Johnson & Johnson MEDICAL DEVICES

A Multicenter Observational Registry to Develop Ablation Parameter Guidance for Microwave Liver Ablation of Soft Tissue Lesions

Protocol Number: NEU_2017_04

Document	Effective Date
Original (version 1.0)	19 April 2019
Amendment 1 (version 2.0)	13 June 2019
Amendment 2 (version 3.0)	20 April 2020
Amendment 3 (version 4.0)	21 July 2021

Sponsor: NeuWave Medical, Inc.

[redacted]

NeuWave Medical, Inc. is a subsidiary of:

Ethicon, Inc.

[redacted]

CONFIDENTIALITY STATEMENT

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is *privileged* or *confidential* and may not be further disclosed by them. These restrictions on disclosure will apply equally to *all* future information supplied to you which is indicated as *privileged* or *confidential*.

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1.0 RESPONSIBLE PARTIES INVOLVED IN THE REGISTRY

A list of all responsible parties, such as laboratories, medical monitors, and contract research organizations, who are involved in the operations of the registry is filed in the Sponsor's Trial Master File. The names of the individuals and corresponding phone numbers who should be contacted regarding the conduct of the registry, adverse events, safety issues, and complaints are provided in the Site Investigator File.

2.0 STATEMENT OF COMPLIANCE

This registry will be conducted in accordance with specific provisions of the associated Institutional Review Board (IRB)/ Ethics Committee (EC) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable national and regional regulatory requirement(s).

3.0 INVESTIGATOR SIGNATURE

I have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practices (GCP), applicable country regulations, the Declaration of Helsinki, the signed clinical trial agreement with Sponsor, and with the protocol outlined herein. I will conduct this registry as outlined therein and will make reasonable effort to complete the registry within the time period designated by the Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this registry. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the registry.

I will fulfill the requirements of my Institutional Review Board (IRB) / Ethics Committee (EC), or other oversight committee, to ensure complete and continual oversight of this clinical registry. I will use an Informed Consent Document approved by the Sponsor and my reviewing IRB/EC.

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events, device-related adverse events, or procedure-related adverse events, as defined in this protocol, to the Sponsor, and comply with all adverse event reporting requirements of my reviewing IRB/EC. I agree to permit the Sponsor, its authorized representatives, my reviewing IRB/EC, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms I have read and understood this protocol and its associated amendments or attachments and will accept respective revisions or amendments provided by the Sponsor. I agree to comply with all other requirements regarding the obligation of clinical investigators and all other pertinent requirements of the Sponsor and government agencies.

_____	_____
Principal Investigator Signature	**Date**
[Principal Investigator printed name]	
Name of the site	
Address of the site	
City, State	
Country	

PLEASE RETAIN A COPY FOR YOUR RECORDS

4.0 PROTOCOL SUMMARY

Full Title	A Multicenter Observational Registry to Develop Ablation Parameter Guidance for Microwave Liver Ablation of Soft Tissue Lesions
Protocol Number	NEU_2017_04
Short Title	NOLA (NeuWave Observational Liver Ablation) Registry
IDE/IND number	N/A
Sponsor	NeuWave Medical, Inc.
Indication	Ablation (coagulation) of soft tissue in percutaneous, open surgical, and in conjunction with laparoscopic surgical settings, including the partial or complete ablation of non-resectable liver tumors.
Registry Article Description	• NEUWAVE Microwave Ablation System and Accessories (originally marketed as the "Certus 240 140 2.45GHz Ablation System and Accessories"; hereafter referred to as "NEUWAVE Microwave Ablation System"). • NEUWAVE Microwave Ablation System with Ablation Confirmation.
Registry Design	This is a multicenter, observational registry that follows patients for a total of 5 years from the date of the first liver ablation procedure with the NEUWAVE Microwave Ablation System.
Sample Size	N = up to 1500 patients ablated.
Registry Population	Patients with at least one soft-tissue liver lesion ablated with the NEUWAVE Microwave Ablation System or NEUWAVE Microwave Ablation System with Ablation Confirmation.
Geographic Areas	Starting at sites in the United States and expanding to regions where NEUWAVE Microwave Ablation Systems are available, including EMEA and Asia.
Registry Duration	Enrollment: ~2 years Follow up: 5 years
Procedure(s) Description	Patients who meet the eligibility criteria will undergo microwave ablation (MWA) with the NEUWAVE Microwave Ablation System with or without Ablation Confirmation of at least one soft-tissue liver lesion, in accordance with the study site's standard-of-care (SOC) practices.
Primary Objective	The primary objective of this registry is to compile data that will be analyzed at various timepoints, to understand the impact of selected parameters on procedure/patient outcomes.

Primary Endpoints	• Technical success (perioperative endpoint) • Technique efficacy (short term endpoint) • Target lesion recurrence (local recurrence) rate (long term endpoint)
Secondary Endpoints	• Secondary efficacy rate • Regional recurrence rate at a separate location in the liver • Recurrence-free survival • Overall survival • Economic impact of ablation • Incidence of reportable Adverse Events/Serious Adverse Events (AEs/SAEs) • Numeric Pain Rating Scale • Quality of Life Questionnaires (QLQ-C30 and QLQ-HCC18)
Inclusion Criteria	1) Patients who underwent or are scheduled to undergo a microwave ablation of one or more liver lesions with the NEUWAVE Microwave Ablation System per the device's Instructions for Use (IFU). 2) Patients with signed informed consent (or waiver approved by IRB/EC) who are willing to comply with the assessment schedule, and willing to have data included in the database. 3) Patients $\geq$ 22 years old at the time of informed consent (or waiver approved by IRB/EC).
Exclusion Criteria	1) Patients with a life expectancy of less than 1 year, in the opinion of the treating physician. 2) Use of microwave ablation purely as a transection tool, rather than focused liver lesion ablation. 3) Patient is currently participating, or planning to participate, in another NeuWave/Ethicon-funded clinical trial or registry studying microwave ablation in the liver. Note: roll-over patients from previous NeuWave trials are permitted.
Safety Assessments	Patients will be assessed per the Schedule of Assessments for AEs that are procedure- or device-related and all SAEs.

Statistical Analysis	Categorical variables will be summarized descriptively by frequencies and associated percentages. Continuous variables will be summarized descriptively by number of patients, mean, standard deviation, median, minimum, and maximum. Confidence intervals will also be provided for procedure-related variables. Models will be built to explore the relationship between technical success, technique efficacy, and secondary efficacy rate, and ablation procedure, patient, and provider parameters. Time to event analyses will be used for target lesion recurrence rate, recurrence-free survival, and overall survival.
Interim Analysis	There are no plans for interim analyses with intent to stop the registry early or to adapt the registry design or planned number of patients.
Determination, if DSMB required	There will not be a DSMB utilized for this observational registry.

Schedule of Assessments Table:

Visit No.	Visit 1:	Visit 2			Visit 3	Visit 4	Visit 5	Visit 6	Visits 7 to 13	Visit 14/EOS	USV
Visit	Screening[22]	Ablation Day			Post-ablation	Post-ablation	Post-ablation	Post-ablation	Post-ablation	Post-ablation	Unsched. Visit[23]
Interval Windows	≤ 60 days pre-ablation	Day 0 = Ablation of target lesions			7 days to < 3 months	3 to < 6 months	6 to < 9 months	9 to < 12 Months	every 6 months	54 to 60 months	N/A
Registry Activity		pre	intra	post							
Eligibility criteria	X	X									
Informed consent / waiver	X										
Demographic information	X										
Patient parameters[1]	X										
Liver tissue assessment[2]	X										
BCLC staging[3]	X										
BMI	X										
ECOG performance[26]	X	X			X	X	X	X	X	X	
Child-Pugh Score[4], ASA	X										
Coagulation tests[5]	X				X	X	X	X	X	X	
Liver function tests[6]	X				X	X	X	X	X	X	
Renal function tests[7]	X				X	X	X	X	X	X	
Complete blood count[8]	X				X	X	X	X	X	X	
Genetic marker levels: AFP, CA19-9, CEA[9]	X				X	X	X	X	X	X	
Concomitant medications[10]	X	X		X	X	X	X	X	X	X	X
Quality of life questionnaires[11]		X[24]			X	X	X	X			
Pain score[12]		X[24]		X[25]	X						
Imaging[13]	X	X	X	X	X	X	X	X	X	X	
Ablation procedure details[14]			X	X							
Healthcare provider details[15]				X							
Recurrence evaluation[16]					X	X	X	X	X	X	X
Relevant concomitant procedures[17]				X	X	X	X	X	X	X	X
Technical success evaluation[18]				X							
Technique efficacy evaluation[19]					X						
Economic impact data[20]			X	X							
Follow-up post-ablation treatment[21]					X	X	X	X	X	X	X
AEs/SAEs			X	X	X	X	X	X	X	X	X

See List of Abbreviations Glossary in Section 22.2

1. Patient parameters, as listed in Section 19.1 Data Elements, subsection 2.
2. Liver tissue assessments, if available, including steatosis, fibrosis/ cirrhosis, liver stiffness, vascular invasion, micro satellite instability
3. If applicable: BCLC staging
4. If applicable: Child-Pugh Score
5. If applicable, per site SOC: Coagulation tests, including INR, PT, and APTT (or PTT).
6. If applicable, per site SOC: Liver function tests, including AST, ALT, GGT, albumin, direct and total bilirubin, and total protein.
7. If applicable, per site SOC: Renal function tests, including BUN, creatinine and electrolytes (sodium, potassium, chloride and bicarbonate).
8. If applicable, per site SOC: Complete blood count test, including differential cell count and platelet count.
9. If applicable, per site SOC: genetic markers include Alpha-fetoprotein (AFP), Carbohydrate antigen 19-9 (CA19-9), Carcinoembryonic antigen (CEA)
10. Record all relevant prior medications taken within 60 days prior to Visit 2 and all relevant concomitant medications taken throughout the registry. Relevant concomitant medications include: chemotherapy, immunotherapy, blood-thinning or coagulation, NSAIDs, those medications used to treat AEs, those used for hepatitis (if concurrently treating), and any others that are relevant in the opinion of the investigator. For post-ablation follow-up visits, relevant concomitant medications may be assessed over the phone, as needed.
11. Quality of Life questionnaires: EORTC QLQ-C30 and liver-specific QLQ-HCC18. The questionnaires may be administered over the phone, as needed.
12. Pain score, using the Numeric Pain Rating Scale. The questionnaire may be administered over the phone, as needed.
13. Use SOC imaging for all study visits.
14. Ablation procedure details, as listed in Section 19.1 of the protocol.
15. Healthcare provider parameters, as listed in Section 19.1 of the protocol.
16. SOC imaging as used at every follow-up visit to determine if there is local or regional recurrence of lesion(s). If there is a recurrence, determine soft tissue lesion details,via CT, MRI, PET, US, and/or X-ray. Scans will be submitted to the Sponsor (refer to NOTE 1).
17. Record only relevant concomitant procedures (i.e. liver or lesion-related). For post-ablation follow-up visits, relevant concomitant procedures may be assessed over the phone, as needed.
18. Technical success, defined as ablation of the target lesion(s) according to the protocol and covered completely, with an adequate margin, as defined by the physician performing the ablation (that is, the ablation zone completely overlaps or encompasses the target lesion plus an ablative margin), as assessed by CT, MRI, PET, US, and/or X-ray, immediately following the procedure. If patient has had any lesions ablated with NeuWave in the post-ablation follow-up visit period, assess Technical success following each ablation.
19. Technique efficacy, defined as ablation of the target lesion(s) according to the protocol and covered completely, with an adequate margin, as defined by the physician performing the ablation (that is, the ablation zone completely overlaps or encompasses the target lesion plus an ablative margin), as assessed by CT, MRI, PET, US, and/or X-ray, at Visit 3.
20. Economic impact data (as available), including the following: length of hospital stay, if applicable; number and types of probes used; and, ablation duration, defined as the time elapsed between first ablation probe puncture and removal of the last probe at the completion of the ablation.
21. Follow-up post-ablation treatment, including the number of successful repeat ablations, if applicable, and if patient has been hospitalized since the procedure. If patient has been re-ablated with NeuWave, record ablation procedure parameters as outlined in section 19.1, subsection 1. Record date of registry completion, when applicable.
22. When applicable, the Screening Visit may occur on the same day as the ablation procedure (Visit 2).
23. Record reason for unscheduled visit, as well as AEs (if applicable), and any updates to the relevant concomitant medications and relevant concomitant procedures.
24. Quality of Life and Pain Questionnaires may be administered up to 72 hours prior to the ablation procedure (Day 0).
25. Post-ablation Pain Score must be administered on the day of ablation (Day 0).
26. For Visit 1 through Visit 3, Eastern Cooperative Oncology Group classification (ECOG) performance status is required. After Visit 3, evaluate ECOG, if applicable per site SOC. ECOG may be assessed over the phone.

NOTE 1: All SOC scans of the abdomen/liver, including CT, MRI, and/or PET, taken at the following timepoints (Screening, Ablation Day, and throughout the 5-year follow-up period) should be submitted to the Sponsor through [redacted]. SOC Ultrasound scans of the abdomen/liver should also be submitted to the Sponsor, when on the Ablation Day or at any re-ablation visits. A subset of scans will be reviewed by the Central Review Committee to reduce the variability between investigators in assessing scans and to minimize potential bias.

NOTE 2: Patients rolling into this registry from a previous NeuWave trial will only have data collected in the Registry database starting from the time they consent to participate in the registry. Any data previously collected on roll-over patients will remain in the original database in which it was entered into.

ADMINISTRATIVE REQUIREMENTS

This registry is sponsored by NeuWave Medical, Inc. and will be conducted in all regions of the world under a single protocol approved by each participating site's Institution Review Board (IRB) / Ethics Committee (EC) prior to implementation. The Principal Investigator (PI) at each site must be qualified by education, experience, and training to perform the registry procedure and to assume responsibility for the conduct of this registry.

The Data Management and Biostatistics groups of Ethicon, Inc. will be responsible for the analysis of data from this protocol. An electronic data capture (EDC) system will be utilized by site personnel to transfer registry data from source records (the first point of clinical data capture) onto common electronic case report forms (eCRFs). This system is a web-based, secure electronic software application [redacted]. This system was designed, developed and maintained by [redacted] in a manner that is compliant with national and international Good Clinical Practice (GCP) data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements.

Protocol Modifications

All protocol amendments must be issued by the Sponsor, signed and dated by the Investigator, and should not be implemented without prior IRB/EC approval, except where necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the registry (e.g., change in monitor, change of telephone number, etc.). The Investigator will report the protocol amendments to the IRB/EC as per their local requirements.

5.0 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

Real World Evidence can provide information on how factors such as clinical setting, health care provider, and health-system characteristics influence treatment effects and outcomes. Importantly, the use of such evidence has the potential to allow researchers to answer these questions efficiently, while yielding answers relevant to broader populations of patients. Prospective registries with planned external controls and high-quality data collection have been accepted for regulatory purposes in the evaluation of medical devices.[1] Ideally, patient registries collect data in a comprehensive manner and, therefore, produce outcome results that may be generalizable to a wide range of patients.[2]

For the NEUWAVE Microwave Ablation System, the microwave ablation procedure parameters (including time, power, number and type of probes used) necessary to obtain desired short-term and long-term results across a range of target lesion characteristics (including size, location, co-morbidities, previous treatments, etc.) have not been studied in a systematic manner, nor is it known how operator factors affect results.

6.0 REGISTRY OBJECTIVES AND ENDPOINTS

6.1 Primary Objective

The primary objective of this registry is to compile data that will be analyzed at various timepoints, to understand the impact of selected parameters on procedure and patient outcomes. The database will capture data related to (1) Ablation Procedure parameters, (2) Patient parameters, and (3) Healthcare Provider parameters.

6.2 Primary Endpoints

The primary endpoints of this registry are below, based on different points in time:

Perioperative endpoint-

1. Technical success, defined as ablation of the target lesion(s) according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (i.e. the ablation zone completely overlaps or encompasses the target lesion(s) plus an ablative margin), as assessed by CT, MRI, PET, US, and/or X-ray, immediately following the procedure.

Short term endpoint-

2. Technique efficacy, ablation of the target lesion(s) according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (i.e., the ablation zone completely overlaps or encompasses the target lesion(s) plus an ablative margin), as assessed by CT, MRI, PET, US, and/or X-ray, at Visit 3 (between 7 days and less than 3 months post-ablation).

Long term endpoint-

3. Target lesion recurrence (local recurrence) rate evaluated at every visit after ablation of the target lesion(s), and overall evaluation at the 5-year follow-up, as assessed by CT, MRI, PET, US, and/or X-ray.

6.3 Secondary Endpoints

The secondary endpoints of this registry are:

1. Secondary efficacy rate, defined as the percentage of soft tissue lesions that have undergone successful repeat ablations (target or non-target) following identification of local soft tissue lesion progression. A successful repeat ablation will be defined as ablation of the lesion according to the protocol and covered completely, with an adequate margin, as defined by the performing physician (i.e. the ablation zone completely overlaps or encompasses the lesion plus an ablative margin), as assessed by CT, MRI, PET, US, and/or X-ray, immediately following the procedure.

2. Regional recurrence rate at a separate location in the liver (outside the initial treatment site(s)), evaluated at every visit after ablation of the target lesion(s), and overall evaluation at the 5-year follow-up, as assessed by CT, MRI, PET, US, and/or X-ray.

3. Recurrence-free survival, evaluated at every visit after ablation of the target lesion(s), and overall evaluation at the 5-year follow-up, as assessed by CT, MRI, PET, US, and/or X-ray.

4. Overall survival, evaluated at every visit after ablation of the target lesion(s), and overall evaluation at the 5-year follow-up.

5. Assess economic impact of ablation by capturing procedure-related items such as: complete procedure duration, ablation duration, number of ablations, length of hospital stay, and number and types of probes used.

6. Incidence of adverse events (AEs) (SAEs) that are deemed at least unlikely related to the procedure or device and all serious adverse events (SAEs) from the start of the ablation procedure through the end of the study.

7. Two QOL questionnaires: European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and liver-specific QLQ-HCC18.

   Note: These two questionnaires were chosen as tools to assess overall health status/quality of life in the patient population with soft-tissue liver lesions.

8. Numeric Pain Rating Score.

7.0 REGISTRY DESIGN

7.1 Overall Registry Design and Plan – Description

This is a multicenter, observational registry that follows patients for a total of 5 years from the date of the first liver ablation procedure with the NEUWAVE Microwave Ablation System. The data gathered from participating sites will be available to be analyzed to develop ablation parameter guidance for ablation approaches under varying patient liver tissue conditions and liver lesions.

This is an "umbrella registry," which was included as an optional component in other NEUWAVE studies; hence, data from consenting patients who are or will be enrolled in other NEUWAVE soft tissue liver lesion ablation studies will be included in this registry. All other patients will be enrolled and followed prospectively, enrolled retrospectively with prospective, longitudinal follow up, or enrolled retrospectively with all retrospective follow up.

7.2 Enrollment

The goal is to create a registry with enrollment ongoing until there are an adequate number of patients with which a statistically sound analysis could be performed. Enrollment for this study will include at least 1,500 patients throughout the world who underwent or are undergoing microwave ablation of one or more soft tissue liver lesions using the NEUWAVE Microwave Ablation System or the NEUWAVE Microwave Ablation System with Ablation Confirmation.

7.3 Inclusion Criteria

1. Patients who underwent or are scheduled to undergo a microwave ablation of one or more liver lesions with the NEUWAVE Microwave Ablation System per the device's Instructions for Use (IFU).

2. Patients with signed informed consent (or waiver approved by IRB/EC) who are willing to comply with the assessment schedule, and willing to have data included in the database.

3. Patients $\geq$ 22 years old at the time of informed consent (or waiver approved by IRB/EC).

7.4 Exclusion Criteria

1. Patients with a life expectancy of less than 1 year, in the opinion of the treating physician.

2. Use of microwave ablation purely as a transection tool, rather than focused liver lesion ablation.

3. Patient is currently participating, or planning to participate, in another NeuWave/Ethicon-funded clinical trial or registry studying microwave ablation in the liver. Note: roll-over patients from previous NeuWave trials are permitted.

7.5 Prior and Concomitant Therapy

Patients may continue with their current medical care throughout the duration of the registry, including medications. Relevant concomitant medications will be recorded on the relevant eCRF page. Relevant concomitant medications include: chemotherapy, immunotherapy, blood-thinning or coagulation, NSAIDs, those medications used to treat AEs, those used for hepatitis (if concurrently treating), and any others that are relevant in the opinion of the investigator.

7.6 Screen Failures

All patients signing consent who do not meet the eligibility or who do not have the ablation procedure initiated will be recorded as screen failures. The relevant eCRF pages (i.e. demographics and reason for screen failure) will be completed for all screen failure patients and thereby included in the registry database.

7.7 Removal of Patients from the Registry

In accordance with the current revision of the Declaration of Helsinki and the Code of Federal Regulations, a patient has the right to withdraw from the registry at any time for any reason without prejudice to his/her future medical care by the physician or the institution. Should a patient (or patient's legally authorized guardian/representative) decide to withdraw from the registry, all efforts will be made to collect all AEs the patient may have experienced.

Participation may be terminated prior to completing the registry for any of the reasons listed below (reasons that do not fit the categories below will be documented as "other").

Withdrawal of Consent:

If a patient chooses to withdraw early from the registry, the patient should contact the site, which will then complete the Subject Completion/Discontinuation eCRF page. When a patient's participation is terminated prior to completing the registry, the reason for withdrawal is to be documented on the eCRF and in the source documentation.

Investigator Decision for Patient Termination:

The Investigator may withdraw a patient for any safety reason, including, but not limited to, the following reasons:

1. Inability of Investigator to locate and target the soft tissue liver lesion.
2. Inability of patient to tolerate the anesthesia.

Note: If a patient experiences an AE during probe puncture and is not ablated, this patient should be followed until AE resolution. If no AE occurred during probe puncture and the patient could not be ablated, the patient should be discontinued.

Death:

When available, the cause of death should be documented in the AE eCRF. The Subject Completion/Discontinuation eCRF also must be completed.

Lost to follow-up:

All patients should be encouraged to return for clinic visits for evaluation during the registry follow-up period. After all attempts to contact the patient have failed and after 2 consecutive missed visits to the site, a patient will be considered lost to follow up. Should the patient return to the site, their status in the database may be updated accordingly and data continue to be collected. For patients who are definitively lost to follow-up, the reason for early termination will be completed in the Subject Completion/Discontinuation eCRF.

Site Termination or Registry Termination:

The Sponsor may terminate a site or the registry at any time. When this occurs all patients at the site will be withdrawn and documented as "early termination." Reasons for site or registry termination may include, but are not limited, to the following:

1. Administrative concerns (e.g., inadequate patient enrollment, investigator/institution non-compliance, change of business strategy, etc.).
2. Safety issues including those due to non-compliance, which substantially affect the risk-to-benefit ratio of the registry patients at a site or for the registry as a whole.
3. Regulatory body mandates.

8.0 REGISTRY POPULATION

The registry population includes patients with one or more soft tissue liver lesions of any size, location, or shape who underwent or will undergo a MWA procedure with the NEUWAVE Microwave Ablation System.

9.0 INVESTIGATOR RESPONSIBILITIES

9.1 Good Clinical Practices

An Investigator is responsible for ensuring that this registry is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the ICH GCP, the signed Clinical Trial Agreement, this Protocol, the institution's IRB/EC policies and procedures, and applicable regulatory requirements.

Prior to the initiation of this clinical registry at each site, the responsible Principal Investigator will approve this Protocol by signing the signature page. This signature confirms that the clinical registry will be performed in compliance with this protocol.

The following documents must be provided to the Sponsor prior to registry start:

1. A copy of the formal written notification to the Investigator regarding approval of the protocol by an IRB/EC that is in compliance with regulatory guidelines.

2. A copy of the IRB/EC approved ICF or ICF waiver and other adjunctive materials (e.g., advertising) to be used in the registry, including written documentation of IRB/EC approval of these items.
3. Name and address of the IRB/EC, and a current list of the IRB/EC members. If accompanied by a letter of explanation from the IRB/EC, a general statement may be substituted for this list, or a general assurance number.
4. Applicable local regulatory documentation.
5. Signed and dated protocol Investigator Signature page.
6. Signed confidentiality agreement between the Investigator and the Sponsor.
7. Signed and dated clinical trial agreement, including financial agreement.
8. Up-to-date signed and dated curriculum vitae for each investigator and sub-investigator.
9. Statement of Investigator.

Other documents may also be required prior to the registry and during the course of the registry.

9.2 Institutional Review Board/Ethics Committee

Participating investigators will ensure that this protocol, corresponding ICF/Waiver, or protocol amendments, and if applicable, any other written information provided to the patients that assist in the decision to participate are reviewed by an IRB/EC that complies with governmental requirements. The approving IRB/EC will be responsible for the initial and continuing review and approval of this registry. Participating investigators will be required to promptly report to the IRB/EC as required by the IRB's/EC's policies. Additionally, investigators will be required to refrain from making any changes in the protocol without Sponsor and IRB/EC approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to registry patients or others.

9.3 Patient Information and Consent

To minimize selection bias, sites should attempt to identify and approach all eligible patients for consent who were ablated or will be ablated for soft tissue liver lesions using the NEUWAVE Microwave Ablation System or the NEUWAVE Microwave Ablation System with Ablation Confirmation. Patients who had liver ablations with NEUWAVE prior to consent are eligible to participate as retrospectively enrolled patients. Retrospective patients can be fully retrospective (all protocol visits have occurred prior to the date of ICF/waiver) or can have some prospective follow-up (applicable protocol visits occur after signing the ICF).

The informed consent process involves the investigator or delegated staff to complete the following activities: giving a patient adequate information concerning the registry, providing adequate time for the patient to consider all available options, responding to the patient's questions, ensuring that the patient has comprehended this information, and finally, prior to a

patient's participation in this registry, an ICF will be signed and dated by the patient and person who conducted the consent discussion. All prospective patients in this registry should be completely informed about the purpose, risks, benefits, and other pertinent details of this registry. The informed consent process is careful to avoid the perception of any coercion or undue influence on, or inducement of, the patient to participate, and does not waive or appear to waive the patient's legal rights. The ICF is presented in native, non-technical language that is understandable to the patient. The patient will be provided with a copy of the signed ICF. Completely retrospective patients will need to have an ICF waiver in place prior to having his or her data collected.

The ICF and any other written materials provided to the patient to assist in the decision to participate must be revised whenever new information becomes available that may be relevant to their willingness to participate or continue participation in this registry. Revision to the ICF and other written materials will receive IRB/EC approval before implementation. Each patient required to sign an amended ICF will receive a copy of the signed ICF. All original signed amended ICFs will also be kept within the patient's medical record.

10.0 REGISTRY INTERVENTIONS

There is no intervention, beyond necessary, standard, clinical care in this registry.

11.0 REGISTRY PROCEDURES AND EVALUATIONS

11.1 Procedure Description(s)

Pseudoanonymized data from all patients who provide consent (or an IRB approved ICF waiver), and who are undergoing or have undergone microwave ablation of one or more soft tissue liver lesions using the NEUWAVE Microwave Ablation System will be included in the registry's clinical database. The ablation will be performed in accordance with the institution's SOC for microwave ablation and per the device's IFU.

11.2 System Overview

The NEUWAVE Microwave Ablation System has a single 2.45 GHz signal microwave source generator and three (3) independent microwave amplifiers, each capable of producing up to 140W each. Generator power is limited based upon the number of probes selected and the types of probes used. One touch-screen user interface controls the system. The User Interface can be set for either Ablation Mode or Surgical Mode. Up to three (3) microwave ablation probes can be connected to and powered by the system at one time. An intermediate junction box or Power Distribution Module (PDM) reduces system set up complexity.

Cooling System Overview

A CO_2 based cooling system ensures the non-active portion of the probe does not exceed temperature requirements. Additionally, the CO_2 enables the Tissu-Loc™ function, which may be used to adhere or stick the probe in place prior to starting ablation therapy. This function is similar in use to the stick function available on cryogenic ablation systems.

The system uses two (2) CO_2 cylinders (size may vary by market). When a tank in use empties, the system will automatically switch to using the other tank and notify the user to replace the empty tank.

The cooling system regulates the flow of high-pressure CO_2 in a cooling gas tube to the PDM and eventually to the probe. Inside the tip of the probe, the cooling gas tube expands from high pressure to low pressure. As the gas pressure reduces quickly, the Joule-Thompson effect causes the probe shaft to cool. This is used for both the Tissu-Loc™ function and to keep probes at a safe temperature while energy is being delivered to the patient.

The PDM is designed to improve the usability of the system by reducing set-up complexity while also helping to minimize the cabling from the probe to the generator. The PDM also allows a larger, lower-loss cable to be used between the microwave generator and PDM. The increased efficiency of the larger cable and PDM allow more power to be safely sent to the ablation probe without an unsafe heating of the probe cable or handle.

System performance is constantly monitored. The NEUWAVE Microwave Ablation System will automatically discontinue delivering microwave energy in the event of system failures.

NEUWAVE Ablation Probes Overview

NEUWAVE Ablation Probes are provided sterile and are intended for single patient use only. Ablation probes are comprised of a sharp trocar on the end of a cannula, a probe handle, a 1.4-meter cable, and a connector assembly.

Each NEUWAVE Ablation probe contains three (3) temperature measurement sensors that help monitor performance and ensure patient and operator safety.

The NEUWAVE ablation probe assembly contains four (4) main sections: a handle, a cannula, a radiating section, and a faceted tip for insertion.

All NEUWAVE Ablation Probes should be used within their cleared indications.

Most commonly used probes are LK and PR. NEUWAVE LK probes are designed to perform optimally, in terms of efficiently transferring energy into tissue, in liver and kidney tissues.

The antenna of the NEUWAVE PR probe is designed to limit the length of the ablation compared to LK probes for instances when a shorter ablation zone is desired. The NEUWAVE PR probes are designed to produce ablations that quickly encompass the tip of the probe while limiting the overall length of the ablation. NEUWAVE PR probes will enable physicians to ablate smaller lesions while limiting necrosis of adjacent tissue when compared with other NEUWAVE probes.

Refer to the NEUWAVE Microwave Ablation System accompanying documents, such as the IFU, for a list of Warnings and Cautions.

11.3 Central Review Committee

An independent, Central Review Committee (CRC) will be used to reduce the variability between investigators in assessing scans and to minimize potential bias. The CRC will assess a subset of scans for prospectively-enrolled patients at each site. The CRC will review these scans and provide assessments including, but not limited to, lesion details at baseline, outcome of ablation, and lesion recurrence/progression during the post-ablation period.

As this is a SOC registry, assessments by the Principal Investigator (PI) will be used for all treatment decisions, as well as all protocol-defined analyses. Review by the CRC will be compared, where applicable, to the assessments made by the PI. The results of these comparisons will be summarized in separate analyses as part of the Clinical Study Report (CSR) and/or publication(s).

12.0 REGISTRY SCHEDULE

The Schedule of Assessments, which is found at the end of the Protocol Summary, serves as a guideline for participating sites regarding data to be collected for this registry. All should closely reflect standard of care.

12.1 Visit 1 – Screening

The screening assessments for this visit may occur over several dates within 60 days prior to Visit 2. If the patient is not seen within a 60 day window of the Ablation Day (Visit 2), the Screening Visit may occur on the same day as the ablation procedure.

Patients will be selected for microwave ablation based on the pre-procedure investigations and the Investigator's opinion. Eligible patients will be provided with the registry information, including the ICF.

The following screening assessments will occur within 60 days prior to the ablation visit (Visit 2):

- Patients must be given ample time to review and sign the ICF, or have a waiver in place, where applicable.
- Collect demographic information (age at time of Visit 1, sex, race, ethnicity).
- Collect patient parameters, as outlined in Section 19.1, subsection 2.
- Perform a liver tissue assessment (if available): steatosis (mild, moderate, severe); fibrosis/cirrhosis (mild, moderate, severe; include pathology results and fibrosis stage, if known); liver stiffness (actual stiffness value in kilopascals, if known); vascular invasion (presence or absence); microsatellite instability (MSI; high [MSI-H], low [MSI-L], or microsatellite stable [MSS]).
- BCLC staging, if applicable

- Evaluate Eastern Cooperative Oncology Group classification (ECOG) performance status.
- Body Mass Index (BMI): height and weight.
- Child-Pugh Score, if applicable and American Society of Anesthesiologists (ASA) Score.
- SOC imaging used to determine the ablation plans (CT, MRI, PET, Ultrasound (US), and/or X-ray), even if not within the screening window, should be used to determine soft tissue liver lesion details (e.g., lesion size, lesion type, location, shape).
    - If a Screening Visit occurs and the patient's SOC scans do not fall within the screening window, then an additional scan is not required for the screening visit.
    - For purposes of this Registry, target lesions are defined as any lesions ablated or intended to be ablated on the Ablation Day (Visit 2). Non-target lesions are defined as any lesions not ablated or not intended to be ablated on the Ablation Day (Visit 2).
    - All SOC scans of the abdomen/liver (CT, MRI, and/or PET) should be submitted to the Sponsor.
- Laboratory tests if applicable, per site SOC; to be done within 60 days of the ablation procedure,
    - Coagulation tests, including, INR, PT and APTT (or PTT).
    - Liver function tests, including AST, ALT, GGT, albumin, direct and total bilirubin, and total protein.
    - Renal function tests, including BUN, creatinine and electrolytes (sodium, potassium, chloride and bicarbonate).
    - Complete blood count (CBC), including differential cell count and platelet count.
    - Genetic markers including: Alpha-fetoprotein (AFP) level, Carbohydrate antigen 19-9 (CA19-9) level, Carcinoembryonic antigen (CEA).
- Review inclusion and exclusion criteria.
- Record all relevant medications taken within 60 days prior to Visit 2: Relevant concomitant medications include: chemotherapy, immunotherapy, blood-thinning or coagulation, NSAIDs, those used for hepatitis (if concurrently treating), and any others that are relevant in the opinion of the investigator.

12.2 Visit 2 – Ablation Procedure

Patients will be under anesthesia during the procedure per the site's SOC. On the day of ablation, SOC imaging will be done at the timepoints listed in the section below.

Pre-ablation

Data collected before the procedure:

- Evaluate ECOG performance status (prior to ablation).

- Confirm that the patient still meets inclusion and exclusion criteria.
- Record all relevant concomitant medications: Relevant concomitant medications include: chemotherapy, immunotherapy, blood-thinning or coagulation, NSAIDs, those used for hepatitis (if concurrently treating), and any others that are relevant in the opinion of the investigator.
- QOL questionnaires, using EORTC QLQ-C30 and liver-specific QLQ-HCC18. The questionnaires may be administered up to 72 hours prior to the ablation procedure. The questionnaires may also be administered over the phone, as needed.
- Pain score, using the Numeric Pain Rating Scale. The questionnaire may be administered up to 72 hours prior to the ablation procedure. The questionnaire may also be administered over the phone, as needed.
- SOC imaging (i.e. CT, MRI, US) to determine soft tissue liver lesion details (e.g. size, location, shape, stage), if performed as part of site's routine SOC.

During ablation

Use SOC imaging to guide the microwave ablation probe to the target soft tissue liver lesion(s) and insert the probe into the lesion(s). Data collected during the procedure:

- Record ablation procedure details as outlined in section 19.1, subsection 1
- Record any applicable AEs/SAEs.

Note: When available, some of the above ablation procedure details will be provided to the site via a report generated from the Call Home Database. The site will review the Call Home report and enter the procedure details into the clinical database, as applicable.

Post-ablation

After the ablation procedure, the following assessments will occur:

- Pain score using the Numeric Pain Rating Scale. The post-ablation pain score must be administered on the day of ablation (Day 0). The questionnaire may be administered over the phone, as needed.
- Relevant concomitant procedures (i.e. liver or lesion-related).
- Record all applicable AEs/SAEs and product complaints.
- Imaging to evaluate technical success, defined as ablation of the target lesion(s) according to the protocol and covered completely, with an adequate margin, as defined by the physician performing the ablation (that is, the ablation zone completely overlaps or encompasses the target lesion plus an ablative margin), as assessed by CT, MRI, PET, US, and/or X-ray, immediately following the procedure.
- Length of hospital stay, measured from post-ablation to discharge.
- Record Healthcare provider parameters as outlined in section 19.1, subsection 3
- Record any remaining ablation procedure details

- Record all relevant concomitant medications: Relevant concomitant medications include: chemotherapy, immunotherapy, blood-thinning or coagulation, NSAIDs, those medications used to treat AEs, those used for hepatitis (if concurrently treating), and any others that are relevant in the opinion of the investigator.

Note: All SOC scans of the abdomen/liver on the day of ablation (CT, MRI, PET, and/or US) should be submitted to the Sponsor.

12.3 Post-ablation Follow-up Visits

The list of assessments is the same for all follow-up visits unless otherwise specified.

At each follow-up visit, the patient will visit the site (or have a tele-visit and/or phone visit when unable to visit the site) and the following assessments will occur:

- Evaluate ECOG performance status (Visit 3 only). After Visit 3, evaluate ECOG, if applicable per site SOC. ECOG may be assessed over the phone.
- Laboratory tests, as follows, if applicable per site SOC:
  - Coagulation tests, including, INR, PT and APTT (or PTT).
  - Liver function tests, including AST, ALT, GGT, albumin, direct and total bilirubin, and total protein.
  - Renal function tests, including BUN, creatinine and electrolytes (sodium, potassium, chloride and bicarbonate).
  - CBC, including differential cell count and platelet count.
  - Genetic markers including: Alpha-fetoprotein (AFP) level, Carbohydrate antigen 19-9 (CA19-9) level, Carcinoembryonic antigen (CEA).
- Record all relevant concomitant medications: Relevant concomitant medications include: chemotherapy, immunotherapy, blood-thinning or coagulation, NSAIDs, those medications used to treat AEs, those used for hepatitis (if concurrently treating), and any others that are relevant in the opinion of the investigator. Relevant concomitant medications may be assessed over the phone.
- QOL questionnaires, using EORTC QLQ-C30 and liver-specific QLQ-HCC18, (Visits 3 through 6). The questionnaires may be administered over the phone, as needed.
- Pain score using the Numeric Pain Rating Scale (Visit 3 only). The questionnaire may be administered over the phone, as needed.
- Technique efficacy evaluation (Visit 3 only).
- Imaging to determine whether there has been a local or regional recurrence of lesion(s). If there is a recurrence, determine soft tissue liver lesion details via CT, MRI, PET, US, and/or X-ray.
  - All SOC scans of the abdomen/liver (CT, MRI, and/or PET) should be submitted to the Sponsor.
- Record relevant concomitant procedures (i.e. liver or lesion-related). Relevant concomitant procedures may be assessed over the phone.

- Record follow-up post-ablation treatment, including the number of successful repeat ablations, if applicable, and if patient has been hospitalized since the procedure. If patient has been re-ablated with NeuWave, record ablation procedure details as outlined in section 19.1, subsection 1.
- Record all applicable AEs/SAEs and product complaints. Assessments for safety may be assessed over the phone.
- Record date of registry completion, when applicable.

Note: in the case a patient has a liver resection or liver transplant, he/she should continue to be followed in the study, as outlined per the study protocol. Post-ablation follow-up visits should occur as per site SOC.

12.4 Unscheduled Visits

The following data will be collected during each unscheduled visit:

- Reason for the unscheduled visit.
- AEs/SAEs, if applicable.
- If applicable, SOC imaging to determine whether there has been a local or regional recurrence of lesion(s). If there is a recurrence, determine soft tissue liver lesion details via CT, MRI, PET, US, and/or X-ray.
    - All SOC scans of the abdomen/liver (CT, MRI, and/or PET) should be submitted to the Sponsor.
- Any follow-up post-ablation treatment, including the number of successful repeat ablations, if applicable, and if patient has been hospitalized since the procedure. If patient has been re-ablated with NeuWave, record ablation procedure parameters as outlined in section 19.1, subsection 1 and product complaints, as applicable. Upload of SOC images on the day of re-ablation with NeuWave should follow the requirements of upload per Visit 2 – Ablation Procedure.
- Any updates to the relevant concomitant medications and relevant concomitant procedures

13.0 ASSESSMENT OF SAFETY

Patients will be assessed and monitored for all AEs that are deemed at least unlikely related to the procedure or device from the day of ablation (from the time of first probe insertion) through the 5-year follow-up visit and all SAEs.

13.1 Adverse Events

Definitions

Adverse Event

For this registry, an adverse event is defined as any undesirable clinical occurrence (sign, symptom, or disease) in a patient. Only AEs that are deemed at least unlikely-related to the procedure or device will be collected. All SAEs, regardless of relationship to the study device or procedure, will be collected.

Expected Morbidity / Anticipated Adverse Events

An expected morbidity/procedural complication is defined as an AE that is known to be common or usual in nature, severity, or incidence during ablation of the liver.

Serious Adverse Event

All SAEs, regardless of relationship to the study device or procedure will be collected. It is the Investigator's responsibility to determine the "seriousness" of an AE using the protocol defined terms, listed below. An SAE is an AE that results in one or more of the following for this registry:

- Resulted in death: An AE that resulted in the patient's death.
- Life-threatening illness or injury: The patient was at imminent risk of dying at the time of the adverse event.
- Permanent impairment: An AE that resulted in permanent impairment of a body function or permanent damage to a body structure.
- Required in-patient or prolonged hospitalization.
- Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body or body function.
- Led to fetal distress, fetal death or congenital abnormality or birth defects.

Notes:

1. Progression of the disease under study should not be reported as an SAE.
2. "Death" should not be reported as an AE. The cause of death should be reported as an AE. The only exception is "Sudden Death" when the cause is unknown.
3. Planned hospitalization for a pre-existing condition is not considered an SAE.

SEVERITY OF ADVERSE EVENTS

It is the Investigator's responsibility to assess the severity of an AE. A change in severity may constitute a new reportable AE.

Also, the following guideline should be used to determine the severity of each adverse event:

- MILD: Awareness of signs or symptoms, but does not interfere with the patient's usual activity or is a transient event that resolves without treatment and with no sequelae.
- MODERATE: A sign or symptom, which interferes with the patient's usual activity.
- SEVERE: Incapacity with inability to do work or usual activities.

RELATIONSHIP OF ADVERSE EVENTS

It is the Investigator's responsibility to assess the relationship between all AEs to the registry device and procedure. All SAEs, regardless of relationship to the study device or procedure will be collected. Adverse events deemed to have an unlikely, possible, probable, or causal relationship to the procedure or device should be captured in source as part of the study and entered in the the AE eCRF. Adverse events deemed to be not related to the procedure or device should only be captured in source. The following guidelines should be used in determining the relationship of an AE to a device, procedure, or other causality:

Not related	Relationship to the procedures or device can be excluded when: • The event is not a known side effect of the product category the device belongs to or of similar device and procedures; • The event has no temporal relationship with the use of the device or the procedures; • The event does not follow a known response pattern to the device (if the response pattern is previously known) and is biologically implausible; • The discontinuation of the device application or the reduction of the level activation/exposure (when clinically feasible) and reintroduction of its use (or increase of the level of activation/exposure), does not impact on the event; • The event involves a body-site or an organ not expected to be affected by the device or the procedure; • The 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); • Harms to the subject are not clearly due to use error; or • To establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedure and the 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 device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/condition and/or an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable*	The relationship with the use of the device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

Causal Relationship*	The event is associated with the 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 device and procedure
	• The event has a temporal relationship with the device uses/application or procedures
	• The event involves a body-site or organ that
	  ○ The device or procedures are applied to
	  ○ The device or procedures have an effect on
	• The 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 event (when clinically feasible)
	• Other possible causes (e.g. an underlying or concurrent illness/clinical condition and/or an effect of another device, drug, or treatment) have been adequately ruled out
	• Harm to the subject is due to error in use
	• To establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedure and the event.

*Denotes “related” to the procedure or device and should be captured (AE) as part of the study.

13.2 Reporting Adverse Events

All procedure-related and device-related AEs (non-serious) and all SAEs from the time of the first probe placement through study completion (Visit 14), or to the time of early withdrawal of the study, must be reported in the AE eCRF. The Investigator will evaluate the severity of the event and its relatedness to the registry device or procedure.

The Investigator is required to report all applicable non-serious AEs to the Sponsor within 2 weeks of becoming aware of the adverse event(s). All SAEs are to be reported as soon as possible, but no later than 72 hours after becoming aware of the event, regardless of relationship to the device or study procedure.

The study site will report applicable AEs and all SAEs to the Sponsor by entering the event into the EDC system via the Adverse Event eCRF, which will trigger an automated email to the Sponsor. Additional information, including the Investigator's assessment, may be added to the eCRF later. Any necessary medical management of the event will be recorded in the patient's medical record/source document. If the Sponsor requires supporting documentation or other information, the Sponsor will contact the study site.

Data related to AEs and SAEs will be collected until event resolution, until the event is considered stable, or until all attempts to determine the resolution of the event are exhausted. All AEs and SAEs that are unresolved at study completion (or early termination) will be recorded as ongoing at study end.

In addition, the following information should be recorded:

- Onset date
- Resolution date or date of death
- Action taken
- Event status (ongoing at registry end or resolved)
- Relationship of AE to the ablation device used in the registry
- Relationship of AE to the registry procedure
- Indication of seriousness.
- Was AE anticipated or not (only for serious, device-related AEs)

The report of an AE or SAE by a site does not constitute an admission that registry personnel or the user facility (hospital/clinic) caused or contributed to the event. The site is responsible for submitting AEs to the reviewing IRB/EC, per their IRB/EC procedures.

For retrospectively enrolled patients, the site should review patient medical records (i.e. through chart review) to look for reportable AEs/SAEs. Collection of AE data and reporting requirements will be the same for retrospective events, however, Sponsor reporting timelines do not apply.

13.3 Product Complaints

Product Complaint Definition

A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, labeling, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution (21CFR 820.3 (b)). A product complaint may or may not be associated with an AE/SAE.

Product complaints may include, but are not limited to:

- Product contamination;
- Defective components;
- Poor packaging or product mix-up;
- Device malfunction (the failure of a device to perform as intended for this registry);
- Labeling concerns;
- User errors.

Reporting Product Complaints

All product complaints related to devices in the procedure shall be documented throughout the registry study.

The registry site must report product complaints related to a device manufactured by NeuWave Medical, Inc., in a timely manner after becoming aware of the event. When any representative of the Sponsor becomes aware of a product complaint, the Sponsor representative must notify the Sponsor's Product Complaint Team with the least practical delay after becoming aware of the event through a Product Complaint Form to the following email address (Productcomplaint1@its.jnj.com) or by calling 1-877-ETHICON, Option 5.

One copy of the processed form should be kept on-site, and the device should be retained. Sponsor representatives will organize collection of the device for evaluation, as needed.

14.0 DEVIATIONS FROM THE CLINICAL REGISTRY PLAN

A protocol deviation is any noncompliance with the registry protocol, Good Clinical Practice, or protocol-specific requirements. A deviation (any activity conducted outside the parameters established by the registry protocol) can be identified from a number of sources. Potential sources include but are not limited to: a member of the Investigator's staff, a Sponsor representative during monitoring visits, or a member of the data management or statistical groups when entering or analyzing data. Regardless of the source, it is crucial to document the deviation in the protocol deviation eCRF. The Investigator will report protocol deviations to the IRB/EC as required by the IRB/EC procedures.

Any deviation from the protocol or procedures should be recorded in the source documents. Assessments or visits that are not completed because they are not SOC at a site, or assessments that were not completed for retrospective patients, should not be considered protocol deviations.

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate sites, the review of protocol procedures with the Investigator and associated personnel prior to the registry, and periodic monitoring visits by the Sponsor. The Sponsor will review eCRFs for accuracy and completeness during monitoring visits; any discrepancies will be resolved with the Investigator or designees, as appropriate.

15.0 REGISTRY PRODUCT

All NEUWAVE Microwave Ablation Systems, the NEUWAVE Microwave Ablation System with Ablation Confirmation, and the NEUWAVE Ablation Probes used in the registry are legally marketed in the countries where they are used. The registry products should be used within their cleared indications as per the Instructions For Use.

16.0 CLINICAL MONITORING

This registry will be monitored by the Sponsor to ensure the following:

- The rights and well-being of the patients are protected.
- Reported registry data is accurate, complete, and verifiable from source documents.
- The conduct of the registry is in compliance with the currently approved protocol/amendment(s), applicable GCPs, and with applicable local regulatory requirements.

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate sites, review of protocol procedures with the Investigator and associated personnel prior to the registry, and periodic monitoring visits by the Sponsor. The Sponsor will review eCRFs for accuracy and completeness during monitoring visits; any discrepancies will be resolved with the Investigator or designees, as appropriate.

The extent and nature of monitoring will be predetermined and based on considerations such as the objective, design, complexity, and endpoints of the registry and mutually agreed to by the Sponsor and investigators. Monitors will comply with established written standard operating procedures as well as procedures (i.e., monitoring plan) specified by the Sponsor for monitoring this registry. These monitoring procedures are characterized in the Monitoring Plan for this registry.

17.0 STATISTICAL METHODOLOGY

17.1 Statistical and Analytical Plans

The Sponsor Data Management and Biostatistics groups will be responsible for the analysis of data from this protocol. A comprehensive and detailed Statistical Analysis Plan (SAP) to supplement the statistical design and analysis described in this section will be finalized prior to the first analysis of data from this protocol.

Categorical variables will be summarized descriptively by frequencies and associated percentages. Continuous variables will be summarized descriptively by number of patients, mean, standard deviation, median, minimum, and maximum. Confidence intervals will also be provided for procedure-related variables.

17.2 Registry Design

This is a multicenter, observational registry that follows patients for a total of up to 5 years from the date of the first liver ablation procedure with either the NEUWAVE Microwave Ablation System or the NEUWAVE Microwave Ablation System with Ablation Confirmation.

This is an “umbrella registry,” which was included as an optional component in other NEUWAVE studies; hence, data from consenting patients who are or will be enrolled in other NEUWAVE soft tissue liver lesion ablation studies will be included in this registry. All other patients will be enrolled and followed prospectively, enrolled retrospectively with prospective, longitudinal follow up, or enrolled retrospectively with all retrospective follow up.

17.3 Treatment Assignment

This is a single-arm registry where all enrolled patients will be ablated using the NEUWAVE Microwave Ablation System as part of the site’s SOC treatment or per protocol for those patients who are also enrolled in other NEUWAVE studies.

17.4 Interval Windows

Interval windows are provided in the Schedule of Assessments, which appears at the end of the Protocol Summary. No additional windows are planned for analysis purposes.

17.5 Primary Endpoint and Associated Hypotheses

This protocol does not have a single primary endpoint and there are no associated hypotheses. Rather, there are several patient-level outcomes of interest that will be investigated through statistical modeling to estimate the relationship between these outcomes and various patient, provider, and ablation-specific parameters. These patient-level outcomes of interest include: technical success, technique efficacy, secondary efficacy rate, target lesion recurrence rate, recurrence-free survival, and overall survival.

17.6 Levels of Significance

No levels of significance are specified as no specific hypotheses about any of the outcomes of interest are being formulated or tested. Significance levels relating to variable selection in a statistical regression model will be specified in the SAP.

17.7 Analysis Sets

All patients contributing data to the registry will be considered eligible for inclusion into planned analyses. Specific rules regarding a minimum or critical number of observed dependent and independent variables for inclusion into statistical modeling analyses will be specified in the SAP.

17.8 Sample Size Justification

This registry will be open to receiving data from all patients who are ablated with microwave ablation of soft tissue liver lesions using the NEUWAVE Microwave Ablation System. Given that the objective of the registry is to investigate the relationships that exist between the stated clinical outcomes, patient and provider parameters, and microwave ablation (MWA) time and power, no power analysis or sample size determination have been performed given the absence of a specific hypothesis to test. Rather, a statistical modeling exercise will occur at pre-specified intervals after sufficient data has been entered to support exploratory statistical modeling. The timing of these analyses will be defined in the SAP. Additional ad-hoc analyses will be conducted throughout the duration of the registry.

17.9 Analyses to be Conducted

Categorical variables will be summarized descriptively by frequencies and associated percentages. Continuous variables will be summarized descriptively by number of patients, mean, standard deviation, median, minimum, and maximum. Confidence intervals will also be provided for procedure-related variables.

Disposition of Registry Patients

Patient disposition will be summarized using counts and percentages. The number and percentage of patients completed and discontinued along with the specific reasons for discontinuation will be tabulated.

Demographic and Baseline Characteristics

Summary statistics will be provided for patient demographics and pre-operative ablation characteristics.

Primary and Secondary Endpoint Analyses

Regression analysis methodologies will be utilized to explore the relationship between dichotomous clinical outcomes (technical success, technique efficacy, and secondary efficacy rate) and ablation procedure, patient, and provider parameters. Time to event analyses will be used for target lesion recurrence, regional recurrence rate, recurrence-free survival, progression free survival, and overall survival.

Complete details regarding all analysis methodologies including approaches to handle multiple lesions per patient, variable selection techniques, data reduction techniques given the number of potential independent variables, as well as subgroup analyses of interest will be specified in the SAP.

The number and percentage of patients achieving technical success will be summarized and a 95% confidence interval will be provided. A similar summary will be provided for technique efficacy, as well as for the primary and secondary efficacy rates, as previously defined.

Target lesion recurrence rates at each post-ablation scheduled visit will be estimated using the Kaplan-Meier method and 95% confidence intervals will be provided. A similar summary will be provided for the 5-year overall rate. Similar summaries will also be provided for regional recurrence rate, overall and progression-free survival rates for the entire observation period from the ablation procedure date through 5 years of follow-up.

Scores from the EORTC QOL questionnaires and Numeric Pain Rating Scales will be summarized with methodology consistent to the recommendations of the specific survey. Additional endpoints will be summarized with descriptive statistics.

Plans for Interim Analysis

There are no plans for interim analyses with an intent to stop the registry early or to adapt the registry design or planned number of patients.

Analysis of Safety

From start of ablation procedure through the 5-year follow-up visit, procedure and device-related AEs, and all SAEs will be collected, and these will be summarized by system organ class and preferred term. Ninety-five percent confidence intervals may be provided for pre-specified adverse events of interest, which are:

- Ascites (accumulation of fluid causing abdominal swelling)
- Biloma/bile leak (buildup of bile within the abdomen)/bile leak)
- Bile duct injury
- Bleeding requiring transfusion, embolization (obstructing of blood vessel or organ to stop bleeding), or prolonged hospital stay
- Intrahepatic hematoma
- Pneumothorax and hemothorax
- Organ injury other than the liver (such as gastrointestinal injury/perforation, diaphragmatic injuries/hernia)
- Fever
- General feeling of tiredness
- Infection

- Liver dysfunction.
- Liver abscess
- Nausea
- Pain
- Pneumonia
- Pleural effusion
- Post ablation syndrome, which is your body's response to the destroyed lesion. You may experience flu-like symptoms, including fever, decreased appetite, and general discomfort. This syndrome generally happens 3 to 5 days after the ablation procedure.
- Skin burn
- Thrombosis (local coagulation or clotting of the blood in the circulatory system, with/without tube drainage)
- Tumor implantation

Handling of Dropouts or Missing Data

Given that this is a registry that will include both retrospective and prospective data, with some patients coming from other NeuWave clinical trials, missing data is expected for both the dependent and independent variables in the regression analyses described above. Specific rules regarding imputation of missing data (e.g. multiple imputation, minimum number of observed variables, sensitivity analyses) will be provided in the SAP.

Multicenter Studies

Analyses will be adjusted for center through the inclusion of the various provider-specific variables described above.

Analysis of Subgroups

Subgroup analyses will be performed for levels of the following variables: Location of lesion (near vessel >3mm, Dome, Subcapsular, Segment); Underlying disease (mild, moderate or severe cirrhosis; presence of fatty liver; post chemotherapy); Type of disease (CRLM, HCC, Cholangiocarcinoma, Other); ASA score; Child-Pugh score; Type of hospital; Experience of the ablationist; AC vs no AC; and gender. Additional subgroups of interest may be identified pending the distribution of various parameters at enrollment. Details regarding the analysis methodologies for these subgroups will be pre-specified in the SAP.

18.0 ETHICS/PROTECTION OF HUMAN PATIENTS

18.1 Institutional Review Board/Ethics Committee

Participating investigators must obtain IRB or EC approval prior to execution of the protocol. Only IRBs/ECs that comply with governmental requirements may approve this registry. Prospective investigators must provide to an IRB/EC this protocol, ICF and/or waiver, , and if applicable, any protocol amendments or other written information provided to the patients. This includes information to be completed by participants or the Investigator and staff, such as survey instruments or questionnaires, and any proposed advertising or recruitment materials. The approving IRB/EC will be responsible for the initial and continuing review and approval of this clinical registry. The participating investigators will be required to promptly report to the IRB/EC as required by the IRB/EC's policies. Additionally, investigators will be required to refrain from making any changes in the clinical registry plan without Sponsor and IRB/EC approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to registry patients or others.

18.2 Applicable Regulations

This registry will be conducted in compliance with Good Clinical Practice and in accordance with the Declaration of Helsinki, as well as any other applicable local and country regulatory requirements.

18.3 Patient Information and Consent

Regulations concerning the protection of patients require that informed consent be obtained, or waiver approved by the IRB/EC where applicable, before a patient may participate in any clinical registry. For this registry, a patient must be consented or waiver approved by the IRB/EC before completing any registry specific procedures. Screening information that are part of SOC procedures may occur and be collected prior to consent, but the data may not be collected for registry purposes until the informed consent form (ICF) has been signed by the patient or waiver from the IRB/EC is received. A patient who signs the consent, or waiver is received, is considered enrolled.

An IRB/EC approved informed consent or waiver, where applicable, must be sought from each patient and must be appropriately documented in the patient's medical record. It is the Investigator's responsibility to obtain written informed consent from prospective patients or retrospectives patients with prospective follow-up prior to registry-specific procedures.The Investigator may delegate this responsibility, if appropriately documented.

19.0 DATA HANDLING AND RECORD KEEPING

19.1 Data Elements

The following three categories of data will be captured in the registry database: (1) ablation procedure parameters, (2) patient parameters, and (3) healthcare provider parameters. The complete list of data parameters requested for this registry database are listed below.

1. Ablation procedure parameters:

a) Procedure type: laparoscopic surgical; open surgical; percutaneous.
b) Complete procedure duration from start of anesthesia administration (start time) to completion of the procedure (end time).
c) Ablation duration for each individual ablation attempt (minutes and seconds).
d) Ablation duration, defined as the time elapsed between first ablation probe puncture and removal of the last probe at the completion of the ablation.
e) Type of anesthesia used during ablation procedure.
f) Anatomical location of ablation.
g) Liver stiffness near ablation site, if obtained prior by ultrasound or MRI.
h) Smallest ablation margin, if available. Note: if less than 5mm margin, include reason (vessel, duct, location, bowel, other).
i) Ablation Zone measurement, if available
j) Use of hydrodissection during ablation procedure.
k) Type of probe(s) (including serial number).
l) Number of probes.
m) Maximum probe temperature, per probe (°C).
n) Power settings used per probe (Watts).
o) Constant power vs ramp-up.
p) Number of probe placement attempts per probe (to get the probe in position).
q) Number of changes in probe placement throughout the ablation (after energy has been delivered).
r) Location of probe placement relative to the target lesion (central, peripheral).
s) Tract ablation (yes/no).
t) If overlap of coagulation zones, provide overlap, if available.
u) Needle navigation/placement guidance method used.
v) Image fusion details, if applicable
w) Identify if ablation procedure guidance software was used (i.e. for target identification, ablation monitoring, and/or ablation confirmation)
    - If NeuWave ablation confirmation software used, note use of the software, tissue contraction percentage, and the software version
    - If other software, note supplier/manufacturer
x) If applicable, total number of CT and Xray scans used for the Ablation and total amount of radiation dose
y) Imaging details (contrast, slice thickness if applicable).

2. Patient parameters:

a) Patient lesion details at baseline:

i. Type/origin of lesion: HCC, CRLM, CC, recurrent lesion (can be local recurrent or other intrahepatic recurrence), or metastatic lesion, if biopsy is performed.
ii. Lesion size (measured in at least two dimensions), shape, and location (by liver segment).
iii. Date of diagnosis of soft tissue liver lesion.
iv. Lesion characteristics: stellate or smooth.
v. Proximity to vasculature (specify name and distance to vasculature, if possible).
vi. Proximity to other critical structures (specify, such as, bowel, stomach, skin, bile ducts, other).
vii. Location of lesion: Superficial, exophytic, deep.
    i. Exophytic: lesion extends beyond the contour of the liver
    ii. Superficial: lesion that is within 10 mm of the capsule
    iii. Deep: lesion that is deeper than 10 mm of the capsule
viii. Modality used for lesion measurements (CT, MRI, PET, US, and/or X-ray)

b) Patient medical, surgical, and radiation histories
    i. Relevant medical history, in the opinion of the investigator
    ii. Pre-treatment embolization or other chemotherapy.
    iii. Relevant surgical history (any abdominal surgery or that is related to the soft-tissue lesion(s)).
    iv. Radiation history.
    v. Thermal ablation history.
    vi. Biliary manipulation history.
    vii. Other treatments for liver lesions.

c) Family and genetic histories, as per SOC:
    i. CRLM family history.
    ii. HCC family history.
    iii. Any other known genetic and molecular diagnostics available.

d) Abuse and exposure histories, if available:
    i. Alcohol history.
    ii. Asbestos history.
    iii. Hepatitis: B virus (HBV) / C virus (HCV), others and DNA level.
    iv. Smoking history; tobacco, marijuana, other.

3. Healthcare provider parameters:

a) Type of provider performing the ablation: abdominal imaging specialist, gastroenterologist, general surgeon, hepatologist, HPB surgeon, interventional radiologist, medical oncologist, surgical oncologist, ultrasonographer, other.

19.2 Source Documents

Source documents are documents on which information regarding patients is first recorded, including printed, optical, or electronic documents. Investigator patient files or hospital records, generally, are the basis of source document information. This includes, but is not limited to, original patient files; certified copies of patient records; hospital/clinic records; original recordings /tracing; digital images from automated instruments (e.g., cameras); radiographs; photographic negatives; and records kept at the site, at the laboratories and at other departments involved in the clinical registry.

Another type of source document is data from NeuWave Medical's Call Home Database. NEUWAVE Microwave Ablation System has a functionality that electronically collects procedure data and information during the ablation procedure and is transmitted by the NEUWAVE Microwave Ablation System to NeuWave Medical, after the conclusion of each ablation procedure; this information is collectively called the "Call Home Database." The procedure data includes, but not limited to, the following: date and time of procedure, anatomical location of ablations, number of ablations and power used for each ablation, type of probes used, and duration of procedure. Some of these relevant ablation procedure details will be provided to the site via a report generated from Call Home Database, if possible. The site will review the report and enter the procedure details into the registry's clinical database. Reports generated from the Call Home Database must be retained by the Investigator as part of the patient's permanent medical record. The report should be retained for review by the monitor. If a site is unable to receive the report generated from the Call Home Database, the relevant ablation procedure details should be manually recorded in the source documents from what is displayed on the NeuWave System monitor screen.

Source documents must be retained by the Investigator as part of the patient's permanent medical record. The information in the source documents is used to complete the eCRFs. All information captured on the eCRFs should be completely and accurately supported in source documentation. Any additional information relevant to the registry should be included in the source documents. In particular, any deviations from the registry protocol or procedures should be recorded in the source documents. The Investigator will retain originals of all source documents, patient consent form, and registry data.

19.3 Electronic Data Capture

An electronic data capture (EDC) system will be utilized by site personnel to transfer registry data from source records (medical records and/or source document worksheets) onto common eCRFs. This system is a web-based, secure electronic software application [redacted]. This system was designed, developed and maintained by [redacted] in a manner that is compliant with national and international GCP data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements. The EDC system will be used to facilitate the collection of all registry data at the site. Designated site personnel will be responsible for entering patient data into the EDC system. All external and Sponsor internal users will be trained on the EDC application at a level dependent on their planned function. An EDC digital User Manual will be available under the help menu within the [redacted] website to assist in the collection and entry of source data into the electronic casebook.

[redacted] also has an image upload option called [redacted], which is where sites will be uploading all required scans.

A 24/7/365 Help Desk Support line (per [redacted] web site) staffed by the outsourced vendor will also be available to respond to site-monitor questions. Contact information for this help desk will be provided during site training.

19.4 Data Collection

Each EDC eCRF will be completed by the PI or PI's designee. Every effort should be made to respond to all monitoring and/or data management questions on each eCRF as completion of the data is required by the protocol. A unique ID number will identify each patient. The patient's unique ID number will be visible on each eCRF. At no time should the patient name appear on the eCRFs.

All data should be recorded accurately and completely. The Investigator is responsible for reviewing and approving each completed eCRF. Assurance of overall review and approval will be documented by the Investigator electronically signing each patient's electronic casebook.

19.5 Medical Dictionary Coding

Medical dictionary coding of medical history, concomitant medications, and verbatim AEs captured on eCRFs will be performed using a coding thesaurus algorithm. The Medical Dictionary for Regulatory Activities (MedDRA) and WHODrug dictionaries will be used after data entry and query resolution, via auto-encoding and interactive coding processes.

19.6 Data Correction

Required data corrections to eCRFs will be prompted via automated electronic edit checks and/or queries manually created by Sponsor reviewers. The change(s), individual making the change(s), and time the change(s) were made to the eCRFs will be automatically captured in the audit trail within [redacted].

19.7 Data Privacy

The collection, use, and disclosure of all personal data, including patient health and medical information, are to be maintained in compliance with applicable personal data protection and security laws and regulations that govern protected health information and the informed consent given by each registry patient. When collecting and processing such personal data, appropriate measures are to be taken to maintain the confidentiality of patient health and medical information and to prevent access by unauthorized persons.

20.0 REGISTRY SUSPENSION OR TERMINATION

The Sponsor may suspend or terminate the registry or one or more sites at any time. When this occurs, all patients at the site will be withdrawn and documented as early termination. Reasons for site or registry termination may include, but are not limited, to the following:

- Administrative concerns (e.g., inadequate patient enrollment, investigator/institution non-compliance, change of business strategy, etc.).
- Regulatory body mandates.

The Investigator also has the right to terminate participation in the registry at any time (e.g., for safety or inability to enroll patients). Should termination of a site be necessary, the Sponsor will provide procedures for termination.

21.0 DATA AND PUBLICATION POLICIES

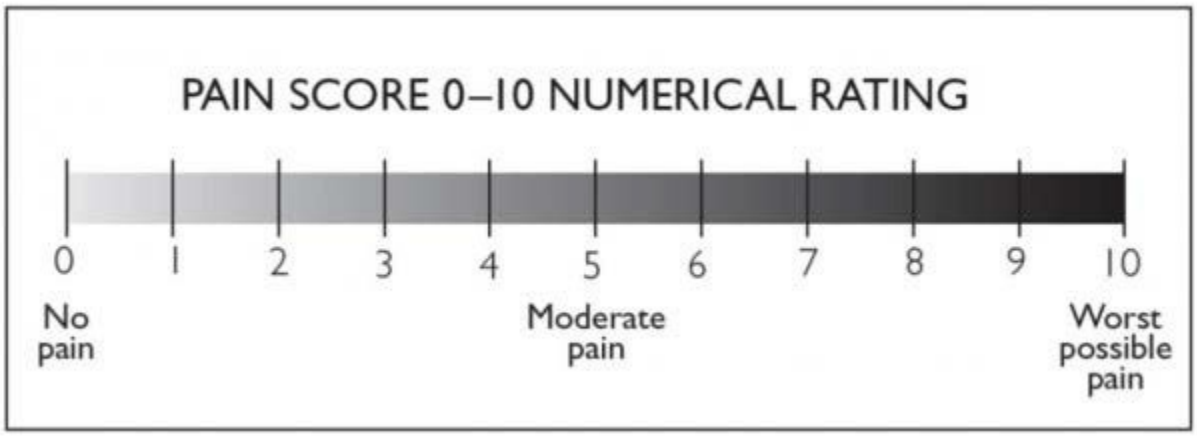
Publication of the results of this registry will be governed by Johnson & Johnson publication policies, including current and applicable Medical Device Publication Policy. Any presentation, abstract, or manuscript will be made available for review by the Sponsor prior to submission. Licensing agreements or copyrights applying to tools, work products or intellectual property used during the registry should be observed and clearly displayed on registry documentation and publications, wherever appropriate.

All manuscripts of data obtained from this clinical registry will be reviewed and approved by the Sponsor and each author prior to any submission. All authors must disclose financial or personal affiliations that could be considered a conflict of interest.

22.0 SUPPLEMENTS

22.1 Numeric Pain Rating Scale

The Numeric Pain Rating Scale (NPRS) can be administered verbally (therefore also by telephone) or graphically for self-completion. As mentioned above, the respondent is asked to indicate the numeric value on the segmented scale that best describes their pain intensity.



22.2 Glossary

Acronyms/ Abbreviations	Terms
2D	2-Dimensional
AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CBC	Complete Blood Count
CC	Cholangiocarcinoma
CFR	Code of Federal Regulations
CRLM	Colorectal Liver Metastases
CT	Computed Tomography
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of Study
FeNo	Fractional Exhaled Nitric Oxide
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transpeptidase
HCC	Hepatocellular Carcinoma
ICF	Informed Consent Form
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
LOS	Length of Hospital Stay
MRCSI	Member of the Royal College of Surgeons (Ireland)
NPRS	Numeric Pain Rating Scale

Acronyms/ Abbreviations	Terms
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PAP	Positive Airway Pressure
PDM	Power Distribution Module
PET	Positron Emission Tomography
PI	Principal Investigator
PT	Partial Prothrombin
PTT	Partial Prothrombin Time
QOL	Quality of Life
SAE	Serious Adverse Event
SOC	Standard-of-Care
USV	Unscheduled (visit)

23.0 DOCUMENT FILING

A copy of all approved versions of the Registry Protocol will be kept by the site, in the Investigator Site File and in the Sponsor Trial Master File.

24.0 SCIENTIFIC REFERENCES

1. Sherman R, Anderson S, Dal Pan G,et al. Real-World Evidence — What Is It and What Can It Tell Us? NEJM 375;23 December 8, 2016.

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3. Aarson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

4. Chie WC, Blazeby JM, Hsiao CF, et al. International cross-cultural field validation of an European Organization for Research and Treatment of Cancer questionnaire module for patients with primary liver cancer, the European Organization for Research and Treatment of Cancer quality-of-life questionnaire HCC18. Hepatology. 2012 Apr;55(4): 1122-9. Epub 2012 Mar 1.

5. Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies Comparing Numerical Rating Scales,Verbal Rating Scales, and Visual Analogue Scales for Assessment of Pain Intensity in Adults: A Systematic Literature Review. Journal of Pain and Symptom Management 2011 June, 41(6)1073-1093.