Statistical Analysis Plan

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Confidentiality Statement

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• *Not Applicable, New Document*	*Yan Zhang, Prin Statistician*

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan (AKA: the protocol)
CRF	Case Report Form
GEE	Generalized Estimating Equation
HF	Heart Failure
ISCC	INTERVENE Study Communication Center
PRN	*pro re nata* or "as needed"
SAP	Statistical Analysis Plan

3. Introduction

This Statistical Analysis Plan (SAP) has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports. This SAP does not limit the analysis in reports, and additional analysis of the study data beyond this plan is expected. This SAP is developed based on Version 3 of the INTERVENE-HF Clinical Investigation Plan (CIP) dated Feb 01, 2016.

Integrated Diagnostics Driven Diuretic and Chronic Medication Management for Heart Failure (INTERVENE-HF) is a prospective, non-randomized, multi-center (US only), investigational, feasibility study. The purpose is to evaluate the INTERVENE-HF research system that combines integrated device diagnostics based risk stratification algorithm with a guided work flow process managed by a centralized communication center to manage HF patients.

The basic INTERVENE-HF research system is comprised of the pre-existing Medtronic, CRT-D device, investigational 2090 programmer software capable of turning ON/OFF the silent OptiVol® wireless CareAlert, and the INTERVENE Study Communication Center (ISCC). The ISCC will reside with the Care Management Service (formerly Cardiocom) business unit of Medtronic. The INTERVENE-HF study will have a dedicated team of licensed nurses at ISCC that will guide and monitor subjects through an individualized, physician prescribed medication intervention for diuretics and other acute volume management drugs after their silent OptiVol CareAlert has been transmitted and medication intervention is warranted.

4. Study Objectives

For purposes of defining study objectives, the INTERVENE-HF research system is termed the "Integrated Diagnostics Medication Intervention Strategy". The study objectives are:

Primary Objectives:

1. To characterize the effectiveness of the Integrated Diagnostics Medication Intervention Strategy in resolving the subject risk.
2. To characterize the safety of the Integrated Diagnostics Medication Intervention Strategy in resolving the subject risk.

Ancillary Objectives:

1. To characterize the occurrence of HF events in the study subjects.

NOTE: Intervention for heart failure decompensation (HF event) is defined as an event requiring invasive intervention (i.e. IV diuretics, ultrafiltration, or equivalent) or inpatient hospitalization.

5. Investigation Plan

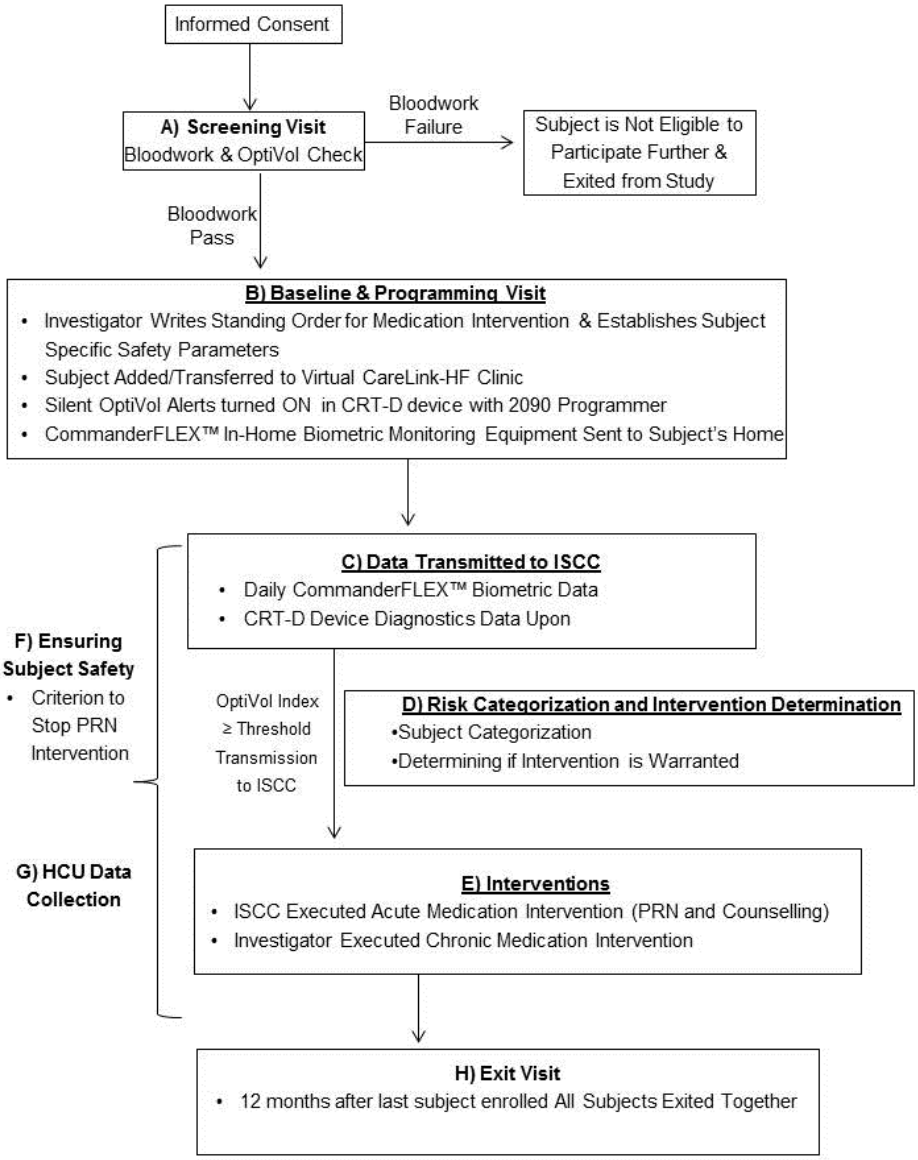
INTERVENE-HF is a prospective, non-randomized, single-arm feasibility study. The study is expected to be conducted at up to 20 centers located in the United States. Up to 400 subjects will be enrolled to yield up to 200 eligible subjects that meet screening criteria. The subject inclusion and exclusion criteria can be found inSection 5.2 of the CIP.

The study process is outlined in

Figure 1 (see also CIP Figure 4). Note that the silent OptiVol CareAlert will be turned ON at the baseline and programming visit with the threshold of OptiVol Fluid Index being programmed uniformly to 70 Ohm-Days for all subjects. Physician adjustment of OptiVol threshold value will not be allowed during the course of the study. If necessary, the OptiVol threshold may be changed during the course of the study. However, this change will be applied uniformly to all study subjects. The CRT-D device will monitor the subject's OptiVol Fluid Index for any threshold crossings. When the OptiVol Fluid Index value crosses the programmed threshold, the device will perform an automatic wireless CareLink transmission of the device diagnostics data to ISCC. The ISCC nurse will then schedule the CRT-D device to transmit data at set intervals within the next 28 days to continue assessment of the fluid index for either therapy initiations, recovery criteria to stop medication intervention, and/or an OptiVol reset when applicable.

Interim analyses of the study objectives will take place and if data are deemed to sufficiently characterize these objectives by the sponsor at one of these analyses, enrollment and/or follow-up will be stopped. In addition, in order to have an early check on the subjects' safety, a preliminary safety interim data analysis will take place after 10 PRN interventions have been implemented and the last completed PRN intervention has been followed up for 14 days. PRN stands for *pro re nata* or 'as needed'. It refers to the medication intervention of transient increase in volume management drugs prescribed by physicians as a standing order that was written at the baseline and programming visit.

Figure 1: General study process for INTERVENE-HF



6. Determination of Sample Size

As a feasibility trial, the INTERVENE-HF study is not designed to be powered for specific endpoints. However, the sample size for this study was chosen with the goal of gaining a first time experience with the Integrated Diagnostic Medication Intervention Strategy in a broad number of patients to understand the safety, effectiveness and potential patient benefit of the strategy.

The study plans to enroll up to 400 subjects to yield up to 200 eligible subjects that meet screening criteria from 20 centers in the US with follow up for at least 12 months. The study is estimated to be completed in approximately 30 months including 18 months of enrollment and 12 months of follow-up from the last enrolled subject. To ensure a widespread distribution of data and minimize center bias in study results, the maximum number of subjects enrolled at a single center is 30.

The unpublished data of a Medtronic sponsored study (OptiLink HF) shows that among the subjects who had had CRT-D implanted for at least nine months and had NYHA class II or III nine months post implantation, 58% had at least one OptiVol crossing within the next 12 months of follow-up (of which 39%, 28%, 19%, 9% and 5% had one, two, three, four and more than four OptiVol crossings, respectively). Furthermore, about two-thirds of the subjects in that study had OptiVol version 1 and the rest had OptiVol version 2 and it is known that OptiVol version 2 generates fewer alerts. Therefore, we assume in the INTERVENE-HF study that:

- 55% of the enrolled subjects who meet screening criteria and complete the baseline and programming visit will have at least one OptiVol crossing within the 12 months of follow-up; and
- The distribution for those experiencing OptiVol crossings during the 12 months of follow up is the same as the results from the unpublished OptiLink HF data.

As shown in Table 1 (see also CIP Table 18), this leads to approximately 233 OptiVol crossings in 110 subjects (55% of 200 subjects) to be observed in the INTERVENE-HF study. Furthermore, literature has indicated that 45% of OptiVol crossings are HF related[20]. This means about 105 out of the 233 OptiVol crossings would require PRN implementation in this study.

Table 1: Number of OptiVol crossings expected from 110 (55% of 200) subjects

Assumption		Estimation	
Crossing(s)	% of subjects having the crossing(s)	Expected # of subjects having the crossings	Expected # of crossings
1	39%	43	43*1=43
2	28%	31	31*2=62
3	19%	21	21*3=63
4	9%	10	10*4=40
>4	5%	5	5*5=25
Total		**110**	**233**

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Subject disposition throughout the course of the study will be summarized using a flow chart.

7.1.2. Clinical Investigation Plan (CIP) Deviations

Events within a study that did not occur according to the CIP will be recorded as study deviations in the Case Report Form (CRF). The CIP describes a few potential study deviations:

- The investigator will be responsible for performing the re-evaluation of the subject's chronic medications or HF treatment. Any changes in baseline medications will need to be reported to the ISCC. If no changes were made, rationale as to why changes were not made will need to be provided. Failing to follow these protocol requirements will result in a study deviation.
- Blood work will be performed by the site if PRN intervention is stopped anytime because of safety concern. Blood work will also be performed if 2 rounds PRNs are completed irrespective of whether the intervention is deemed success or failure after 2 PRNs. Investigators will be required to record creatinine, eGFR, K+ and Na+ in the blood work CRF. Lack of completing this blood work CRF in its entirety will be considered a study deviation.
- Outside of the PRN medication intervention window, subject's blood pressure will be monitored for hypotension per nominal safety threshold of a systolic blood pressure of <85 mmHG or a diastolic blood pressure <40 mm Hg or physician specified threshold, if different. The Investigator will be required to review the 'Exception Report' and determine if clinical actions are necessary. Actions along with rationale will be documented in the CRF. Lack of completing the CRF in its entirety will be considered a study deviation.

Details of the reporting and handling of study deviations can be found in Section 9 of the CIP. Study deviations will be summarized in the study reports based on deviation type, and details of individual study deviations will be listed.

7.1.3. Analysis Sets

For the two primary objectives aiming to characterize the effectiveness and safety of the Integrated Diagnostic Medication Intervention Strategy, a per protocol analysis set will be used. Specifically, all subjects who have received the Integrated Diagnostic Medication Intervention will be included in the analysis for these two objectives.

For the ancillary objective that is to characterize the occurrence of HF events, a per protocol analysis set will be used. Specifically, all the enrolled subjects who have completed the baseline and programming visit will be included.

Per CIP Section 13, all study objectives will be analyzed once the last enrolled subject has completed the 12-month follow-up visit and/or during interim analyses. If data are deemed to sufficiently characterize the study objectives by the sponsor at one of the interim analyses, enrollment and/or follow-up will be stopped. It is planned to conduct the first interim analysis after 100 subjects are enrolled and have completed the baseline and programming visit. If the study continues after the first interim analysis, the second interim analysis will be conducted after 150 subjects are enrolled and have completed the baseline and programming visit.

In additional, there will be a preliminary safety interim data analysis to summarize preliminary safety of PRN intervention. All the subjects who have completed the baseline and programming visit by the time of the analysis will be considered.

7.2. General Methodology

There is no statistical hypothesis for any of the study objectives. Generalized linear models with generalized estimating equation (GEE) will be used to characterize the effectiveness and safety of Integrated Diagnostic Medication Intervention Strategy, and Poisson regression will be used to characterize the occurrence of HF events. These apply to both interim and final analyses. The preliminary safety interim data analysis will be conducted through descriptive statistics.

7.3. Center Pooling

This study could include up to 20 US centers. Data from all the centers will be pooled. For each study objective, center effect will not be considered in the statistical modeling. Instead, for the two primary objectives, the average number of PRN interventions per subject that are effective or safety will be reported for each individual center. Using the effectiveness endpoint as an example, first the percentage of PRNs being effective will be calculated for each subject as the number of effective PRNs divided by the total PRNs that have been implemented for that subject; then the individual percentages will be averaged within each center. Center-specific analysis will not be conducted for the ancillary objective.

7.4. Handling of Missing Data and Dropouts

Because this is a feasibility study and no hypothesis testing is involved in any of the study objectives, the main analysis for each objective will not account for missing data. If missing data becomes a concern, a sensitivity analysis will be considered.

7.5. Adjustments for Multiple Comparisons

There is no statistical hypothesis for any of the study objectives. Therefore, adjustments for multiple comparisons are not applicable.

7.6. Demographic and Other Baseline Characteristics

Subjects' demographic and other baseline characteristics will be summarized using descriptive statistics. For continuous variables, descriptive statistics such as mean, standard deviation, median, the first and third quartiles, and range will be presented. For categorical variables, counts and percentages will be reported.

7.7. Treatment Characteristics

The INTERVENE-HF research system combines integrated device diagnostics based risk stratification algorithm with a guided work flow process handled by a centralized communication center to manage HF patients. Section 7.9.1 and 7.9.2 describe in details the methods that evaluate the effectiveness and safety of this system. Other characteristics of the system will be summarized using descriptive statistics.

7.8. Interim Analyses

In the INTERVENE-HF study, it is planned to have two interim analyses for all study objectives and one preliminary safety interim data analysis.

7.8.1. Interim Analyses

As indicated previously, all study objectives will be analyzed once the last enrolled subject has completed the 12-month follow-up visit and/or during interim analyses. If data are deemed to sufficiently characterize the study objectives by the sponsor at one of the interim analyses, enrollment and/or follow-up will be stopped.

7.8.1.1. Analysis Methods

It is planned to conduct the first interim analysis after 100 subjects are enrolled and have completed the baseline and programming visit. If the study continues after the first interim analysis, the second interim analysis will be conducted after 150 subjects are enrolled and have completed the baseline and programming visit. The same statistical methods will be used for both the interim and final analyses. See section 7.9 for details.

7.8.1.2. Determination of Patients/Data for Analysis

Patients to be analyzed for each study objective at the time of the interim analyses will be determined using the same rules as those described in Section 7.9 for the final analysis. The analysis sets will be per protocol.

7.8.2. Preliminary Safety Interim Data Analysis

This analysis is to summarize preliminary safety of PRN intervention. There is no statistical hypothesis for this analysis. The endpoint includes any adverse event reported per protocol.

7.8.2.1. Analysis Methods

The analysis will occur when 10 PRN interventions have been implemented and the last completed PRN intervention has been followed up for 14 days. Descriptive statistics such as count and percentage will be used. The seriousness and relatedness of adverse events will be based on the Clinical Events Committee (CEC) adjudication. If an adverse event has not been adjudicated by the CEC by the time of the analysis, study investigators' assessment (if available) will be considered. However, the goal of the study team is to have all the adverse events adjudicated for this analysis. The primary interest in the relatedness of adverse events includes but is not limited to safety issues leading to termination of PRN interventions, treatment-related adverse events after implementation of PRN interventions, and HF events occurring during or within 14 days after completion of PRN intervention. Adverse events occurring before and after PRN interventions will be summarized separately.

7.8.2.2. Determination of Patients/Data for Analysis

All the subjects who have completed the baseline and programming visit by the time of the preliminary safety interim data analysis will be included.

7.9. Evaluation of Objectives

7.9.1. Primary Objective #1

To characterize the effectiveness of the Integrated Diagnostic Medication Intervention Strategy in resolving subject risk.

7.9.1.1. Hypothesis

There is no statistical hypothesis for this objective.

7.9.1.2. Performance Criteria and Rationale

Performance criteria and corresponding rationale are not applicable for this objective.

7.9.1.3. Endpoint Definition

Once initiated, the Integrated Diagnostic Medication Intervention Strategy will be regarded as being effective if all the following criteria are met:

- The intrathoracic impedance of a subject recovers per defined criterion after completion of the Integrated Diagnostic Medication Intervention;
- The subject has no HF-related event (as adjudicated by the CEC) during or in the next 14 days after completion of the Integrated Diagnostic Medication Intervention;

  NOTE: Intervention for heart failure decompensation (HF event) is defined as an event requiring invasive intervention (i.e. IV diuretics, ultrafiltration, or equivalent) or inpatient hospitalization.

- The subject has not experienced any adverse events that are related to the Integrated Diagnostic Medication Intervention per CEC adjudication and require medical care.

7.9.1.4. Analysis Methods

For each episode that requires intervention as determined by this protocol, the effectiveness of Integrated Diagnostic Medication Intervention Strategy will be evaluated as a binary outcome variable, where 1 = effective and 0 = not effective. During the course of the study, a subject could experience more than one intervention. Therefore, a generalized linear model with the generalized estimating equation (GEE) method will be used to analyze this correlated binary data. The effectiveness rate and its 95% confidence interval (CI) will be calculated based on the log of odds estimated using the GEE.

In the main analysis, there will be no covariates in the generalized linear model, only intercept (β_0) will be estimated. Let π = probability (Integrated Diagnostic Medication Intervention Strategy is effective), then:

$$\beta_0 = \log\left(\frac{\pi}{1-\pi}\right)$$

To solve for π:

$$\pi = \frac{e^{\beta_0}}{1+e^{\beta_0}}$$

The analysis will be conducted using PROC GENMOD procedure in SAS similar to the following:

```
proc genmod data=effectiveness descending;
   class pt;
   model effective =   /dist=bin link=logit type3;
   repeated subject=pt /type=exch modelse;
   output  out=predict  predicted=pr_success lower=lower_CI upper=upper_CI;
run;
```

In this procedure, 'effective' is the outcome variable with 1=effective and 0=not effective. 'dist=bin' and 'link=logit' indicates this generalized linear model is based on a logistic regression for binomial distribution. In the 'repeated' statement, 'subject=pt' assumes observations from the same subject are correlated, and 'type=exch' means parameter coefficent(s) in the model will be estimated using GEE. 'predicted=' in the 'output' statement gives the estimated probability of Integrated Diagnostic Medication Intervention Strategy being effective, and its 95% confidence interval based on the parameter estimate of the intercept are from 'lower=' and 'upper='.

If it turns out that the majority of subjects included in the analysis received a single Integrated Diagnostic Medication Intervention, a sensitivity analysis will be conducted through the common logistic regression assuming independent interventions within the same subject. In addition, secondary analysis may be considered to explore the association of covariates such as NYHA class with the effectiveness endpoint.

7.9.1.5. Determination of Patients/Data for Analysis

All subjects who have received the Integrated Diagnostic Medication Intervention will be included. The analysis set is per protocol.

7.9.1.6. Sample Size and Measurement Precision

There are no data to help us predict the percentage of OptiVol crossings receiving Integrated Diagnostic Medication Intervention or the effectiveness rate of Integrated Diagnostic Medication Intervention Strategy. Different scenarios have been considered in Table 2 and Figure 2 to estimate the precision on measuring the effectiveness rate of Integrated Diagnostic Medication Intervention Strategy. Figure 2 is a visual illustration of Table 2.

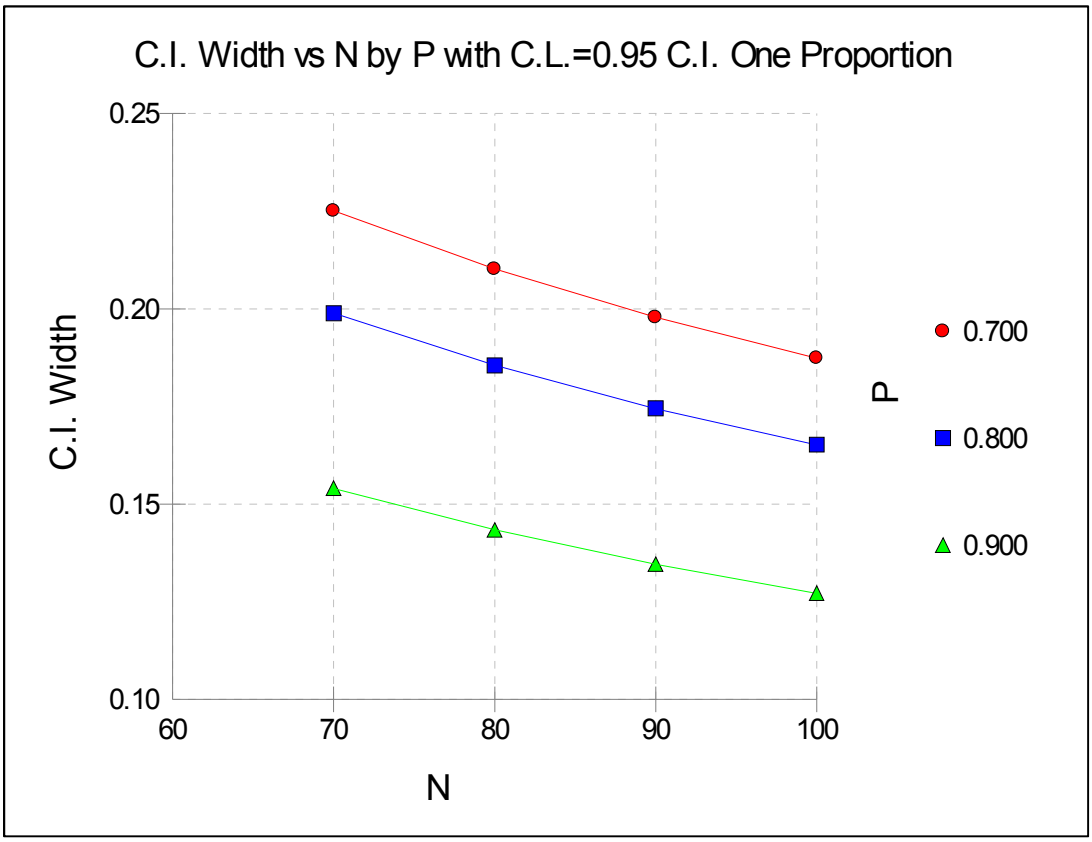
The width of 95% CI for the effectiveness rate represents the measurement precision. Using the first row in Table 2**Error! Reference source not found.** as an example, a total of 70 independent episodes with Integrated Diagnostic Medication Intervention produces a two-sided 95% CI with an actual width of 0.225 when the observed proportion of having effective treatment among those episodes is 0.7. This is based on the exact Clopper-Pearson confidence interval for one proportion assuming independent effectiveness status of Integrated Diagnostic Medication Intervention. Note that each episode is an OptiVol crossing that lead to the initiation of an Integrated Diagnostic Medication Intervention. Note also that for each scenario, we expect a narrower width (i.e. better precision) of 95% CI for the effectiveness rate in the framework of generalized linear model with GEE method. This is because GEE method takes the correlation among the effectiveness status of multiple episodes from the same subject into account, thus presumably results in a smaller standard error of the effectiveness rate.

Table 2: Measurement Precision of Effectiveness Rate for 70-100 Independent Episodes

Sample

Confidence Level	Size (N)	Actual Width	Proportion (P)	Lower Limit	Upper Limit
0.950	70	0.225	0.700	0.579	0.804
0.950	70	0.199	0.800	0.687	0.886
0.950	70	0.154	0.900	0.805	0.959
0.950	80	0.210	0.700	0.587	0.797
0.950	80	0.186	0.800	0.696	0.881
0.950	80	0.143	0.900	0.812	0.956
0.950	90	0.198	0.700	0.594	0.792
0.950	90	0.174	0.800	0.702	0.877
0.950	90	0.135	0.900	0.819	0.953
0.950	100	0.187	0.700	0.600	0.788
0.950	100	0.165	0.800	0.708	0.873
0.950	100	0.127	0.900	0.824	0.951

Figure 2: Illustration of Table 2



7.9.2. Primary Objective #2

To characterize the safety of the Integrated Diagnostic Medication Intervention Strategy in resolving the subject risk.

7.9.2.1. Hypothesis

There is no statistical hypothesis for this objective.

7.9.2.2. Performance Criteria and Rationale

Performance criteria and corresponding rationale are not applicable for this objective

7.9.2.3. Endpoint Definition

Once initiated, the Integrated Diagnostic Medication Intervention Strategy will be regarded as being safe if all the following criteria are met:

- The Integrated Diagnostic Medication Intervention applied to an episode is not terminated due to safety issues;

  NOTE: Safety issues include hypotension with/without patient contact and weight loss with patient contact.
- And, the Integrated Diagnostic Medication Intervention applied to an episode has not caused treatment-related adverse events (as adjudicated by the CEC).

7.9.2.4. Analysis Methods

Similar to the effectiveness endpoint of Integrated Diagnostic Medication Intervention Strategy, the safety endpoint of Integrated Diagnostic Medication Intervention Strategy is a correlated binary outcome with 1=safe and 0=not safe. It will be analyzed using a generalized linear model with GEE method. The safety rate and its 95% CI will be calculated based on the log of odds estimated using GEE.

Similar to Section 7.9.1.4, the analysis will be conducted using PROC GENMOD:

```
proc genmod data=safety descending;
   class pt;
   model safe =   /dist=bin link=logit type3;
   repeated subject=pt /type=exch modelse;
   output  out=predict  predicted=pr_success lower=lower_CI upper=upper_CI;
run;
```

where ‘safe’ is the outcome variable with 1=safe and 0=not safe.

Again, if it turns out that the majority of subjects included in the analysis received a single Integrated Diagnostic Medication Intervention, a sensitivity analysis will be conducted through the common logistic regression assuming independent interventions within the same subject. In addition, secondary analysis may be considered to explore the association of covariates such as NYHA class with the safety endpoint.

7.9.2.5. Determination of Patients/Data for Analysis

All subjects who have received the Integrated Diagnostic Medication Intervention will be included. The analysis set is per protocol.

7.9.2.6. Sample Size and Measurement Precision

The estimated precision of measuring effectiveness rate of Integrated Diagnostic Medication Intervention Strategy under different scenarios illustrated in Table 2 and Figure 2 are applicable to the safety rate as well. Using the first row in Table 2 as an example, a total of 70 independent episodes with Integrated Diagnostic Medication Intervention produces a two-sided 95% CI with an actual width of 0.225 when the observed proportion of having safe treatment among those episodes is 0.7.

7.9.3. Ancillary Objective

To characterize the occurrence of Heart Failure (HF) events in the study subjects.

7.9.3.1. Hypothesis

There is no statistical hypothesis for this objective

7.9.3.2. Endpoint Definition

The endpoint of this objective is the number of HF events per subject, as adjudicated by CEC.

7.9.3.3. Analysis Methods

The number of HF events will be summarized using frequency and percentage, and stratified by the implementation status of Integrated Diagnostic Medication Intervention (1=have ever received the intervention, 0=have never received the intervention). A Poisson regression model will be used to analyze the number of HF events, adjusting for the implementation of Integrated Diagnostic Medication Intervention. The fit of the Poisson regression model will be checked. If over dispersion is a concern, a negative binomial model may be considered.

PROC GENMOD procedure will be used to perform the Poisson regression analysis:

```
proc genmod data=HFevent;
class PRN;
model HFevent = PRN / dist=poisson link=log;
run;
```

where 'HFevent' is the number of HF events per subject, and 'PRN' refers to the implementation status of Integrated Diagnostic Medication Intervention with 1=have ever received the intervention and 0=have never received the intervention.

It is important to note, that those who have received the Integrated Diagnostic Medication Intervention might be sicker when compared to subjects who have never received the Integrated Diagnostic Medication Intervention, and therefore, are more likely to have HF events. Thus, the number of HF events before and after the intervention will be summarized using descriptive statistics for the subjects who have received such intervention.

7.9.3.4. Determination of Patients/Data for Analysis

All the enrolled subjects who have completed the baseline and programming visit will be included.

7.10. Safety Evaluation

Seriousness and relatedness of adverse events per CEC adjudication will be summarized using counts and percentage. Details of individual adverse events will be listed.

7.11. Changes to Planned Analysis

A screening visit was added after the CIP version 1. This led to an adjustment with the definition of 'enrolled subjects'. In CIP version 1, the study was to enroll 200 subjects assuming they all were eligible for the Integrated Diagnostic Medication Intervention. With CIP version 2 and 3, the study was to enroll 400 subjects where 200 subjects meeting the screening criteria that would proceed towards the baseline and programming visit. So, in the statistical considerations of CIP version 2 and 3, 'enrolled subjects' refers to the enrolled subjects who met screening criteria and completed the baseline and programming visit, i.e. those who were eligible for the Integrated Diagnostic Medication Intervention. This has been spelt out in the SAP.

8. Validation Requirements

At minimum, a Level II validation (i.e. peer review) is required when each study objective is analyzed at the first time (e.g. the first interim analysis). When the same analysis is repeated, the minimum requirement could be a Level III validation (i.e. self review).

9. References

N/A

10. Statistical Appendices

N/A