MR5® Prototype Device

A multi-center, triple-blind, placebo-controlled, randomized evaluation of the effect of the MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

MULTI RADIANCE MEDICAL®

Version 2.5

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STUDY INFORMATION

SPONSOR
Multi Radiance Medical
6521 Davis Industrial Parkway
Solon, Ohio 44139 USA
Contact: Douglas Johnson, ATC, EES, CLS
Chief Science Officer, Clinical and Scientific Affairs
Telephone: 440-542-0761
Fax: 440-542-0765
Email: info@multiradiance.com
www.multiradiance.com

PRINCIPAL CLINICAL INVESTIGATORS AND TEST SITES

Principal Clinical Investigator: Ernesto Cesar Pinto Leal Junior, PhD, MSc, PT
Nove de Julho University – UNINOVE, Sao Paulo, Brazil.
Email: ernesto.leal.junior@gmail.com

Three Test Sites:

Test Site #1: Laboratory of Phototherapy and Innovative Technologies in Health
Nove de Julho University
Vergueiro St. 235/249
Liberdade, São Paulo - SP
Brazil, 01504-001
Telephone: +55 11 3385 9134

Test Site #2: Vila Maria Outpatient Clinic
Nove de Julho University
Guaranésia St. 425
Vila Maria, São Paulo - SP
Brazil, 02112-000.

Test Site #3: Core Sport Physical Therapy
Siqueira Campos Ave, 1240
Sumaré, Caraguatatuba - SP
Brazil, 11661-400

.

ETHICS COMMITTEE
Research Ethics Committee of Nove de Julho University
Rua Vergueiro nº 235/249 – 3º subsolo
Liberdade
São Paulo – SP, Brazil 01504-001
Telephone: +55 11 3385 9197
E-mail: comitedeetica@uninove.br
Approval # 3.669.043

MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

DEVICE: MULTI RADIANCE MEDICAL® MR5® Prototype Device

DEVICE DESCRIPTION & DETAILS

The Multi Radiance Medical MR5 Prototype Device is being evaluated in this study for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

The MR5 Prototype Device is designed to provide pain relief and non-invasive treatment of diverse conditions. The device, which may be used in combination with pharmacological methodologies, operates in phototherapeutic modes providing simultaneous penetrative impact of coherent and incoherent light energy. These include infrared and visible red light and are delivered into biological tissues in combination with a surface impact provided by a static magnetic field. Phototherapeutic treatment is carried out by placing the light emitting aperture directly over the affected area according to the study protocol.

Figure 1: MR5 Prototype Device

MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

Figure 2: The Multi Radiance Medical MR5 Prototype Device Technical

MR4 Prototype Settings				
Wavelength	905	850	660	905, 850, and 660
Total Power (Average, W)	0.001375	0.25	0.2	0.451375
Number of Diodes	1	3	3	7
Power per Diode (W)	0.001375	0.083333	0.066667	N/A
Irradiance W/cm2	0.000344	0.062500	0.050000	0.112844
Fluence J/cm2	0.020625	3.750000	3.000000	6.770625
Time Duration (seconds)	60			
Frequency of SPL (Hz)	250			
Laser Peak Pulse Power (W)	50			
Laser Pulse Duration (s)	0.00000011			
Aperture area (cm2)	4			
Laser average power (W)	0.001375			
IR average power (W)	0.25			
Red average power (W)	0.2			

Battery:

Li-polymer battery Voltage	3,7
Capacity, amp-hour	4
Continuous operation with fully charged batteries, hours, no less	6
Battery complete charging time, hours, no more	4
Input voltage of power adapter for battery charging	100...240 VAC, 50/60 Hz
Output voltage of power adapter	12,0 VDC

Laser safety according to:

IEC 60825-1:2007 and IEC 60825-1:2014	Class 1
Electric classification by IEC 60601-1	battery powered device, type BF applied part

Device Specifcations:

Overall dimensions, mm	203x64x70
Net weight, g, no more (w/o adapter)	250
Average lifetime, years	5

Operational Environment

Temperature	Humidity	Atmospheric Pressure
40˚C (104˚F)	<80%	70-106 kPa
10˚C (50˚F)		

Storage/Transport Environment

Temperature	Humidity	Atmospheric Pressure
45˚C (113˚F)	<80%	50-106 kPa
0˚C (32˚F)		

PURPOSE OF STUDY

The purpose of this multi-center clinical study is to determine the effectiveness of the Multi Radiance Medical MR5 Prototype Device manufactured by Multi Radiance Medical (the Company), MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

STUDY DURATION
The estimated total duration of the study is four to five months.

LABELING
Once the device has been cleared for market in the U.S., the device will be labeled as a prescription device, per 21 CFR § 801.109.

PROPOSED INDICATIONS FOR USE
The indication (claim) being sought through support of the results of this clinical study is: "The Multi Radiance Medical MR5 Prototype Device is indicated for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis." It is intended that the results of this clinical study be used to support a DeNovo submission to FDA for clearance to market the device for the intended indication.

EXPECTED RESULTS
Following completion of the study procedure protocol with the Multi Radiance Medical MR5 Prototype Device, it is anticipated that relative to baseline (pain at rest), significantly more subjects in the test group than in the placebo group will show a 30% or greater reduction in self-reported VAS rating in the Lateral Epicondylitis following completion of the three-week study procedure administration phase.

MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

REGULATORY HISTORY

The MR4™ Multi Radiance Therapy and its various emitters and accessories have received the following 510(k) clearances from the United States Food and Drug Administration (FDA):

1. K080102

- *Device Name:* MR4™ Multi Radiance Therapy System, TQ Solo, TQ Solo Pro, and LS50 Accessory
- *Regulatory Class*: Class II
- *Product Code*: ILY, GEX
- *Clearance date*: August 20, 2008
- *Indications for Use*: All four devices are indicated for temporary relief of minor muscle and joint pain, arthritis and muscle spasm, relieving stiffness, promoting relaxation of muscle tissue, and to temporarily increase local blood circulation where heat is indicated.
- *Over-The-Counter (OTC) use*

2. K171354

- *Device Name:* MR4™ Laser
- *Regulatory Class*: Class II
- *Product Code*: NHN
- *Clearance date*: January 13, 2018
- *Indications for Use*: MR4 Laser is indicated for adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin.
- *Prescription use*

TECHNOLOGY, LITERATURE, BACKGROUND, THEORY OF MECHANISM OF OPERATION, PRODUCT OVERVIEW & SAFETY

BACKGROUND:

LATERAL EPICONDYLITIS:

Upper extremity musculoskeletal disorders are common in the general population. These disorders may include diseases such as cervical disc disease, rotator cuff disease, lateral and medial epicondylitis, carpal tunnel syndrome, osteoarthritis, and other conditions[i]. Studies report that these disorders have a negative impact on quality of life[ii],[iii],[iv] since upper extremity pain can cause substantial disability, need for health care, and loss of work time[v]. Among the most common upper extremity disorders are lateral and medial epicondylitis, which have been reported to significantly affect the upper extremity function, causing losses in daily living activities[vi],[vii].

Lateral epicondylitis (LE) is one of the most frequently encountered lesions affecting the upper extremity and is the most common cause of elbow pain in adults. It occurs on the lateral side of the elbow where the common extensors originate from the lateral epicondyle[viii],[ix],[x]. It is defined as an injury involving the wrist common extensor tendons, particularly the carpi radialis brevis and extensor digitorum[xi]. LE is a common term used to describe a group of symptoms, including pain and tenderness over the origin of extensor muscles of the wrist and fingers, and is also known as tennis elbow, as it is frequently seen in racquet sports players[xii],[xiii],[xiv],[xv]. This clinical condition has a significant impact on the healthcare industry and society in general[xvi],[xvii].

LE can be considered an overuse injury which occurs on the lateral side of the elbow in the extensor tendons with repetitive micro-trauma[xviii],[xix]. It typically presents around the lateral epicondyle elicited by forced wrist extension, this is the result of the degenerative angiofibroblastic hyperplasia of wrist extensor tendons due to repeated micro-traumas[xx],[xxi]. This condition is usually related to repetitive occupations or hobbies[xxii]. Besides overuse and repetitive movements, other relevant risk factors include wrong training, misalignment, flexibility problem, age, poor circulation and muscle weakening or imbalance[xxiii],[xxiv]. While the exact pathophysiology behind the condition is not yet clear, and despite the presence of inflammatory cells locally, there are arguments that LE can be regarded as a degenerative process caused by muscle overuse, with subsequent tendinosis, microtrauma and tear of the extensor carpi radialis brevis tendon[xxv],[xxvi].

The prevalence rate of LE is more than 1% in the general population, with a slight predominance among females[xxvii],[xxviii]. It is commonly seen in racquet sports players with a reported incidence of 9 ~ 35% and prevalence of 14 ~ 41% among tennis players[xxix]. The disease mostly affects people between the ages of 35 – 50 years, who have a history of repetitive activities involving the upper limbs, and the dominant upper limb is much more often involved[xxx],[xxxi],[xxxii]. The high prevalence of LE leads to a significant socioeconomic burden[xxxiii]. Diagnosis is usually based on clinical history and physical examination, for a differential diagnosis, multiple exams can be used including simple radiography, ultrasonography, magnetic resonance imaging and electrodiagnosis[xxxiv].

The clinical presentation of LE involves a painful or burning sensation over the humeral insertion of the common extensor tendons[xxxv]. This pain can be exacerbated by wrist extensor activation, passive wrist flexion combined with passive elbow extension[xxxvi], and palpation over the lateral epicondyle or the origin of the wrist extensor muscle groups[xxxvii]. People affected by LE in the lateral epicondyle show increased pain and decreased functional abilities due to the weakening of the rotator cuff and the scapula muscular

systems[xxxviii]. They will commonly present with a loss of grip strength and usually report pain during daily activities such as grasping objects, turning doorknobs and shaking hands[xxxix],[xl]. In some cases, the recovery phase can take several months, potentially impacting the quality of life and sports performance of these individuals[xli],[xlii].

Despite the high incidence of LE, optimal treatment has not been established, and, although treatments are usually non-surgical, such as oral medications, physiotherapy and corticosteroid injection, surgical decompression has been used to treat LE[xliii]. The relatively large number of options currently available for LE treatment could be attributed to the scarce evidence available about the disease etiology and the lack of agreement about definitive treatment for the condition[xliv],[xlv],[xlvi].

Medial epicondylitis (ME) of the elbow is less commonly encountered than the lateral disease but is also a common pathology[xlvii],[xlviii],[xlix]. The relative incidence of ME is 9.8% to 20%,[l],[li], and is often referred to as "golfer's elbow," because in the golf swing significant tension is noted across the medial aspect of the elbow[lii],[liii]. However other activities involving repetitive use have also been implicated, they include tennis, swimming, weightlifting and work-related activities[liv]. With the continuation of sport practice and active use of the elbow in the aging population, it has been diagnosed with increasing frequency[lv].

The underlying etiology of ME is described as an angiofibroblastic tendinosis in the origin of the common flexor-pronator, it has also been characterized as a micro-tearing in the origin of the flexor mass[lvi]. It occurs due to repetitive forced wrist extension and forearm supination during activities involving wrist flexion and forearm pronation causing flexor-pronator tendon degeneration. The confluence of the flexor carpi radialis and pronator teres is frequently a common site of injury[lvii]. A staged process of pathologic change in the tendon can result in structural breakdown and irreparable fibrosis or calcification[lviii].

Patients typically report persistent medial-sided elbow pain that is exacerbated by daily activities, it is usually present with flexion of the wrist and fingers and pronation of the forearm[lix],[lx]. The ME is primarily a condition of the middle aged, most injuries are degenerative in nature, but in some cases an acute trauma may precipitate the symptoms. Once the acute symptomatology is alleviated, focus is turned to flexor-pronator mass rehabilitation and injury prevention[lxi].

Treatment of ME is initiated with nonsurgical modalities, this supportive care includes activity modification, physical therapy, oral medications and corticosteroid injections[lxii]. Conservative treatment has been shown to relieve the pain, however this may depend on the stage of presentation. Surgical treatment via open techniques is typically reserved for patients with persistent symptoms, typically after at least six months of nonsurgical care[lxiii].

Considering the importance and high incidence of these musculoskeletal disorders, LE and ME, a variety of therapeutic modalities has been employed in order to alleviate pain and repair the tissue. Treatment options include therapeutic exercise, bracing, shock wave or ultrasound therapy[lxiv], but many of them lack sufficient evidence of beneficial effects[lxv],[lxvi]. The corticosteroid injections are often used but with limited success[lxvii]. Photobiomodulation therapy (PBMT) has been shown to stimulate tendon healing, this suggests that therapy using laser or light-emitting diodes (LEDs) is efficacious for the symptoms associated with chronic epicondylitis[lxviii].

The PBMT was first used to target soft tissue inflammation and injuries, its applications have expanded to a multitude of musculoskeletal injuries, including tendon injuries[lxix]. PBMT can

be performed using lasers or LEDs and is possible over a range of wavelengths, studies have demonstrated favorable results using PBMT on the tendon repair process, evidenced by improved quality of remodeling and decreased inflammation[lxx],[lxxi],[lxxii],[lxxiii].

The PBMT is non-thermal, thus its effects are related to photochemical and photobiological effects within the tissue and not to heat[lxxiv]. It is non-invasive, therapeutically beneficial and promotes a wide range of biological effects including the enhancement of energy production, gene expression and cell death prevention[lxxv]. The major intracellular molecule absorbing photons is cytochrome c oxidase, an enzyme present in mitochondria, which can be stimulated by PBMT[lxxvi]. So the PBMT modulates biological processes of cells in the mitochondrial level increasing oxygen consumption and production of adenosine triphosphate (ATP)[lxxvii]. The PBMT also has the advantage of not having severe side effects.

Favorable results of PBMT in the tendon repair process have already been demonstrated, it promotes the deposition of collagen fibers in the early and late stages and minimization of inflammatory cells in the lesion area[lxxviii],[lxxix]. These beneficial outcomes of PBMT can be attributed to the modulatory effect of fibroblast metabolism and collagen deposition by matrix metaloproteinases, and activation or inhibition of inflammatory mediators. This also supports the indications that PBMT treated tendons have a higher turnover rate of collagen and higher mechanical integrity when compared to non-treated tendons[lxxx].

Epicondylitis (lateral or medial) has a significant impact on the health care system and society in general[lxxxi]. Therefore, investigating the mechanisms involved in tendon repair in order to encourage the development of novel therapies for epicondylitis treatment is very important. According to the favorable results of PBMT in tendons repair processes, this type of therapy can be used as a therapeutic tool for management in epicondylitis, therefore, more investigations are necessary to establish the ideal parameters. With this in mind, we believe that PBMT, in the appropriate parameters, can significantly decrease pain and improve quality of life of patients presenting epicondylitis diagnosis.

THEORY OF MECHANISM OF OPERATION

The scientific principle underlying laser physics was first developed by Albert Einstein in 1916. The biological effects of low-level laser therapy (LLLT) have been studied globally for over forty years with no unwanted side effects noted.

General Therapeutic Effects and Mechanism of Operation of Low Level Lasers

“Low-energy photon irradiation by low level laser light lasers or LED arrays has been found to modulate various biological processes in cell culture and animal models. This mechanism of photobiomodulation by LLLT lasers or LED arrays at the cellular level has been ascribed to the activation of mitochondrial respiratory chain components, resulting in initiation of a signaling cascade that promotes cellular proliferation and cytoprotection.”
Source: Proc Natl Acad Sci U S A. 2003 Mar18; 100(6): 3439-44. 2003 Mar 07.

L.A.S.E.R. (Light Amplification by Stimulated Emission of Radiation) is a name for a type of intense radiation of the light spectrum. A laser is a beam of light in which high energies can be concentrated. Laser light has unique physical properties of coherence and monochromaticity that other types of light do not have. It is these physical properties that make laser light is so effective compared to other kinds of light in the field of pain reduction and healing. When applied to injuries and lesions, low level laser light has been shown to stimulate healing and reduce pain by accelerating the speed, quality and strength of tissue repair and the reduction of inflammation. Laser therapy has been found to be particularly

effective over other standard therapies in relieving pain and other symptoms associated with chronic problems and injuries as it impacts the complete system of targeted muscles, tendons, ligaments, connective tissue, bone, nerve, and dermal tissues.

The effects of low-level laser treatments are photochemical. Photons enter the tissue and are absorbed in the cell's mitochondria and at the cell membrane by chromophores. These chromophores are photosensitizers that generate reactive oxygen species following irradiation thereby influencing cellular redox states and the mitochondrial respiratory chain. Within the mitochondria, the photonic energy is converted to electromagnetic energy in the form of molecular bonds in ATP (Adenosine Triphosphate). In order to interact with the living cell, laser light has to be absorbed by intracellular chromophores. Cell membrane permeability increases, which causes physiological changes to occur. These physiological changes affect macrophages, fibroblasts, endothelial cells, mast cells, and bradykinin and nerve conduction rates. The clinical and physiological effects are obtained by the way in which tissues absorb laser radiation. This tissue absorption depends on the wavelength of the beam itself and the power to ensure that the laser energy reaches the target tissue at the necessary clinical levels. The improper wavelength of laser light would not penetrate into the tissue to reach the target area. Furthermore, even if one has a laser with the proper wavelength, if the device does not have enough power to drive the energy into the tissue, the target area may not realize the potential benefits. Each type of laser emits light at a very specific wavelength which interacts with the irradiated tissue. It also acts in particular with the chromophores present in the tissue, but in a different way. A chromophore, intrinsic or extrinsic, is any substance, colored or clear, which is able to absorb radiation. Among the endogenous chromophores are water and hemoglobin, nucleic acid and proteins. Among the exogenic chromophores are porphyrins and hematoporphyrins, which are injected into the organism. These are described as photosensitizers because they fix themselves to the tissue making it photosensitive at specific wavelengths.

The level of tissue penetration by the laser beam depends on the beam's optical characteristics, as well as on the concentration and depth of the chromophores, which are absorbed at different percentages according to the laser light's wavelength. For instance, water absorbs almost 100 percent of the laser irradiation at 10,600 nanometers, the wavelength of a CO2 gas laser. That is the reason why this type of laser wavelength is used in surgical applications. Other factors affecting the depth of penetration are the technical design of the laser device and the particular treatment technique used. There is no exact limit with respect to the depth penetrated by the light. The laser light gets weaker the further from the surface it penetrates where eventually the light intensity is so low that no biological effect from it can be measured. In addition to the factors mentioned, the depth of penetration is also contingent on tissue type, pigmentation and foreign substances on the skin surface such as creams or applied oils. Bone, muscles and other soft tissues are transparent to certain laser lights, which means that light can safely penetrate these tissues. The radiation in the visible spectrum, between 400 and 600 nanometers, is absorbed by the melanin, while the whole extension of the visible which goes from 420 to 750 nanometers is absorbed by composite tetrapyrrolics. In the infrared, which covers about 10,000 nanometers of light spectrum, water is the main chromophore. Fortunately, there exists a narrow band in the light spectrum where water is not a highly efficient chromophore, thereby allowing light energy to penetrate tissue that is rich in water content. This narrow band, which extends approximately from 600 to 1,200 nanometers, is the so-called "therapeutic window" and is the range within which the output design of the Multi Radiance Medical® MR5® Prototype Device is based.

In general, laser diodes are either continuous wave or pulsed. Continuous wave (CW) diodes emit laser energy continuously while pulsed diodes emit a radiation impulse with a high

amplitude (intensity) and duration which is typically extremely short: 100-200 nanoseconds. Continuous wave lasers produce a fixed level of power during emission. Although lacking the high peak power of a "true" or "super" pulsed laser, most continuous wave lasers can be made to flash a number of times per second to simulate pulse-like rhythms by interrupting the flow of light rapidly as in turning a light switch “off” and “on”. “True” or “super” pulsed lasers produce a brief high-power level light impulse. It is the high-power level achieved during each pulse that drives the light energy to the target tissue. Even though the pulse peaks at a high-power level there are no deleterious thermal effects in the tissue because the pulses are of such short duration. Therefore, the peak power of a “true” or “super” pulsed laser is quite high compared to its average pulse power. As such, “true” or “super” pulsed lasers are able to more effectively drive light energy into tissue.

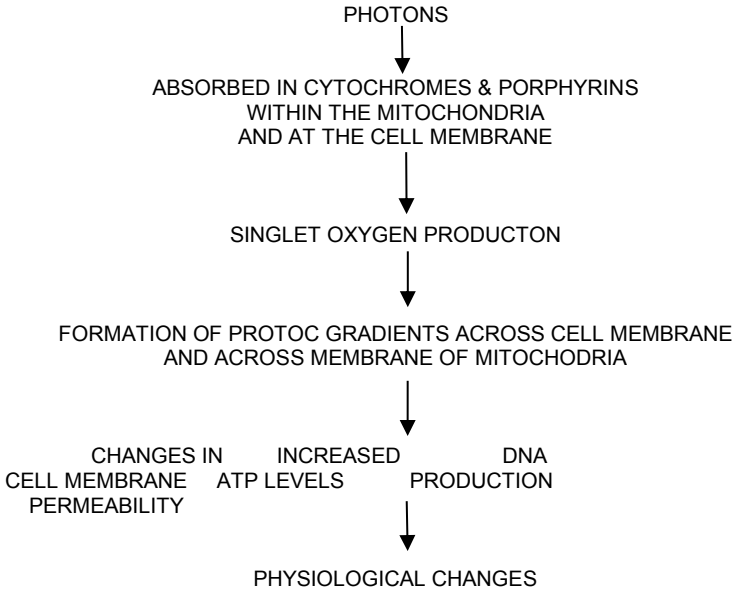
Therefore, in summary, LLLT:

- Promotes healing in many conditions because it penetrates the skin, increases the ATP and activates enzymes in the targeted cells.
- Cultivates a growth factor response within the cells and tissue as a result of increased ATP and protein synthesis.
- Improves cell proliferation.
- Provides pain relief as a result of increased endorphin release.
- Strengthens the immune system response via increasing levels of lymphocyte activity.

Additionally, low level laser light energy will only be absorbed by cells and tissues that are not functioning normally (impaired) and will have no effect on healthy cells.

The process by which low level laser light aids in the production of ATP, thereby providing cells with more energy which in turn means the cells are in optimum condition to play their part in a natural healing process, works as follows:

The effects of low-level laser light are photo-chemical (not thermal), triggering normal cellular function.



Considering the general mechanism of operation of LLLT as explained above, it follows that LLLT provides relief from the Lateral Epicondyle by:

- penetrating the skin of the Lateral Epicondyle region to increase the production of ATP and activate enzymes in the underlying targeted cells of the tissue to promote healing of the micro-tears in the tissue
- cultivating a growth factor response within the cells and tissue as a result of the increased ATP production to promote new, healthier cell and tissue growth to strengthen and support tendons and musculature, to restore strength and flexibility and to protect against further damage
- the anti-inflammatory properties of low-level lasers reduce the inflammation to provide pain relief.
  See ***Appendix A*** *for Supporting Research Abstracts*

PRODUCT OVERVIEW

Like other therapeutic laser and light-emitting commercially available devices. The MR5™ emits visible and infrared photons that are absorbed by skin and tissue via cellular mitochondria which contain chromophores capable of absorbing light energy. This creates a cellular cascade of events that result in an increase in ATP production which allows the cells to function more normally and to resolve or minimize the results of specific diseased states.

The Multi Radiance® Medical devices combine a combination of wavelengths and light sources comprised of Super Pulsed Lasers (GaAs 905 nm), infrared and red LEDs (850 nm and 660 nm) wavelengths. Albuquerque-Pontes et al[lxxxii] investigated the effects of phototherapy with the combination of different light sources to establish if an optimal dose or wavelength was needed to stimulate the enhancement of ATP production. Three different low-level laser therapy (LLLT) wavelengths (660, 875 and 905 nm) were used to analyze cytochrome c-oxidase (CCO), an enzyme in muscle, brain, and other tissues that catalyzes the transfer of a phosphate group from ATP to creatine, producing adenosine diphosphate (ADP) and phosphocreatine (PCr) expression by immunohistochemistry. The results demonstrated that LLLT increased ($p<0.05$) CCO expression mainly with the following wavelengths and doses: 660nm with 1 J, 875nm with 3 J and 905nm with 1 J at each time-point. These specific wavelengths and light sources were selective to optimize the biological effects of the entire phototherapeutic window, provide a greater depth of penetration and eliminate the thermal barrier.

It has been suggested in the literature that other modes, such as super pulsing, may have different skin penetration time profiles. Brondon, et al[lxxxiii] found the super pulsing the laser allows for better penetration through melanin filters, indicating that pulsing may be beneficial in reaching deep target tissue in dark-skinned patients. Joensen et al[lxxxiv] evaluated a super pulsed 904nm LLLT and found the light energy penetrated 2-3 easier through the rat skin barrier than 810nm continuous. There was an interesting linear increase in penetrating energy from 38% (SEM±1.4) to 58% (SEM±3.5) during 150 seconds of exposure during the study. Therefore, the greatest depth of penetration occurs at the 904/905nm wavelengths and that the absorption occurs not just at the superficial layers of the skin, but in deeper layers as well.

Leal-Junior and Albuquerque-Pontes evaluated the depth of penetration time profile (DPTP) of the original ACTIV and Albuquerque-Pontes, et al. performed the same study with the ACTIV PRO to determine the effects of concurrent multiple wavelengths of 660nm Red LED, 875nm IRED and 905nm SPL. Each individual wavelength was tested separately with and without the tissue skin flaps to establish the percentage of energy penetration. Data observed also confirmed what Joenson, et al found regarding the pattern of linearly

increasing penetration of the light over time by the super-pulsed laser. The individual wavelength penetration profiles provided a predicted measurement (summated total of each individual wavelength) to compare with an actual reading of the combined wavelength time profile.

The data suggests and demonstrates a pattern of linearly increasing penetration of the light over time with the device and 49% penetrating beyond the skin. This skin penetration time profile allows for a greater proportion of the available light energy to penetrate beneath the skin. By improving the efficiency of penetration, the necessary energy provided at the surface is significantly less, reduces the conversion into heat and avoids a dangerous rise in tissue temperature.
See ***Appendix B*** *for supporting research studies on Multi Radiance® Medical Technology*

SAFETY
After 50+ years of low intensity level light applications in humans with lasers (or any other optical to near infrared light sources) there are no known reports of any adverse side effects to the best of our knowledge.[lxxxv] The MR4™ Laser Therapy System and many other light devices are cleared (FDA, Health Canada, TGA) and considered safe for both professional and consumer home use (OTC). Low level laser devices have been designated by FDA as non-significant risk. Multi Radiance® Medical also complies with ISO 13485 Certification to ensure good manufacturing practices for consistency in product quality, monitoring and reporting.

The Multi Radiance Medical Super Pulsed Infrared Laser (905 nm) in the ACTIV PRO creates the desired higher peak power, however due to the ultrashort pulses, there is little resulting heat accumulating within the target tissue. Vanin, et al.[lxxxvi] replicated a study by Grandinétti, et al.[lxxxvii] that evaluated the thermal impact of the MR5 Prototype Device on light, medium and dark skin. Baseline measurements were taken prior to the start and skin temperatures were measured using a FLIR thermographic camera. Four doses were applied: placebo, 25 J, 80 J, and 133 J to the skin. The MR5 Prototype Device was set to full power (500 mW and 50 Hz frequency).

	Light	**Intermediate**	**Dark**
Baseline	33.84	34.74	34.48
72 sec	34.28	34.86	34.90
228 sec	34.54	35.45	35.21
380 sec	35.54	36.46	36.06

There was a non-significant increase ($p>0.05$) in temperature (degrees C) for all skin types and with all doses. No groups experienced excessive photothermal effects that may affect patient safety and no threat or concern regarding cytotoxicity in clinical practice exists. The lack of accumulating skin temperature may be attributed to the ultra-short pulse structure related to the frequency of the super pulsed laser and pulsing of the LEDs and IREDs.

DEVICE SAFETY

RISK AND PREVENTION OF EYE INJURY

The MR5 Prototype Device - This product is classified as Class 1 according to EN IEC 60825-1:2007. Access to laser radiation in excess of Class 1 is not possible during normal operation, and/or maintenance functions.

The MR5 Prototype Device is a Class 1 laser device, and as such, protective eye wear is not required. However, for comfort and added caution, Laser Safety Industries shade/tint level 3 goggles that block out the spectrum of light from 600 nm to 950 nm will be provided to the subject and the treating investigator in this clinical study, as follows:

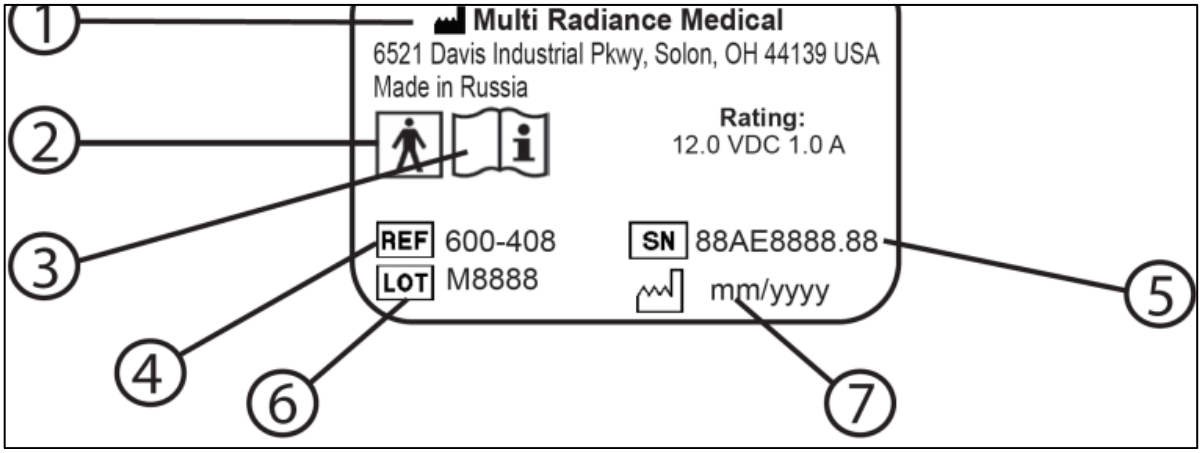
The Laser Safety Industries PN: 100-40-245 light blue laser safety glasses, having the following OD specifications and shown in Figure 6 to the right.

- OD 2+ @ 630-650 nm
- OD 3+ @ 650-690 nm
- OD 6+ @ 690-1330 nm

Figure 3: Laser Safety Industries PN: 100-40-245

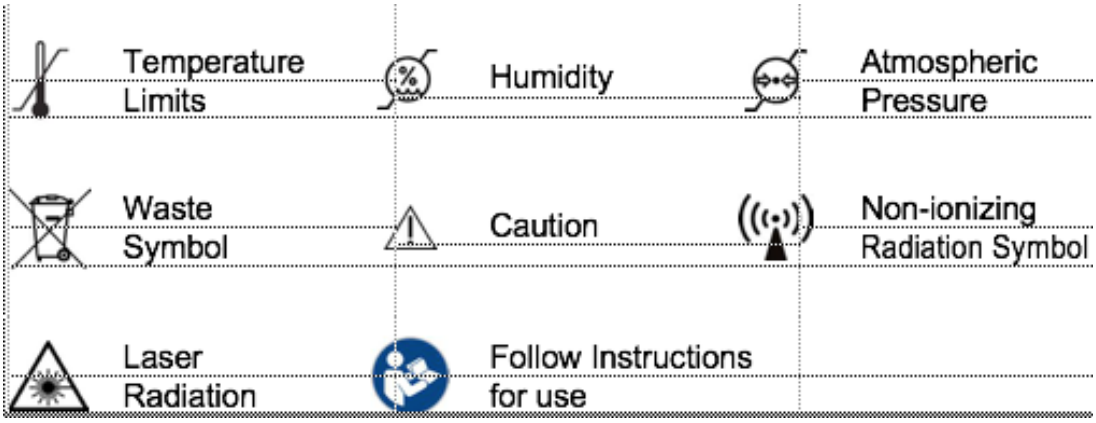
MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

DEVICE LABELING



1. Manufacturer
2. Type BF applied part
3. Attention: see instructions for use
4. Catalog number
5. Serial number
6. Lot number
7. Manufacture date

Symbol Explanation:



MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

OTHER POTENTIAL RISKS

Other potential risks and their mitigation include:

Hazard Category	Hazard	Mitigation Measure
Electrical Energy	Line Voltage	Device was designed and tested to comply with IEC 60601-1: (3.1 Edition) + A1 2012.
	Leakage Current	
Electromagnetic Energy	Electric Fields	Device was designed and tested to comply with IEC 60601-1-2 and EM radiation and emission requirements.
Radiation Energy	Non-Ionizing Radiation	Device was designed and tested to comply with IEC 60825-1:2007 and classified as Class 1 laser device. Device was designed and tested to comply with IEC 60601-2-57:2011 and LED radiation classified in Exempt group.
Thermal Energy		Device was designed and tested to comply with IEC 60601-1: (3.1 Edition) + A1 2012 which includes testing against excessive temperatures.
Mechanical Energy		Device was designed and tested to comply with IEC 60601-1: (3.1 Edition) + A1 2012.
Biological Hazard	Thermal Energy	Statement that Device is not sterile, non-invasive, restrictions in the application of the Device (unbroken skin) and description of methods of cleaning / disinfection of the Device before / between uses have been included in the IFU.
Chemical Hazard	Gravity – Device falling	Device was designed and tested to comply with IEC 60601-1: (3.1 Edition) + A1 2012. Device shelf life and Operating / Storage Environments have been included in the IFU.
Biocompatibility	Vibration	Device was designed and tested to comply with ISO 10993-1, 5, 10. Device was designed and tested to comply with IEC 60601-1: (3.1 Edition) + A1 2012.
Operational	Acoustic Energy	Device was designed and tested to comply with IEC 60601-1: (3.1 Edition) + A1 2012. Device includes self-test feature that will prevent using the Device if levels of laser / LED radiation / magnetic field will be out of specified ranges. Description of the self-test procedure has been included in the IFU.
	Loss or deterioration of function	
	Use error	Device was designed) + A1 2012.- Specifications / statements / warnings about residual risk are added to the IFU.
Labeling	Incomplete instructions for use	Device was designed and tested to comply with IEC 60601-1: (3.1 Edition) + A1 2012.
	Inadequate description of performance characteristics	
	Inadequate specification of intended use	
	Inadequate disclosure of limitations	
	Inadequate specification of pre-use checks	
	Over-complicated operating instructions/ End user does not use the Operating Instructions	
	Warnings	
	Specification of service and maintenance	
Chemical	Fire / Explosion	Device was designed and tested to comply with IEC 60601-1: (3.1 Edition) + A1 2012.

STUDY INDICATION: LATERAL EPICONDYLITIS

Definition
Lateral epicondylitis is the most common overuse syndrome in the elbow. It is an injury involving the extensor muscles of the forearm. These muscles originate on the lateral epicondylar region of the distal humerus. In a lot of cases, the insertion of the extensor carpi radialis brevis is involved.

Statistics
The right elbow was affected in 63% of cases; the left in 25%, with 12% of patients diagnosed with LET in both elbows. The highest incidence occurred in individuals aged 40 to 49, with a 7.8 per 1,000 rate in men and a 10.2 per 1,000 rate in women. Most patients received bracing and NSAIDS as primary treatment[lxxxviii].

Anatomy of the lateral elbow
The elbow joint is made up of three bones: the humerus (upper arm bone), the radius and ulna (two bones in the forearm). At the distal end of the humerus there are two epicondyles, one lateral (on the outside) and one medial (on the inside). The area of maximal tenderness is usually an area just distal to the origin of the extensor muscles of the forearm at the lateral epicondyle. Most commonly, the extensor carpi radialis brevis (ECRB) is involved, but others may include the extensor digitorum, extensor carpi radialis longus (ECRL), and extensor carpi ulnaris. The radial nerve is also in close proximity to this region and divides into the superficial radial nerve and the posterior interosseous nerve.

Etiologies of Lateral epicondylitis
Lateral epicondylitis is classified as an overuse injury that may result in hyaline degeneration of the origin of the extensor tendon. Overuse of the muscles and tendons of the forearm and elbow together with repetitive contractions or manual tasks can put too much strain on the elbow tendons. These contractions or manual tasks require manipulation of the hand that causes maladaptation in tendon structure that lead to pain over the lateral epicondyle. Mostly, the pain is located anterior and distal from the lateral epicondyle.

Epicondylitis occurs at least five times more often and predominantly occurs on the lateral rather than on the medial aspect of the joint, with a 4:1 to 7:1 ratio. It affects 1-3% of the population, with those 35-50 years old most commonly being affected. If a patient is <35 , it is important to consider differential diagnosis (growth plate disorder, referral from the cervical spine. If a patient is >50, consider OA, referred cervical spine pain.

This injury is often work-related, any activity involving wrist extension, pronation or supination during manual labor, housework and hobbies are considered as important causal factors. Lateral epicondylitis is equally common in both sexes. Between the ages of 30-50 years the disease is most prevalent. Obtaining of the condition at the both lateral epicondyle is rare, the dominant arm has the greatest chance of the occurrence of lateral epicondylitis. Twenty percent of cases persist for more than a year.

A systematic review identified 3 risk factors: handling tools heavier than 1 kg, handling loads heavier than 20 kg at least 10 times per day, and repetitive movements for more than 2 hours per day. Other risk factors are overuse, repetitive movements, training errors, misalignments, flexibility problems, aging, poor circulation, strength deficits or muscle imbalance and psychological factors[lxxxix].

There are several opinions concerning the cause of lateral epicondylitis:

1. Inflammation
    a. Although the term epicondylitis implies the presence of an inflammatory condition, inflammation is present only in the earliest stages of the disease process[xc].

2. Microscopic tearing
    a. Nirschl and Pettrone attributed the cause to microscopic tearing with formation of reparative tissue (angiofibroblastic hyperplasia) in the origin of the extensor carpi radialis brevis (ECRB) muscle. This micro-tearing and repair response can lead to macroscopic tearing and structural failure of the origin of the ECRB muscle.
    b. Histology of tissue samples shows "collagen disorientation, disorganization, and fibre separation by increased proteoglycan content, increased cellularity, neovascularization, with local necrosis." Nirschl termed these histological findings bangiofibroblastic hyperplasia. The term has since been modified to bangiofibroblastic tendinosis. He noted that the tissue was characterized by disorganized, immature collagen formation with immature fibroblastic and vascular elements. This grey, friable tissue is found in association with varying degrees of tearing involving the extensor carpi radialis brevis.

3. Degenerative Process
    a. The histopathological features of 11 patients who had lateral epicondylitis were examined by Regan et al. They determined that the cause of lateral epicondylitis was more indicative of a degenerative process than an inflammatory process. The condition is degenerative with increased fibroblasts, vascular hyperplasia, proteoglycans and glycosaminoglycans, and disorganized and immature collagen.
    b. Repetitive eccentric or concentric overloading of the extensor muscle mass is thought to be the cause of this angiofibroblastic tendinosis of the ECRB. Epicondylitis is a degenerative condition in which increased fibrolastic activity and granulation tissue formation occur within the tendon[xci].

4. Hypovascularity
    a. Because this tendinous region contains areas that are relatively hypovascular, the tendinous unit is unable to respond adequately to repetitive forces transmitted through the muscle, resulting in declining functional tolerance[xcii].

Symptoms

The most prominent symptom of epicondylitis lateralis is pain, this pain can be produced by palpation on the extensor muscles origin on the lateral epicondyle. The pain can radiate upwards along the upper arm and downwards along the outside of the forearm and in rare cases even to the third and fourth fingers. It is also often seen that the flexibility and strength in the wrist extensor and posterior shoulder muscles are deficient[xciii].
Furthermore, it is also often seen that the flexibility and strength in the wrist extensor and posterior shoulder muscles are deficient. At least patients report weakness in their grip strength or difficulty carrying objects in their hand, especially with the elbow extended. This weakness is due to finger extensor and supinator weakness[xciv].

Symptoms last, on average, from 2 weeks to 2 years. 89% of the patients recover within 1 year without any treatment except perhaps avoidance of the painful movements[xcv].

MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

Subjective Assessment

- Onset of pain 24-72 hours after provocative activity involving wrist extension
- Pain may radiate down forearm as far as the wrist and hand
- Difficulty with lift and grip (Pain+/- weakness)

Objective Assessment[xcvi]

- Pain and point tenderness over lateral epicondyle and/or 1-2cm distal to epicondyle
- Pain and weakness on resisted wrist extension
- Weakness on grip strength testing (Dynamometer)
- Pain and/or decreased movement on passive elbow extension, wrist flexion and ulnar deviation and pronation
- Weak elbow extensors and flexors

Differential Diagnosis

- Radial Tunnel Syndrome
- Pain in the posterolateral area of the forearm
- Pain sometimes spreads to the dorsal side of the wrist
- Parasthesia
- Weakness (overuse injuries of the musculoskeletal system)
- Posterior Interosseus Syndrome
- Motor deficits
- Elbow osteoarthritis
- Fractures
- Distal Radial Fractures
- Radial Head Fracture
- Olecranon Fracture
- Cervical Radiculopathy
- Radiating arm pain corresponding to the dermatomes
- Neck pain
- Parasthesia
- Muscle weakness in myotome
- Reflex impairment/loss
- Headaches
- Scapular pain
- Sensory and motor dysfunction in upper extremities and neck
- Cervical Disc Disease
- Cervical Myofascial Pain
- Cervical Spondylosis
- Fibromyalgia
- Medial Epicondylitis

Diagnosis

The diagnosis of lateral epicondylitis is substantiated by tenderness over the ECRB or common extensor origin. By the following methods, the therapist or physiotherapist should be able to reproduce the typical pain. To examine the severity of the tennis elbow, there is a dynamometer for strength and the patients must rate their levels of tennis elbow pain and disability from 0 to 10.

Treatment Options

Non-Operative medical management of lateral epicondylitis is initially based on the following principles: relieving pain and controlling inflammation. Relieving pain can be countered by

rest and avoiding painful activities. Inflammation on the other hand can be prevented by NSAIDs in the acute cases. The use of ice three times per day for 15 minutes is also recommended because it reduces the inflammatory response by decreasing the level of chemical activity and by vasoconstriction, which reduces the swelling. Elevation of the extremity is also indicated if an edema of the wrist or fingers is present.

The use of an elbow counterforce brace can be helpful because it plays the role of a secondary muscle attachment site and relieves tension on the insertion at the lateral epicondyle. The brace is applied around the forearm (below the head of the radius) and is tightened enough so that, when the patient contracts the wrist extensors, he or she does not fully contract the muscles.

Injections should be given subperiosteally to the extensor brevis origin. These injections have an early and beneficial effect. During the initial 24-28 hours, increased pain be experienced. A steroid injection should be followed by 1-2 weeks' rest and should not be repeated more than 2 times. Steroid injection seems to be effective for about 3 months, indicating that the patient must continue with the exercise program.

Surgical treatment:
If the symptoms of epicondylitis lateralis will prove to be resistant surgical treatment is indicated. Usually this is after a failed conservative treatment for more than 6 months. Most surgical procedures for tennis elbow involve removing diseased muscle and reattaching healthy muscle back to bone. The right surgical approach for you will depend on a range of factors. These include the scope of your injury, your general health, and your personal needs.

Physical Therapy may include:

- Ultrasound
- Transcutaneous electrical nerve stimulation (TENS)
- Braces/Splints/Straps
- Extracorporeal Shockwave therapy
- Deep transverse frictions for tennis elbow
- Exercise therapy
- Stretching
- Eccentric exercises

Current treatments for pain have yielded mixed results. Pain relief and anti-inflammatory medications remain the primary treatment option of choice; however, only about half of patients who take prescription and/or over-the-counter medication for chronic pain reported ineffective pain relief. Additionally, prescription painkiller use abuse and addiction rates are very high and a major contributor to unintentional drug deaths.

STUDY DESIGN

A multi-center, triple-blind, placebo-controlled, randomized evaluation of the effect of the MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

SUBJECT GROUPS
Each subject will be randomized to one of two test procedure as follows:

MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

Test procedure groups:

A. Subjects randomized to the test procedure group 1 will receive the study procedures with the active (true) Multi Radiance Medical® MR5® Prototype Device (light only).
B. Subjects randomized to the control procedure group will receive the study procedures with a 'fake' (placebo) Multi Radiance Medical® MR5® Prototype Device.

The 'fake' (placebo) MR5 Prototype device will appear to the subject to be an active device but will not produce any therapeutic light output. The placebo laser device is designed to have the same physical appearance as the actual (active test) device, including the appearance of any **visible** light output. Therefore, both the test and control devices emit light when activated that is indistinguishable to the subject. As the laser light does not put out any notable degree of heat or noise, these are not distinguishing factors for subjects between the active and control devices.

Apart from the distinction of whether the subject receives the study procedures with the actual or the fake laser device, all subjects and investigative parties will adhere to all phases of the entire protocol design.

SUBJECTS

Recruitment

Subjects will be recruited from three different sites and among the licensed health care provider's test site's pool of patients who are currently being treated for, or who are seeking treatment for Lateral Epicondylitis, or from patients who respond to the following recruitment materials, if needed.

Flyer

WANTED

ADULTS WITH LATERAL EPICONDYLITIS, ONGOING
FOR ONE MONTH, FOR A CLINICAL STUDY
OF THE EFFECTS OF LOW-LEVEL LASER LIGHT ON REDUCING LATERAL EPICONDYLITIS.

THIS STUDY INVOLVES SIX LASER LIGHT PROCEDURES, TWO TIMES A WEEKS FOR THREE WEEKS WITH THE MULTI RADIANCE MEDICAL® MR5® LASER AT THE TEST SITE.

THERE IS THREE VISITS PRIOR TO LASER LIGHT PROCEDURES WITH ONE MORE VISIT TO THE TEST SITE
ONE MONTH AFTER THE LAST LASER LIGHT PROCEDURE.

YOU WILL RECEIVE $450 IF YOU FINISH THE STUDY.

FOR MORE INFORMATION PLEASE CONTACT:

<PI name>
<test site name & location>
<phone # and/or e-mail>

MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

Newspaper Ad

Lateral Epicondylitis
Research Study

This study is to see if the Multi Radiance Medical® MR5® LASER, a non-invasive, investigational device that uses low-level laser light, can help to relieve symptoms of Lateral Epicondylitis pain longer than one month in duration.

The study involves ten visits to a test site and recording some information at home.

You will receive $450 if you finish the study. Please contact
<PI name> at
<test site name & location> at
<phone and/or e-mail> for details.

Compensation
A subject will be paid a stipend of $450.00 USD for their participation in the study upon completion. Subjects will not be charged for the cost of the study procedures administered with the Multi Radiance Medical® MR5® Prototype Device for the cost of any other directly related evaluations or measurements that occur as part of his or her participation in the study.

Sample size
There will be 60 subjects evaluated for eligibility in this clinical study:

- 30 subjects in the active procedure group
- 30 subjects in the control procedure group (Placebo)

Rationale for sample size
Based on the following parameters established for the purposes of assessing efficacy of the Multi Radiance Medical MR5 Prototype Device in this clinical study using the Fischer's Exact test to assess the primary endpoint.

- Individual subject success criteria is defined as a 30% or greater reduction in self-reported Degree of Pain rating on the 0-100 VAS from baseline to study endpoint evaluation.
- Overall study success criteria of at least a 30% difference between the test device group and the placebo group, comparing the proportion of individual successes in each group.
- It is anticipated that about 50% of subjects in the test device group and about 20% of subjects in the placebo group will meet the individual success criteria, and
- Intended application of a two-tailed test with an alpha value of 0.05 and Power of 0.8

- the sample size of 25 available subjects per group (test group and the control group, separately) has been determined using the following reference calculator: *Hypothesis Testing: Categorical Data - Estimation of Sample Size and Power for Comparing Two Binomial Proportions* in Bernard Rosner's *Fundamentals of Biostatistics.*

For the purposes of sample size calculation, a subject loss-to-follow-up of 20% is anticipated.

Therefore, a minimum starting sample size of 30 evaluable subjects in each group is needed to ensure that a sufficient number remains at the end of the trial (25 subjects per group) for any significant differences found between groups to be considered statistically valid and representative of the general population being sampled. This results in a total of 60 subjects being enrolled in this study across both study procedure groups.

RANDOMIZATION

Subject allocation to procedure group will be via variable block randomization with varying block sizes of two and four used at random to minimize the likelihood of predicting the next procedure group assignment. In addition, randomization will be stratified by Fitzpatrick Skin Type grouping

Randomization will be attained using computer generation sequence methodology, ensuring that the randomization methodology and the generated allocation sequence is concealed from the investigator and subjects.

Concealment will be insured as follows:

- Each computer-generated randomization sequence is unique and will therefore not be able to be replicated.
- Randomization will occur to either 'Test Group A' or 'B' rather than to a tests or placebo group, and only the study Sponsor will know which assignment corresponds to the active devices and which corresponds to the fake device. The Sponsor will not reveal this information to any source (investigators, subjects, or study Monitor) until the final study data analysis is complete.

TRIPLE BLIND DESIGN

This clinical study will be a triple-blind design, such that neither the subject, nor the assessor, nor the therapists will be aware of whether a subject is receiving the study procedure with the active (test procedure group assignment) or the 'fake' (placebo procedure group assignment) Multi Radiance Medical MR5 Prototype Device until after the study is completed. Maintenance of study triple-blind throughout the entire course of the study will be achieved through the following means:

1) Each subject will be randomly assigned to 'Test Group A' or 'B' by the independent study Monitor. Only the study Sponsor will know which label 'Test Group A' or 'B') corresponds to the actual (test) MR5 device and which label corresponds to the 'fake' device until the final study data analysis is complete. The Sponsor will ensure that this information is stored and maintained confidentially at the Sponsor's work site. This knowledge will not be shared with the investigators, the subjects, or the study Monitor until the final data analysis is complete.
2) The fake (placebo) MR5 device is designed to have the same physical appearance as the actual MR5 device, including the appearance of any **visible** light output. Therefore, both the test and sham devices emit light when activated that is indistinguishable to both

the subject and to the investigator. As the laser light does not put out any notable degree of heat or noise, these are not distinguishing factors for subjects between the four groups.

3) There will be two independent investigators interacting with subjects at each test site:
    i. *Administration investigator*: who will be responsible for administrating the study procedures; and
    ii. *Assessment investigator*: who will be responsible for recording the study outcome measures

   Only the administration investigator will be aware of whether a subject is assigned to 'Test Group A' or 'B', although he or she will not be made aware of whether 'Test Group A' or 'B' corresponds to the true or fake laser. Neither the assessment investigator nor the subject will be aware of the subject's A/B Group assignment. In this way, the assessment investigator will not be able to form an association between A/B Procedure Group and active/sham device over the course of the study if a treatment effect is observed.
4) During the MR5 procedures, both the subject and the administration investigator will wear Laser Safety Industries protective eyewear that filter out the laser light spectrum.

TABLE OF SUBJECT EVENTS

The following table provides a progressive summary of subject events throughout this study.

PRE-PROCEDURE ACTIVITIES
1. A potentially well-suited and interested candidate for participation in the study attends the investigator's office. 2. The investigator reviews the informed consent form with the candidate. 3. If the candidate continues to be interested and voluntarily signs the informed consent form, the study qualification evaluation phase of the study is performed. 4. A qualified subject is randomly assigned to procedure group. 5. One-week individualized pain management regimen stabilization phase occurs 6. The following measures are recorded during the Stabilization Phase: ▪ Subject Daily Diary ▪ Degree of Pain Ratings on final three days
PRE-PROCEDURE ASSESSMENT PHASE
CONTINUED STUDY ELIGIBILITY EVALUATION ▪ Review of application of individualized pain management regimen throughout the Stabilization Phase ▪ Evaluation of 3-day average VAS rating **PRE-PROCEDURE MEASURES** ▪ Degree of Pain Rating ▪ PRTEE, Grip Strength and TNFa measurements **PRE-PROCEDURE VARIABLES** ▪ Baseline concomitant medication and treatment/therapy use

- Historical pain medication and treatment/therapy use
- Baseline Lateral Epicondylitis pain variables
- Demographics

PROCEDURE ADMINISTRATION PHASE

Six 9-minute study procedure administrations with the Multi Radiance Medical® Prototype Device, two procedure administrations a week for three consecutive weeks administered at the test site.

PROCEDURE ADMINISTRATION PHASE MEASURES

DAILY THROUGHOUT THE THREE-WEEK PROCEDURE ADMINISTRATION PHASE

- Maintenance of the individualized pain management regimen, as needed
- Subject Daily Diary

WITHIN 24 HOURS OF COMPLETION OF THE FINAL PROCEDURE ADMINISTRATION

- Degree of Pain Rating
- PRTEE, Grip Strength and TNFa measurements
- Subject Satisfaction with Overall Outcome Rating
- Perceived Group Assignment
- Investigator Adverse Events Evaluation

POST-PROCEDURE ADMINISTRATION PHASE

DAILY THROUGHOUT THE ONE MONTH POST-PROCEDURE ADMINISTRATION PHASE

- Maintenance of the individualized pain management regimen, as needed
- Subject Daily Diary

ONE MONTH (30 DAYS) POST-PROCEDURE ADMINISTRATION PHASE (TEST SITE VISIT)

- Degree of Pain Rating
- PRTEE, Grip Strength and TNFa measurements
- Subject Satisfaction with Overall Outcome Rating
- Perceived Group Assignment
- Investigator Adverse Events Evaluation

STUDY PROCEDURE

PRIMARY OUTCOME MEASURE:
The following is a listing of the study measurement tools to be used in this study. At each evaluation point, the precise tools from this list that will be employed will be specified.

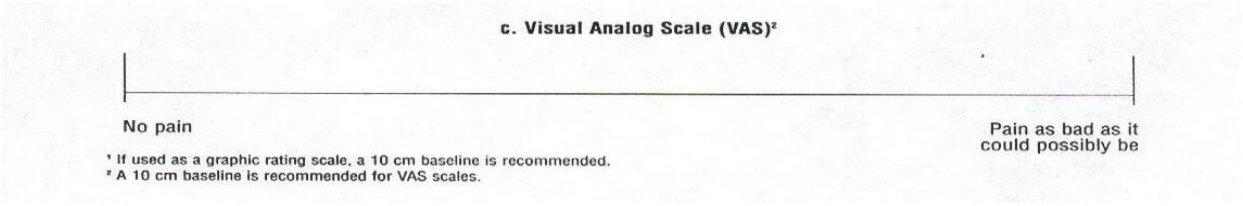
DEGREE OF PAIN RATING: Subjects will be asked to rate the overall degree of pain they are currently experiencing in the Lateral Epidondyle region on the following 0-100 0 cm (100 mm) horizontal ***Visual Analog Pain Scale (VAS).***

The Visual Analog Pain Scale is one of the three most commonly used scales for assessing chronic pain. It is a simple scale that consists of a line anchored at one end by a label such as "NO PAIN" and at the other end "WORST POSSIBLE PAIN". The subject marks on the line the spot for the pain intensity, which is then measured.

Standard guidelines for effective use of the VAS that are followed in this clinical study are:

1) The line should be 10 cm long, as other lengths are less reliable.
2) There should be a small vertical mark at each end and a verbal description.
3) The verbal description must be in absolute terms (e.g. worst discomfort imaginable);
4) The line itself should be clear of any markings and should be horizontal rather than vertical, for more reliable measurements.

Used in the above way, it has been shown that the VAS is a proper ratio scale. Like a thermometer, this means that its two ends are rooted, and a doubling of the score does accurately reflect a doubling of the pain. Consequently, sensitive t-tests and ANOVA methods can be used in the analysis, so that significant differences can be identified with relatively small sample sizes or small differences between groups.
Source: Measuring Pain by Adrian White, Acupuncture in Medicine, November 1998 – Vol 16 No. 2



The subject will be instructed not to record a VAS pain rating (whenever indicated) any sooner than four hours after having consumed a dosage of any pain relief medication. This is to ensure that the effect of the pain relief medication does not influence the effect of the study procedures with the Multi Radiance Medical MR5 Prototype Device. That is, a VAS rating is only to be recorded once the effect of any previously consumed pain relief medication has dissipated. The subject may take another dosage of his or her study-approved pain relief medication immediately after recording the VAS rating, if needed.

Throughout the course of his or her study participation, a subject can continue to take any other over-the-counter and/or prescription medication(s) that he or she usually takes for any other (non-pain relief) indication(s), as he or she usually takes them, as reported at Baseline evaluation and approved by the study investigator. Subjects will be required to record consumption of all medication throughout the course of study participation.

MR5® Prototype Device for temporary adjunctive use to relieve pain associated with Lateral Epicondylitis.

SECONDARY OUTCOMES

Patient Related Tennis Elbow Evaluation *- PRTEE*
The PRTEE, formerly known as the Patient-Rated Forearm Evaluation Questionnaire (PRFEQ), is a 15-item questionnaire designed to measure forearm pain and disability in patients with lateral epicondylitis (also known as "tennis elbow"). The PRTEE allows patients to rate their levels of tennis elbow pain and disability from 0 to 10, and consists of 2 subscales: PAIN subscale (0 = no pain, 10 = worst imaginable) and FUNCTION subscale (0 = no difficulty, 10 = unable to do) In addition to the individual subscale scores, a total score can be computed on a scale of 100 (0 = no disability), where pain and functional problems are weighted equally.

The PRTEE is a reliable, reproducible, and sensitive instrument for assessment of chronic lateral elbow tendinopathy. It is at least as sensitive to change as Visual Analog Scale (VAS); the Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire, and the Upper Extremity Function Scale. The PRTEE may become the standard primary outcome measure in research of tennis elbow.[xcvii]

For a group using the questionnaire, mean PRTEE score reductions of at least 11 points - or an improvement of 37% on the mean baseline score - is necessary to consider that a substantial improvement has taken place. Using a less stringent criterion, falls of 7 points or 22% of the baseline score can be interpreted as indicating a limited but meaningful improvement.[xcviii]

Grip Strength Test
The grip strength will be measured using a digital grip dynamometer type Jamar® Plus Digital Hand Dynamometer (Patterson Medical, Warrenville, IL, USA). The grip dynamometer will be placed on the second knuckle of the finger to measure the grip strength between the thumb and the other fingers, and the subject will grip the grip dynamometer for five seconds within the range where no pain will be felt, with both arms naturally lowered while ensuring that the grip dynamometer will not be shaken or put into contact with the body. This measurement will be conducted three times and the average value will be used (Lee et al. 2018).
Lee JH, Kim TH, Lim KB. Effects of eccentric control exercise for wrist extensor and shoulder stabilization exercise on the pain and functions of tennis elbow. J Phys Ther Sci. 2018; 30(4):590-594.

TNF-α Marker *- Blood Collection*
Blood samples (5 ml) will be collected by puncture of the antecubital vein. The collections will be performed by a qualified professional who will use sterile gloves, disposable syringes and needles. The collected material will be placed in centrifuge tubes. Fifteen minutes after obtaining the blood sample, it will be centrifuged and the supernatant (serum) stored at -80°C for further analysis. An analysis of the concentration the inflammatory marker the cytokine TNF-α (Tumor Necrosis Factor-alpha) will be performed by means of the enzyme-linked immunosorbent assay (ELISA), following the instructions of the commercial kit.

1) Risks and discomforts: Blood collection can generate discomfort at the puncture site (antecubital vein) during the procedure and for a few minutes later. A mild hematoma may occur at the puncture site after the procedure.

2) Inclusion and Exclusion Criteria: Subjects with hemophilia or any type of blood clotting disorder, or diagnosed with a chronic immune impairment, will be excluded from the study.

BACKGROUND/RATIONALE*: EPICONDYLITIS - TNF-α*
It is known that matrix remodeling is being enabled by the balance of matrix metalloproteinases (MMPs) and their inhibitors. The imbalance in the expression of MMPs and inhibitors can contribute to tendon matrix degradation[xcix],[c]. The tendon matrix degradation is initiated by MMPs and involves the release of inflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukins as IL-1, IL-6 and IL-10[ci]. The presence of these cytokines is directly related to the progression of inflammation and painful processes after tendon disorder[cii],[ciii].

TNF- α is a pleiotropic cytokine related to cell survival and proliferation but also to cell death in the apoptotic process expressed by tenocytes in inflammatory conditions[civ]. It may be the key cytokine in the origin of several musculoskeletal diseases such as arthritis and tendinitis, the TNF-α expression is increased in tendons with installed inflammatory processes, such as after surgery or injuries[cv].. The long persistence of inflammation can increase the pro-inflammatory mediators extending the inflammatory phases and favoring the outbreak of scar tissues which alter the characteristics of original tendon[cvi]. So, in this context, it is important that treatment aims to modulate the inflammation process, promoting a quality tissue repair.

ADVERSE EVENTS EVALUATION: Adverse events evaluation will include, but not be limited to, the following unlikely, but potentially feasibly events that may occur from application of the Multi Radiance Medical® MR5® Prototype Device to the treatment site:

- skin irritation
- discoloring
- rash
- indentations
- infection
- increased pain or tenderness

SUBJECT SATISFACTION WITH OVERALL OUTCOME RATING: The subject is asked to indicate how satisfied he or she is with any change in his or her Lateral Epicondylitis pain following completion of the procedure administrations with the MR5®, by responding to the following question by selecting the most appropriate category from the following five-point Likert scale: "*How satisfied or dissatisfied are you with any change you may have noticed in the pain in your neck/shoulder after getting the procedures with the study device?*"

- ✓ Very Satisfied
- ✓ Somewhat Satisfied
- ✓ Neither Satisfied nor Dissatisfied
- ✓ Not Very Satisfied
- ✓ Not at All Satisfied

PERCEIVED GROUP ASSIGNMENT: The subject, the Administration Investigator and the Assessment Investigator will each be asked (separately) to state whether he or she believes the subject to have received the active procedure administrations with the actual Multi Radiance Medical® MR5® Prototype Device or the 'fake' procedures with the 'placebo' MR5® device, and the reasons for those beliefs.

STUDY PROCEDURE PROTOCOLS

All study procedure protocol activities listed below will be conducted by a licensed health care provider at the test site. The study licensed health care provider will be a suitably qualified and licensed medical/healthcare professional who is trained and experienced in treating individuals with Lateral Epicondylitis, in evaluating according to the study qualification parameters, in recording the study outcome measures such as range of motion and medication history, and in performing adverse events evaluations.

PRE-PROCEDURE ACTIVITIES

The pre-procedure activities will be conducted at the test site prior to commencement of the study procedure administration.

STUDY QUALIFICATION

ATTAINMENT OF INFORMED CONSENT PROCESS

Informed consent is an agreement between the individual investigator (a licensed medical/healthcare professional) and each individual subject, having the capacity to understand and to make an informed decision. Informed consent is a process that is initiated prior to the potential subject agreeing to be considered for participation in the study and continues throughout the duration of the individual's study participation.

A written consent form describing in detail the purpose of the study, the study intervention, the study procedures, and the risks involved in taking part in the study is given to and reviewed with each subject, with voluntarily signed and dated documented informed consent required from the subject *prior to* starting any study subject activity, including study qualification evaluation. No other consent documents will be provided to subjects in this study. The consent form will be IEC-approved with supporting documentation.

The informed consent process will occur in a private room and be between the investigator and the subject.

The step-by-step processing for attainment of informed consent will be as follows:

1. The subject will be provided with the written informed consent form and asked to carefully read and review the entire document or the investigator will read it to the subject if alternatively requested by the subject.

2. The investigator will then also provide a verbal review of the written information contained in the consent form ensuring subject awareness of the:
   - purpose of, the intervention, and the procedures involved in, the study.
   - reasonably expected benefits the subject might receive, as well as any risks or potential discomfort that are involved.
   - alternative treatments available to the subject for the study condition being evaluated.
   - fact that the subject's records will remain confidential, but that the FDA and the IEC has the right to inspect those records.
   - Subject's rights as a research subject.

- name and method of contacting the appropriate person(s) to answer the subject's questions about the research and in the event of the occurrence of a research-related injury.

3. The investigator will emphasize to the subject that their participation in the study is strictly voluntary, and that they may decline to participate in the study or withdraw their consent to participate in the study at any time, for any reason, without prejudice, such that the quality of their medical care will not be adversely affected.

4. The investigator will answer any questions the subject may have about the study and their participation in it and verify that the subject has correctly understood the information in the consent form.

5. Subjects will be given the opportunity and encouraged to take the consent form home to discuss the study with their family and/or to think about it some more before signing for as long as desired provided enrollment is ongoing at the time the decision to sign is made.

6. The subject must voluntarily and willingly, without coercion or duress, or force or influence from the investigator or sponsor or any other party, sign and date the written informed consent document that is witnessed and verified by the investigator's dated signature prior to commencement of any study procedures or activities.

7. A copy of the informed consent document will then be given to the subject for their records.

8. Completion of the informed consent process will be documented in the source document (CRF), and the subject and investigator signed and dated consent form will be filed according to the procedure in the site's Informed Consent SOP.

The informed consent form that will be used in this clinical study is contained in ***Appendix D***.

ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBER

The subject will be assigned a unique subject identification number based upon his or her order of entry into the study.

Additional information about the informed consent and subject ID number assignment is contained in a later section of the protocol titled, "SAFETY AND CONFIDENTIALITY ISSUES."

STUDY QUALIFICATION EVALUATION: INCLUSIONS/EXCLUSION CRITERION

INCLUSION CRITERIA
To be eligible for study participation, a subject must satisfy each of the following criteria.

Patient history: History of one or more the following:

- Patients with a history of pain around the Lateral Epicondyle for at least 1 month;
- Tenderness localized to the epicondyle and anterodistal region of the epicondyle with palpation;

- 2 of 4 positive results of provocative tests comprising of Maudsley's, Cozen's, Thomsen and Mill's tests (Whaley, Baker 2004);
- Aged between 18 and 50 years;
- Both genders.

Reference - *Whaley AL, Baker CL. Lateral epicondylitis. Clin Sports Med. 2004; 23(4):677-691*

Medication Use History: Where applicable, history of attaining relief from Lateral Epicondyle pain from taking over-the-counter and/or prescription muscle relaxants; nonsteroidal anti-inflammatories (NSAIDs) such as ibuprofen or naproxen, and acetaminophen.

Previous Records Review (x-rays, MRI, CT scans, etc.): where pre-existing and available, previous records review that indicates muscle or ligament injury and the absence of Degenerative Joint Disorder (DJD)

Physical Examination of the Lateral Epicondyle Region.

- Painful range of motion
- Pain and weakness upon grip strength and wrist extension
- Muscles in Lateral Epicondyle feel hard, tight or knotted upon palpation
- Muscles in Lateral Epicondyle feel hard, tight or knotted upon palpation
- Lateral Epicondyle pain is persisting over one month
- Self-reported Degree of Pain rating on the 0-100 VAS pain scale for the Lateral Epicondyle region is 50 or greater
- Subject is willing and able to maintain his or her current pre-study Lateral Epicondyle pain management regimen of pain relief medication and/or treatment/therapy use throughout the course of study duration, whilst refraining from consuming other OTC and/or prescription medication(s) and/or herbal supplements intended for the relief of pain and/or inflammation, including muscle relaxants, and/or partaking in other treatments/therapies including conventional therapies such as physical therapy, occupational therapy and hot or cold packs, as well as alternative therapies such as chiropractic care and acupuncture.
- 18 years of age or older
- Male or female
- Subject is fluent in Portuguese

EXCLUSION CRITERIA

A subject who satisfies any of the following criteria will be excluded from study participation:

- hemophilia or any type of blood clotting disorder
- chronic immune impairment neoplasia
- neurologic deficits
- cervical radiculopathy
- peripheral nerve disease
- rheumatoid arthritis
- shoulder disease
- radial tunnel syndrome
- previous surgery of the affected upper extremities
- congenital or acquired bony deformity in the ipsilateral upper extremity
- the initiation of opioid analgesia or corticosteroid or analgesic injection interventions within the previous 6 months

- physical therapy intervention on the upper extremity in the previous year
- bilateral epicondylosis
- secondary orthopedic problems.

Physical Examination of the Lateral Epicondyle Region:

- Lateral Epicondyle pain is acute, defined as having persisted over less than the last 1 month
- Self-reported Degree of Pain rating on the 0-100 VAS pain scale for the Lateral Epicondyle region is less than 50
- Local corticosteroids and/or botulinum toxin (Botox®) injection for Lateral Epicondyle pain relief within the prior 30 days
- Medical tx; such as chiropractic care and acupuncture within last 30 days
- Current, active chronic pain disease: chronic fatigue syndrome, fibromyalgia, endometriosis, inflammatory bowel disease, interstitial cystitis diabetic neuropathic pain
- Cancer or treatment for cancer in the past 6 months, including tumors of the spinal cord
- Diabetes Type 1
- Significant heart conditions including CHF and implantable heart devices such as a pacemaker
- Active infection, wound, or other external trauma to the areas to be treated with the laser
- Medical, physical, or other contraindications for, or sensitivity to, light therapy
- Pregnant, breast feeding, or planning pregnancy prior to the end of study participation
- Serious mental health illness such as dementia or schizophrenia; psychiatric hospitalization in past two years
- Developmental disability or cognitive impairment that in the opinion of the investigator would preclude adequate comprehension of the informed consent form and/or ability to record the necessary study measurements
- Involvement in litigation and/or receiving disability benefits related in any way to the parameters of the study
- Subject is less than 18 years of age
- Participation in a clinical study or other type of research in the past 30 days
- Subject is not fluent in Portuguese

SUBJECT GROUP RANDOMIZATION

A fully qualified subject is randomly assigned to 'Test Group A' or 'B' following the methodology outlined above in the STUDY DESIGN section of the protocol.

INDIVIDUALIZED PAIN MANAGEMENT REGIMEN STABILIZATION PHASE:

During the one-week period immediately preceding commencement of the pre-procedure assessment phase, subjects will partake in a pain management stabilization phase. See **Appendix C** for Individualized Pain Medication Regimen Details.

ESTABLISHMENT OF PROCEDURE ADMINISTRATION VISIT SCHEDULE

To implement consistency in the time of day when VAS pain ratings are recorded across all evaluation points throughout the study duration, the visit schedule times for each of the six procedure administration visits will be established at this time within a one-hour time frame. For example, between 2 p.m. and 3 p.m. for each of the six procedure administration visits, or between 10 a.m. and 11 a.m. for each of the six procedure administration visits, etc.

INDIVIDUALIZED PAIN MANAGEMENT REGIMEN STABILIZATION PHASE MEASURES
During the two-week stabilization phase, the subject records the following, as applicable.

- Subject Daily Diary
- Degree of Pain Rating on the 0-100 VAS on each of the last three days of the baseline stabilization phase, each measurement to be recorded within 15 minutes of the procedure administration visit times scheduled. For example, if the procedure administration visit schedule is established as between 2 p.m. and 3 p.m., the latest time a required VAS recording can be made is 3:15 p.m. The subject will record the exact time that he or she marks the VAS recording.

PRE-PROCEDURE ASSESSMENT PHASE

The pre-procedure assessment phase will commence following successful completion of the individualized pain management regimen stabilization phase and just prior to commencement of the procedure administration phase.

CONTINUED STUDY ELIGIBILITY EVALUATION
Prior to the subject commencing the Pre-Procedure Assessment phase of the study, the investigator will:

- review the subject's recordings of use/application of his or her individualized pain management regimen to ensure it was correctly applied and recorded, and that there are no deviations significant enough to warrant withdrawal of the subject from the study prior to entry to the pre-procedure assessment phase; and
- calculate the average of the 3 VAS degree of pain scores recorded during the last three days of the individualized pain management regimen stabilization phase. In order for the subject to proceed, the 3-day average VAS score must be 50 or greater. If it is less than 50, the subject's participation in the study ends at this time.

PRE-PROCEDURE MEASURES

- Degree of Pain Rating. This will occur within 15 minutes prior to the initial procedure administration. The exact time the VAS rating is recorded will be noted.
- PRTEE, Grip Strength and TNFa measurements will be noted.

PRE-PROCEDURE VARIABLES

- Baseline concomitant medication and treatment/therapy use
- Historical pain medication and treatment/therapy use
- Baseline Lateral Epicondyle pain variables
- PRTEE, Grip Strength and TNFa measurements and Fitzpatrick Skin Type Classification will be noted.
- Demographics

PROCEDURE ADMINISTRATION PHASE

PROCEDURE ADMINISTRATION PROTOCOL

- The procedure administration phase of the study will commence within 15 minutes subsequent to completion of the pre-procedure assessment phase.
- The procedure administration phase comprises a total of six procedure administrations with the Multi Radiance Medical® MR5® Prototype Device: two

procedures a week for three consecutive weeks*, each procedure administration three to four days apart.

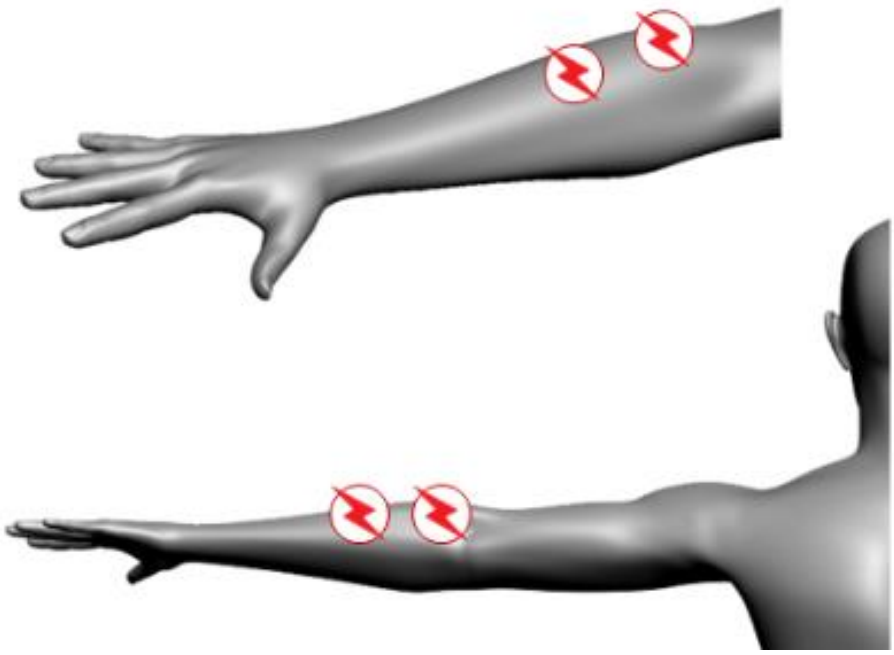
- *Three weeks, 2 times a week... Follow-up at 4th week after administration phase*
- *Emanet SK, Altan LI, Yurtkuran M. Investigation of the effect of GaAs laser therapy on lateral epicondylitis. Photomed Laser Surg. 2010 Jun;28(3):397-403. doi: 10.1089/pho.2009.2555. PubMed PMID: 19877824.*
- Each of the six procedure administration visits will occur within the same on-hour timeframe, as explained above under 'ESTABLISHMENT OF PROCEDURE ADMINISTRATION VISIT SCHEDULE' above.
- Each procedure administration lasts 20 minutes.
- The procedure administrations with the MR5® Laser is administered by the procedure administrator at the test site.
- Prior to administration of treatment protocol skin should be cleansed and verify there is no broken skin.

The study procedure administration protocol is as follows:

1. The subject enters the procedure administration room and is situated in a seated position.
2. The skin should be prepared for treatment by cleansing skin and verification of no broken skin.
3. The subject is correctly fitted with the safety glasses.
4. The procedure administrator puts on the safety glasses and selects the Multi Radiance Medical® MR5® Prototype Device A or B according to the subject's procedure group randomization.
5. The Prototype Device emitter is statically held by direct contact with the skin on each of the target areas:
   Identified in diagram (over the Lateral Epicondyle) for the light administration phase for 60s each location.
6. The total procedure administration duration is 5 minutes for the laser portion of the treatment.

Laser

		1 SPL	IR	Red	Total
	Photons/sec	5.69E+15	1.10E+18	6.75E+17	1.78E+18
Time,sec	Irrad, W/cm2	0.002841	0.0625	0.05	1.15E-01
60	Energy, J	0.075	15	12	2.71E+01
	Fluence, J/cm2	0.170455	3.75	3	6.92E+00



PROCEDURE ADMINISTRATION PHASE MEASURES

Daily throughout the three-week procedure administration phase, the subject will continue at home to:

- maintain application of his or her individualized pain management regimen, as during the two-week stabilization phase, and
- complete the Subject Daily Diary, as applicable

WITHIN 24 HOURS OF COMPLETION OF THE FINAL (6TH) PROCEDURE ADMINISTRATION

- Degree of Pain Rating. The exact time the VAS rating is recorded will be noted.
- PRTEE, Grip Strength and TNFa measurements will be noted.
- Subject Satisfaction with Overall Outcome Rating
- Perceived Group Assignment
- Investigator Adverse Events Evaluation

POST-PROCEDURE ADMINISTRATION PHASE

The post-procedure administration phase encompasses the one-week period immediately following completion of the procedure administration phase and comprises the following evaluation points and associated measures.

POST-PROCEDURE ADMINISTRATION PHASE EVALUATION POINTS AND MEASURES

Daily throughout the one-week post-procedure administration phase, the subject will continue at home to:

- maintain application of his or her individualized pain management regimen, as during the two-week stabilization phase and the three-week procedure and phase, and
- complete the Subject Daily Diary, as applicable

ONE MONTH POST-PROCEDURE ADMINISTRATION PHASE (TEST SITE VISIT)

- Degree of Pain Rating: This time will be within the same one-hour time-frame as the prior post-procedure administration phase VAS ratings were recorded, 1 month after the final procedure administration; e.g., if the prior 3 post-procedure administration VAS recordings were made between 1:30 p.m. and 2:30 p.m. on each of the three days, then the 1 week post-procedure VAS recording will also be made between 1:30 p.m. and 2:30 p.m. The exact time the VAS rating is recorded will be noted.
- PRTEE, Grip Strength and TNFa measurements will be noted.
- Subject Satisfaction with Overall Outcome Rating
- Perceived Group Assignment
- Investigator Adverse Events Evaluation

ADVERSE EVENTS

At each evaluation and measurement point throughout the clinical study, and at any other time throughout the duration of the clinical trial that is necessary, any and all potential adverse events reported by a subject or observed by an investigator will be recorded on the case report form, and subsequently evaluated by the investigator for its relation to the study procedure and whether or not any corrective action needs to be taken. All potential adverse events recorded will be appropriately reported to the governing IRB, as applicable.

It is unlikely and not expected that any adverse events will result from implementation of this clinical study protocol. Prior clinical trials using low level laser light have not typically yielded any adverse events or reactions. However, potential adverse events that may feasibly occur from application of the Multi Radiance Medical® MR5® Prototype Device include, but are not necessarily limited to; skin irritation, discoloring, rash, indentations and infection.

PRIVACY AND CONFIDENTIALITY

Records for each subject in this clinical study will be maintained in separate files in a locked filing cabinet at the test site. The investigator at the test site will be responsible for ensuring that all records for a subject pertaining to his or her participation in the clinical study are stored in that subject's file at all times other than when information is being recorded on them.

The Laboratory of Phototherapy in Sports and Exercise will have access to the files for the purposes of data monitoring and auditing. Once the study is complete, copies of all of the subject case report forms will be made and supplied to Laboratory of Phototherapy in Sports and Exercise for analysis of results. Laboratory of Phototherapy in Sports and Exercise will

maintain these copies in a separate clinical study file that is kept in a locked filing cabinet on their premises. The original records will be maintained at the respective test sites upon completion of the study in their original files and stored in a locked filing cabinet.

Subjects' identities will be kept confidential by assigning each subject a subject ID upon acceptance into the study. The subject ID will comprise the investigator's two initials (first and last name initials) and a three-digit number from 001 to 100 that will be based upon the subject's order of entry into the clinical study. For example, the eighth subject to be enrolled at the test site would have a subject ID of EL008. Neither the study Sponsor nor Laboratory of Phototherapy in Sports and Exercise will receive any additional identifying information about a subject and will therefore have no way of linking a subject ID to a particular subject and his or her results.

MONITORING OF THE CLINICAL STUDY

The study Monitor will assure that the test site and the investigator is executing the protocol exactly as outlined and intended. This includes insuring that a signed informed consent form has been attained from each subject prior to commencing the protocol, and that all study evaluations are recorded using the specified methods and correctly and fully recorded on the appropriate clinical case report forms. The investigator will be trained by the same study Monitor to this end, including insuring that the investigator understands how to watch for, to evaluate and to handle, the occurrence or potential occurrence of an adverse event.

STATISTICAL ANALYSIS

PRIMARY EFFICACY OUTCOME MEASURE:
CHANGE IN SUBJECT SELF-REPORTED VAS PAIN RATING FROM BASELINE TO STUDY ENDPOINT

Primary efficacy outcome measure for this clinical study will be a statistically significant difference in the proportion of subjects between test and control groups who achieve a clinically meaningful and statistically significant decrease in self-reported VAS pain rating from baseline to study endpoint.

Subjects meeting Individual Success Criteria

The individual subject success criteria is defined as a 30% or greater decrease in self-reported VAS pain rating at study endpoint relative to baseline.

Overall Study Success Criteria.

Overall study success criteria is defined as at least a 30% difference between procedure groups, comparing the proportion of individual successes in each group. It is anticipated that about 50% of subjects in the test group will meet the individual success criteria and about 20% of subjects in the control group will meet the individual success criteria.

Evaluation Time Points

The study end evaluation time point at which study success will be analyzed is within 24 hours following completion of the three-week procedure administration phase with the Multi Radiance Medical® MR5® Prototype Device. Study success will be evaluated at endpoint relative to baseline.

Hypotheses

- *Null Hypothesis*: There will be no statistically significant difference in the proportion of individual successes, as defined, between the test and control groups.

- *Alternative Hypothesis*: There will be a statistically significant difference in the proportion of individual successes, as defined, between the test and control groups, to the effect of 30% or greater.

PRIMARY EFFICACY OUTCOME STATISTICAL EVALUATION METHODS

Intent to Treat (ITT) Principle: Primary efficacy analysis will be according to the intent to treat (ITT) principle; wherein subjects will be included in the analysis if they were randomized to study procedure group, had a valid baseline (pre-procedure) visit including the required Lateral Epicondylitis pain VAS recordings; and received at least the first study procedure administration.

Missing data will be handled through all of the following methods:

- *Last Observation Carried Forward (LOCF)*: by carrying forward the last recorded observation to fill in the subsequent missing value.
- *Tipping Point Analysis:* Tipping point analysis will be used to examine the impact of missing data on the study conclusion. Tipping point analysis is defined as the difference in means (for continuous data) or the difference in the number of events (for binary data) between treatment groups in the missing cohort at which the study conclusion is changed. A tipping point analysis replaces the missing value with other values so that the resulting p-value is equal to the pre-specified significance level (i.e. α=0.05, 2-sided).
- *Multiple Imputation Analysis*: Multiple imputation analysis is a strategy to handle missing values in a clinical trials wherein each missing value is replaced with a set of plausible values that represent the uncertainty about the right value to impute. Multiple imputation does not attempt to estimate each missing value through simulated values, but rather to represent a random sample of the missing values. This process results in valid statistical inferences that properly reflect the uncertainty that results from missing values, such as valid confidence intervals for parameters.

  Multiple imputation inference involves three distinct phases:

  1. The missing data are filled in m times to generate m complete data sets.
  2. The m complete data sets are analyzed by using standard statistical procedures.
  3. The results from the m complete data sets are combined for the inference.

  Multiple imputation usually assumes that the data are missing at random (MAR). That is, for a variable Y, the probability that an observation is missing depends only on the observed values of other variables, not on the unobserved values of Y.

Pre-Protocol Analysis will also be performed for the set of all subjects who were randomized to procedure group and completed the study according to the full protocol.

Primary analysis of efficacy will be according to intent to treat (ITT) analysis through the application of:

1) **Fisher's exact test** to compare the proportion of success between the test and the control groups, considering that randomization has been diligently conducted and important covariates between the two groups are well balanced.

2) **Parametric ANCOVA model** analysis with the mean change from baseline to study endpoint in Lateral Epicondyle pain ratings on the VAS as the dependent variable, procedure group as the independent variable of interest and baseline average Lateral Epicondyle pain VAS rating as a covariate. A two-tailed significance level of 5% will be considered to be statistically significant.

Covariates: The following potential covariate baseline variables will be adjusted, as applicable, through application of an ANCOVA analysis for the continuous variables and linear regression analysis for categorical variables.

- Baseline Lateral Epicondyle pain VAS rating
- Fitzpatrick Skin Type Classification
- Age
- Gender
- Demographics

SUPPORTIVE OUTCOME MEASURES

The following supportive outcome measures will be evaluated:

a. Mean and individual subject changes in Degree of Pain VAS ratings across and between all study evaluation time points, within and between procedure groups
b. Mean and individual subject changes in each of the PRTEE, grip strength and TNFa levels measurements across and between all evaluation points, within and between procedure groups
c. Differences in satisfaction with Study Outcome Ratings between procedure groups at both evaluated time points, and any change between

SUPPORTIVE MEASURES STATISTICAL EVALUATION METHODS

a. Supportive measures that are continuous variables will be analyzed through parametric analysis using ANCOVA. A two-way significance level of 5% will be statistically significant.
b. Supportive measures that are categorical will be evaluated through linear regression analysis.
c. Satisfaction with Study Outcome Ratings: will be tabulated according to category and reported as percentages. Satisfaction levels will be correlated with subject individual study success and recorded changes in Lateral Epicondyle pain VAS ratings from baseline to endpoint evaluations.

STATISTICAL EVALUATION OF APPLICATION OF PAIN MANAGEMENT REGIMEN

The impact of pain management regimen use on the study outcome measure will be evaluated through application of the following analyses:

a. **Fisher's exact test** to compare the proportion of subjects requiring use of his or her individualized pain management regimen between the test and the control groups.
b. **Parametric ANCOVA model** analysis with the mean change from baseline to study endpoint in Lateral Epicondyle pain ratings on the VAS as the dependent variable, procedure group as the independent variable of interest and average dosage/frequency of use any component of the individualized pain management regimen. A two-tailed significance level of 5% will be considered to be statistically significant.
c. **T-test analysis** to compare the frequency of usage of the pain management regimen across study duration between treatment groups.

d. **Linear regression analysis** to evaluate the impact of frequency of usage of the pain management regimen across study duration on the primary outcome measure between procedure groups
e. **Log Rank statistics** to evaluate differences in the time to first use of the pain management regimen between test and placebo procedure groups

BLINDING EFFICACY EVALUATION
Statistical evaluation of blinding efficacy will be performed as follows:

(i) The percentage of subjects who correctly perceived their procedure group assignment and the percentage of subjects who did not correctly perceive their procedure group assignment will be calculated.
(ii) The percentage of times the administration investigators correctly perceived subjects' procedure group assignment and the percentage of times the assessment investigators did not correctly perceive subjects' procedure group assignment will be calculated.
(iii) The percentage of times the assessment investigators correctly perceived subjects' procedure group assignment and the percentage of times the assessment investigators did not correctly perceive subjects' procedure group assignment will be calculated.
(iv) The **Fischer's Exact categorical analysis technique** for comparison of proportion of successes (accurate procedure group assignment determination) and failures (inaccurate procedure group assignment determination) between subject groups will be performed for each of the subject, administration investigator and assessment investigator determinations.
    - Comparisons will be made to evaluate if the proportion of correctly guessed subject procedure group assignments is greater than the proportion of incorrectly guessed subject group assignments.
    - Comparison will be made for each of the groups of subjects, administration investigators and assessment investigators, within and between treatment groups.
    - In performing these evaluations, the numerical design and analysis of the blinding assessment will follow that outlined in Bang, et al. (Bang H, Ni L, Davis CE, Assessment of blinding in clinical trials. Control Clin Trials. 2004; 25:143-56)
(v) **Qualitative analysis confirmation:** Evaluation of the comments provided by the subject, administration investigators and assessment investigators in the rationale section to explain the guess at group alignment will be evaluated and interpreted as follows to either support or negate the numerical findings:
    - *Positive blinding efficacy* will be supported through qualitative assessment of comments provided to support perceived group assignment that pertain to the determination being made based on treatment efficacy or lack thereof; e.g.: 'I can move my head from side to side easily and without it hurting and I couldn't do that before, so I believe I got the real treatment' or 'I haven't noticed any change in my Lateral Epicondyle pain, so I believe I got the fake treatment.'
    - *Blinding will be determined to have failed* if comments provided to support perceived group assignment pertain to factors such as sensation/visual clues, such as 'I saw/didn't see a light go on', or other factors that pertain to blinding having been compromised such as 'I overheard the doctor saying I wasn't getting the real treatment.'

Sample stratification distribution plan

Sample Stratification

In order to account for the possibility that skin phototype could affect the absorption of the energy emitted from the study device, and to ensure that the study sample is representative of the range of skin phototypes in the intended U.S. clinical patient population, recruitment and enrollment of the final 50 study subjects will be further stratified by Fitzpatrick skin type, as determined according to race, according to the process of proportionate allocation using a sampling fraction in each of the strata that is proportional to that of the total sample population.

According to the United States Census Bureau (www.census.gov), the distribution of race throughout the United States population as of 2014 is as follows:

- White (not Hispanic/Latino): 62%
- Hispanic/Latino: 17%
- African American: 13%
- Asian: 5%
- Other (including Hawaiian/Pacific Islander, America Indian, Alaskan and 2+ races): 3%

Applying stratification according to the process of proportionate allocation using a sampling fraction in each of the strata that is proportional to that of the total sample population, the following formula is applied:

X = x1*X + x2*X + x3*X + x4*X + x5*X; where
• X = Total Sample Population = 50 subjects
• x1 = Subpopulation: White = 0.62; 0.62*50 = 31 subjects
• x2 = Subpopulation: Hispanic/Latino = 0.17; 0.17*50 = 8.5 subjects
• x3 = Subpopulation: African American = 0.13; 0.13*50 = 6.5 subjects
• x4 = Subpopulation: Asian = 0.05; 0.05*50 = 2.5 subjects
• x5 = Subpopulation: Other = 0.03; 0.03*50 = 1.5 subjects

Furthermore, in the following reference …
Sauer's Manual of Skin Disease; Brian J Hall, John C. Hall; 2012
Chapter 35: Skin Disease in Ethnic Skin; Cheryl M Burgess, MD & Beverly A. Johnson, MD
… Fitzpatrick Skin Type is associated with race, as follows:

• "White": (Not Hispanic/Latino): Fitzpatrick Skin Types I, II &III
• "Ethnic" (Hispanic/Latino; African American, Asian): Fitzpatrick Skin Types IV, V & VI

In consideration of the distribution of race in the U.S population as determined above, this results in the need to recruit:
Ø 31 subjects with Fitzpatrick Skin Type I, II or III
Ø 19 subjects with Fitzpatrick Skin Type IV, V or VI (17 Hispanic/Latino+13 African American+5 Asian+3 'Other')

For ease and uniformity of randomization, given that there will be three test sites, and two procedure administration groups the sampling plan is rounded to even numbers within individual groups, as follows:

	Test Site #1	
	Skin Type I, II & III	Skin Type IV, V & VI
Test Group	7	5
Placebo Group	8	4

	Test Site #2	
	Skin Type I, II & III	Skin Type IV, V & VI
Test Group	4	3
Placebo Group	4	3

	Test Site #3	
	Skin Type I, II & III	Skin Type IV, V & VI
Test Group	4	2
Placebo Group	4	2

While every effort will between made to recruit subjects evenly across the range of Fitzpatrick Skin Types within each of the two categories, it is anticipated that the majority of recruited Skin Types will fall within the range of II to V, inclusive, proportionate within the respective categories, as Fitzpatrick Skin Types I and VI and the least predominant Skin Types amongst the U.S. population.

Once a Fitzpatrick Skin Type category has been filled at a test site, no additional subjects will be enrolled in that category at that site.

FITZPATRICK SKIN TYPE CLASSIFICATION SCALE: The Fitzpatrick Skin Type Classification Scale is a numerical classification schema for human skin color developed in 1975 by Harvard Medical School dermatologist, Thomas Fitzpatrick, MD, PhD. The scale classifies a person's complexion and their tolerance of sunlight.

The Fitzpatrick Classification Scale classifies skin type from I through VI according to the applicable criteria contained in the chart below.

Skin Type	Skin Color	Characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel, or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark Brown; mid-eastern skin types	very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

POOLABILITY EVALUATION

The primary efficacy outcome is a binary variable, with success defined as a 30% or greater reduction in self-reported Degree of Pain rating on the 0-100 VAS from baseline to study endpoint evaluation. Poolability analysis for this primary binary outcome will be via the Breslow-Day test for homogeneity of odds ratios.

Furthermore, poolability analysis will also be conducted for the continuous outcome of mean change from baseline to study endpoint in self-reported Degree of Pain ratings on the 0-100 VAS through a treatment-by-subgroup interaction term applying a logistic regression model that also includes the main effect terms of all treatment groups.

SAFETY ANALYSES

Safety analyses will be based on all subjects who were randomized to the test or to the placebo procedure group. Safety will be assessed by evaluating and comparing frequency and incidence of observed and/or reported adverse events between test and placebo procedure groups. A chi-square test with a continuity correction will be performed to compare the percentage of subjects who had adverse events between test and placebo group subjects.

CASE REPORT FORMS

The case report forms that will be used to collect the data from each subject in this clinical study can be found in ***Appendix E***.

REFERENCES

[i] Boocock MG, Collier JM, McNair PJ, Simmonds M, Larmer PJ, Armstrong B. A framework for the classification and diagnosis of work-related upper extremity conditions: systematic review. Semin Arthritis Rheum. 2009;38:296-311.

[ii] Huisstede BM, Wijnhoven HA, Bierma-Zeinstra SM, Koes BW, Verhaar JA, Picavet S. Prevalence and characteristics of complaints of the arm, neck, and/or shoulder (CANS) in the open population. Clin J Pain 2008;24:253-9.

[iii]McDonald M, DiBonaventura Md, Ullman S. Musculoskeletal pain in the workforce: the effects of back, arthritis, and fibromyalgia pain on quality of life and work productivity. J Occup Environ Med 2011;53:765-70.

[iv] Spreeuwers D, de Boer AG, Verbeek JH, van Beurden MM, de Wilde NS, Braam I, et al. Work-related upper extremity disorders: one-year follow-up in an occupational diseases registry. Int Arch Occup Environ Health. 2011;84:789-96.

[v] Walker-Bone K, Palmer KT, Reading I, Coggon D, Cooper C. Prevalence and impact of musculoskeletal disorders of the upper limb in the general population. Arthritis Rheum. 2004;51:642-51.

[vi] Roquelaure Y, Ha C, Leclerc A, Touranchet A, Sauteron M, Melchior M, et al. Epidemiologic surveillance of upper-extremity musculoskeletal disorders in the working population. Arthritis Rheum. 2006;55:765-78.

[vii] Moon DK, Park YJ, Song SY, Kim MJ, Park JS, Nam DC, Kim DH, Na JB, Lee SI, Hwang SC, Park KS. Common Upper Extremity Disorders and Function Affect Upper Extremity-Related Quality of Life: A Community-Based Sample from Rural Areas. Yonsei Med J. 2018;59(5):669-676.

[viii] Moon DK, Park YJ, Song SY, Kim MJ, Park JS, Nam DC, Kim DH, Na JB, Lee SI, Hwang SC, Park KS. Common Upper Extremity Disorders and Function Affect Upper Extremity-Related Quality of Life: A Community-Based Sample from Rural Areas. Yonsei Med J. 2018;59(5):669-676.

[ix]Hoogvliet P, Randsdorp MS, Dingemanse R, Koes BW, Huisstede BM. Does ffectiveness of exercise therapy and mobilisation techniques off er guidance for the treatment of lateral and medial epicondylitis? A systematic review. Br J Sports Med. 2013;47(17):1112-19.

[x] Wilhelm A. Lateral epicondylitis review and current concepts. J Hand Surg Am. 2009;34:1358–9. author reply 1359–1360.

[xi] Fernández-Carnero J, Fernández-de-las-Peñas C, de la Llave-Rincón AI, Ge HY, Arendt-Nielsen L. Bilateral myofascial trigger points in the forearm muscles in patients with chronic unilateral lateral epicondylalgia: a blinded, controlled study. Clin J Pain. 2008;24(9):802-807.

[xii] Rayan F, Rao VS, Purushothamdas S, Mukundan C, Shafqat SO. Common extensor origin release in recalcitrant lateral epicondylitis-role justified? J Orthop Surg Res. 2010;5(31), 1–3.

[xiii] Inagaki K. Current concepts of elbow-joint disorders and their treatment. J Orthop Sci. 3013;18(1):1–7.

[xiv] Agir I, Caypınar B, Topkar OM, Karahan M. The effect of autologous platelet rich plasma in treatment lateral epicondylitis . Dicle Med J. 2011;38:40-3.

[xv] Pluim BM, Staal JB, Windler GE, Jayanthi N. Tennis injuries: occurrence, aetiology, and prevention. Br J Sports Med. 2006;40:415–23.

[xvi] Bisset L, Paungmali A, Vicenzino B, Beller E. A systematic review and meta-analysis of clinical trials on physical interventions for lateral epicondylalgia. Br. J Sports Med. 2005;39(7), 411–422.

[xvii] Cohen M, Motta Filho GDR. Lateral epicondylitis of the elbow. Rev Bras de Ortop. 2012;47(4):414–420.

[xviii]Kraushaar BS, Nirschl RP. Tendinosis of the elbow (tennis elbow). Clinical features and findings of histological, immunohistochemical, and electron microscopy studies. J Bone Joint Surg Am. 1999;81:259–78.

[xix] Clancy WG Jr. Tendon trauma and overuse injuries. In: Leadbetter WB, Buckwalter JA, Gordon SL, editors. Sports-Induced Inflammation: Clinical and Basic Science Concepts. Park Ridge (IL): American Academy of Orthopaedic Surgeons. 1990;609-18.

[xx] Cho YT, Hsu WY, Lin LF, Lin YN. Kinesio taping reduces elbow pain during resisted wrist extension in patients with chronic lateral epicondylitis: a randomized, double-blinded, cross-over study. BMC Musculoskeletal Disorders. 2018;19:193.

[xxi] Faro F, Wolf JM. Lateral epicondylitis: review and current concepts. J Hand Surg Am. 2007;32:1271–9.

[xxii] Buchbinder R, Green SE, Struijs P: Tennis elbow. BMJ Clin Evid. 2008;1117.

[xxiii] Almekinders LC, Temple JD: Etiology, diagnosis, and treatment of tendonitis: an analysis of the literature. Med Sci Sports Exerc. 1998;30:1183–90.

[xxiv] Bongers PM, Kremer AM, ter Laak J: Are psychosocial factors, risk factors for symptoms and signs of the shoulder, elbow, or hand/wrist?: A review of the epidemiological literature. Am J Ind Med. 2002;41:315–342.

[xxv] Osborne H. Stop injecting corticosteroid into patients with tennis elbow, they are much more likely to get better by themselves!. J Sci Med Sport. 2010;13(4):380–381.

[xxvi] Walz DM, Newman JS, Konin GP, Ross G. Epicondylitis: Pathogenesis, Imaging, and Treatment 1. Radiographics. 2010;30(1):167–184.

[xxvii] Shiri R, Viikari-Juntura E, Varonen H, HeliovaaraM (2006) Prevalence and determinants of lateral and medial epicondylitis: a population study. Am J Epidemiol. 2006;164(11):
1065–74.

[xxviii] Shiri R, Viikari-Juntura E. Lateral and medial epicondylitis: role of occupational factors. Best Pr Res Clin Rheumatol. 2011;25(1): 43–57.

[xxix] Pluim BM, Staal JB, Windler GE, Jayanthi N. Tennis injuries: occurrence, aetiology, and prevention. Br J Sports Med. 2006;40:415–23.

[xxx] Johnson GW, Cadwallader K, Scheffel SB, Epperly TD (2007) Treatment of lateral epicondylitis. Am Fam Physician. 2007;76(6):843–848.

[xxxi] Küçüksen S, Yilmaz H, Salli A, Ugurlu H. Muscle energy technique versus corticosteroid injection for management of chronic lateral epicondylitis: randomized controlled trial with 1-year follow-up. Arch Phys Med Rehabil. 2013;94(11):2068–74.

[xxxii] Smidt N, Lewis M, Van Der Windt DA, Hay EM, Bouter LM, Croft P. Lateral epicondylitis in general practice: course and prognostic indicators of outcome. J Rheumatol. 2006;33:2053– 9.

[xxxiii] Richer N, Marchand AA, Descarreaux M. Management of Chronic Lateral Epicondylitis With Manual Therapy and Local Cryostimulation: A Pilot Study. Journal of Chiropractic Medicine. 2017;16(4):279-288.

[xxxiv] Kwak SH, Lee SJ, Jeong HS, Do UM, Suh KT. Subtle elbow instability associated with lateral epicondylitis. BMC Musculoskeletal Disorders. 2018;19:136.

[xxxv] Richer N, Marchand AA, Descarreaux M. Management of Chronic Lateral Epicondylitis With Manual Therapy and Local Cryostimulation: A Pilot Study. Journal of Chiropractic Medicine. 2017;16(4):279-288.

[xxxvi] Waseem M, Nuhmani S, Ram CS, Sachin Y. Lateral epicondylitis: a review of the literature. J Back Musculoskelet Rehabil. 2012;25(2):131-142.
[xxxvii] Richer N, Marchand AA, Descarreaux M. Management of Chronic Lateral Epicondylitis With Manual Therapy and Local Cryostimulation: A Pilot Study. Journal of Chiropractic Medicine. 2017;16(4):279-288.
[xxxviii] Day JM, Bush H, Nitz AJ, et al.: Scapular muscle performance in individuals with lateral epicondylalgia. J Orthop Sports Phys Ther. 2015;45:414–424.
[xxxix] Taylor SA, Hannafin JA. Evaluation and management of elbow tendinopathy. Sports Health. 2012;4(5):384-393.
[xl] Rompe JD, Overend TJ, MacDermid JC. Validation of the patient-rated tennis elbow evaluation questionnaire. J Hand Ther. 2007;20(1):3-10.
[xli] Smidt N, Assendelft WJ, van der Windt DA, Hay EM, Buchbinder R, Bouter LM. Corticosteroid injections for lateral epicondylitis: a systematic review. Pain. 2002;96:23–40.
[xlii] Alizadehkhaiyat O, Fisher AC, Kemp GJ, Frostick SP. Pain, functional disability, and psychologic status in tennis elbow. Clin J Pain. 2007;23:482–9.
[xliii] Wilhelm A. Lateral epicondylitis review and current concepts. J Hand Surg Am. 2009;34:1358–9. author reply 1359–1360.
[xliv] Ahmad Z, Siddiqui N, Malik SS, Abdus-Samee M, Tytherleigh-Strong G, Rushton N. Lateral epicondylitis: a review of pathology and management. Bone Jt J. 2013; 95(9):1158–64.
[xlv] Chesterton LS, Mallen CD, Hay EM (2011) Management of tennis elbow. Dovepress J. 2011;(2):53–59.
[xlvi] Ben-Nafa W, and Munro W. The effect of corticosteroid versus platelet-rich plasma injection therapies for the management of lateral epicondylitis: A systematic review. SICOT-J. 2018;4:11.
[xlvii] Ciccotti MC, Schwartz MA, Ciccotti MG. Diagnosis and treatment of medial epicondylitis of the elbow. Clin Sports Med 2004;23:693-705.
[xlviii] Ciccotti MG, Ramani MN. Medial epicondylitis. Tech Hand Up Extrem Surg 2003;7:190-6.
[xlix] Nirav H. Amin; Neil S. Kumar; Mark S. Schickendantz. Medial Epicondylitis: Evaluation and Management Journal of the American Academy of Orthopaedic Surgeons. 2015;23(6):348–355.
[l] Gabel GT, Morrey BF. Medial epicondylitis. In: Morrey BF, Sanchez-Sotelo J, editors. The elbow and its disorders. Philadelphia: Saunders. 2008;638-44.
[li] Amrit V, Vinod BA, Glen Ross MD. An effective approach to diagnosis and surgical repair of refractory medial epicondylitis. J Shoulder Elbow Surg. 2015;24: 1172-77.
[lii] Nirav H. Amin; Neil S. Kumar; Mark S. Schickendantz. Medial Epicondylitis: Evaluation and Management Journal of the American Academy of Orthopaedic Surgeons. 2015;23(6):348–355.
[liii] Yen-Ting Cho, Wen-Yen Hsu, Li-Fong Lin, Yen-Nung Lin. Kinesio taping reduces elbow pain during resisted wrist extension in patients with chronic lateral epicondylitis: a randomized, double-blinded, cross-over study Cho et al. BMC Musculoskeletal Disorders. 2018;19:193.
[liv] Ciccotti MG, Charlton WPH. Epicondylitis in the athlete. Clin Sports Med 2001;20:77-93.
[lv] Ciccotti MG, Ramani MN. Medial epicondylitis. Tech Hand Up Extrem Surg 2003;7:190-6.
[lvi] Ollivierre CO, Nirschl RP, Pettrone FA. Resection and repair for medial tennis elbow a prospective analysis. Am J Sports Med 1995;23:214-21.
[lvii] Gabel GT, Morrey BF. Operative treatment of medial epicondylitis. Influence of concomitant ulnar neuropathy at the elbow. J Bone Joint Surg Am 1995;77:1065.
[lviii] Nirav H. Amin; Neil S. Kumar; Mark S. Schickendantz. Medial Epicondylitis: Evaluation and Management Journal of the American Academy of Orthopaedic Surgeons. 2015;23(6):348–355.
[lix] Nirav H. Amin; Neil S. Kumar; Mark S. Schickendantz. Medial Epicondylitis: Evaluation and Management Journal of the American Academy of Orthopaedic Surgeons. 2015;23(6):348–355.
[lx] Ciccotti MG, Charlton WPH. Epicondylitis in the athlete. Clin Sports Med 2001;20:77-93.
[lxi] Nirav H. Amin; Neil S. Kumar; Mark S. Schickendantz. Medial Epicondylitis: Evaluation and Management Journal of the American Academy of Orthopaedic Surgeons. 2015;23(6):348–355.
[lxii] Stahl S, Kaufman T. The efficacy of an injection of steroids for medial epicondylitis. A prospective study of sixty elbows. J Bone Joint Surg Am 1997;79:1648-52.
[lxiii] Amrit V, Vinod BA, Glen Ross MD. An effective approach to diagnosis and surgical repair of refractory medial epicondylitis. J Shoulder Elbow Surg. 2015;24: 1172-77.
[lxiv] Wilhelm A. Lateral epicondylitis review and current concepts. J Hand Surg Am. 2009;34:1358–9. author reply 1359–1360.
[lxv] Smidt N, Van Der Windt DA, Assendelft WJ, Devillé WL, Korthals-de Bos IB, Bouter LM. Corticosteroid injections, physiotherapy, or a wait-and-see policy for lateral epicondylitis: a randomised controlled trial. Lancet. 2002;359:657–62.
[lxvi] Smidt N, Assendelft WJ, Arola H, Malmivaara A, Greens S, Buchbinder R, van der Windt DA, Bouter LM. Effectiveness of physiotherapy for lateral epicondylitis: a systematic review. Ann Med. 2003;35:51–62.
[lxvii] Stahl S, Kaufman T. The efficacy of an injection of steroids for medial epicondylitis. A prospective study of sixty elbows. J Bone Joint Surg Am 1997;79:1648-52.
[lxviii] Roberts DB, Kruse RJ, Stoll SF. The effectiveness of therapeutic class IV (10 W) laser treatment for epicondylitis. Send to Lasers Surg Med. 2013;45(5):311-7.
[lxix] Bjordal JM, Lopes-Martins RA, Iversen VV. A randomised, placebo controlled trial of low level laser therapy for activated Achilles tendinitis with microdialysis measurement of peritendinous prostaglandin E2 concentrations. Br J Sports Med. 2006;40(1):76–80.
[lxx] Bastos JLN, Lizarelli RFZ, Parizotto NA. Comparative study of laser and LED Systems of Low Intensity Applied to Tendon Healing. Laser Phys. 2009; 19(9): 1925-931.
[lxxi] Casalechi HL, Nicolau RA, Casalechi VL, Silveira L Jr., Paula AMB, Pacheco MTT. The effects of low level light emitting diode on the repair process of Achilles tendon therapy in rats. Lasers Med. Sci. 2009;24:659-665.
[lxxii] Xavier M, David DR, de Souza RA, Arrieiro AN, Miranda H, Santana ET, Silva JA Jr., Salgado MA, Aimbire F, Albertini R. Anti-inflammatory effects of low-level light emitting diode therapy on Achilles tendinitis in rats. Lasers Surg Med. 2010;42(6):553-8.
[lxxiii] Xavier M, de Souza RA, Pires VA, Santos AP, Aimbire F, Silva JA Jr., Albertini R, Villaverde AB. Low-level light-emitting diode therapy increases mRNA expressions of IL-10 and type I and III collagens on Achilles tendinitis in rats. Lasers Med Sci. 2014;29:85-90.

[lxxiv] Grandinétti, VD, Miranda, EF, Johnson, DS, et al. The thermal impact of phototherapy with concurrent super-pulsed laser and red and infrared LEDs on human skin. Lasers Med Sci. 2015;30:1575-81.
[lxxv] Barrett DW, Gonzalez-Lima F. Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. Neuroscience. 2013;230:13–23.
[lxxvi] Karu TI, Pyatibrat LV, Kolyakov SF, Afanasyeva NI. Absorption measurements of a cell monolayer relevant to phototherapy: reduction of cytochrome c oxidase under near IR radiation. J Photochem Photobiol B Biol. 2005;81:98–106
[lxxvii] Huang, Y-Y, Chen, ACH, Carroll, JD, et al. Biphasic Dose Response in Low Level Light Theraphy. Dose Response. 2009;7:358-83.
[lxxviii] Tavares, MR, Mazzer N, Pastorello, M. Efeitos do laser terapêutico na cicatrização tendinosa: estudo experimental em ratos. Fisioterapia Barsil.2005;6(2):96-100.
[lxxix] Casalechi HL, Nicolau RA, Casalechi VL, Silveira L Jr., Paula AMB, Pacheco MTT. The effects of low level light emitting diode on the repair process of Achilles tendon therapy in rats. Lasers Med. Sci. 2009;24:659-665.
[lxxx] Marcos RL, Leal-Junior EC, Arnold G, Magnenet V, Rahouadj R, Wang X, Demeurie F, Magdalou J, de Carvalho MH, Lopes-Martins RA. Low-level laser therapy in collagenase-induced Achilles tendinitis in rats: analyses of biochemical and biomechanical aspects. J Orthop Res. 2012;30(12):1945–1951
[lxxxi] Cohen M, Motta Filho GDR. Lateral epicondylitis of the elbow. Rev Bras de Ortop. 2012;47(4):414–420.
[lxxxii] Albuquerque-Pontes GM, Leal-Junior EC, et al. Effect of different doses, wavelengths and application intervals of low-level laser therapy on cytochrome c-oxidase activity in intact skeletal muscle in rats. Lasers Med Sci June, 2014 Epub ahead of print]
[lxxxiii] Brondon P, Stadler I, Lanzafame RJ. Pulsing influences photoradiation outcomes in cell culture. Lasers Surg Med. 2009;41(3):222–226. [PubMed]
[lxxxiv] Joensen J, Ovsthus K, Reed RK, Hummelsund S, Iversen VV, Lopes-Martins RÁ, Bjordal JM.; Skin penetration time-profiles for continuous 810 nm and Superpulsed 904 nm lasers in a rat model.; Photomed Laser Surg. 2012 Dec;30(12):688-94. doi: 10.1089/pho.2012.3306. Epub 2012 Oct 1.
[lxxxv] Tata, D. B., & Waynant, R. W. (2011). Laser therapy: A review of its mechanism of action and potential medical applications. Laser & Photonics Reviews, 5(1), 1-12.
[lxxxvi] Vanin AA, Grandinetti VS, Johnson DS, Leal-Junior EC. Thermal impact of a photobiomodulation therapy (PBMT) portable device with combination of super-pulsed laser, red and infrared LEDs in human skin. [article in preparation]
[lxxxvii] dos Santos Grandinétti, V., Miranda, E. F., Johnson, D. S., de Paiva, P. R. V., Tomazoni, S. S., Vanin, A. A., ... & Leal-Junior, E. C. P. (2015). The thermal impact of phototherapy with concurrent super-pulsed lasers and red and infrared LEDs on human skin. Lasers in medical science, 1-7.
[lxxxviii] Sanders Jr, T. L., Maradit Kremers, H., Bryan, A. J., Ransom, J. E., Smith, J., & Morrey, B. F. (2015). The epidemiology and health care burden of tennis elbow: a population-based study. The American journal of sports medicine, 43(5), 1066-1071.
[lxxxix] Van Rijn RM, Huisstede BM, Koes BW, Burdorf A. Associations between work-related factors and specific disorders at the elbow: a systematic literature review. Rheumatology (Oxford). May 2009;48(5):528-36.
http://rheumatology.oxfordjournals.org/content/48/5/528.full.pdf (accessed 17 Nov 2010)
[xc] Baker CL, Plancher KD. Operative treatment of elbow injuries. New York: Springer, 2002.
[xci] Tuomo Pienimäki, M.D Ph.D et al. Associations Between Pain, Grip Strength, and Manual Tests in the Treatment Evaluation of Chronic Tennis Elbow . The clinical journal of pain 18: 164-170 2002. Level of Evidence: 3B.
[xcii] Fenwick, S. A., Hazleman, B. L., & Riley, G. P. (2002). The vasculature and its role in the damaged and healing tendon. Arthritis Research, *4*(4), 252–260.
[xciii] Whaley AL, Baker CL. Lateral epicondylitis. Clin Sports Med 2004; 23: 677– 691. Level of Evidence: 1C.
[xciv] Van Rijn RM, Huisstede BM, Koes BW, Burdorf A. Associations between work-related factors and specific disorders at the elbow: a systematic literature review. Rheumatology (Oxford). 2009;48(5):528-36.
[xcv] Wright JG. Evidence-based orthopaedics: the best answers to clinical questions. Philadelphia: Saunders Elsevier, 2008.
[xcvi] Brukner P. Brukner & Khan's clinical sports medicine. North Ryde: McGraw-Hill; 2012.
[xcvii] Validation of the Patient-rated Tennis Elbow Evaluation Questionnaire, Rompe, Jan D.Overend, Tom J.MacDermid, Joy C. et al., Journal of Hand Therapy, Volume 20, Issue 1, 3 - 11
[xcviii] Poltawski, L., & Watson, T. (2011). Measuring clinically important change with the Patient-rated Tennis Elbow Evaluation. Hand Therapy, 16(3), 52-57.
[xcix] Buhrmann C, Mobasheri A, Busch F, Aldinger C, Stahlmann R, Montaseri A, Shakibaei M. Curcumin modulates NF-{kappa} B-mediated inflammation in human tenocytes in vitro: role of the phosphatidylinositol 3-kinase-Akt pathway. J Biol Chem. 2011; 286:28556–66.
[c] Casalechi HL, Leal-Junior EC, Xavier M, Silva JA Jr, de Carvalho PT, Aimbire F, Albertini R. Low-level laser therapy in experimental model of collagenase-induced tendinitis in rats: effects in acute and chronic inflammatory phases. Lasers Med. Sci. 2013; 28(3):989-95.
[ci] John T, Lodka D, Kohl B, Ertel W, Jammrath J, Conrad C, Stoll C, Busch C, Schulze-Tanzil G. Effect of pro-inflammatory and immunoregulatory cytokines on human tenocytes. J Orthop Res. 2010; 28:1071–1077.
[cii] Hayer S, Redlich K, Korb A, Hermann S, Smolen J, Schett G. Tenosynovitis and osteoclast formation as the initial preclinical changes in a murine model of inflammatory arthritis. Arthritis Rheum. 2007; 56(1):79–88.
[ciii] Torres-Silva R, Lopes-Martins RA, Bjordal JM, Frigo L, Rahouadj R, Arnold G, Leal-Junior, EC, Magdalou J, Pallotta R, Marcos RL. The low level laser therapy (LLLT) operating in 660 nm reduce gene expression of inflammatory mediators in the experimental model of collagenase-induced rat tendinitis. Lasers Med Sci. 2015; 30(7):1985-90.
[civ] Hosaka Y, Kirisawa R, Ueda H, Yamaguchi M, Takehana K. Differences in tumor necrosis factor (TNF)alpha and TNF receptor-1-mediated intracellular signaling factors in normal, inflamed and scarformed horse tendons. J Vet Med Sci. 2005; 67(10):985–991.
[cv] Akesen B, Demirag B, Budak F. Evaluation of intra-articular collagenase, TIMP-1, and TNF-alpha levels before and after anterior cruciate ligament reconstruction. Acta Orthop Traumatol Turc. 2009; 43(3):214–218.
[cvi] Alves AC, Albertini R, dos Santos SA, Leal-Junior EC, Santana E, SerraAJ, Silva JAJr, de Carvalho PD. Effect of low-level laser therapy on metalloproteinase MMP-2 and MMP-9 production and percentage of collagen types I and III in a papain cartilage injury model. Lasers Med Sci. 2014; 29(3):911–919.