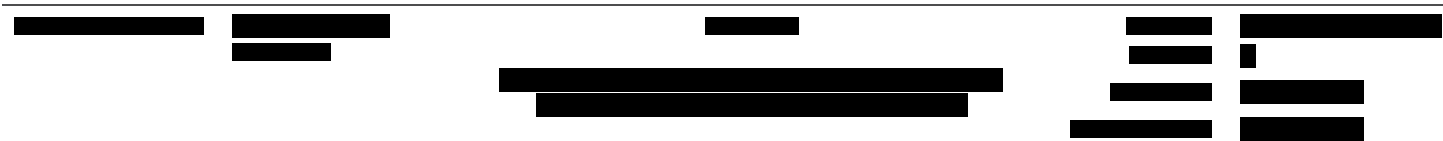
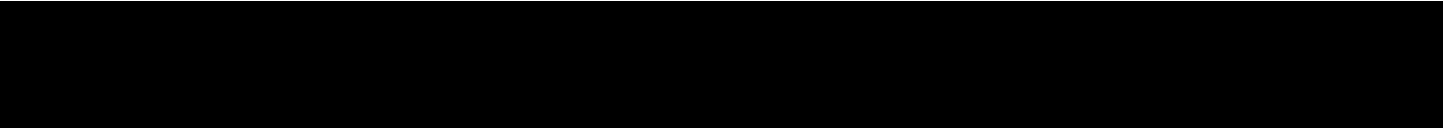


STUDY NUMBER: CR-RR-2020-005	PLAN VERSION: 2.0	PLAN VERSION DATE: 28 MAY 2024
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Statistical Analysis Plan: CR-RR-2020-005


Study Title:	Evaluation of Oscillation and Lung Expansion (OLE) using The Volara® System for treatment of respiratory complications in patients with neuromuscular disease in the home setting
Study Number:	CR-RR-2020-005
Study Phase:	Post Market
Study Design	The study is a multi-center, non-randomized, open-label, decentralized pilot study using an observational design comparing a retrospective control period to an active treatment period to evaluate the impact of Oscillation and Lung Expansion (OLE) to treat respiratory complications in 70 patients with neuromuscular disease in the home setting. The study will be conducted at 6 to 10 sites in the United States.
Product Name:	The Volara® System
Indication:	The Volara® System is an FDA 510k cleared device (k192143), powered by an internal blower, that delivers oscillation and lung expansion (OLE) therapy using both continuous high-frequency oscillation (CHFO) and continuous positive expiratory pressure (CPEP). The therapy is indicated for mobilization of secretions, lung expansion therapy and the treatment and prevention of pulmonary atelectasis. The device can also provide





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supplemental oxygen when used with
an oxygen supply.

Statistician: 

Sponsor: Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, Illinois 60015, USA

Responsible Medical Officer: 

Final Date: 28 MAY 2024

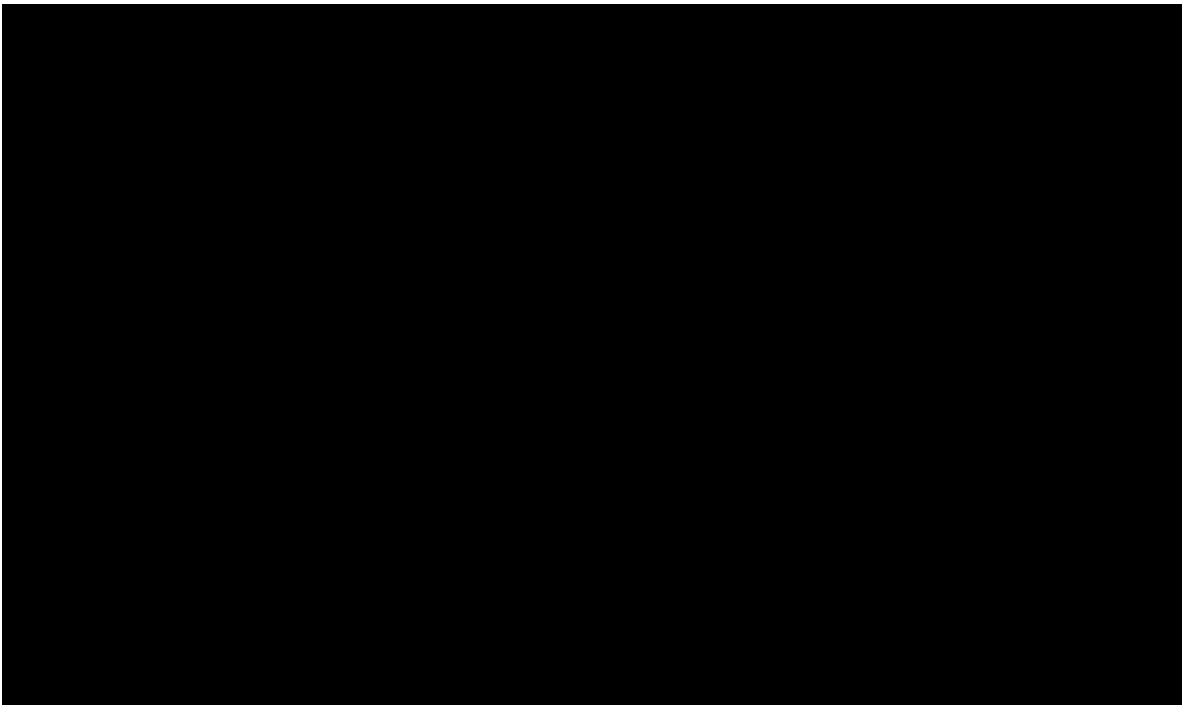


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[illegible]

Study Title:	Evaluation of Oscillation and Lung Expansion (OLE) using The Volara® System for treatment of respiratory complications in patients with neuromuscular disease in the home setting
Study Number:	CR-RR-2020-005
Statistician:	

I have read this report and confirm that to the best of my knowledge it accurately describes the planned analyses of the study.

Prepared by and Date : XXXXXXXXXX

Worldwide Medical, Baxter Healthcare Corporation

Approved by and Date: _____

Worldwide Medical, Baxter Healthcare Corporation

Approved by and Date: _____

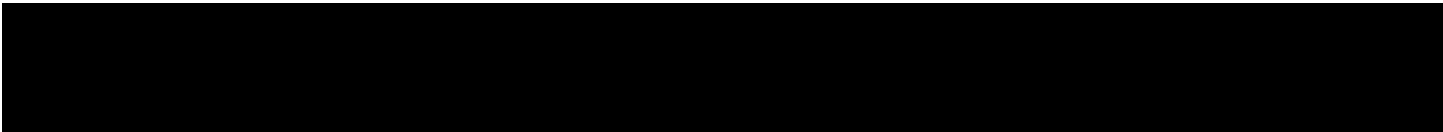
Worldwide Medical, Baxter Healthcare Corporation

Approved by and Date: _____

Worldwide Medical, Baxter Healthcare Corporation

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ATS	American Thoracic Society
BMI	body mass index
CI	confidence interval
eCRF	electronic case report form
ED	emergency department
FAS	full analysis set
FDA	Food and Drug Administration
ICF	informed consent form
ICU	intensive care unit
ID	identification
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MIP	maximal inspiratory pressure
N	sample size
NMD	neuromuscular disease
OLE	oscillation and lung expansion
PCF	peak cough flow
PPS	per protocol set
PT	preferred term
QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SD	standard deviation



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SOC	system organ class
SPO2	oxygen saturation
SRI	severe respiratory insufficiency
SS	safety analysis set
SVC	slow vital capacity
US	United States
WHO	World Health Organization

1. STUDY DETAILS

This statistical analysis plan (SAP) is provided to describe the framework for the reporting, summarization, and statistical analysis methodology of the safety and efficacy parameters measured throughout the study. It is based on clinical trial protocol CR-RR-2020-005 Revision D, dated 11 MAY 2022.

1.1 Study Objectives and Endpoints

The objective of the study is the evaluation of the impact of Oscillation and Lung Expansion (OLE) therapy to treat respiratory complications of neuromuscular disease in patients.

Primary Endpoint:

- Frequency of exacerbations of pulmonary disease requiring medical intervention (e. g. one or more of the following):
 - Hospitalization
 - Emergency Department (ED) Visit
 - Unscheduled Antibiotics for Respiratory Infection
 - Unscheduled outpatient visit

Secondary Endpoints:

- Pulmonary function tests
 - Slow Vital Capacity (SVC)
 - Peak Cough Flow (PCF)
 - Resting Oxygen Saturation (SPO2)
 - Maximal Inspiratory Pressure (MIP)
- Number of hospital admissions
- Total hospital length of stay
- Number of intensive care unit (ICU) admissions

1.2.1 Overall Study Design and Plan

The study will be a multi-center, non-randomized, open-label, pilot study. It is a decentralized study using an observational design comparing a retrospective control period to an active treatment period. Approximately 70 patients will be enrolled from identified clinics that currently treat neuromuscular disease (NMD) patients. All enrolled subjects will receive Oscillation and Lung Expansion (OLE) treatment during the active treatment period. Subjects will be recruited from 6 to 10 sites in the United States (US).

1.2.2 Determination of Sample Size

1.2.3 Blinding

1.2.4 Schedule of Visits and Procedures

1.3 Analysis Populations

1.3.1 Definition of Analysis Populations

Deviations that could be considered for exclusion in a PPS analysis

- Treatment errors
- Use of prohibited medication known to influence the primary endpoint
- Key exclusion criteria such as:

- Diagnosis with rapidly progressing NMD such as certain types of Motor Neuron Disease (MND)
- Requirement for continuous mechanical ventilation
- Anticipated requirement for respiratory related hospitalization within the next six months
- History of pneumothorax within past 6 months
- History of hemoptysis requiring embolization within past 12 months
- Home use of OLE therapy within the past 12 months
- Inability or unwillingness to perform OLE therapy or study procedures as required

Deviations that should not lead to exclusion of data in a PP analysis

- Patients who violate inclusion/exclusion criteria relating to patient safety
- Issues with documentation of informed consent
- Issues with SAE reporting

Safety analysis set (SS): the set of all patients who have received OLE therapy with The Volara® System.

1.3.2 Protocol Deviations

Protocol deviations will be summarized for all patients in the FAS pooled together. Patient counts and number of deviations will be presented for minor protocol deviations, major protocol deviations, and for each category of major protocol deviation.

Protocol deviations will also be listed for the FAS. The listing will include patient ID, age, verbatim description of the protocol deviation, the assigned category of protocol deviation, and major/minor status.

1.3.3 Safety Variables

1.3.3.1 Adverse Events

The safety profiles are evaluated by:

- Adverse Events (AEs) / Adverse Device Effects (ADE)

Change from baseline variables will be calculated as the post-treatment value minus the value at baseline.

2.1.2 Study Periods

The study periods include the 12-month pre-treatment historical control period, 6-month pre-treatment historical control period, and the active treatment period. The active treatment period begins once a subject has started therapy with The Volara® System.

2.1.3 Visit Windows

The study visits for the active treatment period can be obtained from the eCRF and need not be derived programmatically. The visits will be displayed as: Baseline, 1-month, 2-month, 3-month, 4-month, 5-month, 6-month.

Results from unscheduled study visits will not be included in table summaries. These values will only be presented in the listings.

2.1.4 Completion and Discontinuation

A patient is considered to have completed the study when he/she ceases active participation in the study because the patient has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations). Any other cases are classified as discontinuation.

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation electronic case report form (eCRF), including:

- Protocol Violation
- Withdrew Consent
- Lost to Follow-Up
- Adverse Device Effect
- Other

Regardless of the reason, all data available for the patient up to the time of completion/discontinuation should be recorded on the appropriate eCRF.

2.2 Patient Disposition

Patient disposition will be summarized and will include:

- Number of patients screened
- Number of patients who screen fail. These patients will also be summarized by primary reason for screen failure from the study. The percentage associated with each reason will have the total number of patients who screen fail as the denominator.
- Number of patients enrolled
- Number of patients included in chart review for 12-month pre-treatment period
- Number of patients eligible for treatment
- Number of patients treated with study device
- Number of patients in the FAS
- Number of patients in the PPS
- Number of patients in the SS
- Number of patients who completed the study
- Number of patients who discontinued (withdrew early) from the study. These patients will also be summarized by primary reason for withdrawal from the study. The percentages associated with each reason for early withdrawal will have the total number of patients who withdrew early as the denominator.

A listing of all patients enrolled in the study will be created including patient ID, age, sex, completion status, reason for discontinuation (if applicable), and the number of days that the patient remained in the study. The number of days the patient was in the study will be calculated using the following:

$$(\text{Date of Study Completion/Discontinuation} - \text{Date of Enrollment}) + 1$$

2.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized descriptively for the FAS population. A listing will also be provided for this population.

2.3.1 Demographics

Demographics (age, race, ethnicity, sex) will be summarized descriptively.

2.3.2 Other Baseline Characteristics

Baseline characteristics including height, weight, and BMI will be summarized descriptively.

2.3.3 Medical History

All neuromuscular disease and pulmonary disease medical history will be listed.

2.3.4 Concomitant Medications

All pulmonary and respiratory related concomitant medications will be listed.

2.4 Endpoint Analyses

2.4.1 Primary Endpoint

The primary endpoint analysis will be carried out on the FAS with a supportive analysis performed on the PPS.

2.4.1.1 Derivation of Primary Endpoint

Exacerbations of pulmonary disease are defined as changes in respiratory status requiring intervention. Documentation of pneumonia or respiratory infection, change in chest x-ray, changes in requirement for respiratory support necessitating any of the interventions below will be considered an exacerbation of pulmonary disease:

- Hospitalization
- ED Visit
- Unscheduled Antibiotics for Respiratory Infection
- Unscheduled outpatient visit

Total hospital length of stay will be determined for each study subject by calculating the number of days spent in the hospital for each admission, from time of admission to time of discharge. Date of admission and date of discharge will be recorded in the data for each study period. The sum of all hospital days for each subject will be calculated for the 6-month pre-treatment and active treatment periods. The number of days spent in the hospital for each admission will be calculated as follows (standardized to the number of days):

Total ICU length of stay will be analyzed descriptively by study period (active treatment and 6-month pre-treatment) using n, mean, standard deviation, minimum, median, and maximum.

The number of antibiotic use days for pulmonary exacerbation will be analyzed descriptively by study period (active treatment and 6-month pre-treatment) using n, mean, standard deviation, minimum, median, and maximum.

QOL assessments for the overall Respiratory Complaints scale score will be analyzed descriptively at each time-point (Baseline, 1-month, 3-month, 6-month) using n, mean, standard deviation, minimum, median, and maximum. Change from baseline values will also be presented in a similar manner. Individual responses to each Respiratory Complaints survey question will be summarized descriptively using frequencies and percentages. The Severe Respiratory Insufficiency Questionnaire guidance for scoring the Respiratory Complaints scale will be implemented.¹

Guidance for scoring

Please provide the following values for each item:

completely untrue	=>	1
mostly untrue	=>	2
sometimes true	=>	3
mostly true	=>	4
always true	=>	5

The majority of items need to be recoded following the instructions given below:

value		recoded value	Items which need to be recoded:
1	→	5	1, 2, 4, 5, 6, 8, 11, 12, 13, 14, 15, 16, 17, 19, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31, 34, 35, 38, 39, 40, 42, 43, 45, 46, 47, 48.
2	→	4	
3	→	3	
4	→	2	
5	→	1	

Next, the scales need to be calculated as indicated below. For this purpose at least 50% of the items per scale must be correctly addressed. Please find the item number indicated in brackets [a, b, c.....]. This process of transformation produces a score between 0 and 100 with higher values indicating a better health-related quality of life according to content of the scale.

Respiratory Complaints

$$SRI - RC = \frac{\text{Mean} [2,5,12,19,22,24,25,29] - 1}{4} \bullet 100$$

[illegible]

- Adverse event listings will be sorted by patient ID, and adverse event start date. They will include SOC, PT, verbatim term, adverse event start and end date and its duration, relationship to study device, severity, action taken, and seriousness.

Table Number	Analysis Population	Table Name
14.1.1	N/A	Patient Overview
14.1.2	FAS	Patient Disposition

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14.1.3	FAS	Protocol Deviations
14.1.4	FAS	Categorical Demographic and Baseline Characteristics
14.1.5	FAS	Continuous Demographic and Baseline Characteristics
14.2.1.1	FAS	Primary Endpoint: Exacerbations of Pulmonary Disease Requiring Medical Intervention
14.2.1.2	PPS	Primary Endpoint: Exacerbations of Pulmonary Disease Requiring Medical Intervention
14.2.2	FAS	Pulmonary Function Tests
14.2.3	FAS	Medical Interventions for Exacerbations of Pulmonary Disease
14.2.4.1	FAS	Quality of Life Assessment - Respiratory Complaints Overall Score
14.2.4.2	FAS	Quality of Life Assessment - Respiratory Complaints
14.2.5.1	FAS	Patient/caregiver Satisfaction with Prior Therapy at Baseline
14.2.5.2	FAS	Patient/caregiver Satisfaction with The Volara® System
14.3.1.1.1	SS	Summary of Adverse Events
14.3.1.1.2	SS	Treatment Emergent Adverse Events by SOC and Preferred Term
14.3.1.1.3	SS	Serious Treatment Emergent Adverse Events by SOC and Preferred Term
14.3.1.1.4	SS	Treatment Emergent Adverse Events Related to Study Device by SOC and Preferred Term
14.3.1.1.5	SS	Serious Treatment Emergent Adverse Events related to Study Device by SOC and Preferred Term
14.3.1.1.6	SS	Treatment Emergent Adverse Events Leading to Discontinuation by SOC and Preferred Term
14.3.1.1.7	SS	Treatment Emergent Adverse Events Leading to Death by SOC and Preferred Term

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14.3.1.1.8	SS	Treatment Emergent Adverse Events in $\geq 5\%$ of Patients by SOC and Preferred Term
14.3.1.2.1	SS	Treatment Emergent Adverse Events by SOC, Preferred Term, and Severity
14.3.1.2.2	SS	Serious Treatment Emergent Adverse Events by SOC, Preferred Term, and Severity
14.3.1.3.1	SS	Treatment Emergent Adverse Events by SOC, Preferred Term, and Relationship with Study Device
14.3.1.3.2	SS	Serious Treatment Emergent Adverse Events by SOC, Preferred Term, and Relationship with Study Device

Listing Number	Analysis Population	Listing Name
16.2.1	N/A	Patient Disposition
16.2.2	FAS	Protocol Deviations
16.2.3.1	N/A	Patient Overview
16.2.4.1	FAS	Demographic and Baseline Characteristics
16.2.4.2	FAS	Medical History
16.2.4.3	FAS	Pulmonary Concomitant Medications
16.2.4.4	FAS	Respiratory Support and Respiratory Concomitant Medications
16.2.6.1	FAS	Exacerbations of Pulmonary Disease Requiring Medical Intervention
16.2.6.2	FAS	Pulmonary Function Tests
16.2.6.3	FAS	Medical Interventions for Exacerbations of Pulmonary Disease
16.2.6.4.1	FAS	Quality of Life Assessment - Respiratory Complaints Overall Score
16.2.6.4.2	FAS	Quality of Life Assessment - Respiratory Complaints
16.2.6.5	FAS	Patient/caregiver Satisfaction with Prior Therapy and The Volara® System
16.2.7.1.1	SS	Pre-Treatment Adverse Events
16.2.7.1.2	SS	Treatment Emergent Adverse Events
16.2.7.1.3	SS	Serious Pre-Treatment Adverse Events

