Title:	A Retrospective Registry Study to Evaluate the Long-Term Efficacy and Safety of Superficial Radiation Therapy (SRT) in Individuals with Non-Melanoma Skin Cancer (NMSC)
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SITE INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Retrospective Registry Study to Evaluate the Long-Term Efficacy and Safety of Superficial Radiation Therapy (SRT) in Individuals with Non-Melanoma Skin Cancer (NMSC)

Short Title: Long-Term Efficacy and Safety of SRT for NMSC

Lead Investigator:

Protocol Version And Date: Version 1.0; Aug 22, 2018.

I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated.

Site Principal Investigator Name: _____

Site Principal Investigator Signature _____

Date: _____

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
AAD	American Academy of Dermatology
AJCC	American Joint Committee on Cancer
BCC	Basal Cell Carcinoma
ºC	Degrees Celsius
CAP	College of American Pathologists
CM	Centimeters
EBT	Electronic Brachytherapy
ECT	Electrochemotherapy
ED&C	Electrodesiccation and Curettage
`HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
MMS	Mohs Micrographic Surgery
NCCN	National Comprehensive Cancer Network
NMSC	Non-Melanoma Skin Cancer
PDT	Photodynamic Therapy
PHI	Protected Health Information
RT	Radiation Therapy
SCC	Squamous Cell Carcinoma
SRT	Superficial Radiation Therapy
U.S.	United States
U.S. FDA	United States Food and Drug Administration
UV	Ultraviolet

ABSTRACT

Context

Non-melanoma skin cancer (NMSC) is the most common cancer in the United States (U.S.), with prevalence and incidence rapidly rising. Superficial radiation therapy (SRT) has been used for the treatment of NMSC since the 1900s, though its use declined since the development of Mohs micrographic surgery. With advances in radiation technology, there is a resurgence in the use of radiation therapy, more specifically, superficial radiation therapy in the treatment of NMSC. Superficial radiation therapy provides a viable treatment for NMSC but current literature on efficacy and long-term cure rates are needed.

Objectives

- The primary objective of this retrospective analysis is to evaluate long-term efficacy and safety of SRT when applied with the Sensus Healthcare SRT-100™ in the treatment of NMSC.
- The secondary objectives of this study are to evaluate the data for potential differences in cure rates with respect to lesion variables (tumor size, location and type) and patient demographics; and to evaluate the relationship between outcomes and treatment dosage/fractionation.

Study Design

- The study is a retrospective data registry design.
- The data will be used only as applicable to the objectives of this study.

Setting/Participants

- Retrospective data will be collected from medical records of patients treated for NMSC with the SRT-100™ prior to January 1, 2015, with follow-up data available.
- There will be multiple participating study sites in the United States who have access to the required patient population medical records.
- The number of participants will be determined by the number of qualifying patient files identified cross all participating sites.
- Medical record retrospective data will be included for males and females treated with SRT-100™ prior to January 1, 2015

- January 1, 2015 and for whom follow-up data is available. Subjects will have NMSC pathological diagnosis of confirmed squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) with Histopathological Grade of G1 (well differentiated); G2 (moderately differentiated) or Gx (not assessed in report), Qualifying subjects had a single lesion treated, or more than one lesion treated with a minimum 5 mm gap between the edges of the lesion margins.

Data/Specimen Collection Procedures and Frequency

- Study data will be retrospectively collected from already existing documentation in patient files at the participating sites.
- Study staff will perform an initial review of the existing patient charts for patients who were treated with SRT-100™ for NMSC prior to January1, 2015. The selected charts will be further reviewed for satisfaction of inclusion criteria and presence of required data elements. The study staff will extract the required information from the patient charts and enter it into an Excel database provided by the study Sponsor.
- The data elements of patient demographics, lesion diagnostic variables and characteristics, lesion size and margins, treatment duration, treatment dosage and schedule, treatment outcomes (particularly cured vs, non-cured) and follow-up outcome variables (particularly incidence of lesion recurrence) will be recorded.
- Data collection will be ongoing until no additional qualifying patient charts are identified at the respective study sites.

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 STUDY CONDITION: NON-MELANOMA SKIN CANCERS (NMSC)

Non-Melanoma Skin Cancers (NMSC) predominantly (98%) include Basal Cell Carcinomas (BCC) and Squamous Cell Carcinomas (SCC).

1.2 BASAL CELL CARCINOMA (BCC)

Basal cell carcinomas (BCC) are abnormal, uncontrolled growths or lesions that arise in the skin's basal cells that line the deepest layer of the epidermis. BCCs typically appear as open sores (possible oozing or crusting) that don't heal or recur; raised red patches that may itch; pink, red, translucent, shiny or pearly bumps with possible darker areas; pink growths with raised edges; or scar-like lesions. They can be fragile and bleed easily such as with shaving or a minor injury. BCCs tend to develop on sun-exposed body areas, most commonly the face, head and neck. Slow-growing cancers, BCCs rarely metastasize to body regions beyond the original lesion site but have the potential to do so if left untreated. Delayed or ineffective treatment can also lead to disfigurement of the lesion. If not removed completely, BCCs can recur in the same location. Prior BCCs increase the likelihood of future BCCs.

1.3. SQUAMOUS CELL CARCINOMA (SCC)

Squamous cell carcinomas (SCC) are uncontrolled growths of abnormal cells arising from the squamous cells in the epidermis producing keratin. SCCs may appear as scaly red patches (that may crust or bleed); open sores (possibly oozing or crusting) that don't heal or recur; or wart-like or elevated growths with a central depression. SCCs typically develop on sun-exposed body areas such as the face, ears, neck, lips, back of the hands, arms and legs. The skin in these areas often contain signs of sun damage such as wrinkles, pigment changes, freckles, "age spots," loss of elasticity and broken blood vessels. SCCs may also develop in scars or chronic skin sores elsewhere on the body, including the genitals, and occasionally in actinic keratoses. The natural history of SCCs also varies, from slowly enlarging to rapidly growing with significant tenderness and pain. They may become disfiguring and fatal if left untreated and allowed to grow.

1.4. STATISTICS

NMSC is the most commonly occurring type of skin cancer, and skin cancers are the most common of all types of cancer (about one-third of all cancers). It is estimated that about 3.3 million people in the United States (U.S.) are diagnosed with NMSC annually, equating about 5.4 million BCCs and SCCs. The diagnosis and treatment of NMSC in the U.S. increased by 77% between 1994 and 2014. It is believed that the increasing incidence of NMSC is due to better skin cancer detection, increasing sun exposure, and longer lifespans.

The incidence of basal cell carcinoma is about 4 times that of squamous cell carcinoma. An estimated 4.3 million cases of BCC are diagnosed annually in the U.S. resulting in over 3,000 deaths. Over 1 million cases of SCC are diagnosed in the U.S. annually, resulting in over 15,000 deaths. SCC has a 4% annual incidence of metastasis.

About 90% of NMSC is associated with exposure to ultraviolet (UV) radiation from the sun.

1.5. CAUSE OF NON-MELANOMA SKIN CANCER (NMSC)

NMSC primarily results from repeated and unprotected skin exposure to ultraviolet (UV) rays from sunlight and man-made sources such as tanning beds. UV rays can damage the DNA inside skin cells that comprise genes that control cell function.

It is believed that most NMSC are the result of DNA changes from UV ray exposure that affect the tumor suppressor genes in cells. Tumor suppressor genes are those that keep cell growth in check by slowing down cell division or causing cells to die at the right time. The gene most often altered in SCC is TP53, the tumor suppressor gene that normally functions to cause cells with damaged DNA to die. When TP53 is altered, these abnormal cells may live longer and proceed to become cancerous.

In BCC, the most common mutated gene is PTCH1, a tumor suppressor gene that typically functions to keep cell growth in check. Changes to PTCH1 permit cells to grow out of control.

These are not the only gene changes that play a role in the development of skin cancer. There are likely to be many others as well.

Additional risk factors for the development of NMSC include radiation therapy, lighter skin, prolonged immunosuppression, human immunodeficiency virus (HIV), human papilloma virus (HPV), and certain syndromes or genetic disorders.

Increased risk of multiple NMSC lesions is associated with males, tumor locations in the trunk and extremities, superficial histologic subtype, younger age at initial diagnosis, and red hair phenotype.

1.6. CONFIRMATORY DIAGNOSIS OF NMSC

Dermoscopy is commonly used as an initial aid for early evaluation, identification and diagnosis of NMSC. Confirmatory diagnosis is subsequently made through clinical (physical) examination followed by histological excision (biopsy – most commonly punch or shave biopsy).

(i) Clinical assessment of the lesion involves evaluation of tumor size (diameter) and anatomical location; determination of lesion recurrence; determination of lesion connection to underlying structures such as muscle, cartilage or bone; classification/grading of the borders (SCCs); and notation of evidence of prior surgery or treatment. If an SCC is suspected, lymph nodes are examined for potential metastasis.

(ii) Histological examination of NMSC is critical to confirming the clinical assessment, confirming the histopathological type as BCC or SCC, and if applicable, the degree of differentiation of SCC. Histopathological assessment involves evaluation of tumor depth; presence of ulceration (BCCs); morphological subtype; histopathological features (SCCs); and perineural or vascular involvement.

1.7. BCC AND SCC VARIANTS

BCC and SCC variants are listed in the table below.

BCC Variants	SCC Variants
BCC nodular	SCC in situ/Bowen's disease
BCC superficial	SCC invasive
BCC infiltrative/Morpheaform	SCC clear-cell
BCC Basosquamous (metatypical) carcinoma	SCC Spindle Cell
BCC spindle cell	SCC De Novo
BCC carcinosarcoma	SCC lymphoepitheliomatous
BCC pigmented	SCC Verrucous
BCC micronodular	SCC Acantholytic
BCC trichoblastic	SCC Desmoplastic
BCC with follicular differentiation	SCC HPV induced
Fibroepithelioma of pinkus	SCC bowenoid papulosis
BCC cystic	
BCC adenoid cystic	
BCC keloidal	

1.8. TREATMENT OPTIONS

The range of available treatment options for NMSC includes surgery, cryotherapy, curettage and electrodessication, radiation therapy including superficial radiation therapy, photodynamic therapy, various forms of brachytherapy, and chemotherapeutic agents. Treatment decisions may be based on tumor type, anatomical location, patient age, tumor stage and classification, physician preference, and treatment setting. The choice of treatment becomes more complex among the elderly due to frailty, limited life-expectancy, and comorbidities. Anatomical location also becomes an important factor as NMSC lesions commonly occur on the ears, eyes and nose where treatment may have significant cosmetic consequences.

This study will focus on evaluation of outcomes of Superficial X-ray Therapy (SRT), a non-surgical option for patients with primary non-aggressive BCC and SCC and for patients who decline surgery or are poor surgical candidates.

2 STUDY JUSTIFICATION AND RATIONALE

Non-melanoma skin cancers are the most common form of cancers with the incidence increasing at a rapid rate. Current guidelines (e.g. National Comprehensive Cancer Network (NCCN) and American Academy of Dermatology (AAD)) suggest that surgical treatments remain the most effective option for the management of most cases of BCC and SCC.

Clinical recommendations for radiation therapy (RT) are typically based on consideration of RT as a single category without differentiating between the different applications of the different available modalities. As different radiotherapy modalities and dosing have been shown to result in widely varying outcomes, with recurrence rates ranging from 2.8% to 30%, such generalized recommendations can be misleading. AAD guidelines group newer technologies such as high-dose electronic brachytherapy (EBT) and SRT as new therapies. Though the AAD has since clarified these modalities in an addendum position statement it continues to refer to SRT as a “new” technology that “differs substantially from traditional external beam radiation therapy” and one in need of “research on long term outcomes.”

This retrospective study has been designed to focus on efficacy and safety of superficial radiation therapy (SRT) for NMSC and to specifically address this AAD-highlighted deficiency and need for long-term evaluation of ’new’ technologies for the treatment of NMSC. Evaluation of SRT for NMSC in this study will be via review of retrospective data for procedures delivered by the Sensus Healthcare SRT-100™. Sensus Healthcare’s SRT-100™ has been cleared by the U.S. Food and Drug Administration (U.S. FDA) for the treatment of non-melanoma skin cancer and keloids.

The SRT-100™ delivers a precise, calibrated dose of superficial radiation therapy that only penetrates skin deep, resulting in a virtually painless treatment can be safely administered in the physician’s office.

Low-dose SRT effectively destroys BCC and SCC without any invasive cutting, bleeding or stitching. There is no need for anesthesia, no risk of infection or scarring and no need for reconstructive plastic surgery. Healing time is quick with minimal to no post-treatment downtime or lifestyle restrictions. It is therefore both a viable and highly desirable alternative to invasive, painful and higher-risk surgical procedures.

While formal long-term outcome evaluations may be lacking, there is much existing data. This study will utilize retrospective chart analysis to evaluate the outcomes of SRT-100™ therapy on NMSC lesions over a long-term post-treatment period. Long-term cure rate is considered the primary outcome, with secondary outcome evaluation focused on the impact on cure rate and other treatment outcomes of key variables such as lesion type, location, patient characteristics and treatment parameters such as treatment dosing and fractionation.

3. SUPPORTIVE LITERATURE

The following study published in 2012 is similar in design and purpose to the current retrospective trial.

Superficial x-ray in the treatment of basal and squamous cell carcinomas: A viable option in select patients
J Am Acad Dermatol December 2012 Volume 67, Issue 6, Pages 1235–1241
Armand B. Cognetta, MD, Brett M. Howard, BA, Henry P. Heaton, BA, Earl R. Stoddard, MD, Hyokyoung Grace Hong, PhD, and W. Harris Green, MD

The abstract from this publication is presented below.

Background: Effective nonsurgical modalities are limited in the treatment of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).
Objective: We sought to evaluate the efficacy and viability of superficial x-ray therapy in the treatment of BCC and SCC in an outpatient setting.
Methods: A retrospective analysis was performed on 1715 histologically confirmed primary cutaneous BCC and SCC treated with superficial x-ray therapy at Dermatology Associates of Tallahassee in Florida between 2000 and 2010.
Results: Of the 1715 tumors reviewed during this period, 712 were histologically proven BCC (631 nodular and 81 superficial), 994 were SCC (861 SCC in situ and 133 invasive SCC), and 9 displayed distinct features of both BCC and SCC in the same biopsy specimen. Kaplan-Meier estimates (with 95% confidence intervals) of cumulative recurrence rates of all tumors at 2 and 5 years were 1.9% (1%-2.7%) and 5.0% (3.2%-6.7%), respectively; of BCC at 2 and 5 years were 2% (0.8%-3.3%) and 4.2% (1.9%-6.4%),

respectively; and of all SCC at 2 and 5 years were 1.8% (0.8%-2.8%) and 5.8% (2.9%-8.7%), respectively. Tumors on male patients and those with a diameter greater than 2 cm were associated with a statistically significant increase in recurrence likelihood.
Limitations: This study represents only patients treated in 1 dermatology office in North Florida and may not be representative of the general patient population.
Conclusions: Superficial x-ray therapy remains a viable nonsurgical option for the treatment of primary BCC and SCC in patients where surgical intervention is declined, unadvisable, or potentially associated with significant cosmetic or functional limitations.

The present study's design and intent is to confirm and expand upon these findings. In particular, the limitation of the prior study of homogeneity of the population source from which the data was drawn will be overcome in the present study, as data from numerous sources will be collated and evaluated collectively such that the findings will be representative and generalizable to the general patient population.

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Guidelines of care for the management of cutaneous squamous cell carcinoma
Journal of the American Academy of Dermatology, Volume 78, Issue 3, 560 - 578
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Additional Sources

American Cancer Society website: www.cancer.org
Skin Cancer Foundation website: www.skincancer.org
American Academy of Dermatology (AAD) NMSC 2018 Guidelines

5. STUDY DESIGN

5.1. STUDY OBJECTIVES

The purpose of this study is to collate information from existing medical records for patients who received treatment with the Sensus Healthcare SRT-100™ for non-melanoma skin cancer (NMSC), both SCCs and BCCs, into a central registry database for the purpose of retrospective evaluation.

5.1.1. Primary Objective

The primary objective of this study is to evaluate the treatment outcomes of the retrospective data for long-term safety and efficacy of application of SRT-100™ for the treatment of NMSC (SCC and BCC), including long-term cure rates.

5.1.2. Secondary Objectives

The secondary objectives of this study are to evaluate the retrospective data for potential differences in treatment outcomes, including cure rates, based on lesion variables (such as tumor size and location, tumor type), patient characteristics (such as demographics), and treatment dosage/fractionation differences.

5.2. INVESTIGATIONAL PLAN

5.2.1. Collecting Sites

There will be multiple participating sites located in the United States selected based upon having access to the required patient population medical records. There is no limit on the potential number of participating sites. Each identified and qualifying site that is willing to participate in the study will be included.

5.2.2. Data Collection Methodology

Patient data will be retrospectively collected from the medical records and other source documentation already existing in patient files at the participating sites.

5.2.3. Ethical Considerations

This retrospective chart review qualifies for 'exempt' status under human subject regulations. Exempt studies are not subject to certain federal research requirements and do not require yearly recertification. The determination of 'exempt status' for this study is based on satisfaction of the following criteria: 1) The study involves the use of existing data, documents and records, with 'existing' defined as 'materials that are already in existence at the time of the study protocol development'; 2) The protocol specifies a date for data collection and review, that is, this study will only collect information that has been recorded in charts for patients who were treated for NMSC using the SRT-100™ prior to 01/01/2015; and 3) Information recorded will not contain any individual subject identifying information or data elements that may potentially link a patient to his or her data. That is, it will not be possible to figure out what data belongs to which patient once the data has been recorded in the central study database.

This retrospective study will meet Health Insurance Portability and Accountability Act (HIPAA) Privacy Requirements by satisfying the criteria for waiver of privacy authorization according to the following criteria: 1) There is an adequate plan to protect identifiers from improper use and disclosure; 2) There is an adequate plan to destroy any identifiers at the earliest opportunity; 3) Protected health information (PHI) will not be re-used or disclosed for another purpose; 4) The research could not practicably be conducted without the waiver of privacy authorization; and 5) The research could not practicably be conducted without the use of PHI.

5.3. STUDY DURATION, ENROLLMENT AND NUMBER OF SITES

5.3.1. Duration of Study

Applicable data elements to be reviewed in this study will be collected from patient records whose treatment of NMSC with the SRT-100™ occurred prior to 01/01/2015. All applicable and available data elements as specified in this study protocol will be recorded for each patient from the time of treatment forward to the most recent follow-up data entry date.

Therefore, the study duration of patient participation in this study according to the duration of the review of their medical records will vary individually based upon their initial SRT-100™ treatment date.

The entire study duration with respect to time from start of patient data identification and collation to completion of the final patient data entry will be dependent upon the time needed to identify all potential participating study sites and to collate all of the required available data from all qualifying patient records at each of those sites.

5.3.2. Total Number of Study Sites/Total Number of Subjects Projected

There will be multiple participating study sites, all located in the United States. Each will be selected based upon having access to the required medical records of patients who were treated at their site for NMSC with the SRT-100™ prior to January 1, 2015, and for whom follow-up data is available. There is no limit on the potential number of participating sites. Each identified and qualifying site that is willing and able to participate in the study will be included.

Subject data will be retrospectively collected from the existing medical records in the identified qualifying patient files at the participating sites as those who were treated with the SRT-100™ for one or more NMSCs, who have follow-up data and who subsequently satisfy all of the inclusion criteria and none of the exclusion criteria for inclusion of their retrospective data in this study. There is no limit on the potential number of study subjects. The applicable retrospective data for each identified and qualifying subject at each participating study site will be included in the retrospective analysis.

5.4. STUDY POPULATION

The study population comprises patients who were treated at one of the participating study sites with the SRT-100™ for one or more NMSCs, who have follow-up data and who satisfy each of the study inclusion criteria and none of the exclusion criteria.

5.4.1. Inclusion Criteria

1. Male or female.
2. Treatment with SRT-100™.
3. Treatment date of December 31, 2015 or earlier.
4. Non-Melanoma Skin Cancer (NMSC) pathological diagnosis of confirmed squamous cell carcinoma (SCC) or basal cell carcinoma (BCC).

5. Histopathological Grade: G1 (well differentiated); G2 (moderately differentiated) or Gx (not assessed).
6. One lesion is treated, or more than one lesion is treated with a minimum of a 5 mm gap between the edges of the lesion margins.
7. Required retrospective data is existing and sufficient.

5.4.2. Exclusion Criteria

1. Lesions of etiology other than non-melanoma skin cancer (NMSC).

6. STUDY PROCEDURES

6.1. RESEARCH DATA SOURCE

The research data source in this study is existing recorded information in patient files at the study test sites from patients who received SRT-100™ treatment for NMSC prior to January 1, 2015 and for whom follow-up data is available. This study is a pure retrospective analysis. No additional information will be collected for any subject in this study other than the required information that is already existing in their patient file.

6.2. DATA COLLECTION

Study staff at each of the study test sites will perform an initial review of the existing patient charts for those who received a diagnosis of NMSC for which they received SRT-100™ treatment prior to January 1, 2015 and for which post-procedure follow-up data is available. From this initial review, selected charts will be further reviewed for the satisfaction of inclusion criteria and presence of required data elements. The study staff will extract the required data elements from the patient charts and enter them directly into the Excel database provided by the study Sponsor.

6.3. DATA ELEMENTS

The following demographic, lesion, diagnostic, treatment and outcome variables will be recorded from the suitably identified existing patient medical records.

A. <u>Patient Information and Demographics</u>:
   1. Gender
   2. Age at treatment start

3. Ethnicity
4. Significant comorbidities

B. Lesion Diagnostic Variables and Characteristics:

1. Pathology diagnosis
2. Diagnosis subtype/variant
3. Other pathology
4. Recurrent lesion (yes/no)
5. Previous treatment if recurrent
6. Lesion location (no restrictions): scalp, mastoid, forehead, cheek, nose, ear, chin, lips, neck, upper arm, lower arm, hand, upper leg, lower leg, foot.

C. Lesion Size and Margins:

1. Lesion size
2. Treatment margin
3. Lead cutout size
4. Applicator size

D. Treatment Dosage and Schedule:

1. Treatment dose
2. Number of treatments
3. Number of treatments per week
4. Treatment span(days)
5. TDF
6. TX energy KV: 50, 70, 100
7. Total dose
8. Break duration (days or N/A)

E. Outcomes:

1. Cured: Yes/No
2. Adverse Events: yes, no
3. Adverse Events description (as applicable)
4. Notes (as applicable)

F. Follow-Up:
   1. Time in months since the most recent follow-up since end of treatment
   2. Recurrence: Yes/No
   3. Recurrence treatment and outcome (as applicable)
   4. Follow-up notes (as applicable)

7. REGISTRY ADMINISTRATION

Existing patient medical records will only be reviewed by study site staff who already have access to the files and who have been trained to the study protocol. Once a qualifying patient medical record is identified, the study site staff member will extract only the required data elements and enter them directly into an Excel database provided by the study Sponsor.

There will be no identifying information entered into the database that could potentially connect an individual data record to an individual patient. Unique de-identified codes will be used for each patient data set entered into the database.

The collected retrospective data will only be used for the purposes of evaluating the primary and secondary objectives of this study.

The parties who will have access to the retrospective data and database will be study site investigators and designated study site staff, the study Sponsor and the study biostatistician.

Access to the database will not be given to outside parties at any time during the data collation and analysis process or in the future for any reason.

7.1. COMPLIANCE STATEMENT

The investigators will perform the study in accordance with this protocol. Identification, collection and recording of data will be accurate and will ensure the privacy, health, and welfare of patients during and after the data collection process.

7.2. DATA COLLECTION AND MANAGEMENT

Primary records (source documents) will continue to be maintained in the study site patient medical record files as before. The extracted study data elements will be directly entered into an Excel database to which only the designated study staff, the study Sponsor and the study biostatistician will have access.

7.2.1. Confidentiality and Privacy

Privacy of subjects and confidentiality of the collected data elements will be secured through use of a de-identified coding system that will comprise the first and last name initials of the investigator at a test site followed by the order of entry of the subject's data into the database from 001 onwards, as applicable. For example, the third suitable patient record to be identified at Dr. John Black's study site would have a de-identified entry code of JB003.

A separate sheet containing the link between the code and the subject's medical file will be maintained in a separate location at each respective test site until such time that all the pertinent data has been collated, entered into the database and double-checked for accuracy and completeness. At this time, all copies of the sheets containing the link between the code and the subject's medical file at each study site will be destroyed.

7.2.2. Providing Results to Subjects

Results will not be provided to subjects as there is no diagnostic or otherwise medical purpose associated with this retrospective analysis that could in any potential way benefit the patients whose data was included in the analysis or alert them to potential risks or issues in any other regard.

7.3. REGULATORY AND ETHICAL CONSIDERATIONS

7.3.1. Risk Assessment

The only potential risk to subjects in this study is breach of privacy and confidentiality. The application of a de-identified coding system to record patient data has been established to minimize this risk.

7.3.2. Potential Benefits of Participation

There is no direct benefit to the study subject from participation in this registry trial. Indirect benefit to potential future patients is the provision of data and information to physicians who treat individuals with NMSC that may enable them to consider non-invasive SRT as a viable treatment option.

7.3.3. Risk-Benefit Assessment

The Risk-Benefit assessment reveals no negatives in conducting this retrospective analysis.

7.4. RECRUITMENT STRATEGY

Initially, eligible study sites will be identified and selected as those who have treated NMSC patients with SRT-100™ prior to January 1, 2015 and for whom follow-up data is available. This study is a pure retrospective analysis. No additional

information will be collected for any subject in this study other than the required information that is already existing in their patient file.

At each study site, designated and trained study staff will perform an initial review of the existing patient charts for those who received a diagnosis of NMSC for which they received SRT-100™ treatment prior to January 1, 2015 and for whom follow-up data is available. From this initial review, selected charts will be further reviewed for the satisfaction of inclusion criteria and presence of required data elements.

7.5. INFORMED CONSENT

This retrospective study meets the criteria for waiver of consent, assent and HIPAA authorization according to the following criteria: 1) There is an adequate plan to protect identifiers from improper use and disclosure; 2) There is an adequate plan to destroy any identifiers at the earliest opportunity; 3) Protected health information (PHI) will not be re-used or disclosed for another purpose; 4) The research could not practicably be conducted without the waiver of privacy authorization; and 5) The research could not practicably be conducted without the use of PHI.

All of the data is collected retrospectively from information already recorded in existing patient medical files.

7.6. PAYMENT TO SUBJECTS

Patients whose data is collected in this retrospective analysis will not receive payment or any other form of compensation.

7.7. CONFIDENTIALITY

All data and records generated during this study will be kept confidential in accordance with HIPAA regulations on subject privacy. The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Coded de-identifiers will be used for all data entries.

8. SAFETY MANAGEMENT

Safety management, including adverse event evaluation and reporting, is not applicable to this registry trial as all evaluations are being performed on prior existing data.

9. PUBLICATION

It is intended that the outcome of this retrospective registry analysis be written up for publication in a peer-reviewed journal. In any potential publication, there will be no identifiable information for any individual subject and no individual case studies will be profiled.

10. RESULTS ANALYSIS

10.1. PRIMARY ANALYSIS

Primary analysis of the retrospective data set will be assessment of cure rates and incidence of reoccurrence of lesions.

10.1.1. Cure Rate

Cure rate will be calculated as the percentage of lesions that attained complete cure following treatment completion, reported as the overall success rate.

10.1.2. Recurrences and Complications

Each identified incidence of lesion recurrence, complication or adverse event recorded at any point throughout the treatment and follow-up evaluation phase will be explored descriptively. Statistical evaluation of recurrences will be as follows:

(i) *Kaplan-Meier Survival Probability Estimates* will be calculated across the duration of available follow-up data, reporting survival probability estimates, and lower and upper limits of the 95% Confidence Interval by follow-up year.

(ii) *Log-Rank Test* will be performed to evaluate for differences in recurrence-free survival between lesion types.

(iii) *Multivariate Cox Regression Analysis* will be performed to account for the contribution of the potential influential factors of gender, age, lesion type, lesion size, total treatment dosage and TDF to recurrence-free survival.

10.2. SECONDARY ANALYSIS

Secondary analysis of the retrospective data set will be both descriptive and statistical, as follows.

10.2.1. Subject Demographics

Descriptive evaluation (mean, standard deviation and range) of the subject demographics of age and gender will be performed on a subject rather than lesion basis.

10.2.2. Lesion Variables

(i) *Lesion Type and Location*: The distribution (number and percentage) of lesion type (BCC and SCC) and the distribution of lesion subtype within each lesion type will be

calculated. The distribution of the location of lesions on the body will also be calculated. The findings will be presented descriptively in table and chart format.

(ii) *Comorbidities*: The distribution (number and percentage) of comorbidities for lesions overall and by lesion type will be calculated and presented descriptively in table and chart format.

(iii) *Lesion Size*: Descriptive evaluation (mean, standard deviation and range) of baseline lesion size (diameter) in centimeters (cm) will be calculated for lesions overall and by lesion type. T-test analysis for two independent samples will be applied to assess for any difference in lesion size between lesion types. A two-tailed p value of <0.05 will be considered statistically significant and indicative of a clinically meaningful difference. The categorical distribution (number and percentage) of lesion size for all lesions and by lesion type will also be calculated.

10.2.3. Treatment and Follow-Up

(i) *Treatment Period*: Descriptive evaluation (mean, standard deviation and range) of the number of treatment days will be calculated for lesions overall and by lesion type. T-test analysis for two independent samples will be applied to assess for any difference in the number of treatment days (the treatment administration period) between lesion types. A two-tailed p value of <0.05 will be considered statistically significant and indicative of a clinically meaningful difference.

(ii) *Follow-Up Evaluation Period*: Descriptive evaluation (mean, standard deviation and range) of the number of follow-up months will be calculated for lesions overall and by lesion type. T-test analysis for two independent samples will be applied to assess for any difference in the number of follow-up months (the follow-up evaluation period) between lesion types. A two-tailed p value of <0.05 will be considered statistically significant and indicative of a clinically meaningful difference. The categorical distribution (number and percentage) of the follow-up evaluation period by year for all lesions and by lesion type will also be calculated.

10.2.4. Treatment Dosage and Schedule

(i) *Treatment Dosage*: Descriptive evaluation (mean, standard deviation and range) of the treatment dosage variables of total dosage, Fx Dose, TDF and KV will be calculated for lesions overall and by lesion type. T-test analysis for two independent samples will be applied to assess for any differences in each of the dosage variables between lesion types. A two-tailed p value of <0.05 will be considered statistically significant and indicative of a clinically meaningful difference.

(ii) *Treatment Frequency*: Descriptive evaluation (mean, standard deviation and range) of treatment frequency (number of treatment visits and number of treatment visits per week) will be calculated for lesions overall and by lesion type. T-test analysis for two independent samples will be applied to assess for any difference in treatment frequency between lesion types. A two-tailed p value of <0.05 will be considered statistically significant and indicative of a clinically meaningful difference.

Furthermore, the categorical distribution (number and percentage) of the number of treatment visits and of the frequency of treatment visits per week will be calculated for lesions overall and by lesion type.