Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study 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
Study Product Name	Barrx™ Flex Radiofrequency Ablation System
Sponsor/Local Sponsor	**US Sponsor** [redacted] Director Global Clinical Affairs, Early Technologies Medtronic, Minimally Invasive Therapies Groups [redacted] [redacted] Clinical Project Manager | Clinical Affairs Medtronic, Minimally Invasive Therapies Groups [redacted] **China Sponsor** Medtronic MITG, Greater China [redacted]
Document Version	7.0, 15-Mar-2018

Lead Investigator(s)	[redacted] Cancer Institute and Hospital Chinese Academy of Medical Sciences (CICAMS) Beijing, People's Republic of China [redacted]

Confidentiality Statement

1. Investigator Statement

Study product Name	Barrx™ Flex Radiofrequency Ablation System
Sponsor	Medtronic, Minimally Invasive Therapies Groups, Early Technologies
Clinical Investigation Plan Identifier	COVB3050540
Version Number/Date	Version 7.0/15-Mar-2018
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to comply with Declaration of Helsinki, ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), and China regulations. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.	
Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

Table of Contents

1. Investigator Statement 3

Table of Contents 4

2. Glossary 7

3. Synopsis 9

4. Introduction 14

4.1. Background 14

4.2. Purpose 16

5. Objectives and Endpoints 17

5.1. Objectives 17

5.1.1. Primary Objective(s) 17

5.2. Endpoints 17

5.2.1. Primary Endpoint 17

5.2.2. Secondary Endpoint(s) 18

6. Study Design 18

6.1. Duration 18

6.2. Rationale 19

7. Product Description 20

7.1. General 20

7.2. The Barrx™ Circumferential Radiofrequency Ablation System 20

7.3. The Barrx™ Focal Radiofrequency Ablation System 21

7.4. Regulatory Approval in China 21

7.5. Product Training Requirements 21

7.6. Study Supplies and Device Accountability 21

8. Selection of Subjects 22

8.1. Study Population 22

8.2. Subject Enrollment 22

8.3. Inclusion Criteria 22

8.4. Exclusion Criteria 24

9. Study Procedures 25

9.1. Schedule of Events 25

9.1.1. Tissue Specimen Processing and Histopathological Interpretation 27

9.2. Subject Screening 28

9.3. Subject Consent 29

9.4. Treatment Assignment 29

9.4.1. Treatment Phase 29

9.4.2. Follow-up Phase 36

9.4.3. Escape treatment: Endoscopic (EMR or ESD) or Non-Endoscopic Therapy during Treatment or Follow-up Phase 37

9.5. Assessment of Efficacy 39

9.6. Assessment of Safety 39

9.7. Recording Data 39

9.8. Deviation Handling 40

9.9. Subject Withdrawal or Discontinuation 40

9.10. Definitions 41

10. Risks and Benefits 42

10.1. Potential Risks 42

10.2. Potential Benefits 43

10.3. Risk-Benefit Rationale 43

11. Adverse Events and Device Deficiencies 43

11.1. Definitions/Classifications 43

Adverse Event (AE) 43

Serious Adverse Event (SAE) 43

Adverse Device Effect (ADE) 44

Serious Adverse Device Effect (SADE) 44

Adverse Event Severity Classification 44

Adverse Event Relationship Classification 45

Adverse Event Outcome Classification 47

11.2. Reporting of Adverse Events 47

Notification to Authorities 48

11.3. Device Deficiencies 49

12. Data Review Committees 49

Independent Medical Advisors 49

13. Statistical Design and Methods 49

13.1. General Principles 49

13.2. Sample Size Determination 50

13.3. Analysis Populations 50

13.4. Effectiveness Analysis 50

13.5. Safety Analysis 50

13.6. Additional Analyses 51

14. Ethics 51

14.1. Statement(s) of Compliance 51

14.2. Protocol Compliance 52

15. Study Administration 52

15.1. Monitoring 52

15.2. Data Management 53

15.3. Direct Access to Source Data/Documents 53

15.4. Confidentiality 53

15.5. Liability 54

15.6. CIP Amendments 54

15.7. Record Retention 54

15.8. Publication and Use of Information 55

15.9. Suspension or Early Termination 56

16. References 56

17. Appendices 60

18. Version History 61

2. Glossary

Term	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

Term	Definition
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. Synopsis

Title	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 Study Type	Prospective, multi-center, non-blinded, single-arm (non-randomized) post-market study
Product Name	Barrx™ Flex Radiofrequency Ablation System
Sponsor	Medtronic, Minimally Invasive Therapies Groups, Early Technologies
Local Sponsor	Medtronic MITG, Greater China [redacted]
Indication under investigation	Esophageal squamous cell neoplasia (ESCN)
Investigation Purpose	To measure the effectiveness and durability of the Barrx™ Flex Radiofrequency Ablation System in the eradication of diseased epithelium at 12 months post-treatment and up to 5 years in subjects with early flat-type -defined as type 0-IIb lesions on White Light Endoscopy (WLE) and Lugol's chromoendoscopy- esophageal squamous cell neoplasia (ESCN), defined as moderate-grade squamous intraepithelial neoplasia (MGIN) or high-grade squamous intraepithelial neoplasia (HGIN).
Product Status	The Barrx™ Flex Radiofrequency Ablation System obtained China Food and Drug Administration (CFDA) approval in January 2015 for use in China. The Barrx Flex System is indicated for the clinical treatment of lesions limited to the mucosa in the gastrointestinal tract, specifically flat intraepithelial neoplasia and Barrett's esophagus.
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 early flat-type -defined as type 0-IIb lesions on White Light Endoscopy (WLE) and Lugol's chromoendoscopy- esophageal squamous cell neoplasia (ESCN), defined as moderate-grade squamous intraepithelial neoplasia (MGIN) or high-grade squamous intraepithelial neoplasia (HGIN).

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
Study Design	Multicenter, prospective cohort clinical trial in greater China. Patients will be followed-up for up to 5 years post initial RFA.
Sample Size	Up to 100 subjects will be included in the cohort, in up to 10 clinical sites. This is excluding up to 50 “run-in” subjects, defined as up to 5 patients for each endoscopist that is inexperienced with RFA or has had no onsite RFA training from CICAMS. Data from the run-in patients will be analyzed separately from the cohort.
Inclusion/Exclusion Criteria	Inclusion Criteria

	1. Patient is 18-85 years of age 2. Patient has evidence of ESCN, within the last 3 months, patient demonstrated a new diagnosis or a reconfirmed diagnosis of squamous MGIN or HGIN of the esophagus 3. On endoscopic examination, subject has at least one USL that measures at least 3 cm in at least one dimension and is greater than ¼ of the esophageal circumference and has MGIN or HGIN on biopsy, confirmed by central pathologist 4. All lesions in the esophagus are completely flat (Paris type 0-IIb), both on WLE and Lugol's chromoendoscopy 5. The maximum allowable linear length of "USL-bearing esophagus" is 12 cm 6. Baseline endoscopic ultrasound (EUS) (if applicable) shows no exclusionary findings for the trial 7. Computed tomography (CT) scan of chest and upper third of the abdomen (if applicable) shows no exclusionary findings for the trial 8. Based on the judgment of the study endoscopist, the patient is eligible for treatment, and follow-up endoscopy and biopsy as required by the protocol 9. EMR or ESD occurred > 3 months before enrollment, patients may be eligible for the study if procedure was curative (negative margins and no risk of lymph node involvement) and the patient has no other findings concerning for cancer 10. The subject is willing to provide written, informed consent to participate in this clinical study and understands the responsibilities of trial participation Exclusion Criteria 1. Patient has esophageal squamous cell carcinoma (ESCC) 2. Any non-flat (Paris type 0-I, 0-IIa, 0-IIc, 0-III) abnormalities anywhere in the esophagus 3. Any abnormalities under WLE, Lugol's or NBI that are suspicious for ESCC anywhere in the esophagus (e.g. 'pink sign' USL, defined as a color change after Lugol's staining: initially whitish yellow and pink 2-3 minutes later) 4. Any USL with MGIN or worse on biopsy outside the treatment area 5. Esophageal stricture preventing passage of a therapeutic endoscope 6. Prior endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) which occurred < 3 months before enrollment.

	7. Any esophageal dilation in the past 12 months 8. Any history of a non-squamous cell cancer of the esophagus, or any history of a squamous cell cancer of the esophagus (any stage) 9. Any previous ablative therapy within the esophagus (photodynamic therapy, multipolar electrical coagulation, argon plasma coagulation, laser treatment, cryoablation, or other) or any radiation therapy to the esophagus. 10. Previous esophageal surgery, except fundoplication without complications (i.e., no slippage, dysphagia, etc.) 11. Evidence of esophageal varices detected within last 6 months or at initial RFA procedure 12. Patient has active reflux esophagitis grade C or D. 13. Evidence of eosinophilic esophagitis on endoscopy and/or histology 14. Inner diameter of the esophagus measuring less than 18mm 15. Report of uncontrolled coagulopathy with international normalized ratio (INR) > 2 or platelet count <75,000 platelets per µL (note: a complete blood count is not required for all subjects in this study) 16. Patient is using anti-thrombotic agents that cannot be discontinued 7 days before and after therapeutic sessions 17. Patient has an implantable pacing device (examples: automated implantable cardioverter defibrillator, neurostimulator, cardiac pacemaker) and has not received clearance for enrollment in this study by specialist responsible for the pacing device 18. Patient has life expectancy less than 5 years 19. Patient suffers from psychiatric or other illness and/or has a known history of unresolved drug or alcohol dependency that would limit ability to comprehend or follow instructions related to informed consent, post- treatment instructions, or follow-up guidelines 20. Patient is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity) 21. The subject has participated in an investigational drug or device research study within 30 days of enrollment that would interfere with this study 22. Patient is pregnant or has plans to become pregnant in the ensuing 12 months (confirmation of non-pregnant status in women of child-bearing age and ability required with urine or blood test to be eligible)
Study Procedures and Assessments	Subject's duration of involvement expected to be up to 60 months. The overall study duration expected to last a total of 6 years.

	First 12 months will be indicated as “treatment phase”. Subject eligibility will be documented at a Baseline Qualifying Exam (BQE) as part of regular care. Eligible subjects will be consented and will undergo primary circumferential radiofrequency ablation (12J/cm^2 applied once with no cleaning of coagulum) within three months after BQE. All subjects will return 3, 6 and 9 months later for a repeat standardized chromoendoscopy. Flat USLs found within the previously treated area will be biopsied and treated again with RFA. Patients with ESCC in biopsies, non-flat visible lesions or lesions otherwise suspicious for ESCC (exceedance of initial inclusion criteria) found during follow-up will undergo escape treatment (see section 9.4.3 for description). If subsequent pathology assessment shows progression, defined as ESCC in any biopsy/resection specimen will be considered a failure of the primary endpoint. All subjects will return at 12 months after the primary RFA for biopsy to evaluate the primary endpoint of “complete response.” Subsequent study duration after 12 months until 60 months will be defined as “follow-up phase.” Patients with a complete response at 12 months will directly enter the follow-up phase, whereas patients with residual ESCN at 12 months (“treatment failures”) will undergo escape treatment per investigator’s discretion under the hospital standards of care. The follow-up phase consists of yearly Lugol’s endoscopies with biopsies. If any flat USL will be found in TA, additional RFA treatment will be performed. If subsequent biopsies show MGIN or worse, an extra FU endoscopy will be performed within 3 months. A maximum of 4 consecutive RFA sessions are allowed and if CR won’t be re-established thereafter, escape-treatment will be indicated. Escape treatment is directly indicated for patients with ESCC in biopsies, non-flat lesions and lesions otherwise suspicious for ESCC (in line with the treatment phase) in TA. Escape treatment may consist of endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or non-endoscopic therapy such as surgery, radiotherapy or chemotherapy, at the discretion of the physician under the hospital standard of care. As long as pathology indicates endoscopic treatment (i.e.: sm1 disease, well/moderate differentiation, no lymphovascular infiltration and

	negative vertical resection margins), trial participation will be continued. All patients, regardless of failure of the primary endpoint or use of escape treatment during the trial, will be followed to study termination to assess secondary endpoints. A patient that has not been withdrawn or otherwise disqualified from the study, will have completed the study when the patient has finished all follow-up visits and the study has been terminated.
Safety Assessments	Adverse events will be reported by number, severity, and relationship to the study procedures and devices.
Statistics	The primary study hypothesis is that 80% of treated subjects will have a complete response at 12 months after the initial treatment session (per protocol analysis). Descriptive statistics will be used to summarize primary and secondary endpoints along with 95% confidence intervals or precisions as appropriate.

4. Introduction

4.1. Background

Esophageal cancer is the 9th most common cancer and the 6th most common cause of cancer death world-wide, with 442,000 new cases and 440,000 deaths in 2013 (1).

The incidence rate of esophageal cancer varies widely by region, with highest rates found in Eastern and Central Asia and Eastern and Southern Africa (1, 2). In China in 2011, esophageal cancer was the 4th leading cause of cancer death among both men and women, behind lung, liver, and stomach cancer (3).

In high-risk areas of Central Asia and North-Central China, esophageal squamous cell carcinoma (ESCC) represents 90% of esophageal cancer cases, compared to approximately 26% among Caucasians in the United States where esophageal adenocarcinoma is more common (2).

Risk factors for the development of ESCC include alcohol consumption, tobacco use, very hot drinks, and exposure to certain carcinogens found in salted vegetables and preserved fish (4, 5).

ESCC develops from the epithelial cells that line the esophagus. The precursor lesion to ESCC is esophageal squamous intraepithelial neoplasia (6, 7), also known as esophageal squamous cell neoplasia (ESCN), which is defined histologically as nuclear atypia (enlargement, pleomorphism and hyperchromasia), loss of normal cellular polarity, and abnormal tissue maturation (6).

Intraepithelial neoplasia is graded according to the proportion of the epithelial thickness that contains neoplasia (6). Lesions are categorized as either low-grade intraepithelial neoplasia (LGIN) or high-grade intraepithelial neoplasia (HGIN) depending on the extent of the neoplasia within the epithelium. In China where the incidence of ESCC is high, many pathologists adhere to a three-tier classification for intraepithelial squamous neoplasia, as shown below.

Table 1. Three-tier Classification for Intraepithelial Squamous Neoplasia

Class	Description
LGIN	Intraepithelial neoplasia confined to the lowest third of the epithelium (mild dysplasia)
MGIN	Intraepithelial neoplasia involving the lower two thirds of the epithelium (moderate dysplasia)
HGIN	Intraepithelial neoplasia involving all thirds of the epithelium (severe dysplasia)

Follow-up studies in China have shown that the rate of progression to ESCC differs significantly between the grades of intraepithelial neoplasia. At 3.5 years and 13.5 years, respectively, the progression rates were 5% and 24%, respectively for LGIN; 27% and 50% for MGIN; and 65% and 74% for HGIN (8, 9).

Once diagnosed, the prognosis for ESCC is often quite poor and depends on the stage of disease at diagnosis. Worldwide 5-year survival rates (2001-2007) have been estimated at 37%, 18%, and 3% for localized, regional, and distant disease, respectively (7, 10).

Thus, early screening and endoscopic treatment of MGIN and HGIN before the progression to ESCC may improve outcomes (11).

Management of ESCN commences with an extensive staging work-up, which typically includes chromoendoscopy, multiple biopsies of the esophagus with targeting of unstained lesions (USLs) on chromoendoscopy and any irregularities of the mucosa, endoscopic resection (ER) of any mucosal irregularity, and in some cases endoscopic ultrasound and computed tomography (CT) to rule out deeply invading lesions or metastatic cancer (12). Review of all histopathology is performed to determine the grade of neoplasia and the depth of invasion, when applicable.

Based on neoplastic progression rates, LGIN is generally managed with endoscopic surveillance and biopsies. Given the higher risk of progression to ESCC, patients with MGIN and HGIN are typically offered therapy. These therapies have consisted of wide-field endoscopic mucosal resection (EMR) or

endoscopic submucosal dissection (ESD), focal ablation, and surgical esophagectomy. Each intervention has specific risks and benefits that have been reported in the literature.

For wide-field EMR, resecting more than a 4 cm length of the esophagus or involving more than 50% of the inner circumference has a very high stricture rate, and the procedure is technically demanding. In addition, recurrence has been reported in up to 26% of cases (13).

ESD allows en bloc removal of neoplastic tissue regardless of length (13, 14). However, post-procedural side effects remain a challenge; strictures have been reported to complicate more than 90% of cases of esophageal ESD involving the entire lumen circumference, with resultant dysphagia requiring multiple sessions of dilations, with decrease in patients' quality of life. This procedure is even more technically demanding, requiring a high level of expertise, especially for large lesions. In addition, a long learning period is required to successfully perform ESD, and therefore this procedure can only be performed in high capacity institutions (15, 16).

Both EMR and ESD enable en bloc resection of neoplasia and allow for a pathological assessment to evaluate the curability (13-16).

Surgical esophagectomy is curative for ESCN, but the operative mortality at high-volume centers remains 3% or higher and the morbidity of the resulting gastric pull-up is substantial. Morbidity and mortality rates may even be higher for cases located in the upper 2/3 of the esophagus (17).

Radiofrequency ablation (RFA) is an endoscopically guided procedure which uniformly removes the diseased squamous epithelium without the need for removing the entire organ, as in surgery (11, 18, 19). RFA has been shown to safely, effectively, and durably eradicate early neoplasia in Barrett's esophagus, the precursor of esophageal adenocarcinoma (20-22). Several studies have demonstrated the potential of RFA to treat early ESCN as well (11, 19, 23-25). In a retrospective analysis of 65 patients with flat-type ESCN, RFA was also shown to provide similar effectiveness to ESD in the short-term treatment of ESCN, but with fewer adverse events, especially in lesions extending more than ¾ of the circumference (26).

This clinical study will 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.

4.2. Purpose

To measure the effectiveness and durability of the Barrx™ Flex Radiofrequency Ablation System in the eradication of diseased epithelium at 12 months post-treatment and up to 5 years in subjects with early flat-type -defined as type 0-IIb lesions on White Light Endoscopy (WLE) and Lugol's chromoendoscopy-

esophageal squamous cell neoplasia (ESCN), defined as moderate-grade squamous intraepithelial neoplasia (MGIN) or high-grade squamous intraepithelial neoplasia (HGIN).

5. Objectives and Endpoints

5.1. Objectives

5.1.1. 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).

5.1.2. 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.

5.2. Endpoints

5.2.1. Primary Endpoint

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 who are included in the cohort will be assessed for the primary endpoint. The run-in patients will not be included for the primary endpoint analysis.

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 analysis. MGIN or worse noted in any biopsy from outside this region are not considered failures of ablation for the purposes of the primary endpoints.

5.2.2. 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, are defined as the first 5 subjects enrolled per endoscopist that is inexperienced with RFA or has had no RFA onsite training from CICAMS, 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.

6. Study Design

This 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.

6.1. Duration

Enrollment of up to 100 subjects is expected to take 12 months. 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.

6.2. Rationale

This study design is a prospective, multi-center, non-blinded, single-arm (non-randomized), post-market study. This study design was selected given the desire to evaluate treatment efficacy (RFA) on a disease state (ESCN) with generally well understood natural history. Two recently published reports have evaluated the Barrx™ Flex Radiofrequency Ablation System for the eradication of ESCN (11, 18). Bergman et al. 2011 reported on 29 subjects (18 MGIN, 10 HGIN, and 1 ESCC) treated with circumferential RFA followed by focal RFA every 3 months until the complete histological eradication of MGIN or worse. Two energy applications were administered at 10 J/cm^2 or 12 J/cm^2, with and without cleaning of the coagulum between passes. The primary endpoint was complete response at 12 months, defined as the histological absence of MGIN, HGIN, or ESCC. The rate of complete response was 86% at 3 months after the primary RFA session and 97% at 12 months after the primary RFA session (11). Four strictures (14%) were reported, all dilated to resolution. The authors concluded that RFA was associated with a high rate of histological complete response for the eradication of ESCN with no neoplastic progression (11). Because the stricture rate was slightly higher than typically reported in studies assessing RFA for the treatment of Barrett's Esophagus, the authors concluded that technique and dose may contribute to stricture formation and proposed further evaluation of dosimetry to preserve the high rate of complete response while reducing the stricture rate (11).

The authors continued the study to a total enrollment of 96 subjects (45 MGIN, 42 HGIN, and 9 ESCC). In that analysis, the complete response rate was 73% after 3 months (1 RFA session) and 84% after 12 months. The stricture rate was 21%. However, when using a circumferential RFA dose of 12J/cm^2 with one application and no cleaning of the coagulum, the stricture rate was only 6%, with complete response rates of 65% and 82% at 3 months and 12 months respectively. This regimen had additional benefit of procedural simplicity. However, only a total of 17 patients were treated with this regimen (18).

Although preliminary, results for the long-term follow-up of this study will be shortly discussed. Sustained CR during 5 years follow-up was observed in 86% (67/78 patients). Recurrence occurred in 9% (7/78 patients, MGIN 5, HGIN 1). 5 were managed with RFA, one with ESD. Progression of baseline disease occurred in another 5% (4/78 patients; HGIN (n=1), sm-ESCC (n=3)); all were treated with ESD. Two progressor lesions were normally stained after Lugol's and with repeatedly negative biopsies, and were therefore left untreated. Later both lesions were considered suspicious for cancer and escape treatment was performed, with pathology assessment for one case showed submucosal cancer buried under normal epithelial cells. Pathology assessment for the second case is pending.

However, protocol violations during follow-up occurred in the majority of patients (59%) resulting in prolonged follow-up intervals, lesions left untreated or no adequate follow-up after detection of recurrent or progressive disease. This might have interfered with the results, and those might have been better with strict follow-up protocols.

The 12 patients with residual ESCN suffered a poorer prognosis. Fifty-eight percent (7/12 patients) developed progressive disease and were treated with either ESD (n=2) or non-endoscopic treatment (n=5), suggesting that RFA failures should directly be managed with an alternative treatment like EMR or ESD.

Therefore, to further assess the safety, effectiveness, and durability of the Barrx™ Flex Radiofrequency Ablation System for the eradication of ESCN, the current study will employ methods similar to the 2 studies reported above but with a consistent primary RFA dose of 12 J/cm2 with one application and no cleaning of the coagulum, and with subsequent 5-years follow-up according to strict study protocols.

7. Product Description

7.1. General

The Barrx™ Flex Radiofrequency Ablation System uses radiofrequency (RF) energy to coagulate (ablate) the thin layer of diseased squamous epithelium of the esophagus. RF is used for the purpose of coagulation and ablation in many other target tissue sites. The heat generated by RF delivery results in tissue vaporization or coagulation. Specific to the esophagus, the study device has been evaluated extensively in the treatment of Barrett's esophagus, a glandular metaplastic disease of the esophagus related to gastroesophageal reflux disease.

There are two Barrx™ Flex Radiofrequency Ablation Systems, each with a specific role in the treatment of diseased esophageal epithelium.

Each part of the Barrx™ Flex Radiofrequency Ablation System is assembled in a Medtronic manufacturing facility. Each part of the process from the raw materials to the finished device is diligently controlled to ensure the quality and effectiveness of each product.

7.2. The Barrx™ Circumferential Radiofrequency Ablation System

The Barrx™ Circumferential Radiofrequency Ablation System includes an energy generator (Model 1190A-115A), ablation catheters (Model 32041-18, 32041-22, 32041-25, 32041-28, 32041-31), and sizing balloons (Model 3441C). The circumferential ablation catheters will be used for independent treatment or main treatment. The energy generator is used to inflate a sizing balloon positioned within the esophageal body, in order to measure the inner diameter of the targeted portion of the esophagus. Upon determination of the inner diameter size (mm), an appropriately sized ablation catheter is selected for ablation. The ablation catheter has a balloon at its distal end, wrapped with an electrode having tightly spaced bipolar electrode bands. The generator inflates this ablation catheter within the esophagus and delivers the controlled amount of RF energy to achieve the desired ablation effect. At

the recommended energy density and number of applications, the maximum depth of ablation in previous studies is the muscularis mucosae.

7.3. The Barrx™ Focal Radiofrequency Ablation System

The Barrx™ Focal Radiofrequency Ablation System (Model 90-9100, 90-9200, 90-9300: additional models may be used for the study after CFDA approval is obtained) consists of a similar energy generator and a cap-based electrode that is mounted on the distal end of an endoscope. The focal ablation catheters will be used for supplementary topical treatment. This device is introduced with the endoscope to provide more focally targeted ablation of small areas of disease, either primary or secondary therapy. The Barrx™ Focal Radiofrequency Ablation System is substantially equivalent to the Barrx™ Circumferential Radiofrequency Ablation System in terms of energy delivery and ablation depth, having the same electrode design. The difference is that the surface area is smaller, allowing more focal selective ablation of residual diseased tissue, and this device is attached to the endoscope, rather than to a balloon catheter.

7.4. Regulatory Approval in China

The Barrx™ Flex Radiofrequency Ablation System obtained CFDA approval in January 2015 for the following indication for use: The Barrx Flex System is indicated for the clinical treatment of lesions limited to the mucosa in the gastrointestinal tract, specifically flat intraepithelial neoplasia and Barrett's esophagus.

In this proposed clinical trial, the Barrx Flex RFA Generator will be utilized in accordance with the indications for use in the labeling for the device. All study device catheters are single use, disposable medical devices. See the Clinical Evaluation Report, REG-0023 and REG-0022 for additional information.

7.5. Product Training Requirements

Each Investigator participating in the clinical trial and the associated clinical study staff will receive training on the clinical protocol, IRB-approved ICF and additional training materials as per the study training plan, as well as hands-on training in the use of the Barrx™ Flex Radiofrequency Ablation System for the treatment of ESCN. All endoscopies will be observed by an expert from CICAMS. The tissue specimen review and histopathological interpretation will be centralized at CICAMS by expert pathologists who are the process developers, hence do not require additional training.

7.6. Study Supplies and Device Accountability

The Barrx™ Flex Radiofrequency Ablation System will be provided to each site upon Sponsor collection and approval of all required regulatory documentation. Up to 8 catheters per patient (including both

balloon catheters and focal catheters) may be used during the study protocol (including both treatment phase and follow-up phase). This number may be exceeded depending on extent of disease during follow-up and the number of energy applications needed per session. The device should be stored in a secure (locked) area under the appropriate storage conditions. The study devices shall be used according to the CIP. Access should be limited to designated study staff only. Device accountability logs will be provided to the site. It is the site's responsibility to document the receipt date, device identification, disposition of the product (per subject use including date, including amount used, amount remaining, etc.), transfer (if applicable) and return of all unopened expired or malfunctions study devices.

8. Selection of Subjects

8.1. Study Population

The study cohort will be subjects with early ESCN, defined as MGIN or HGIN.

8.2. Subject Enrollment

Up to 100 subjects are planned for enrollment in the primary analysis cohort. With up to 10 sites and 1-2 endoscopists at each site, up to 50 'run-in' patients will be included in this study. Run-in patients are defined as up to 5 patients for each endoscopist that is inexperienced with RFA or has had no RFA onsite training from CICAMS. Data from the run-in patients will be analyzed separately from the cohort.

Patients shall be reviewed according to the following inclusion and exclusion criteria. An answer of "no" to any inclusion criterion or an answer of "yes" to any exclusion criterion disqualifies a subject from participating in this study. Complete the **Eligibility CRF**.

Definitive eligibility can only be assured during the primary RFA endoscopy, e.g. if a severe stricture or a non-flat abnormality is present, patient is not eligible. Therefore, the subject is considered as enrolled after insertion of the RFA catheter.

8.3. Inclusion Criteria

1. Patient is 18-85 years of age
2. Patient has evidence of ESCN, within the last 3 months, patient demonstrated a new diagnosis or a reconfirmed diagnosis of squamous MGIN and/or HGIN of the esophagus
3. On endoscopic examination, subject has at least one USL that measures at least 3 cm in at least one dimension and greater than ¼ of the esophageal circumference and has MGIN or HGIN on biopsy, confirmed by central pathologist

4. All lesions in the esophagus are completely flat (Paris type 0-IIb), both on WLE and Lugol's chromoendoscopy
5. The maximum allowable linear length of "USL-bearing esophagus" is 12 cm
6. Baseline endoscopic ultrasound (EUS) (if applicable) shows no exclusionary findings for the trial
7. Computed Tomography (CT) scan of chest and upper third of the abdomen (if applicable) shows no exclusionary findings for the trial
8. Based on the judgment of the study endoscopist, the patient is eligible for treatment, follow-up endoscopy, and biopsy as required by the protocol
9. EMR or ESD occurred > 3 months before enrollment, patients may be eligible for the study if procedure was curative (negative margins and no risk of lymph node involvement) and the patient has no other findings concerning for cancer
10. The subject is willing to provide written, informed consent to participate in this clinical study and understands the responsibilities of trial participation

8.4. Exclusion Criteria

1. Patient has esophageal squamous cell carcinoma (ESCC)
2. Any non-flat (Paris type 0-I, 0-IIa, 0-IIc, 0-III) abnormalities anywhere in the esophagus
3. Any abnormalities under WLE, Lugol's chromoendoscopy or NBI that are suspicious for ESCC anywhere in the esophagus (e.g. 'pink sign' USL, defined as a color change after Lugol's staining: initially whitish yellow and pink 2-3 minutes later)
4. Any USL with MGIN or worse on biopsy outside the treatment area
5. Esophageal stricture preventing passage of a therapeutic endoscope
6. Prior endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) which occurred < 3 months before enrollment
7. Any esophageal dilation in the past 12 months
8. Any history of a non-squamous cell cancer of the esophagus, or any history of a squamous cell cancer of the esophagus (any stage)
9. Any previous ablative therapy within the esophagus (photodynamic therapy, multipolar electrical coagulation, argon plasma coagulation, laser treatment, or other) or any radiation therapy to the esophagus
10. Previous esophageal surgery, except fundoplication without complications (i.e., no slippage, dysphagia, etc.)
11. Evidence of esophageal varices detected within last 6 months or at initial RFA procedure
12. Patient has active reflux esophagitis grade C or D
13. Evidence of eosinophilic esophagitis on endoscopy and/or histology
14. Inner diameter of the esophagus measuring <18 mm
15. Report of uncontrolled coagulopathy with international normalized ratio (INR) > 2 or platelet count <75,000 platelets per µL (note: a complete blood count is not required for all subjects in this study)
16. Patient is using anti-thrombotic agents that cannot be discontinued 7 days before and after therapeutic sessions
17. Patient has an implantable pacing device (examples: automated implantable cardioverter defibrillator, neurostimulator, cardiac pacemaker) and has not received clearance for enrollment in this study by specialist responsible for the pacing device
18. Patient has life expectancy less than 5 years
19. Patient suffers from psychiatric or other illness and/or has a known history of unresolved drug or alcohol dependency that would limit ability to comprehend or follow instructions related to informed consent, post- treatment instructions, or follow-up guidelines
20. Patient is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity)
21. The subject has participated in an investigational drug or device research study within 30 days of enrollment that would interfere with this study
22. Patient is pregnant or has plans to become pregnant in the ensuing 12 months (confirmation of non-pregnant status in women of child-bearing age and ability required with urine or blood test to be eligible)

9. Study Procedures

9.1. Schedule of Events

For patients who meet all of the inclusion criteria and none of the exclusion criteria, step-wise endoscopic RFA will be performed in 3month intervals +/- 4 weeks from the first RFA 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.

Study procedures are summarized in Table 2 and described in detail below.

Table 2. Study Schedule and Assignments

	BQE (1 week to 3 months before first RFA)	Baseline assessments	Primary RFA	3-Month Follow-Up visit (from primary RFA, +/- 4 weeks)	6-Month Follow-Up Visit (from primary RFA, +/- 4 weeks)	9-Month Follow-Up Visit (from primary RFA, +/- 4 weeks)	12-Month-Primary Endpoint (from primary RFA, +/- 4 weeks)	2-3-4-5 Year Follow-up (from primary RFA, +/- 4 weeks)
	BQE is part of regular care		***After insertion of RFA catheter, patient is considered enrolled in the study: treatment phase***					***Follow-up phase***
Informed Consent		X						
Patient History CRF		X						
Baseline Qualifying CRF		X						
Confirmation of Study Eligibility CRF		X						
Upper Endoscopy using Lugol's Solution	X			X	X	X	X	X
Circumferential RFA at 12 J/cm^2			X					
Endoscopy CRF			X	X	X	X	X	X
Table of findings CRF			X	X	X	X	X	X

	BQE (1 week to 3 months before first RFA)	Baseline assessments	Primary RFA	3-Month Follow-Up visit (from primary RFA, +/- 4 weeks)	6-Month Follow-Up Visit (from primary RFA, +/- 4 weeks)	9-Month Follow-Up Visit (from primary RFA, +/- 4 weeks)	12-Month-Primary Endpoint (from primary RFA, +/- 4 weeks)	2-3-4-5 Year Follow-up (from primary RFA, +/- 4 weeks)
Circumferential or focal RFA at 12 J/cm^2				X	X	X		X
Biopsy	X			X	X[1]	X[1]	X	X
Central pathology review (BQE biopsy)		X						
Central pathology review				X	X	X	X	X
2nd pathologist assessment		X					X	X[2]
Pathology CRF		X		X	X	X	X	X
Study Exit CRF								X[4]
Safety Assessment			X	X	X	X	X	X
Observation of endoscopy by CICAMS expert			X	X	X	X	X	X
Keyhole biopsy if diagnosis of suspicious/visible lesion needed before escape treatment				X	X	X	X	X
Escape treatment (see section 9.4.3) for ESCC/ disease suspicious for ESCC				X	X	X		X
Escape treatment if residual ESCN							X	X[3]

Remarks:

[1] Biopsies at 6 and 9 months will be performed only if USL are detected after CR

[2] Only recurrent or progressive disease during FU will be assessed by a second expert pathologist. This includes biopsies indicating recurrent or progressive disease, and eventual EMR/ESD/surgery specimens.

[3] If persistent after 4 additional RFA sessions

[4] Study completion is defined as when all follow-up visits have been completed, all data has been entered, reviewed, monitored, and database has been locked.

9.1.1. Tissue Specimen Processing and Histopathological Interpretation

In order to ensure uniform tissue specimen preparation, staining technique, and histopathological evaluation, all study tissue specimen processing using the same laboratory practices. All slides will be stained with hematoxylin and eosin.

All baseline tissue specimens obtained from the esophagus will be independently reviewed by two expert GI pathologists at the lead study site (CICAMS) to confirm eligibility per the inclusion and exclusion criteria. Eventual discrepant results will be resolved by joint reading. All results are entered on the pathology CRF.

All biopsies obtained after the initial RFA procedure at any time of the study will also be reviewed by the lead study site pathologist. This includes biopsies from all USLs, biopsies from a normal staining post-RFA esophagus to confirm CR, and any new USL or lesion outside the treated area (TA). All results are entered onto the pathology CRF.

All biopsies obtained at the 12 month primary endpoint, and all pathology specimens for recurrent or progressive disease (including biopsies and EMR/ESD/surgical specimens, if applicable) will be independently read by two expert gastrointestinal (GI) pathologists at the lead study site with results entered on a CRF. Any discordance between reviewer results will be resolved with a non-blinded consensus review between the pathologists.

For histopathological interpretation for specimens obtained at baseline or follow-up sessions, as described above, each specimen from each slide will be read out as follows according to the worst cell type observed:

1. Squamous epithelium without intra-epithelial neoplasia
2. Glandular (gastric or intestinal metaplasia) +/- normal squamous epithelium
3. Squamous epithelium with low-grade intra-epithelial neoplasia
4. Squamous epithelium with moderate-grade intra-epithelial neoplasia
5. Squamous epithelium with high-grade intra-epithelial neoplasia
6. Invasive squamous cell carcinoma (depth and grade determined if possible, given limitations of biopsy method versus EMR or ESD)

In a biopsy fragment where multiple grades of intraepithelial neoplasia co-exist, the highest grade will represent the diagnosis for that biopsy fragment. The final subject diagnosis is represented by the worst

histological grade of any fragment for that biopsy session. The study site data will be recorded on a case report form that will include all individual biopsy diagnoses, all lesion diagnoses, and the final subject diagnosis for the individual endoscopy session.

9.2. Subject Screening

If a possibly eligible patient is detected during a regular care endoscopy, a member of the research team will enter those subjects into the provided **screening log**. If the endoscopy fulfills all BQE requirements listed below, this endoscopy is mentioned as the BQE. Additional tests like EUS or CT will be performed if clinically indicated. More detailed eligibility criteria will be assessed by reviewing medical records and subject history.

Baseline Qualifying Endoscopy (BQE)

It is permissible for a site to have performed the baseline qualifying endoscopy prior to a particular subject's enrollment as standard of care, provided the time interval was less than 3 months and at least 1 week prior to primary RFA and all steps as outlined below were completed. Otherwise, the baseline qualifying endoscopy will be performed prospectively.

1. Start WLE to document landmarks and to check all selection criteria that can be assessed endoscopically (e.g. appearance of the lesion, strictures, presence of varices, eosinophilic esophagitis, reflux esophagitis, etc.)
2. Upper endoscopy using Lugol's solution ~1.25% is performed to identify all diseased squamous epithelium of the esophageal body. The only allowable lesions are type 0-IIb.
3. Confirmation of at least one flat (type 0-IIb) USL with a minimum diameter greater than or equal to 3 cm in at least one dimension and greater than 1/4 of esophageal circumference (including a USL mosaic where the entire lesion is at least 3 cm in one dimension). At least one biopsy from at least one such a 'qualifying USL' must demonstrate MGIN or HGIN, and no biopsy can demonstrate ESCC.
4. Confirm that no abnormalities under WLE or Lugol's chromoendoscopy are suspicious for ESCC anywhere in the esophagus (e.g. any non-flat [Paris type 0-I, 0-IIa, 0-IIc, 0-III] abnormalities; 'pink sign' USL, defined as a color change after Lugol's staining: initially whitish yellow and pink 2-3 minutes later). No lesions suspicious for ESCC may exist in the esophagus.
5. Confirmation that the total linear length of the esophagus containing USLs is 12 cm or less is required. This area (plus one additional centimeter proximal and distal) defines the Treatment Area (TA) that will be treated with RFA at the primary RFA session. Only flat type (type 0-IIb) USLs containing LGIN or less may be present outside the TA.
6. Only one continuous TA is permitted per subject, and may by definition include any number of individual USLs. For example, two 4 cm TAs may not be created to treat two separate areas of USLs.
7. The location of the USLs and targeted TA will be documented by obtaining video recordings and still images (with high-resolution endoscopy (optional) and Lugol's staining) of the entire TA at 1 cm intervals. The insertion depth of the endoscope at the proximal and distal margins will be documented in the CRF. Locations of individual USLs are described in the CRF.
8. Biopsies from the BQE and USLs are obtained using standardized localization technique as described in section 10.4.1 and are processed per instructions in section 10.1.1 :

- Biopsies are obtained first from the distal portion of the esophagus, working proximally so as to minimize obscuring subsequent biopsy targets with blood from the biopsy sites.
- The maximum number of biopsy specimens per specimen jar is 2
  - Targeted biopsies are obtained from each USL and each USL should have a unique jar(s) for its biopsies.

9.3. Subject Consent

If the subject is deemed eligible after BQE and medical record reviewing, the research team member may then approach the potential subject to discuss participation in the study, including background of the proposed study, inclusion and exclusion criteria, the benefits and risks of the procedures and the follow-up requirements. If the study is of interest to the subject, the informed consent form (ICF) will be discussed and presented. The subject must sign the ICF prior to enrollment. This form must have prior approval of institutional review board (IRB)/ ethics committee (EC) for all participating sites. Failure to obtain informed consent will render the subject ineligible for the study.

Patients will be approached to obtain written informed consent prior to any study specific procedures being performed. The purpose of the study and the benefits and risks of the procedures will be explained to the subject in their local language. The consent process must be documented accordingly in the medical record. Patients who agree to study participation must sign an IRB/EC-approved ICF. Subjects will be informed that their participation in this study is voluntary and they may refuse to participate or discontinue from the study at any time. Subjects will be given the opportunity to ask the investigator questions so that they are adequately informed about the research. A copy of the signed informed consent must be provided to the subject and the informed consent process will be documented in source documents.

If new information becomes available that may affect a subject's decision to continue to take part in the study, this information will be discussed with the subject by the investigator.

Subjects will be assured that they may withdraw from the study at any time for any reason.

9.4. Treatment Assignment

9.4.1. Treatment Phase

Patient History

After the subject signs the ICF, the **Patient History CRF** is completed for that subject.

Baseline Qualifying Tests

Results from the subject's BQE including pathology review and baseline staging tests (EUS and/or CT where applicable) are entered onto the **Baseline Qualifying CRF.** Afterwards, definitive eligibility will be assessed by completing the **Eligibility CRF.**

Primary Radiofrequency Ablation

If the subject is found to be eligible for the study after BQE, central review of the BQE pathology results and reviewing medical records, he or she will proceed to the primary ablation session within 1 week - 3 months after BQE. Primary RFA will be observed by an expert from CICAMS.

1. Start WLE to document landmarks and to check all selection criteria that can be assessed endoscopically (e.g. appearance of the lesion, confirmed absence of non-flat lesions, strictures, presence of varices, eosinophilic esophagitis, reflux esophagitis, etc.)
2. Lugol's staining and assessment of all endoscopic selection criteria
3. Assessment of definitive eligibility of the subject.
4. Marking on the estimated TA with electrocoagulation (preference is not to use APC for this).
5. Measuring will be performed. If the inner diameter of the esophagus is less than 18mm, the patient is ineligible for the study.
6. Primary RFA is performed with the Barrx™ Circumferential Radiofrequency Ablation System. The ablation zone must encompass the entire TA. The energy density setting is 12 J/cm2, applied once, using the default power set by the RF generator according to catheter size, with no cleaning of coagulum.
7. Beginning proximally, the electrode is deployed so that the proximal margin of the electrode is aligned with the proximal marker. The balloon is automatically inflated and ablation energy is delivered.
8. After automated deflation of the balloon, air is insufflated by the endoscope and the catheter carefully advanced distally avoiding denuding of the ablated mucosa. The proximal margin of the electrode is aligned with the distal margin of the first ablation zone minimizing overlap between zones. Ablation is performed.
9. These steps are repeated until the ablation overlaps the distal markings.
10. Tattoos are placed in at least 2 quadrants at the most proximal and distal extent of TA (providing at least 1 cm margin between proximal tattoo and most proximal USL, and at least 1 cm margin between distal tattoo and most distal USL).

All data from the RFA procedure are entered onto the **Endoscopy CRF.**

3, 6, 9 months (from primary RFA, +/- 4 weeks) Follow-up Endoscopy, Biopsy, and Additional RFA

After baseline treatment, patient will return for standardized endoscopies at 3, 6 and 9 months, (from primary RFA, +/- 4 weeks), to endoscopically assess the TA for USLs using Lugol's iodine. All endoscopies in the treatment phase will be observed by an expert from CICAMS. The following two treatment scenarios are possible based on the presence or absence of USLs. For every endoscopy, the **Endoscopy CRF**, the **Table of findings CRF** and the **Pathology CRF** will be completed.

Scenario #1: No USLs are present

At the 3 months FU visit, (from primary RFA, +/- 4 weeks), biopsy sampling of TA will be performed to confirm absence of occult MGIN or worse: Using a maximum capacity forceps or larger (for example, Boston Scientific Radial Jaw 3 or 4) and commencing at the most proximal extent of the original USL-bearing portion of the esophagus and tattoos as reference points, 2 biopsy specimens are obtained for every 2 cm segment of the original USL-bearing esophageal segment. The most distal biopsies are obtained 1 cm above the distal Tattoo. All fragments from a particular 2 cm level are placed in the same pathology specimen container and labeled as to their location (cm from the incisors). In this manner, the portion of the esophagus that originally contained USLs is well-sampled (tissue at baseline that was both USL and non-USL), with the allowance of focusing some biopsies at each level in certain areas based on original USL location (referring to baseline imaging and CRF's). Re-tattoos will be performed if necessary.

***Example**: Baseline USL-bearing portion of the esophagus is 30-36 cm (therefore, TA 29-37 cm). A total of 6 biopsies would be obtained (approximately two fragments each at 30-32, 32-34, and 34-36). Biopsies of the 1 cm "safety zone" at either end of TA are **not** obtained in any biopsy session.*

At the 6 and 9 months FU visit, (from primary RFA, +/- 4 weeks), no biopsies will be performed from normally stained TA.

No RFA is applied in "Scenario #1: no USLs are present."

In the very unlikely scenario that any biopsy subsequently shows MGIN+ despite a normally stained esophagus, the entire TA is treated once again with circumferential or focal RFA (to ensure complete treatment of any occult neoplasia.)

Scenario #2: USLs are present in the TA

If there are **residual flat USLs within the original TA**, the investigator records the extent of the USLs (length, diameter, location) and obtains biopsies of each USL starting distally and moving proximally as follows:

For each two centimeters in length, 1 level of biopsies will be performed. The number of biopsies per level depends on the circumferential extent of the USL as follows:

- <25% of circumference: 1 biopsy per level
- 25 – 49% of circumference: 2 biopsies per level
- 50 – 74% of circumference: 3 biopsies per level
- ≥75% of circumference: 4 biopsies per level.

***Example:** for a USL of 3 centimeter in length covering 60% of circumference, 2 levels with 3 biopsies per level will be performed, summing up to a total of 6 biopsies.*

Each set of unique USL samples are placed in individual containers, and labeled as to their location. If 3 or more biopsies are obtained from a single USL, use multiple jars for that USL with a maximum of 2 biopsies per jar. The investigator designates the staining characteristic of each tissue area prior to biopsy, and enters this information on the Table of findings CRF. It is presumed that biopsies from USLs are unstained, while biopsies from the non-USL TA are "stained". The CRF also contains information about each specimen/USL location.

Treatment of USL

In general, all residual flat USLs during follow-up will be treated with RFA.

USLs that are deemed clearly reactive can be biopsied without need for additional treatment. Clearly reactive USLs will be defined as any USL with stain code III (lightly stained) that is deemed as non-suspicious for ESCN and reactive after RFA on both WLE and NBI by the Investigator. If a USL will be deemed reactive and therefore left untreated, and if subsequent biopsies do show MGIN or worse, the USL will then be treated on the next endoscopy, independent of the endoscopic appearance.

If subsequent biopsies show cancer, patients is defined as progressor will be considered a failure for the primary endpoint and he will be offered escape treatment (see section 9.4.3. for description), at the discretion of the physician under the hospital standard of care.

If an indication for additional RFA exists, the investigator will determine whether to provide secondary RFA with the circumferential or focal device, based on the extent of disease:

- If lesions involve more than 3/4 of the circumference, circumferential RFA will be used
- If lesions involve less than 3/4 of the circumference, focal RFA will be used
    - It is presumed that all secondary RFA procedures will be performed with the focal device, and this presumption is reflected in Figure 1.

If focal RFA is selected, it is important to note that the effect of Lugol's may significantly wane during the biopsy procedures therefore it may be necessary to reapply the Lugol's in order to target the remaining USLs. Or simply use the biopsy sites for targeting. Each USL is treated so that the ablation effect overlaps at least 5 mm onto the normal staining esophageal mucosa surrounding the USL. The energy density setting is 12 J/cm^2 and the power density setting is 40 W/cm^2. Each USL is ablated 3x without changing the position of the catheter. Upon completing focal RFA of USL(s), biopsies are obtained from the TA avoiding all acute RFA sites. Two biopsy fragments are obtained from every 2 cm of the original USL-bearing esophagus that was not treated at this session (see Figure 1).

Example: TA from 30-40, USL bearing esophagus 31-39. One USL at 3 months from 31-32. Sample USL, then RFA USL. Then obtain 2 biopsy fragments from every 2 cm starting at 33-35, 35-37, and 37-39 cm. The area of the USL is avoided (31-33 cm).

In the unlikely event that circumferential RFA is selected for a follow-up RFA, the entire extent of original TA is treated, using same technique as at the primary RFA session.

If necessary, a maximum of four RFA sessions will be performed in total for each patient in this study. If USLs with MGIN or worse in the TA persist after four sessions, the subject is considered a failure for the primary endpoint. Such patients will undergo escape treatment.

Scenario #3: Lesions Suspicious for ESCC Are Present in the TA

If any **non-flat USL (Paris type 0-I, 0-IIa, 0-IIc, 0-III) is detected, independent of its staining characteristics upon Lugol's staining, or WLE, NBI or Lugol's chromoendoscopy show a lesion suspicious for ESCC (e.g. 'pink sign' USL, defined as a color change after Lugol's staining: initially whitish yellow and pink 2-3 minutes later), or if previous biopsies from this lesion showed ESCC,** subject will be managed with escape treatment (see section 9.4.3 for description), at the discretion of the physician under hospital standard of care depending on the lesion type. If histology is needed before

escape treatment, a keyhole biopsy should be performed, but the Investigator can perform escape treatment if deemed necessary, regardless of the biopsy result. The patient will be considered a failure for the primary efficacy endpoint only if escape treatment histology shows progression to ESCC. If histology does not show ESCC, the patient will return in 3 months from escape treatment for possible RFA and will be eligible for success in the primary endpoint. For continuation on trial, please refer to section 9.4.3.

Scenario #4: USLs are present outside the TA

If any **new USL(s) is (are) detected outside the TA** during follow-up prior to 12 months, it is biopsied and the biopsy fragments are placed in a separate container and labeled as to their location. This finding does not alter the plan for RFA inside TA for that particular procedure, and the USL outside the TA is treated according the standard practice under hospital standard of care.

During all endoscopies, re-tattoos will be performed if necessary. If clinically indicated, extra endoscopies can always be performed.

12 Months Follow-up Endoscopy

No RFA is provided to any subject at the 12-month primary endpoint biopsy visit.

For the biopsy methodology for the primary endpoint:

1. If there are no USLs within the TA, see Section 10.4, “Scenario #1: No USLs are present”
2. If there are one or more persistent USLs within the TA, see Section 10.4, “Scenario #2: USLs are present”

If there are any USLs discovered outside the original USL bearing esophagus, these may be biopsied or resected, but must be submitted in separate containers are not considered in the primary endpoint analysis.

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

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. 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.

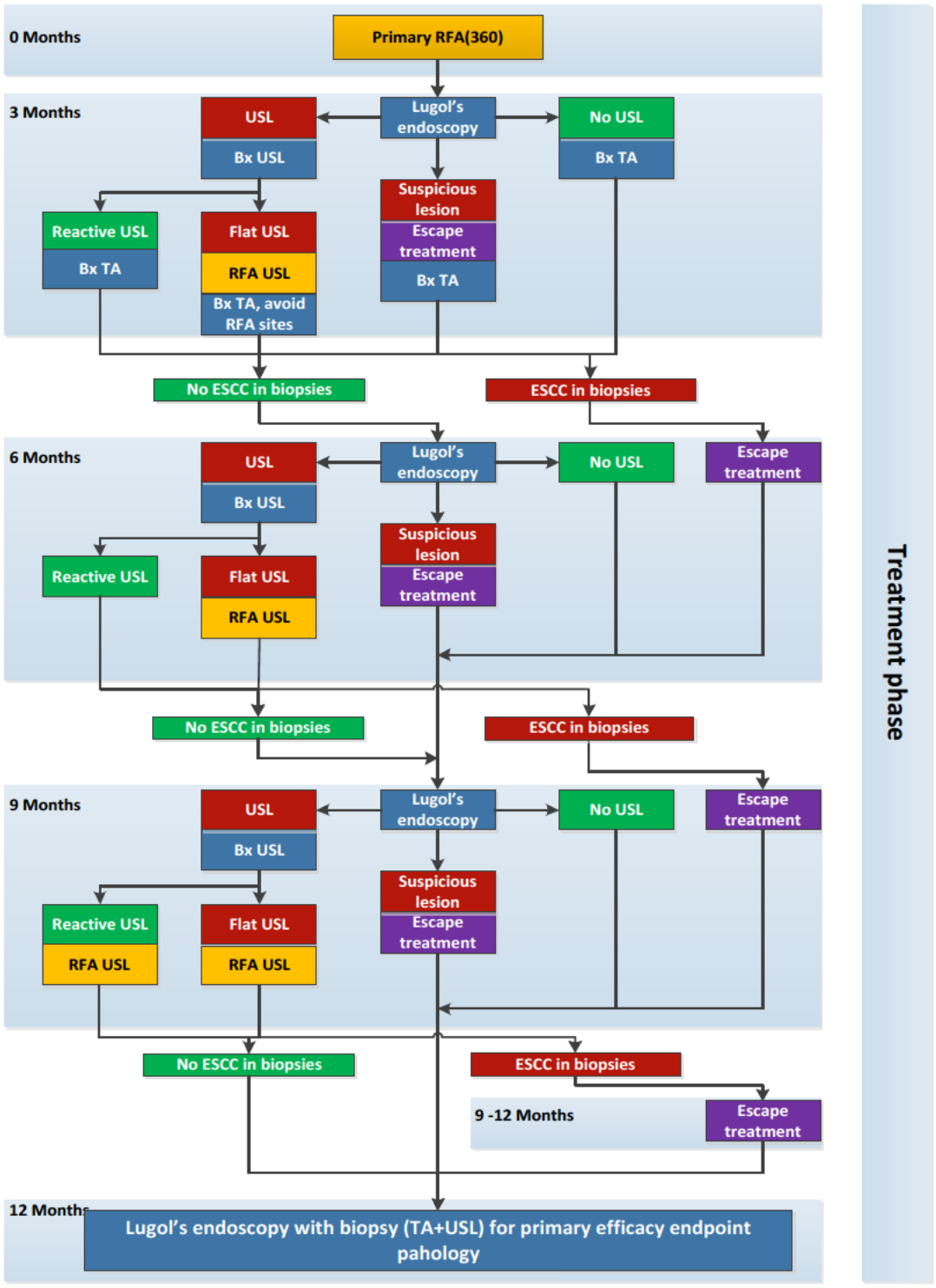

Figure 1. Decision Tree for Subject Flow Through in Treatment Phase (adapted from He et al., 2014 **(18)**)

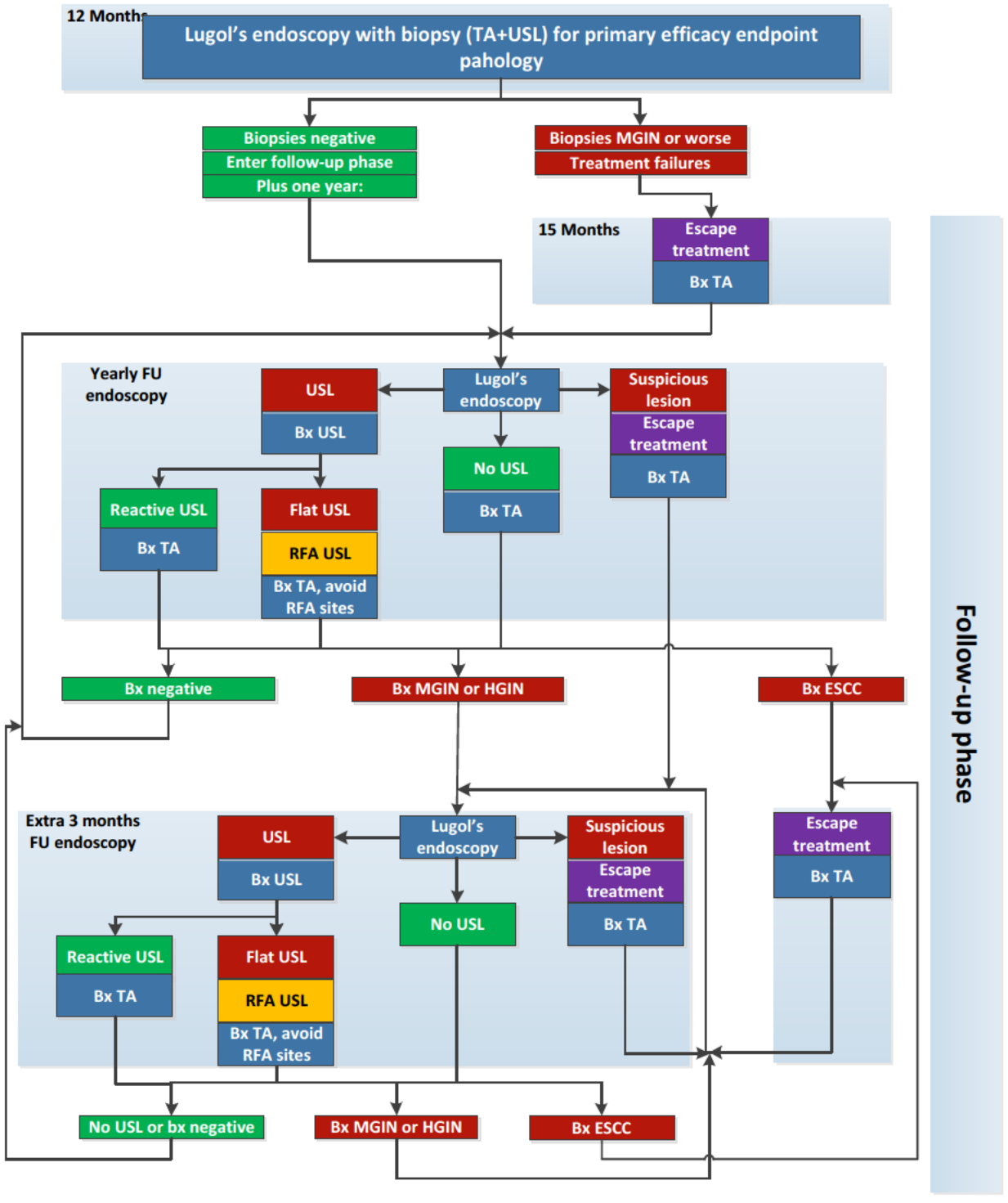

Figure 2. Decision Tree for Subject Flow in Follow-Up Phase (adapted from He et al., 2014 (18))

9.4.2. Follow-up Phase

All subjects with a CR at 12 months will immediately enter follow-up phase. All patients with residual ESCN at 12 months who achieve CR upon endoscopic escape treatment will also enter the follow-up phase. All patients who progress to ESCC and require escape treatment during the trial, including non-endoscopic, will enter the follow-up phase regardless of primary endpoint failure to assess secondary endpoints. All endoscopies in the follow-up phase will be observed by an expert from CICAMS.

Follow-up procedures include (fig 2):

Annual follow-up endoscopy visit:

- upper endoscopy
- re-tattoo the TA, as necessary
- stain the esophagus with Lugol's solution
- map the entire esophagus for USLs

For TA:

i. If no USLs in TA, perform biopsies of TA (2 biopsy specimens are obtained for every 2cm segment of the original USL-bearing esophageal segment)
ii. If unstained lesion (USLs) are found in the TA, each lesion will be biopsied (as described in section 9.4.1, scenario #2). In addition, 2 biopsy specimens are obtained for every 2cm segment of the original USL-bearing esophageal segment that does not now contain USLs. All flat USLs will be treated with RFA. One exception needs to be addressed in line with the treatment phase: clearly reactive USLs may be biopsied and left untreated.
iii. Any non-flat lesion or lesion suspicious for ESCC (e.g. 'pink sign') in TA will be treated with escape treatment (see section 9.4.3 for description), at the discretion of the physician under hospital standard of care.
iv. Subsequent follow-up will be determined by pathology results:
    1. If biopsies show LGIN or less: next follow-up endoscopy will occur in a year.
    2. If any biopsies are found to have MGIN or HGIN, endoscopy with RFA will be repeated at 3 month intervals until resolution of MGIN or HGIN is demonstrated. If patient still harbors MGIN or HGIN after a maximum of 4 consecutive 3-monthly RFA sessions, escape treatment will be performed.
    3. If ESCC is found in any biopsy, the patient will be treated with escape treatment.

Outside the TA:

v. If no USLs, biopsies will not be necessary
vi. If USLs are found outside the TA, each lesion should be biopsied and treated per investigator's discretion.

1. If any biopsies from outside the TA are found to be MGIN or worse, patient will be treated and followed-up at the discretion of the physician under hospital standard of care.

- Central pathology review of biopsies for all biopsies or resection specimens during FU, with independent reading from two pathologists in case of recurrent or progressive disease.
- Safety assessment

If clinically indicated, Investigator may always perform extra endoscopies in addition to figure 2.

9.4.3. Escape treatment: Endoscopic (EMR or ESD) or Non-Endoscopic Therapy during Treatment or Follow-up Phase

Several indications for escape treatment exist:

- Any non-flat lesion (Paris type 0-I, 0-IIa, 0-IIc, 0-III) during treatment or follow-up phase
- Any abnormality under WLE or Lugol's chromoendoscopy that is suspicious for ESCC (e.g. 'pink sign' USL, defined as a color change after Lugol's staining: initially whitish yellow and pink 2-3 minutes later)
- ESCC in biopsies during treatment or follow-up phase (defined as progression of disease)
- Presence of MGIN or worse in any biopsies from TA at the 12 months endoscopy
- Persistent MGIN or worse during follow-up phase despite a maximum of 4 consecutive 3-monthly RFA sessions
- If clinically indicated per Investigator's discretion

Escape treatment can be performed endoscopically (EMR or ESD), or non-endoscopically (surgery, radiotherapy or chemotherapy) per investigator's discretion under the hospital's standards of care. All patients, regardless of treatment used or failure of the primary endpoint, will be followed to study termination for assessment of secondary endpoints:

- Patients who undergo non-endoscopic therapy will be considered a failure for the primary endpoint, but will be tracked through the 5-year follow-up to assess secondary endpoints.
- For patients who undergo endoscopic treatment, final pathology is required:
    - If the disease stage is eligible for endoscopic escape treatment (i.e.: good to moderate differentiation and negative vertical resection margins and m1/m2/m3/sm1 disease and without lymphovascular infiltration), further treatment and/or follow-up endoscopies after the escape treatment will occur according to

the study protocol. The application of RFA after endoscopic resection may be performed after minimally 8 weeks later.

- If the disease stage exceeds the limits for endoscopic treatment (i.e.: either one of: poor differentiation, positive vertical resection margins, sm-2 or sm-3 invasion or lymphovascular invasion), patient will be considered a failure for the primary endpoint. The Investigator will decide which escape treatment to perform, and the patient will be followed to study termination for assessment of secondary endpoints.
- If histology does not demonstrate ESCC, patient will remain eligible for inclusion as a success in the primary and secondary endpoints. The application of RFA after endoscopic resection may be performed after minimally 8 weeks later.

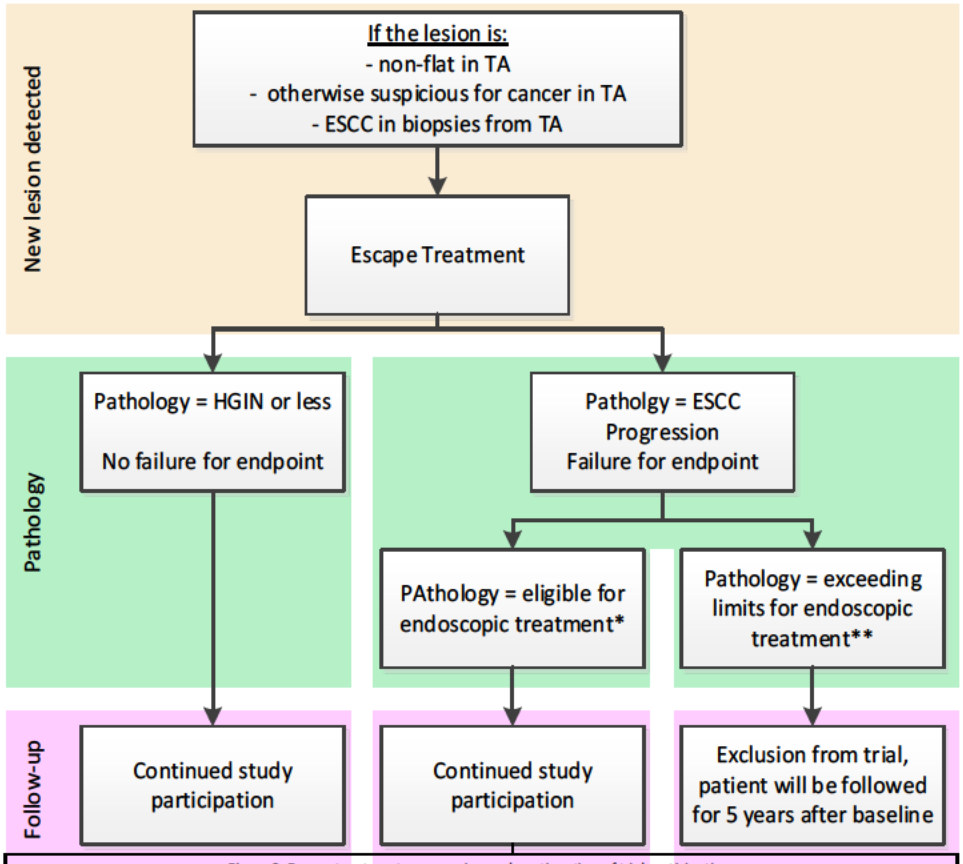

Figure 3. Escape treatment, progression and continuation of trial participation.
* Pathology eligible for endoscopic treatment = sm1; and good to moderate differentiation; and without lymphovascular infiltration; and with negative vertical resection margins.
**Pathology exceeding limits for endoscopic treatment = sm2/3; or poor differentiation; or lymphovascular infiltration; or positive vertical resection margins
Abbreviations: ESCC = esophageal squamous cell cancer; HGIN = high grade intra-epithelial neoplasia; TA = treatment area

Discharge Instructions after RFA Procedures

- Liquid acetaminophen with narcotic per oral as needed for pain
- Liquid antacid, lidocaine, and sucralfate slurry or Almagate Suspension for first 5 days, as needed
- Liquid diet for 3 days, then soft diet for 4 days, then normalize
- At the direction of the physician, anti-thrombotic agents should be avoided for 7 days before and after any RFA procedure.
- All patients commence proton pump inhibitor (PPI) medication (esomeprazole 40 mg bid) after the Primary RFA to allow restoration of a normal epithelium. Patients will continue PPI after each RFA session until endoscopy and biopsy demonstrate no further MGIN+ and no need for further RFA.
- Contact physician for any vomiting, shortness of breath, pain not controlled on medication, fever, or bleeding.
- Subject is educated to not eat very hot foods including soups, and not drink very hot liquids as such behavior can delay healing and potentially promote stricture formation and prolonged pain. Subject is instructed to not eat or drink anything in which they are unable to comfortably place their finger for at least 10 seconds prior to ingesting.

9.5. Assessment of Efficacy

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 will be summarized separately.

9.6. Assessment of Safety

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.

9.7. Recording Data

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. All data recorded on the eCRF will be supported by a source document. Examples of source data are hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries

or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

This study will utilize electronic Case Report Forms (eCRFs). The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained.

9.8. Deviation Handling

The investigator must notify Medtronic and the reviewing IRB of any deviation from the protocol when specific to the protection of the life or physical well-being of a subject in an emergency. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency has occurred. Except in such an emergency, prior written approval by Medtronic and the site IRB/EC is required for changes in or deviations from the plan. All deviations will be reported per the site's IRB/EC deviation policy. Should any deviations from the protocol occur, these will be reviewed by Medtronic for their clinical significance. If the event is performed without written approval from all parties, the investigator may be terminated from the study. Corrective and preventive actions and principal investigator disqualification will be included in the Clinical Study Management Plan. If further escalation is needed, it may result in Corrective and Preventive Action (CAPA), suspension, or termination. When conducting clinical research, an investigator must comply with all applicable rules and regulations. The falsification of information, actions determined to fraudulent or criminal in nature, failure to comply with investigator's responsibilities, failure to appropriately fulfill all study-related responsibilities or failure to disclose relevant financial interests may lead to the investigator being disqualified. If it is determined that there is investigator fraud, or strong evidence of fraud, the course of action may include, but is not limited to: potential exclusion from analyses, site closure, notification of the responsible IRB/EC of the actions to be taken, notification of key stakeholders and/or study team of the actions to be taken, notification of appropriate regulatory authority(ies) and/or restrictions on future participation in clinical studies.
Protocol deviations identified by the Monitor during a monitoring visit should be discussed with the Principal Investigator/ Study staff involved at the time of discovery. Protocol non-compliance will be documented accordingly and communicated again in writing to the site within the follow-up letter. Monitors will also escalate the deviations significant in nature to the study manager (or designee), as soon as possible.

9.9. Subject Withdrawal or Discontinuation

Any subject who wishes to withdraw from this investigation on his/her own accord and for whatever reason is entitled to do so without obligation and prejudice to further treatment. In addition, the

Principal Investigator or study endoscopist may decide for reasons of medical prudence, to withdraw a subject.

In either event, the Principal Investigator or study endoscopist will clearly document the date and reason(s) for the subject's withdrawal from this investigation on the Study Exit CRF and should indicate whether or not he considers it related to the device.

Every attempt will be made to contact subjects who are noncompliant. Subjects will be considered "Lost to Follow-up" once the following steps have been taken:

1. Two phone calls should be made to the subject. Each attempt should be clearly documented in the source documents and the response or lack thereof should be captured.
2. If there is no response to the phone calls, then an official letter should be written to the subject. A copy of the letter should be retained in the subject's source document.
3. Additionally, the site should attempt to reach out to the subject's general practitioner to determine the status of the subject.
4. After a period of four (4) weeks, after all of the above steps have been taken, the subject will be considered "Lost to Follow-up". The sponsor should be notified and the Study Exit CRF should be completed.

All patients, regardless of failure of the primary endpoint or use of escape treatment during the trial, will be followed to study termination to assess secondary endpoints. A patient that has not been withdrawn or otherwise disqualified from the study, will have completed the study when the patient has finished all follow-up visits and the study has been terminated.

9.10. Definitions

-CR = complete response

Absence of MGIN or worse in biopsies from TA at a single endoscopy.

- Escape treatment

Escape treatment is indicated for lesions with (i) ESCC in biopsies, (ii) non-flat lesions, or (iii) lesions otherwise suspicious for ESCC (e.g. pink-sign positive lesions). Escape treatment will be performed by investigator's distinction and per hospital's standards of care. Subsequent pathology assessment determines whether patient is defined as progressor and failure for the efficacy endpoint.

- Progressive disease

This term is applicable during the whole study. Progressive disease is defined as ESCC in any biopsy or resection specimen. Progressive disease on biopsy will always be treated with escape treatment.

Patients with progressive disease within the first 12 months are a failure for the primary efficacy endpoint, whereas progression patients in subsequent 4 years of follow-up are a failure for the durability endpoint. Progressive disease can be classified into 2 categories based on pathology:

- Eligible for endoscopic treatment, if all of the following characteristics are met: good to moderate differentiation, negative vertical resection margins, m1/m2/m3/sm1 disease and without lymphovascular infiltration.
- Exceeding the limits for endoscopic treatment, if any of the following characteristics was found: poor differentiation, positive vertical resection margins, sm-2 or sm-3 invasion or lymphovascular invasion.

- Treatment failure

This term is applicable to the first 12 months of study. All patients with residual ESCN at the 12 months endoscopy, and patients who progressed to ESCC before 12 months, will be defined as treatment failures.

- Sustained CR

This term is applicable during follow-up, to all patients that were not defined as treatment failures at 12 months. Sustained CR is defined as sustained eradication of MGIN or worse in biopsies from TA, during all FU endoscopies until 60 months.

- Recurrent disease

This term is applicable during follow-up, to all patients that were not defined as treatment failures at 12 months. Recurrent disease is defined as flat (Paris type 0-IIb) USLs with MGIN or HGIN in biopsies from TA during FU, independent of baseline pathology. Recurrent disease will be treated with RFA initially, or escape treatment if persistent, as described in section 9.4.3

10. Risks and Benefits

10.1. Potential Risks

Potential risks of the use of the Barrx™ Flex Radiofrequency Ablation System for treatment of ESCN have been evaluated in Clinical Evaluation Reports for the Barrx™ Circumferential Radiofrequency Ablation System (REG-0023, Revision C, August 12, 2014), the Barrx™ Focal Radiofrequency Ablation System (REG-0022, Revision B, December 6, 2013), and the product Instructions for Use (Ref 32041-18, 32041-22, 32041-25, 32041-28, 32041-31, 3441C; Version 717-0050-01 B and Ref 90-9100, 90-9200, 90-9300; Version 717-0053-01 B).

10.2. Potential Benefits

Potential benefits to the subject include the potential for complete eradication of ESCN, which has been reported in the literature with rates between 50% and 100% (11, 18, 19, 23-25, 27, 28).

10.3. Risk-Benefit Rationale

As described in the Clinical Evaluation Reports referenced above, risk analyses for the Barrx™ Circumferential Radiofrequency Ablation System and the Barrx™ Focal Radiofrequency Ablation System was conducted in compliance with ISO 14971-Risk Management for Medical Devices. The overall evaluation of the residual system risks found no unacceptable design or process hazards of significant impact to the safety and reliability of the Barrx™ Radiofrequency Ablation System. The residual risks have been rated as either broadly acceptable or as low as possible.

11. Adverse Events and Device Deficiencies

11.1. Definitions/Classifications

Adverse Events

Adverse event (AE) definitions used in this study are based on ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice). Adverse events will be collected starting from enrollment into the study.

Adverse Event (AE)

An Adverse Event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1 This definition includes events related to the investigational medical device or the comparator.
NOTE 2 This definition includes events related to the procedures involved.
NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

Serious Adverse Event (SAE)

A Serious Adverse Event is an adverse event that has

a) Led to death,

b) Led to serious deterioration in the health of the subject, that either resulted in

1) A life-threatening illness or injury, or

2) A permanent impairment of a body structure or a body function, or

3) In-patient or prolonged hospitalization, or

4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.

Adverse Device Effect (ADE)

An Adverse Device Effect is an adverse event related to the use of an investigational medical device.

NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)

An Unanticipated Serious Adverse Device Effect (USADE) is defined as serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Adverse Event Severity Classification

Severity will be defined according to the following criteria:

Mild	Awareness of event, but easily tolerated
Moderate	Discomfort enough to cause some interference with activities of daily living (ADL)

Severe	Incapacitating, with an inability to perform ADL

An AE can be classified as severe and not deemed a SAE. Similarly, a SAE is not automatically severe in nature.

Adverse Event Relationship Classification

Causality assessments define the relationship between the use of the medical device (including the medical-surgical procedure) and the occurrence of each adverse event. During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the Clinical Evaluation Report and the Risk Management Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each AE and SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures:

- *Not related*: relationship to the device or procedures can be excluded when:
  - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures
  - the event has no temporal relationship with the use of the investigational device or the procedures;
  - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
  - the event involves a body-site or an organ not expected to be affected by the device or procedure;
  - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
  - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
  - harms to the subject are not clearly due to use error;
  - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- *Unlikely*: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- *Possible*: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- *Probable*: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
- *Causal relationship*: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
  - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has a temporal relationship with investigational device use/application or procedures;
  - the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
  - the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
  - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);

- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The sponsor and the investigators will distinguish between the serious adverse events related to the device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as “possible”.

Adverse Event Outcome Classification

Outcome of the event will be defined according to the following:

- *Resolved:* The event has fully resolved at the end of the study.
- *Resolved with sequelae*: The event has resolved, but retained pathological conditions resulting from the prior disease or injury.
- *Continuing:* The event is ongoing at the end of the study.
- *Death:* This event is determined to be the cause of death.

11.2. Reporting of Adverse Events

Assessment of the occurrence of an AE will be based on changes in the subject’s physical examination, laboratory results and/or signs and symptoms. Adverse events will be monitored until a subject completes the study. Medical care will be provided, as defined in the informed consent, for any AE related to study participation. Adverse events will be collected on an AE CRF and applicable source documentation. To the extent possible, the event to be recorded and reported is the event diagnosis as opposed to event symptoms (e.g., fever, chills, nausea and vomiting in the presence of a clinically diagnosed infection is to be reported as infection only). For the purposes of this protocol, only those AEs occurring after enrollment will be recorded.

The following should not be considered an AE:

- A condition requiring a preplanned procedure unless the condition worsened since enrolment
- A preexisting condition found as a result of screening, unless the condition has worsened since enrollment.

All responses to the above events that require treatment beyond the institution's standard procedures will be reported as AEs.

All AEs observed during the course of this study, regardless of severity or relationship to the device will be recorded on the appropriate CRF.

Notification to Authorities

The following events are generally considered reportable during the course of this study and should be reported to the sponsor:

- any AE, ADE, SADE, USADE, or SAE
- any Device Deficiency
- new findings/updates in relation to already reported events.

Type	Report to	Reporting Timeframe (from time of learning of event)
Device Deficiency	Sponsor	Within 48 hours
AE/ ADE	Sponsor	Recommended within 10 working days
	IRB/EC	Per IRB/EC reporting requirements
SAE/ SADE/USADE	Sponsor	Within 24 hours
	IRB/EC	Within 10 working days, unless stricter reporting is required by local regulations or IRB/EC
DD with SADE potential	Sponsor	Within 24 hours
	IRB/EC	Within 10 working days, unless stricter reporting is required by local regulations or IRB/EC
Death	Sponsor	Within 24 hours
	IRB/EC	Required within 10 working days, unless stricter reporting is required by local regulations or IRB/EC

- Events will be reviewed by sponsor or designee to determine any reporting obligations to National Competent Authorities and IRB/EC.
- According to the CFDA Notice No. 766-2008, Provisions of Adverse Events Surveillance and Revaluation of Medical Device (Trial),
  1) Death events should be reported to the local provincial technical institution of medical device adverse events surveillance within 5 working days;
  2) Events led to serious injury or potentially led to serious injury or death, should be reported to the local provincial technical institution of medical device adverse events surveillance within 15 working days.

Any Adverse Event will be recorded on the **Adverse Event CRF.**

11.3. Device Deficiencies

A device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance, such as malfunction, misuse or use error and inadequate labeling.

All device deficiencies will be documented on the Device Complaint CRF (1 for each Device Deficiency), and the device should be returned to the Sponsor for analysis, if possible. Instructions for returning the device will be provided. Device deficiencies should also be documented in the subject's medical record.

Device Deficiencies that led to an AE are reported on the AE CRF and the Device Complaint CRF.

12. Data Review Committees

Independent Medical Advisors

The Sponsor will utilize Independent Medical Advisor(s) to provide an independent medical review and adjudication of pre-specified adverse events in support of protocol defined endpoint data. The Independent Medical Advisor(s) will be qualified, board-certified physicians.

During the review of adverse events or overall study utility, efficacy, and safety data, the Independent Medical Advisor(s) will be blinded to the investigational site.

13. Statistical Design and Methods

13.1. General Principles

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.

13.2. Sample Size Determination

The proposed sample size of up to 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 (18). 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.

13.3. Analysis Populations

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.

13.4. Effectiveness Analysis

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 will be summarized separately.

13.5. Safety Analysis

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.

13.6. Additional Analyses

Subgroup analysis will be performed for potential confounding factors such as study center, age, gender, use of escape treatment, 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.

Additionally, interim data summaries may be performed, as needed, for requirements related to abstract submission, IRB requests, or Independent Medical Advisor requests. Considering the feasibility nature of the study, no multiplicity adjustment is considered. Efficacy and safety will be specifically assessed after enrollment of up to 50 patients.

Any departure or deviation from these planned statistical methodologies will be documented and discussed in the Statistical Analysis Plan (SAP) that will include the statistical rationale for divergence.

14. Ethics

14.1. Statement(s) of Compliance

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), and any regional or national regulations, as appropriate. The principles of the Declaration of Helsinki have all been implemented by means of the

patient informed consent process, EC approval, study training, clinical study registration, preclinical testing, risk benefit assessment, and publication policy. Pediatric, legally incompetent, or other vulnerable subjects are not eligible for the study.

The clinical investigation will not begin until all necessary approvals/favorable opinions are obtained from the appropriate EC/IRBs or regulatory authority, as appropriate. Should an EC/IRB or regulatory authority impose any additional requirements, they will be followed.

Information regarding the study and study data will be made available via publication on clintrials.gov. Additionally, the results of this study will be submitted for publication in an appropriate journal.

14.2. Protocol Compliance

No changes to the protocol will be permitted without the written approval from the Sponsor and the IRB/EC. The investigator must notify the Sponsor and the reviewing IRB/EC of any deviation from the Investigational Plan when specific to the protection of the life or physical well-being of a subject in an emergency. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency has occurred. Except in such an emergency, prior written approval by the Sponsor and the site IRB/EC is required for changes in or deviations from the Plan. All deviations will be reported per the site's IRB/EC deviation policy. Should any deviations from the Investigational Plan occur, these will be reviewed by the Sponsor for their clinical significance. If the event is performed without written approval from all parties, the investigator may be terminated from the study.

15. Study Administration

15.1. Monitoring

Site visits will be conducted by an authorized Sponsor representative to inspect study data, subjects' medical records, and CRFs in accordance with the respective local and national government regulations and guidelines (if applicable). The Study Investigator and the investigating site will permit authorized clinical research personnel and clinical monitors from the Sponsor and/or designee(s) employed by the Sponsor to review completed CRFs, IRB decisions, and Investigator, clinical site records, and facilities relevant to this study at regular intervals throughout the study per the monitoring plan. Additionally, subject charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. The accuracy and quality of the data obtained from the investigator and maintained by the Sponsor will be confirmed through a structured program of clinical field auditing and internal review detailed in the monitoring plan. In instances where data protection regulations prohibit the direct examination of hospital records by the study Sponsor or designee(s), the Investigator will cooperate in a system of source data verification with the Sponsor. Monitoring may be performed with in person visits or remotely, when applicable.

To ensure the rights, safety, and welfare of study subjects are being maintained, the monitor will review training records to ensure all study staff are trained on the study protocol and use of the study devices. If the monitor discovers that an investigator is not complying with the signed Investigator Agreement, the investigational plan, applicable laws, or any conditions of approval imposed by the reviewing IRB or Competent Authority, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, device shipments to the investigator may be discontinued and the investigator's participation in the investigation terminated. The monitor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

15.2. Data Management

This study will utilize an electronic database and eCRF. All data requested on the CRF are considered required. Data points not collected and/or recorded will be considered deviations unless otherwise specified. The Principal Investigator must ensure the accuracy and completeness of the recorded data and then provide his/her signature on the appropriate CRFs. The Investigator's electronic signature for specific CRFs will be documented in compliance with local regulations. Changes to data previously submitted to the sponsor will require a new electronic signature by the Investigator to acknowledge/approve the changes.

Visual and/or computer data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Oracle remote data capture (RDC) system and will be issued to the site for appropriate response. The site staff will be responsible for resolving all queries in the database.

15.3. Direct Access to Source Data/Documents

The investigator must agree to the inspection of study-related records by the Regulatory Authority/Sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/Sponsor representatives/EC representatives.

15.4. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will be kept confidential. Only the subject number and initials will be recorded in the CRF, and if the subject name appears on any other document, it must be obliterated. In cases were the local low does not allow using the subject initials, an identifying number will be assigned.

A Subject Log will be maintained in a secure locked location by the Investigator to enable tracing of specific case study numbers to subjects, in the event required.

Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor, IRBs, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Subjects will also be informed that information regarding the study that does not include subject identifiers will be posted on clinicaltrials.gov.

If the results of the trial are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

15.5. Liability

Medicine is not an exact science and no guarantees can be made as to the results. The procedure to be followed in this study may involve risks and discomforts, as with any procedure. All the risks of being treated with the Barrx™ Flex Radiofrequency Ablation System are the same whether in clinical trials or not. Nevertheless, study related insurance will be available.

The sponsor shall be responsible for any medical expense and will provide compensation for injury or death resulting from participation in the study. However, it shall be excluded from the sponsor's responsibility if the injury or death is in a result of medical institute or the investigator's fault.

In the event of physical injury or physical illness resulting from participation in this study, any medical treatment that is needed will be provided. The expense of any relevant medical treatment for physical injury or physical illness resulting from participation in this study will be reimbursed by Medtronic.

15.6. CIP Amendments

Changes or clarifications to the protocol may be described in a formal protocol amendment as needed, including a summary of changes and a rationale for the changes. Changes to the CIP will not be implemented until all necessary approvals/favorable opinions are obtained from the appropriate IRB/ECs or regulatory authority, as appropriate.

15.7. Record Retention

The investigator will maintain the records of the study including all pertinent correspondence, the study protocol with any/all amendments, all correspondence with and approval from the IEC, the clinical trial

agreement, the Investigator Agreement, device accountability records, individual subject records, and signed ICFs. Subject files and other source data must be kept for a period of not less than 2 years after the latter of the following two dates: the date on which this investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket application. Records may need to be maintained by the Principal Investigator for a longer duration if national regulations require or if agreed to in writing with the Sponsor. All data and documents should be made available if requested by relevant authorities. The sponsor must keep study records for no less than 15 years.

15.8. Publication and Use of Information

The Medtronic Publication and Authorship Policy is aligned with the International Committee of Medical Journal Editors (ICMJE) recommendations (www.icmje.org). The Sponsor will seek to publish, in appropriate peer-reviewed journals and scientific conferences, results of clinical studies where human subjects are involved, regardless of outcome. While study results are owned by the Sponsor, all data on which a publication is based will be made available to all authors as required for their participation in the publication process. Furthermore, data may be published or used by study investigators provided that such publication or use is in accordance with this protocol, the Medtronic Publication and Authorship Policy, and the Clinical Investigation Agreement. Investigators must submit a copy of all manuscripts and/or abstracts to the Sponsor for review and comment 30 days prior to planned submission. Medtronic acknowledges that its right to review and comment shall relate solely to the proprietary, licensing, and/or confidential rights Medtronic may have in such proposed publication, rather than whether such results and/or opinions are favorable to Medtronic.

The publication of substudies, post-hoc analyses, regional results, or single-center experiences based on multicenter clinical studies should not precede that of the primary multicenter publication, and should cite the primary publication whenever possible, as required by specific journal and scientific meeting guidelines.

Medtronic involvement in a publication (e.g., funding of the study; sponsor of the study; collection, analysis, and interpretation of data; professional writing assistance) must be disclosed according to journal-specific policies, submission requirements, and prevailing editorial standards, in addition to those specified by International Committee of Medical Journal Editors. Authors must ensure that an acknowledgement/disclosure statement is included in the body of the manuscript for Medtronic to review for accuracy. All authors must also disclose financial or personal affiliations that could be considered conflicts of interest as per journal/conference requirements.

To enable health care providers, payers, and patients access to the wealth of Medtronic's research, Medtronic will report its scientific data in accordance with the principles outlined in the Guidance Document on Registration and Reporting Results of Company-Sponsored Clinical Trials Under FDAAA 2007 (Title VIII).

15.9. Suspension or Early Termination

The Sponsor reserves the right to discontinue the study at any stage, with suitable written notice to all investigators; all reviewing institutional review boards (IRBs) or ethic committees (ECs). Similarly, investigators may withdraw from the study at any time, subject to providing written notification to the Sponsor 30 days prior to the date they intend to withdraw. However, the Sponsor and investigators will be bound by their obligation to complete the follow-up of subjects already participating in the study. The subjects must be followed according to the clinical protocol, and information obtained during subject follow-up shall be reported to the Sponsor on the appropriate CRF.

16. References

1. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al. The Global Burden of Cancer 2013. JAMA oncology. 2015;1(4):505-27. doi: 10.1001/jamaoncol.2015.0735. PubMed PMID: 26181261; PubMed Central PMCID: PMC4500822.

2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108. doi: 10.3322/caac.21262. PubMed PMID: 25651787.

3. Chen W, Zheng R, Zeng H, Zhang S, He J. Annual report on status of cancer in China, 2011. Chinese journal of cancer research = Chung-kuo yen cheng yen chiu. 2015;27(1):2-12. doi: 10.3978/j.issn.1000-9604.2015.01.06. PubMed PMID: 25717220; PubMed Central PMCID: PMC4329176.

4. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. World journal of gastrointestinal oncology. 2014;6(5):112-20. doi: 10.4251/wjgo.v6.i5.112. PubMed PMID: 24834141; PubMed Central PMCID: PMC4021327.

5. Zhang HZ, Jin GF, Shen HB. Epidemiologic differences in esophageal cancer between Asian and Western populations. Chinese journal of cancer. 2012;31(6):281-6. doi: 10.5732/cjc.011.10390. PubMed PMID: 22507220; PubMed Central PMCID: PMC3777490.

6. Dawsey SM, Lewin KJ, Liu FS, Wang GQ, Shen Q. Esophageal morphology from Linxian, China. Squamous histologic findings in 754 patients. Cancer. 1994;73(8):2027-37. PubMed PMID: 8156507.

7. Taylor PR, Abnet CC, Dawsey SM. Squamous dysplasia--the precursor lesion for esophageal squamous cell carcinoma. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2013;22(4):540-52. doi: 10.1158/1055-9965.EPI-12-1347. PubMed PMID: 23549398; PubMed Central PMCID: PMC3681095.

8. Dawsey SM, Lewin KJ, Wang GQ, Liu FS, Nieberg RK, Yu Y, et al. Squamous esophageal histology and subsequent risk of squamous cell carcinoma of the esophagus. A prospective follow-up study from Linxian, China. Cancer. 1994;74(6):1686-92. PubMed PMID: 8082069.

9. Wang GQ, Abnet CC, Shen Q, Lewin KJ, Sun XD, Roth MJ, et al. Histological precursors of oesophageal squamous cell carcinoma: results from a 13 year prospective follow up study in a high risk population. Gut. 2005;54(2):187-92. doi: 10.1136/gut.2004.046631. PubMed PMID: 15647178; PubMed Central PMCID: PMC1774842.

10. Giri S, Pathak R, Aryal MR, Karmacharya P, Bhatt VR, Martin MG. Incidence trend of esophageal squamous cell carcinoma: an analysis of Surveillance Epidemiology, and End Results (SEER) database. Cancer causes & control : CCC. 2015;26(1):159-61. doi: 10.1007/s10552-014-0485-0. PubMed PMID: 25376829.

11. Bergman JJ, Zhang YM, He S, Weusten B, Xue L, Fleischer DE, et al. Outcomes from a prospective trial of endoscopic radiofrequency ablation of early squamous cell neoplasia of the esophagus. Gastrointest Endosc. 2011;74(6):1181-90. doi: 10.1016/j.gie.2011.05.024. PubMed PMID: 21839994; PubMed Central PMCID: PMC3505032.

12. Ohashi S, Miyamoto S, Kikuchi O, Goto T, Amanuma Y, Muto M. Recent Advances From Basic and Clinical Studies of Esophageal Squamous Cell Carcinoma. Gastroenterology. 2015;149(7):1700-15. doi: 10.1053/j.gastro.2015.08.054. PubMed PMID: 26376349.

13. Lee CT, Chang CY, Tai CM, Wang WL, Tseng CH, Hwang JC, et al. Endoscopic submucosal dissection for early esophageal neoplasia: a single center experience in South Taiwan. Journal of the Formosan Medical Association = Taiwan yi zhi. 2012;111(3):132-9. doi: 10.1016/j.jfma.2010.12.002. PubMed PMID: 22423666.

14. Teoh AY, Chiu PW, Yu Ngo DK, Wong SK, Lau JY, Ng EK. Outcomes of endoscopic submucosal dissection versus endoscopic mucosal resection in management of superficial squamous

esophageal neoplasms outside Japan. Journal of clinical gastroenterology. 2010;44(9):e190-4. doi: 10.1097/MCG.0b013e3181ce52fb. PubMed PMID: 20844363.

15. Isomoto H, Yamaguchi N, Minami H, Nakao K. Management of complications associated with endoscopic submucosal dissection/ endoscopic mucosal resection for esophageal cancer. Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society. 2013;25 Suppl 1:29-38. doi: 10.1111/j.1443-1661.2012.01388.x. PubMed PMID: 23368404.

16. Funakawa K, Uto H, Sasaki F, Nasu Y, Mawatari S, Arima S, et al. Effect of endoscopic submucosal dissection for superficial esophageal neoplasms and risk factors for postoperative stricture. Medicine (Baltimore). 2015;94(1):e373. doi: 10.1097/MD.0000000000000373. PubMed PMID: 25569662; PubMed Central PMCID: PMC4602840.

17. Wang GQ, Jiao GG, Chang FB, Fang WH, Song JX, Lu N, et al. Long-term results of operation for 420 patients with early squamous cell esophageal carcinoma discovered by screening. The Annals of thoracic surgery. 2004;77(5):1740-4. doi: 10.1016/j.athoracsur.2003.10.098. PubMed PMID: 15111177.

18. 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.

19. Wang WL, Chang IW, Chang CY, Lin JT, Mo LR, Wang HP, et al. Circumferential balloon-based radiofrequency ablation for ultralong and extensive flat esophageal squamous neoplasia. Gastrointest Endosc. 2014;80(6):1185-9. doi: 10.1016/j.gie.2014.07.025. PubMed PMID: 25257127.

20. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2013;11(10):1245-55. doi: 10.1016/j.cgh.2013.03.039. PubMed PMID: 23644385; PubMed Central PMCID: PMC3870150.

21. Shaheen NJ, Overholt BF, Sampliner RE, Wolfsen HC, Wang KK, Fleischer DE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology. 2011;141(2):460-8. doi: 10.1053/j.gastro.2011.04.061. PubMed PMID: 21679712; PubMed Central PMCID: PMC3152658.

22. Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. The New England journal of medicine. 2009;360(22):2277-88. doi: 10.1056/NEJMoa0808145. PubMed PMID: 19474425.

23. Pouw RE, Gondrie JJ, Curvers WL, Sondermeijer CM, Ten Kate FJ, Bergman JJ. Successful balloon-based radiofrequency ablation of a widespread early squamous cell carcinoma and high-grade dysplasia of the esophagus: a case report. Gastrointest Endosc. 2008;68(3):537-41. doi: 10.1016/j.gie.2008.03.1086. PubMed PMID: 18760181.

24. van Vilsteren FG, Alvarez Herrero L, Pouw RE, ten Kate FJ, Visser M, Seldenrijk CA, et al. Radiofrequency ablation for the endoscopic eradication of esophageal squamous high grade intraepithelial neoplasia and mucosal squamous cell carcinoma. Endoscopy. 2011;43(4):282-90. doi: 10.1055/s-0030-1256309. PubMed PMID: 21455869.

25. Haidry RJ, Butt MA, Dunn J, Banks M, Gupta A, Smart H, et al. Radiofrequency ablation for early oesophageal squamous neoplasia: outcomes form United Kingdom registry. World journal of gastroenterology. 2013;19(36):6011-9. doi: 10.3748/wjg.v19.i36.6011. PubMed PMID: 24106401; PubMed Central PMCID: PMC3785622.

26. Wang WL, Chang IW, Chen CC, Chang CY, Mo LR, Lin JT, et al. Radiofrequency Ablation Versus Endoscopic Submucosal Dissection in Treating Large Early Esophageal Squamous Cell Neoplasia. Medicine (Baltimore). 2015;94(49):e2240. doi: 10.1097/MD.0000000000002240. PubMed PMID: 26656367.

27. Zhang YM, Bergman JJ, Weusten B, Dawsey SM, Fleischer DE, Lu N, et al. Radiofrequency ablation for early esophageal squamous cell neoplasia. Endoscopy. 2010;42(4):327-33. doi: 10.1055/s-0029-1244017. PubMed PMID: 20235007; PubMed Central PMCID: PMC2848283.

28. Kajzrlikova I, Vitek P, Falt P, Urban O, Kominek P. Recurrent oesophageal intramucosal squamous carcinoma treated by endoscopic mucosal resection and subsequent radiofrequency ablation using HALO system. BMJ case reports. 2010;2010. doi: 10.1136/bcr.08.2010.3211. PubMed PMID: 22802374; PubMed Central PMCID: PMC3027413.

17. Appendices

Questions regarding safety or medical procedures should be directed to Medical Affairs. All other questions including reporting of serious adverse events and serious adverse device effects should be directed to Clinical Affairs.

Clinical Affairs	Medical Affairs
[redacted] Director of Global Clinical Affairs Early Technologies Medtronic, GI Solutions Minimally Invasive Therapies Group [redacted]	[redacted] Director of Global Medical Affairs Early Technologies Medtronic, GI Solutions Minimally Invasive Therapies Group [redacted]

Clinical Affairs	Medical Affairs
[redacted]	[redacted]

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted] PhD/Medical Writer
2.0	• Study procedure and follow up schedule • Effectiveness assessment • Eligibility criteria • DSMB • Transitioned into new Medtronic Template	[redacted] MD, PhD Fellow [redacted] Sr. Clinical Research Specialist
3.0	• Additional Site/PI information • Changed investigational device to device • Clarified languages in section 12	[redacted] Sr. Clinical Research Specialist [redacted] Clinical Project Manager

	• Clarified Table 2. Study Schedule and Assignments • Discharge instruction (Page 30): added "or Almagate Suspension"	
4.0	• Clinical Project Manager information change • Medical device model number corrected • Follow-up extension added • Additional secondary endpoints added • Clarified failures for the primary endpoint • Edited Table 2 and Figure 1 • Added Figure 2 • DSMB removed • Added +/- 4 weeks window to all visits post initial RFA procedure	[redacted] MD, PhD Director, Global Medical Affairs [redacted] Director, Global Clinical Affairs
5.0	• Local sponsor information change • Number of sites changed from 5 to up to 10 • Exclusion criteria revised to include patients who have had EMR > 3 months prior. • BQE changed to 1 week from 2 weeks prior to RFA	[redacted] Director, Global Medical Affairs [redacted] Director, Global Clinical Affairs
6.0	• Exclusion criteria # 6 revised to exclude patients who have had EMR or ESD <3 months prior. • Inclusion criteria #9 revised to include "EMR or ESD occurred > 3 months before enrollment, patients may be eligible for the study if procedure was curative (negative margins and no risk of lymph node involvement) and the patient has no other findings concerning for cancer." • Included 5 satellite sites of CICAMS • Run-in patients defined as up to 5 patients for each endoscopist that is inexperienced with RFA or has had no RFA onsite training from CICAMS.	[redacted] Director, Global Clinical Affairs
7.0	• Remove reference to 5 satellite sites of CICAMS	[redacted] Director, Global Clinical Affairs [redacted] Clinical Research Specialist