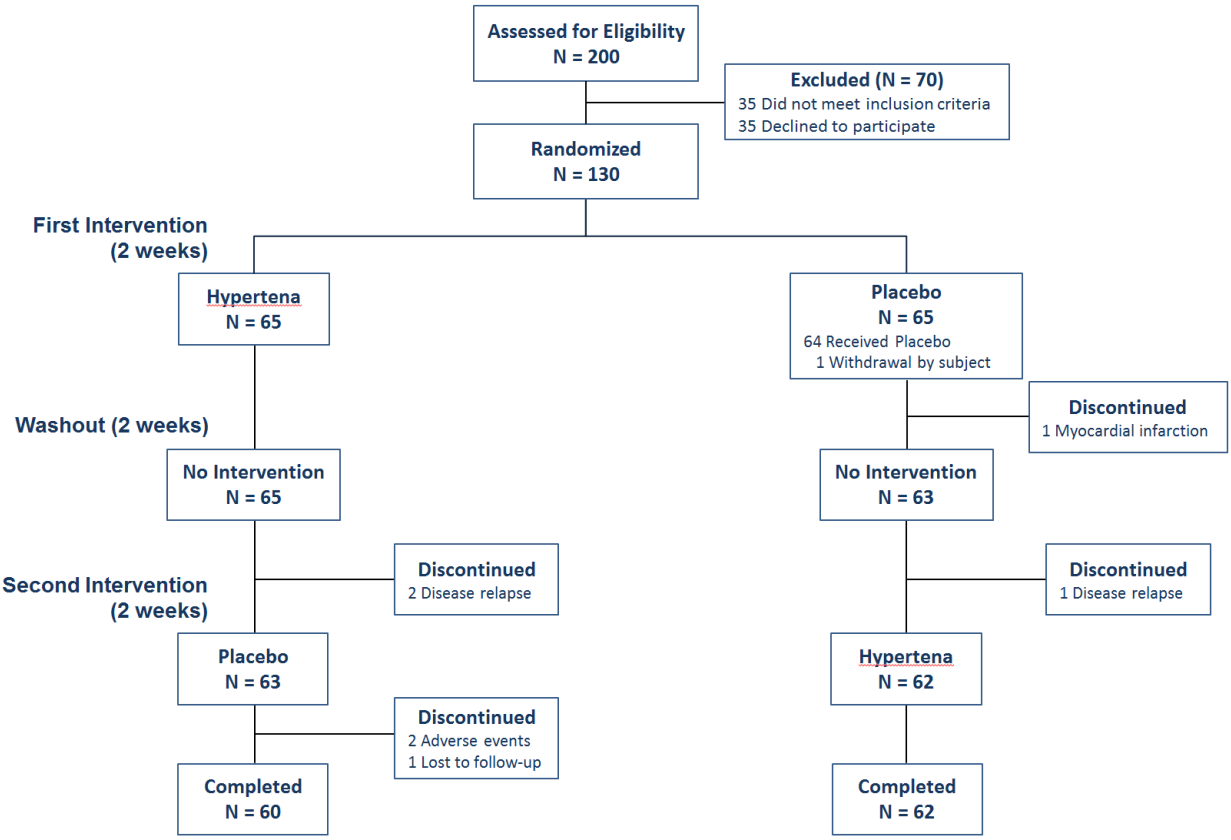

Figure 1. Enrollment, Randomization, and Retention of Study Participants.

Table 2. Change from baseline in mean sitting systolic and diastolic blood pressure at 2 weeks.

Measure	**Hypertena** (n = 127) *mean (SD)*	**Placebo** (n = 123) *mean (SD)*	**p-value***
Sitting Systolic Blood Pressure (mmHg)			
Baseline	146 (19.7)	148 (18.6)	
Change at 2 weeks	-13.7 (1.7)	-7.0 (1.8)	<0.001
Sitting Diastolic Blood Pressure (mmHg)			
Baseline	92 (9.2)	91 (9.1)	
Change at 2 weeks	-6.8 (1.3)	-2.7 (0.7)	<0.001

*ANCOVA models with the trough SBP or DBP at baseline, body weight, and age as covariates, and the treatment group and study site as factors were used.

Table 3. All participants with adverse events during the 2 weeks on each intervention.*

Adverse Events	**Hypertena** *n = 127*	**Placebo** *n = 127*
Cardiac Disorders		
Myocardial Infarction**	0	1
Gastrointestinal Disorders		
Nausea	10	5
Infections and Infestations		
Influenza	2	1
Nervous System Disorders		
Dizziness	11	6
Headache	20	16
Restlessness	5	4
Psychiatric Disorders		
Depression	1	1

*A participant could have experienced the same adverse event more than once during the 2 weeks monitored. 3 participants had more than one headache while receiving Hypertena, and 1 participant had more than one headache while receiving Placebo.
**Event resulted in hospitalization