Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	REACH: A multicenter trial of endoscopic radiofrequency ablation for macroscopically flat type high-grade and medium-grade intraepithelial squamous neoplasia using the Barrx™ Flex Radiofrequency Ablation System
Clinical Investigation Plan Identifier	COVB3050540
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	New Document	[redacted]
2.0	• Add document version/date on header and footer • Delete document reference # • Revise the content based on the CIP V4.0	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
BQE	baseline qualifying endoscopy
CFDA	China Food and Drug Administration
CICAMS	Cancer Hospital/Institute of the Chinese Academy of Medical Sciences
CR	complete response
CRF	case report form
CT	computed tomography
EC	ethics committee
ESD	endoscopic submucosal dissection
EMR	endoscopic mucosal resection
ER	Endoscopic resection

ESCC	esophageal squamous cell carcinoma
ESCN	esophageal squamous cell neoplasia
EUS	endoscopic ultrasound
GCP	good clinical practice
HGIN	high-grade intraepithelial neoplasia
ICF	informed consent form
INR	international normalized ratio
IRB	institutional review board
ISO	International Organization for Standardization
LGIN	low-grade intraepithelial neoplasia
MGIN	mid-grade intra-epithelial neoplasia
RFA	radiofrequency ablation
SAE	serious adverse event
SADE	serious adverse device effect
SCCA	squamous cell carcinoma
TA	treated area
USADE	unanticipated serious adverse device effect
USL	unstained lesion
VAS	visual analog scale
WLE	white light endoscopy

3. Introduction

The REACH study is a multicenter, prospective cohort clinical study to assess (i) the effectiveness of radiofrequency ablation (RFA) using the Barrx™ Flex Radiofrequency Ablation System in the eradication of diseased epithelium at 12 months post-treatment, and (ii) the durability of established eradication of disease during 5 years of follow-up, in subjects with early ESCN, defined as MGIN or HGIN.

This statistical analysis plan (SAP) provides a detailed description of the statistical methods and procedures to be implemented during the analysis of the REACH study. The document is intended to support the generation of a Clinical Study Report (CSR) for the Clinical Investigational Plan (CIP) v4 , dated July 03, 2017.

4. Study Objectives

4.1. Primary Objective(s)

The primary objective is to measure the effectiveness of the Barrx™ Flex Radiofrequency Ablation System in the eradication of diseased epithelium at 12 months post-treatment in subjects with macroscopically flat-type – defined as Paris type 0-IIb on white light endoscopy (WLE) and Lugol's endoscopy- early esophageal squamous cell neoplasia (ESCN), defined as moderate-grade squamous intraepithelial neoplasia (MGIN) or high-grade squamous intraepithelial neoplasia (HGIN).

4.2. Secondary Objective(s)

The secondary objectives are to assess safety, to measure durability of complete response during long-term follow-up, and to measure overall ESCC progression and associated mortality after treatment.

5. Investigation Plan

This multicenter, prospective cohort clinical study will evaluate a subject population having macroscopically flat type (type 0-IIb) esophageal lesions with histological evidence of MGIN or HGIN in biopsy specimens obtained from the esophagus.

For patients who meet all of the inclusion criteria and none of the exclusion criteria, step-wise endoscopic RFA will be performed in 3 month intervals per the Patient Flow Diagram (Figure 1). Each decision point in the flow diagram regarding endoscopy, staining, RFA, biopsy, and patient advancement to subsequent study visits is fully delineated in the diagram. The study primary endpoint biopsies are obtained at 12 months from the initial treatment.

Subject's duration of involvement in the study is expected to be up to 60 months (estimated based on primary RFA plus 12 months of treatment phase and 48 months of follow-up). The overall study is expected to last a total of 6 years if enrollment is completed in a timely manner.

Patients with a CR at 12 months will enter the follow-up phase as described in figure 2 and section 9.4.2 of the CIP..

Patients with residual ESCN at 12 months will be defined as treatment failures, and will undergo escape treatment within 3 months (+/- 4 weeks). If CR will be re-established after escape treatment, patients will stay in the trial and will be followed-up and treated if necessary, according to figure 2 of the CIP. If non-endoscopic treatment is performed at 12 months, or if pathology indicates non-endoscopic treatment, patients won't be treated and/or followed-up according to the study protocol, but will still be followed-up until 5 years after baseline to assess secondary endpoints.

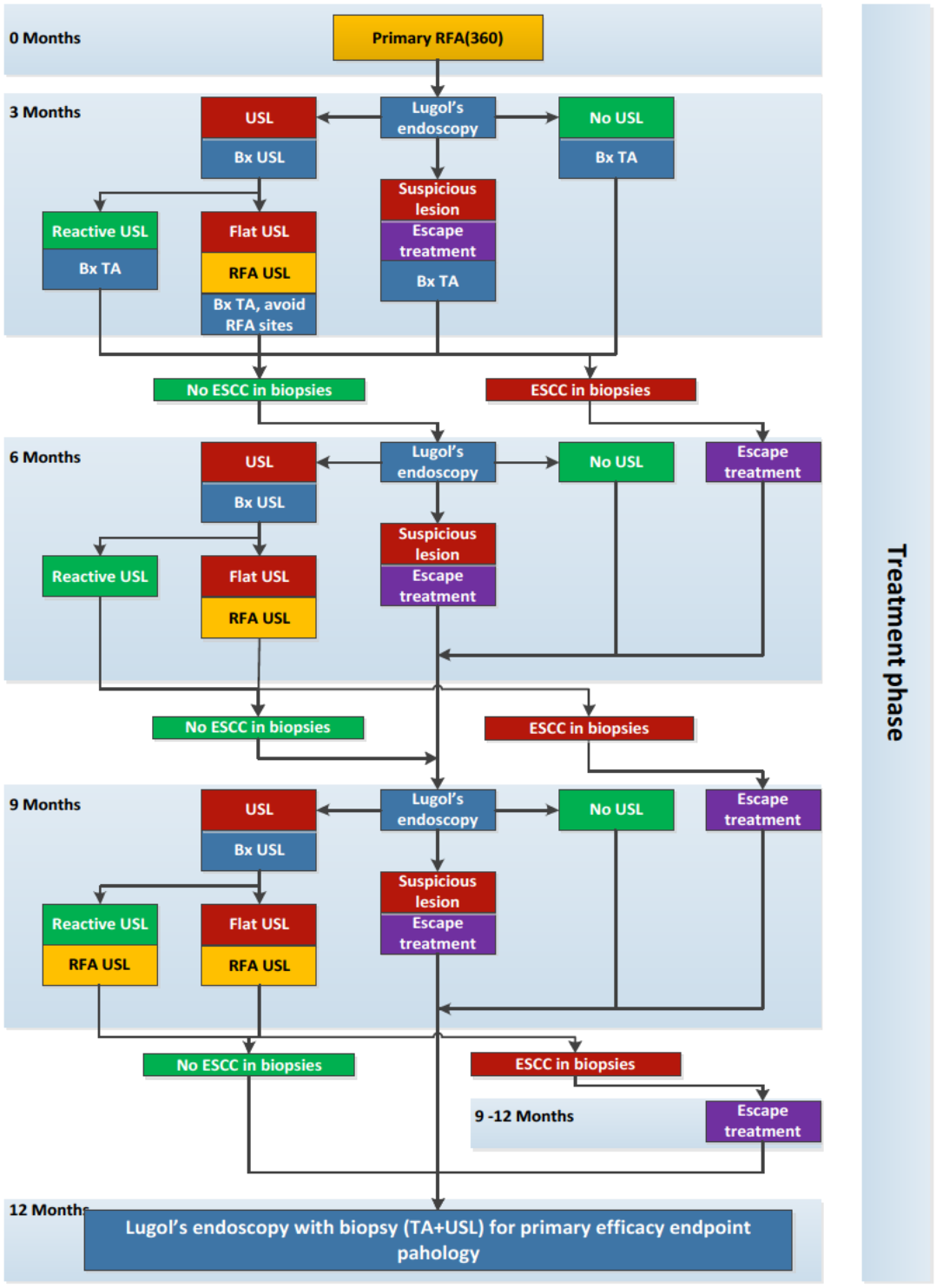

Figure 1. Decision Tree for Subject Flow through Treatment (adapted from He et al., 2014)

6. Determination of Sample Size

The proposed sample size of 100 subjects is considered adequate for the study objective. From published data, a complete response rate of 80%-90% of the RFA treatment is expected at 12 months post-treatment for the subject population (He et al., 2015). With 100 study subjects, a precision (half 95% CI width) of 6%-8% will be achieved for estimating the primary endpoint of complete response rate. For safety, a sample of 100 subjects will have greater than a 99% chance to detect a rare event of 5% incidence or an 85% chance to detect a rare event of 2% incidence. The NIH defines an acceptable dropout rate at 20% or less. However, over 70% of all high-quality clinical studies in China had a dropout rate lower than 10%. For example, the dropout rate at CICAMS was 3% in a previous ESCN study.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Subject disposition (e.g., number completing the study, number lost-to-follow-up) will be summarized with frequency tables.

7.1.2. Clinical Investigation Plan (CIP) Deviations

A CIP deviation is defined as an event where the Investigator or study personnel did not conduct the study according to the CIP. Deviations shall be reported regardless of whether medically justifiable or taken to protect the subject in an emergency.

The total number of protocol deviations and total number of subjects with deviations will be provided by deviation type for all enrolled subjects. Number of protocol deviations and number of subjects with deviations by each investigational site will also be provided.

7.1.3. Analysis Sets

The primary analysis will be based on a per-protocol basis. Subjects who enrolled into the study (a patient is defined as enrolled after introduction of RFA catheter at primary RFA), and had valid study outcomes with no major protocol violations will be included in the analysis. Only the 100 cohort patients will be included for primary analysis.

Additional analyses based on subsets of the study subjects or combining run-in subjects may be performed to provide further support to the study results.

All enrolled study subjects will be included in the safety analysis.

7.2. General Methodology

In general, descriptive statistics will be used to summarize study outcomes. For continuous variables, the number of available observations, mean, standard deviation, median, minimum and maximum values will be provided. For categorical variables, frequency and percentage will be used. Unless otherwise specified, statistical assessments will be based on two-sided tests at an alpha level of 0.05, which include Student-t or Wilcoxon rank-sum test for continuous variables, and Chi-square or Fisher's exact test for categorical variables. Other statistical methods may be used as appropriate. Statistical analysis will be performed using SAS Version 9.2 or higher (SAS Institute Inc., Cary, NC) or other valid statistical software.

7.3. Center Pooling

This is a multi-center clinical study, with standardization of subject enrollment, data entry and adverse event reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms. All the data will be pooled for reporting.

7.4. Handling of Missing Data and Dropouts

The number and proportion of subjects eligible for and compliant with each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated with reasons for withdrawal. Sensitivity analysis for discontinuations or missing data will be conducted to assess the robustness of study results which may include last observation carried forward, multiple imputations, and tipping point analysis, as appropriate.

7.5. Adjustments for Multiple Comparisons

Considering the feasibility nature of the study, no multiplicity adjustment is considered.

7.6. Demographic and Other Baseline Characteristics

The demographic, baseline charactersitics, patient history, BQE and pathology will be summarized. Discrete variables will be presented using frequency distributions and cross tabulations. For continuous variables, statistics will include the number of observations, mean, standard deviation, median, minimum, and maximum.

7.7. Treatment Characteristics

The procedure characteristics, including primary RFA and additional RFA as well as the endoscopy information will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, median, minimum and maximum) and frequency tables for discrete variables.

7.8. Interim Analyses

Efficacy and safety will be specifically assessed after enrollment of 25 and 50 patients. Additional interim data analyses may be performed, as needed, for requirements related to abstract submission, IRB requests, or DSMB requests.

7.9. Evaluation of Objectives

The primary effectiveness will be measured as the percentage of subjects with complete response within the treatment area. The response rates and 95% confidence intervals will be summarized. Run-in subjects, defined as the first 5 subjects enrolled per endoscopist, will be summarized separately.

7.9.1. Primary Endpoint

The primary endpoint is the percentage of subjects with "complete response (CR)", defined as complete eradication of squamous histological abnormalities (MGIN or worse) within the treatment area (TA) at 12 months after the initial treatment session (per-protocol analysis). Patients who show ESCC in biopsies or resection samples are defined as failures for this endpoint, even if subsequent biopsies at 12 months indicate CR.

The primary study hypothesis is that 80% of treated subjects will have a complete response.

Patients

All 100 patients that are included in the cohort will be assessed for the primary endpoint. The run-in patients will not be included for the primary endpoint analyses.

Biopsies
Only biopsies obtained from the original USL bearing portion of the esophagus (the treatment area) will be used in the analysis for the primary endpoint at 12 months. At 12 months, MGIN or worse noted in any biopsy from outside this region are not considered failures of ablation for the purposes of the primary endpoint.

7.9.2. Secondary Endpoint(s)

1. The percentage of subjects with a sustained CR during long-term follow-up, defined as patients with a CR at 12 months that sustained this absence of squamous abnormalities (MGIN or worse) during all subsequent FU endoscopies through 60 months.
2. Proportion of patients with CR after primary RFA, defined as absence of MGIN or worse in any of the biopsies from the treatment area, at the three month visit.
3. Proportion of patients demonstrating progression within the treatment area (TA), defined as detection of ESCC in biopsy or resection specimen at any time within the first 12 months.
4. Occurrence of serious adverse device effects (SADE) after RFA treatment.
5. Proportions of "run-in" subjects, defined as the first 5 subjects enrolled per endoscopist, with a CR at 3 and 12 months after the initial treatment session, and with sustained CR during follow-up.

6. Proportion of patients with CR at 12 months who subsequently developed recurrent disease in TA, defined as MGIN or HGIN for patients with MGIN at baseline, and MGIN or HGIN for patients with HGIN at baseline.
7. Proportion of patients with CR at 12 months who subsequently developed progressive disease in TA, defined as ESCC in biopsy or resection specimen.
8. Durability after reiterative RFA, defined as proportion of patients with a CR at 12 months who sustain or re-establish CR upon reiterative RFA treatment sessions during FU.
9. Durability after additional endoscopic treatment, defined as proportion of patients with CR at 12 months who sustain or re-establish CR upon endoscopic treatment (RFA and eventually in combination with EMR or ESD) during FU.
10. Esophageal squamous cell cancer mortality.
11. Proportion of patients demonstrating MGIN or worse outside the TA during treatment phase or follow-up.

7.10. Safety Evaluation

For safety analyses, adverse events will be summarized using frequency counts and percentages. Descriptive statistics will be provided by event type, severity and relationship to study procedures and devices. Event rates along with 95% confidence intervals will be provided based on subject or event. Individual listings of adverse events, including event type, start date, duration, severity, and device-relatedness will be provided as appropriate.

Safety will be closely monitored during the course of the study. If the incidence of severe or serious adverse events is higher than expected (stricture/stenosis requiring dilation >10%, any mucosal laceration requiring intervention, any perforation, any bleed or infection requiring intervention, or any other severe or serious unexpected adverse event), or a statistically significant trend is observed, the medical advisors will notify the sponsor, review all available data, and make a recommendation regarding continuation of the study.

7.11. Additional Analyses

Subgroup analysis will be performed for potential confounding factors such as study center, age, gender and disease severity (moderate vs. high grade). A multivariate analysis will be conducted to further examine the predictors of compete response. Potential predictive factors to be considered will include but not limited to: age, gender, and grade (MGIN vs. HGIN).

The number and proportion of subjects eligible for and compliant with each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated with reasons for withdrawal. Sensitivity analysis for discontinuations or missing data will be conducted to assess the robustness of study results which may include last observation carried forward, multiple imputations, and tipping point analysis, as appropriate.

For study monitoring and learning curve evaluations, summary data will be provided for the primary and secondary endpoints between the first half of subjects enrolled versus the second half of subjects

enrolled for each site and overall. Furthermore, CR-rates at 3 and 12 months for the run-in cases will be analyzed.

8. Validation Requirements

Primary and secondary endpoints will be validated by level I validation and the rest of the tables, listings and figures will be validated by level II validation.

Level I: The peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer.

Level II: The peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

9. Reference

- He S, Bergman J, Zhang Y, Weusten B, Xue L, Qin X, et al. Endoscopic radiofrequency ablation for early esophageal squamous cell neoplasia: report of safety and effectiveness from a large prospective trial. Endoscopy. 2015;47(5):398-408. doi: 10.1055/s-0034-1391285. PubMed PMID: 25668428.