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

Example Factorial Study Design

(A Phase III Double-Blind, Placebo-Controlled, Randomized, Factorial Design Trial of Two Doses of Marvistatin and Omega-3 Supplement in Patients with Heart Failure)

Methods

Study Design

This multicenter, double-blind (subject/investigator), randomized, placebo-controlled interventional, factorial design study enrolled patients hospitalized with Heart Failure from 5 research sites in the United States: Brigham and Women's Hospital at Harvard Medical School (Boston, MA), Children's Hospital Montefiore (Bronx, NY), Duke University Medical Center (Durham, NC), Thomas Jefferson University Hospital (Philadelphia, PA), University of Texas Medical Branch at Galveston (Galveston, TX).

Patients entered a run-in period during which they received Marvistatin 5 mg tablet once daily and placebo Omega-3 Softgel Supplement for 2 months. Eligible patients who completed run-in were then randomized in a 2x2 factorial blinded design between Marvistatin 80 mg tablet once daily versus Marvistatin 5 mg tablet once daily and Omega-3 Softgel Supplement (900 mg EPA, 5 g DHA) once daily versus placebo Omega-3 Softgel Supplement once daily (See Table 1).

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

Table 1. 2x2 Factorial Design Randomization

	Marvistatin 5 mg	Marvistatin 80 mg	Total
Omega-3 Supplement	100 participants[a]	100 participants[b]	200
Placebo	100 participants[c]	100 participants[d]	200
Total	200	200	400

[a] Reasons for drop out: Lack of Efficacy (2); Physician Decision (1); Pregnancy (1); Did Not Follow Protocol (2); Died (10); Adverse Event (17)
[b] Reasons for drop out: Lack of Efficacy (1); Died (9); Adverse Event (16)
[c] Reasons for drop out: Lack of Efficacy (3); Physician Decision (1); Moved Out of Country (1); Died (10); Adverse Event (16)
[d] Reasons for drop out: Lack of Efficacy (1); Did Not Follow Protocol (1); Died (8); Adverse Event (16)

Patients

Inclusion Criteria

Patients, regardless of gender, at least 18 years of age and hospitalized for the management of Class III or IV Heart Failure (HF) using the New York Heart Association (NYHA) Functional Classification[1] or diagnosed with Class III (Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.) or Class IV (Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.) Heart Failure within 72 hours of hospitalization for another reason were eligible for the trial. Patients 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 having received an antihistamine for more than 2 days prior to randomization or those unable to be treated by Marvistatin were excluded. Additional exclusion criteria included history of acute liver injury (e.g., hepatitis) or severe cirrhosis; pregnancy or breast-feeding; allergy to Marvistatin or Omega-3 Supplement; and participation in a study of an investigational medication within the past 30 days.

Primary Endpoint

The motivation for this study came from indications in the literature that Omega-3 supplements may have a protective and/or ameliorative clinical effect on heart failure. Since statins are frequently prescribed for certain patients with heart failure, it was a primary goal to see if Omega-3 had any short-term protective clinical effect for patients receiving statins and secondarily whether the effect, if any, had an interaction with the statin dose.

The primary composite endpoint was rehospitalization for heart failure or death from any cause during the period from randomization to day 30 by intervention, summing all participants who received each intervention regardless of the paired combination (i.e., Marvistatin 5 mg; Marvistatin 80 mg; Omega-3 Supplement; and Placebo). Rehospitalization and fatal events within 30 days after randomization were reviewed and categorized by an independent, blinded clinical-events committee.

The following criteria were required for rehospitalization events to be classified as due to heart failure: typical clinical manifestations of worsening heart failure and the addition of (or increase in) interventions specifically for worsening heart failure with an intravenous pharmacologic agent, or mechanical or surgical intervention or ultrafiltration, hemofiltration, or dialysis specifically for management of persistent or worsening heart failure. Hospitalized patients who remained in the hospital at 30 days because of heart failure were counted as being rehospitalized for heart failure in the analysis of the primary composite end point.

Secondary Endpoints

Secondary endpoints included the composite endpoint of rehospitalization for heart failure and death from any cause during the period from randomization to day 30 by randomization group; and safety.

Safety

Safety was assessed by the number of adverse events (AEs). AEs were collected by systematic assessment using terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 11.1.

Results

Of the 600 patients screened during the run-in period between July 1998 and September 2007, 67% (N = 400) were randomized to the four intervention groups (Table 1). The last patient completed in May 2008.

Participant characteristics by randomization and by intervention are shown in Tables 2 and 3, respectively.

Table 2. Demographic Characteristics of Participants by Randomization Group

	Marvistatin 5 mg + Omega-3 *n = 100*	**Marvistatin 80 mg + Omega-3** *n = 100*	**Marvistatin 5 mg + Placebo** *n = 100*	**Marvistatin 80 mg + Placebo** *n = 100*	**Total** *n = 400*
Age in Years *Mean (SD)*	63.9 (4.7)	64.5 (5.0)	64.0 (4.8)	64.6 (5.1)	64.2 (4.9)
Gender					
Male	95	96	94	95	380
Female	5	4	6	5	20
NYHA HF Class					
Class III	92	84	97	89	362
Class IV	8	16	3	11	38
Heart Failure Diagnosis					
Pre-hospitalization	57	52	66	63	238
During hospitalization	43	48	34	37	162

SD = Standard Deviation

Table 3. Demographic Characteristics of Participants by Intervention

	Marvistatin 5 mg *n = 200*	**Marvistatin 80 mg** *n = 200*	**Omega-3** *n = 200*	**Placebo** *n = 200*	**Total** *n = 400*
Age in Years *Mean (SD)*	63.9 (4.7)	64.6 (5.2)	64.2 (4.9)	64.3 (5.0)	64.2 (4.9)
Gender					
Male	289	291	291	289	380
Female	11	9	9	11	20
NYHA HF Class					
Class III	189	173	176	186	362
Class IV	11	27	24	14	38
Heart Failure Diagnosis					
Pre-hospitalization	123	115	109	129	238
During hospitalization	77	85	91	71	162

SD = Standard Deviation; NYHA HF = New York Heart Association Heart Failure

The primary and secondary clinical endpoints are reported in Table 4. Statistical analysis was performed with chi square, and a p-value<0.05 was considered statistically significant. There was no significant improvement for rehospitalization or death when analyzed by intervention (p = 0.96) or by randomization group (p = 0.97).

Cumulative probabilities for the primary clinical endpoint for the Omega-3 and Placebo analysis populations were estimated using Kaplan-Meier product-limit method and Greenwood's formula for 95% confidence intervals. For Omega-3, the estimated cumulative probability of rehospitalization or death at 30 days was 0.28 (95% CI: 0.17 to 0.39). For Placebo, the cumulative probability was 0.26 (95% CI: 0.15 to 0.37)

Adverse events are shown in Table 5. If a participant experienced the same serious adverse event more than once, then each event would have been recorded as a distinct event. However, no participant experienced the same serious adverse event more than once. If a participant experienced the same non-serious adverse event more than once, then it was only recorded as one adverse event.

References

[1]American Heart Association. Classes of Heart Failure Web site. http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp#.T1eG2vW-32k . Accessed October 12, 2012.

Table 4. Primary and Secondary Clinical Endpoints from Randomization through Day 30: Rehospitalization for Heart Failure and Death from Any Cause

Primary	
Marvistatin 5 mg: no./total no. (%)	53/200 (26.5)
Marvistatin 80 mg: no./total no. (%)	49/200 (24.5)
Omega-3: no./total no. (%)	52/200 (26.0)
Placebo: no./total no. (%)	50/200 (25.0)
Secondary	
Marvistatin 5 mg + Omega-3: no./total no. (%)	27/100 (27.0)
Marvistatin 80 mg + Omega-3: no./total no. (%)	25/100 (25.0)
Marvistatin 5 mg + Placebo: no./total no. (%)	26/100 (26)
Marvistatin 80 mg + Placebo: no./total no. (%)	24/100 (24)

Table 5. Adverse Events through Day 30*

	Marvistatin 5 mg + Omega-3 *n = 100*	**Marvistatin 80 mg + Omega-3** *n = 100*	**Marvistatin 5 mg + Placebo** *n = 100*	**Marvistatin 80 mg + Placebo** *n = 100*
Total**/Total Other	30/20	26/22	27/27	27/28
Myocardial Infarction**	17	16	16	16
Death**	10	9	10	8
Palpitations	5	8	1	5
Ventricular tachycardia	8	4	6	7
Chest pain	6	4	4	1
Hyperglycemia	5	3	4	2
Hyperlipidemia	2	4	5	6
Hemorrhagic stroke**	2	1	0	1
Hemorrhagic transformation stroke**	1	0	1	2
Dizziness	2	6	9	3
Headache	4	4	8	3
Dyspnea	5	4	10	6
Hypertension	1	8	9	13
Ischemia	7	1	5	8

*If a participant experienced the same serious adverse event more than once, then each event was recorded as a distinct event. If a participant experienced the same non-serious adverse event more than once, then it was only recorded as one adverse event.

**Event classified as “Serious” (i.e., Death or Resulting in Death, requiring either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in a congenital anomaly/birth defect).