Document Date: August 29, 2014

Official Title: Safety and Preliminary Efficacy of Combination Photodynamic Therapy with 5-aminolevulinic Acid and Microcurrent Therapy for the Treatment of Acne Vulgaris

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Nova Southeastern University
Institutional Review Board for Research with Human Subjects (IRB)
New Protocol Submission

FUCC Review - JA 8-27-14

Received
AUG 29 2014
Institutional Review Board

Center Rep: Leonard A. Mazzi	To be completed by IRB Office
Date Sent to IRB:	Protocol Number:

Instructions: In order to comply with federal regulations and with the university's IRB guidelines, the Principal Investigator (PI) is required to complete all of the following items. After completing, submit this document and all consent forms and research instruments (questionnaires, interviews, etc.) to the appropriate IRB College/Center Representative. You can find your college/center representatives using the following link: http://www.nova.edu/irb/membership.html.

- If your study qualifies for center level exemption from further review, the Center Representative will exempt your study, provide you with a memo to that regard, and give you copies of the stamped, approved consent/assent form(s), if applicable. The Center Representative will log your study into the IRB database and forward a copy of the complete submission to the IRB office.
- If your study appears to qualify for expedited review, then once the Center Representative believes the submission is complete, the Center Representative will log your study into the IRB database and forward ONE complete submission packet to the IRB office for review.
- If full review is required, the Center Representative will log the study into the IRB database and will provide the PI with instructions for submitting 23 stapled or rubber banded copies (AND 1 unstapled original) of the submission and all supporting materials (research protocol, consent/assent forms, letters of authorization, etc.) to IRB. Please note: ONLY ONE copy of all research instruments (tests instruments, interview protocols, etc.) needs to be submitted. The completed package must be received by the IRB by the last business day of the month prior to the next scheduled IRB meeting. Because mail, including express delivery, takes at least a day to be delivered within the university, please make allowance for this in your planning. Incomplete submissions will delay review by the IRB. The IRB reserves the right to postpone review of protocols at convened meetings due to needed revisions.

Use a word processor to complete this form. You do not need to be concerned about where page breaks fall. You are to complete all **BLUE** sections. Be sure that all pages, including any appendices or attachments, except for consent/assent forms and advertisements, are numbered sequentially. For further information, refer to http://www.nova.edu/irb/manual/policies.html and http://www.nova.edu/irb/process.html

Do **not** approach subjects about being in the research study until you have received NSU IRB approval.

Form Version: December 2009

1. General Information

1.A. Research Project Title:

Safety and preliminary efficacy of combination photodynamic therapy with 5-aminolevulinic acid and microcurrent therapy for the treatment of acne vulgaris

1.B. Insert Principal Investigator's (PI) Last Name and Date of Submission in the footer.

1.C. Brief Overview (Max 250 Words):

Acne vulgaris is a multifactorial, highly prevalent dermatologic condition that results in visible lesions that can be quite disfiguring. Consequently, individuals with acne often suffer from a wide range of psychological manifestations. Although there is consensus that combination therapy is most effective in treating acne, researchers are constantly striving to develop new treatment. Microcurrent therapy (MCT) is a non-invasive modality that has successfully been used to promote wound healing and has been routinely used in aesthetics. Use of MCT alone or in combination with current successful treatment such as photodynamic therapy using 5-aminolevulinic acid (ALA-PDT), may hold promise for acne treatment. We

propose to conduct a small randomized control trial to determine the safety and preliminary efficacy of combination ALA-PDT and MCT for the treatment of acne. We will recruit up to 60 males and females and randomly assign them to one of 3 treatment arms: 1) ALA-PDT, 2) MCT, and combination therapy (ALA-PDT and MCT). We will assess physiological parameters (number of acne lesions, amount of sebum produced, degree of acne severity) and psychosocial factors (dermatologic quality of life, social anxiety, depressive symptomatology, self-esteem). Participants will complete a baseline assessment prior to initiating treatment and two follow-up assessments at 4 and 12 weeks post termination of treatment. We will conduct intermediary assessments at weeks 3 and 5 and 1 week post termination of the treatment. We will use measures of central tendency to describe the sample and repeated measures analysis of variance to compute the main and interaction effects.

1.D. Principal Investigator (PI) Information

Name	Sergey Arutyunyan	Medical Student	
Mailing Address (for Students)	9118 SW 20th Ct #A, Davie, FL 33324		
Interoffice Mail Code (for Faculty/Staff)		Student	X
Daytime Phone	772-485-5574	Faculty	
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NSU Email Address	sa1096@nova.edu	NSU Center/College/Dept	
Alternate Email Address	serjik2005@gmail.com	College of Osteopathic Medicine	
Degree/Academic Information	Research Fellow in the Doctor of Osteopathic Medicine Program	PI CITI Completion Date*	7/10/2014

Please briefly describe your applicable professional, educational, employment, professional licensure, and research experience. Do NOT attach your vitae.

Sergey Arutyunyan, MS, DO candidate (2017), completed his undergraduate education at Mendeleev University of Chemical Technology of Russia. After graduating from Mendeleev University with highest honors, he moved to the United States to pursue graduate education at Bowling Green State University (BGSU). While at BGSU he conducted research under the guidance of Dr. Douglas Neckers working on design and synthesis of multifunctional molecule for treatment of acne. As well, he served as a teaching assistant to Professor Emeritus Dr. Thomas Kinstle. He graduated BGSU with Masters of Science in 2005. Upon graduation he joined Torrey Pines Institute for Molecular Studies (TPIMS) as a Research Associate and was promoted to the position of Chemistry Lab Manager within his first year at TPIMS working under the direction of TPIMS founder Dr. Richard Houghten – pioneer of tea-bag technology for synthesis of peptides and small molecular compounds, and Director of Chemistry Dr. Adel Nefzi. While at TPIMS he managed research-oriented chemistry laboratory through product design and development of novel organic molecules as potential drug candidates, supervising team of 6 including 3 post-doctoral fellows As part of the interdisciplinary team, he was involved in the design and development of a novel molecule that directly induced tumor cell apoptosis and was subsequently licensed to San Diego based oncology research and development company Apoptos Inc. Student doctor Arutyunyan was among the few employees offered to relocate to Port St. Lucie, FL to help establish TPIMS east coast branch after the State of Florida awarded TPIMS with $90 million and built 100,000-sq.-ft facility in Port St. Lucie. At TPIMS he helped to establish a start-up company Smart Biomolecules Inc. that specializes in custom synthesis of chemical building blocks. Student doctor Arutyunyan co-authored 6 publications in scientific journals, including highly ranked American Chemical Society Journals. One of his publications titled "Solid-Phase Synthesis of

Aminothiazoles" was selected by experts in the field and reprinted by SYNFACTS – a source which highlights current innovative research in organic chemistry. Currently, he is a research fellow in the College of Osteopathic Medicine at Nova Southeastern University, under the mentorship of Dr. M Isabel Fernandez. Dr. Fernandez will be guiding him in the development of his research project.

1.E. Co-Investigators (Co-I) Information (including faculty advisers)

	Co-Investigator 1	Co-Investigator 2	Co-Investigator 3
Name	Maria Isabel Fernandez	Tracy Favreau	Michael A. Carranza
Mailing Address	2000 South Dixie Highway, Suite 108 Miami, FL 33133	3200 South University Drive, Ziff Clinic Davie, Florida 33328	9742 NW 7th Circle Apt 816 Plantation, FL 33324
Contact Phone Number	305-860-8710	954-262-4104	813-541-1176
Email Address	mariafer@nova.edu	tfavreau@nova.edu	mc2423@nova.edu
Degree/Academic Information:	Ph.D	D.O	M.S. D.O. Candidate (2017)
CITI Completion Date*	10/30/13		7/21/14

Please briefly describe applicable professional, educational, employment, professional licensure, and/or research experience for all co-investigators. Do NOT attach vitae.

Maria Isabel Fernández, Ph.D., Professor of Public Health and Preventive Medicine at the College of Osteopathic Medicine at Nova Southeastern University (NSU) and director of the Behavioral Health Promotion Program is an internationally known HIV researcher with a strong and diversified portfolio of research grants. A community psychologist by training, Dr. Fernández has worked in HIV for almost two decades; as a community-based provider, a scientist at CDC and NIH, and for the last 16 years, as a university-based researcher. Dr. Fernández has a strong track record of extramural research support and from diverse funding entities including the National Institute of Mental Health, the National Institute of Child Health and Human Development, the National Institutes on Drug Abuse, the National Institute of Nursing Research, the Centers for Disease Control and Prevention, and the Substance Abuse and Mental Health Services Administration. Her publication record is equally impressive. Her work has appeared in leading peer reviewed journals such as *American Journal of Public Health, AIDS and Behavior, Drug and Alcohol Dependence* and others. She is the Vice-Chair of the Executive Committee of National Institute of Child Health and Human Development's Adolescent Trials Network, and Co-Chair of its Behavioral Leadership Group. She chaired American Psychological Association's Committee on Psychology and AIDS and is a member of NIDA's National Hispanic Network on Drug Abuse. Prior to joining NSU's faculty, Dr. Fernández was Associate Professor of Epidemiology and Public Health at the University of Miami. She was a Health Scientist Administrator at the National Institute of Mental Health, Office on AIDS and served as the staff collaborator in the National Institute of Mental Health, Multi-Site HIV Prevention Trial supported in collaboration with National Institutes on Drug Abuse, National Institute of Child Health and Human Development, CDC, and HRSA. While at the CDC. she served as Project Officer for the national/regional minority HIV prevention grants program, and was the Latina spokesperson for the America Responds to AIDS campaign. She served as behavioral scientist in the office of the Deputy Director, HIV, National Center for Prevention Services, CDC, and was responsible for evaluating HIV counseling and testing, health education, and risk reduction programs.

Tracy Ann Favreau D.O., is an Assistant Professor of Dermatology and Chair of the Department of Dermatology at the College of Osteopathic Medicine at Nova Southeastern University. Dr. Favreau graduated from NSU COM c/o 2001 and went on completing family medicine and dermatology residencies. She is board certified in both family medicine and dermatology. Dr. Favreau also serves as Director of

Dermatology Residency program where she directs a team of 9 residents. Dr. Favreau and her team evaluate and treat all diseases and conditions of the skin, hair, and nails, including skin cancers, acne, chronic dermatitis, eczema, psoriasis and many others. In the past year, Dr. Favreau examined 1,787 patients on campus. Dr. Favreau is affiliated with Broward Health Medical Center. At the community clinics - the Specialty Care facility on Broward Boulevard in Fort Lauderdale and the Broward Health Medical Center outpatient clinic - Dr. Favreau treated almost 2,000 patients last year. Her work has appeared in leading peer reviewed journals such as Journal of Clinical and Aesthetic Dermatology, Journal of Drugs in Dermatology, and Journal of the American Academy of Dermatology. Dr. Favreau has presented her work at the various conferences and meetings as well as contributed her expert opinion on local media such as NBC Miami.

Michael A. Carranza, MS, DO candidate (2017), completed his undergraduate education in anthropology at The University of Florida in 2010. It is here that he was first exposed to clinical research in neurology and movement disorders. He served as a research volunteer with the McKnight Brain Institute, where he was responsible for managing a variety of data forms measuring visuospatial abilities in patients with Parkinson's disease, which were collected at the neurology and movement disorders clinic at UF. He was fascinated by the videos of essential tremor, Parkinson's disease, ataxia, and dystonia that were recorded at the UF clinic. After graduating from UF, Michael completed his Master's of Science in Medical Science degree with a concentration in Pharmacology at the University of South Florida College of Medicine. While at USF's Ataxia Research Center/Frances J. Zesiewicz Foundation and Center for Parkinson's Disease, Michael was involved with various stages of clinical research in movement disorders, from protocol development to neuropsychiatric assessment and manuscript writing. He has experience administering a variety of clinical scales and questionnaires for neurologic conditions. His research areas of interest in movement disorders are Parkinson's disease, essential tremor, ataxia, and progressive supranuclear palsy. During his time under the mentorship of Dr. Theresa Zesiewicz, Michael was able to successfully author and co-author several articles published in Movement Disorders and Tremor and Other Hyperkinetic Movements. Michael also authored a book entitled "Parkinson's disease: A Guide to Medical Treatment" along with several of his colleagues and Dr. Zesiewicz. Currently, he is a Research Fellow in the College of Osteopathic Medicine at Nova Southeastern University. Dr. Isa Fernandez will be his mentor throughout the fellowship year in all aspects of research design and methodology.

1.F. Research Assistant Information (if applicable)

	Research Assistant 1	Research Assistant 2	Research Assistant 3
Name			
Mailing Address			
Phone Number			
Email Address			
CITI Completion Date*			

*NOTE: CITI must have been completed within the last 3 years. If a member of the research team is affiliated with another institution, please include a copy of that individual's training certification.

1.G. Funding Information

Funding status	Unfunded	Funding Applied For	Funded
	X		

If you indicated "Funded" or "Funding Applied For," complete the following.

Source of Funding				
Project Title (if different from above)				
Principal Investigator (if different from above)				
Type of Application	Grant	Subcontract	Contract	Fellowship
Award Amount:				

1.H. Management of Conflict of Interest

Read the conflict of interest guidelines at http://www.nova.edu/ogc/forms/ogc9906.pdf

I certify that I, as PI, have read these guidelines, and have verified that my co-investigators and research assistants also have read these guidelines. PI Initials: SA

Do any investigators have a significant financial interest (as defined by NSU policy) in relation to this study? Yes: ☐ No: X

If yes, please describe the nature of the conflict of interest below

If you answered yes, please be sure to include the following statement, or a similar statement, within the description section of the consent forms: "The principal investigator and/or co-investigator(s) of this research study have a significant financial interest as it relates to this study." Continue, describing the conflict in the consent/assent documents.

1.I. Dates and Phases of Study

Proposed Start Date			
Shortly after IRB approval	X	Other (list date)	

Proposed Duration of Research (including analysis of the results)	
One year or less ☐	Other (describe, please note minimum annual continuing review required): 2 years

Is this a multi-part study? Yes: ☐ No: X

If "Yes," please note that procedures used in later phases may affect the review status of this study. Briefly describe the later stages.

1.J. Multiple Site Information

Will the study be conducted at an NSU location? Yes: X No: ☐

If "Yes," provide the location within NSU, e.g. department or clinic.

Clinical portion of the study will be conducted at NSU Ziff Clinic Division of Dermatology while data analysis and management will be conducted at the NSU COM Office of Behavioral Health Promotion program

Will the study be conducted at a non-NSU location?	Yes	No
		X

Will any of the activities be done online or via telephone (e.g., completion of surveys, delivery of instructional content)?	Yes	No
	X	

If "Yes", for the Internet based activities, will these be done via a secure site?
We are only using the telephone for describing the study and conducting a preliminary screen; not the internet.

	Yes	No
	X	

If "Yes," please complete the following for the non-NSU sites.
Include these sites on the consent form in the "site information" section.

	Site 1	Site 2	Site 3
Site Name			
Address			
Phone Number			

You will need documentation of permission to conduct the research at non-NSU sites. Attach the permission letter(s) or IRB approvals to this document.
*While all data entry/analysis will be conducted at NSU, data will be collected at venues such as conferences, meetings, coffee shops, beaches, cafeteria, and other places where medical students congregate.

1.K. Cooperative Research

Cooperative research projects are those that involve more than one institution or when an investigator is employed at or is an agent of an institution other than NSU, (For more information, see http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html). Each participating institution is responsible for safeguarding the rights and welfare of human subjects and for complying with all regulations.

Does this research involve cooperative research?	Yes	No
		X

Has this proposal been submitted or will the proposal be submitted to another Institutional Review Board (or authorizing individual, entity, or ethics review board) for review?	Yes	No
		X

If "Yes," please complete for each site. Please attach documentation of approval.
(Copy the section of the table and add if there are multiple sites.)

Name of Institution			
IRB/Administrative Decision (check applicable)			
Approved	Submitted (not yet approved)	Not yet submitted	NSU IRB approval required prior to submission
Date of Review	Contact Person		Level of Review (if IRB Reviewed)
	Phone Number		Exempt / Expedited / Full

2. Subject/Participant Information

2.A. Overview of Proposed Subjects/Participants

(complete all that apply and provide maximum number proposed within each category):

Subject Group	Fetus in Utero/ non-viable fetuses/ abortuses	Newborns or Infants	Children (aged 2-6)	Children (age 7-12)	Adolescents (aged 13-17)	Adults (18+)	Pregnant Women	Adults with Guardians
Mark X for each proposed subject type						X		
# of Proposed Subjects*						60		

Please briefly describe your potential subjects:

Participants will be males and females with mild to moderate facial acne (mild to moderate acne is operationally defined as being acne severity grade 2-4 on the Leeds grading system). To be eligible, participants must: 1) be ages 18 to 30; 2) have mild to moderate facial acne; 3) have skin type II-V as measured in the Fitzpatrick Scale; 4) be able to understand written and/or spoken English; and 5) be able to provide written informed consent.

*By proposed subjects, the IRB means subjects who will consent to be in the study and begin the study activities.

2.B. Subject Vulnerability

Do any subjects have limited decision-making autonomy, have communication problems that would limit ability to dissent to study procedures, belong to a group that is vulnerable to coercion, or belong to a group defined by regulation as requiring greater care?	Yes	No
		X

If you indicated "Yes", please mark with an X next to each applicable category in the column to the right and complete the remainder of this section

Prisoners	
Pregnant Women	
Cognitive impairment or emotional problems that potentially limit decision making	
Communication impairments that may preclude communicating a decision to discontinue participation or refuse participation	
Students of the investigator or investigator's department	
Employees of the investigator or investigator's department	
Children (minors)	
Terminally ill	

Other (specify):

If you indicated any of the above, please justify your rationale for including these subjects.

If you are using potentially vulnerable subjects as described above (infants, children, pregnant women/fetuses, terminally ill, decision-impaired, communication-impaired, students/employees, or prisoners), does the research create greater than minimal risk?	Yes	No

If your subjects have a vulnerability that arises from their being students in your class or department, you will be asked for more information in Section 3.G. If the subjects have one of the other vulnerabilities, please describe proposed safeguards to protect vulnerable subjects.

If not evident from the researcher qualification information in 1.D. or 1.E., please describe the researcher(s) qualifications for working with vulnerable subjects

2.C. Study Design and Methodology

Part 1 – Purpose

Please briefly describe the **purpose** of your study. Note: Examples of study purposes are "to determine if a new reading intervention program improves 4th graders' reading scores" or "to survey patients on their perception of physical therapy services".

The goal of this study is to conduct a small randomized control trial (RCT) to test the safety and preliminary efficacy of a novel combination therapy to treat acne vulgaris. We will also explore the effects of the treatments on psychosocial factors (Dermatology Life Quality Index (DLQI), social anxiety, depressive symptomatology, and self-esteem).

Part 2 – Goals and Justification

Briefly elaborate on the main **goals and justification** for the study. Summarize the background, rationale, nature, and significance of the proposed research. Include a brief overview of your prior research in the area, or literature that supports the need for this study. This section should be a brief overview, and typically is not more than a few paragraphs in length. You will be asked about procedures and instruments later in the submission.

Acne vulgaris is one of the most common problems in dermatology affecting almost 80% of adolescents and young adults 11–30 years of age. [1, 2] Acne is a multifactorial disease of the pilosebaceous unit, involving abnormalities in sebum production, follicular epithelial desquamation, bacterial proliferation, and inflammation. [4-6]. Acne results in physical symptoms such as scarring, soreness, itching, and pain, [7] but most importantly it manifests as comedones, papules, pustules and erythematous skin on highly visible areas of the body, including the face – a vital area of social display. Because of its physical manifestations, individuals with acne often suffer from a wide range of psychological manifestations such as depression, social anxiety, low self-esteem and reduced quality of life. [8-11] A variety of therapeutic options to treat acne are currently available. Traditional treatments of acne include retinoids and antibiotics. More recently, photodynamic therapy using aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) have become part of the treatment armamentarium. It is now widely accepted that combination therapy more effective than any single therapy alone. Researchers and clinicians are consistently seeking new and improved combination therapies for the treatment of acne. A promising modality that is yet to be explored in acne treatment is microcurrent therapy.

Microcurrent therapy is a non-invasive therapeutic modality that has successfully been used to promote wound healing among other applications Microcurrent therapy transmits gentle, electrical currents into the tissues, mimicking endogenous electric energy of the human body and stimulating body's natural healing mechanisms by improving blood flow and lymphatic drainage, stimulating ATP production [21], and promoting faster tissue repair and growth. [22, 23] It has been shown that microcurrent therapy

accelerates the natural anti-inflammatory "cascade" to significantly reduce edema and pain, while decreasing both recovery time and the use of pain medication and other pharmacologic agents. [28] Since acne patients experience inflammation, pain, edema, tissue damage and scarring, it is possible that microcurrent therapy may be a promising approach for the treatment of acne vulgaris.

Given the prevalence of acne and the deleterious impact it has on mental health and quality of life, coupled with the efficacy of existing combination treatment approaches, development of more effective and innovative treatment combination that may promote healing and reduce side effects, such as microcurrent therapy, are warranted.

The goal of this study is to conduct a small randomized control trial (RCT) to test the safety and preliminary efficacy of a novel combination therapy to treat acne vulgaris. We will also explore the effects of the treatments on psychosocial factors (Dermatology Life Quality Index (DLQI), social anxiety, depressive symptomatology, and self-esteem). The RCT will have 3 arms: 1) Standard treatment: photodynamic therapy with 5-aminolevulinic acid (ALA-PDT); 2) Microcurrent therapy (MCT); and 3) combination therapy (ALA-PDT + MCT). The main outcomes will be: 1) number of acne lesions; 2) amount of sebum produced, 3) degree of acne severity; and 4) improvement in dermatologic quality of life. The specific aims of the study are:

Aim 1: To examine the safety and preliminary efficacy of MCT for the treatment of acne vulgaris

Aim 2: To examine the safety and preliminary efficacy of combination therapy (ALA-PDT + MCT) for the treatment of acne vulgaris

Aim 3: To determine if combination therapy is a more effective treatment (fewer number of acne lesions, decreased amount of sebum produced, lesser degree of acne severity and greater improvement in dermatologic quality of life) for acne than either type of monotherapy.

Aim 4: To explore the effects of the three therapeutic modalities on psychosocial factors (social anxiety, depressive symptomatology, and self-esteem).

Part 3 – Steps in the Research Study

In the box below, please outline in detail the **steps in the research study** in order as they will occur after consent has been secured. If there are different requirements for different groups/types of subjects within the study, please separate out the steps per group. Indicate how long the subject spends completing the different steps/procedures. Be specific about the tests given and/or treatments used, when they will occur, and their frequency.

After obtaining informed consent, trained research staff will ask participants if they wish to participate in a lottery to win one of three $150 cash prizes and record their decision on the enrollment form. Next, we will randomly assign participants to one of the 3 treatment arms. Treatments will be administered by Dr. Favreau and the student investigators trained and supervised by Dr. Favreau. Each participant will be assigned a unique identification number, not tied to their name, that will be used to identify their data. Assessment will consist of both physiological and psychosocial parameters. The physiological parameters will be: 1) number of acne lesions; 2) amount of sebum produced; and 3) degree of acne severity. The psychosocial factors will be: 1) dermatologic quality of life; 2) social anxiety; 3) depressive symptomatology; and 4) self-esteem. Regardless of the treatment arm assigned, each participant will complete a baseline, 3 intermediary, and 2 follow-up assessments. All assessments will be done prior to receiving treatment.

Baseline and the 2 follow-up assessment will consist of: 1) counting number of acne lesions; 2) measuring the amount of sebum produced; 3) computing the degree of acne severity (take digital photographs of the affected areas of the face and compute the severity following procedures published by Hayashi et al, [2008]); 4) dermatologic quality of life; 5) social anxiety; 6) depressive symptomatology; and 7) self-esteem. Each of these assessments will take approximately 45 to 60 minutes to complete.

Intermediary assessments will be done at week 3, 5, 6 and will include: 1) number of acne lesions; 2) amount of sebum produced; and 4) dermatologic quality of life. Each of the intermediary assessments will take approximately 15 to 25 minutes to complete.

Specific steps in the research study are as follows:

1. Using block randomization procedures, we will randomize participants into the three conditions in blocks of 6 using a computerized randomization program. The data manager will prepare a set of sealed envelopes containing the condition assignment as determined by the randomization program and place the envelopes into a box in sequential order. Select the next-in-line pre-prepared envelope and inform participant of their treatment arm. Determine if participant has sufficient time to complete the initial study visit. If not schedule the initial study visit. If yes, then continue with step 2.
2. Conduct baseline assessment as described above.
3. Administer first treatment as per assigned arm. Within each arm, participants receive the same treatment.
   a) Arm1: Photodynamic therapy with 5-aminolevulinic acid (ALA-PDT). We will apply a formulation of ALA called Levulan® Kerastick to the affected areas of the participant's face. After 1 hour incubation, the affected areas will be exposed to a light source using photodynamic machine between 15 to 20 minutes. Each treatment will take approximately 90 minutes. Schedule an appointment for next treatment.
   b) Arm 2: Microcurrent therapy (MCT).We will place one electrode of the microcurrent machine in one of the regional areas of the lymph nodes or affected area (i.e. the forehead) and move the second electrode systematically from the affected area towards the stationary electrode. Once the entire affected area has been covered, the staff will move the first electrode to another regional area of the lymph nodes or affected area and the process will be repeated. This will continue until all of the affected areas have been treated. This will take approximately 45 minutes. Schedule an appointment for next treatment.
4. Arm 3: Combination therapy (ALA-PDT and MCT). Participants will receive 3 sessions of combined photodynamic therapy with aminolevulinic acid and microcurrent therapy and 2 sessions of microcurrent therapy alone. We will first administer MCT portion of combination treatment as described in 3a followed by ALA-PDT portion as described in 3b. Schedule an appointment for next treatment. Each of these combined sessions will last approximately 135 minutes and the microcurrent therapy will last approximately 45 minutes.
5. Administer the remaining treatments as determined by condition assignment

	Arm 1	Arm 2	Arm 3
Week 1	ALA-PDT	MCT	ALA-PDT+MCT
Week 2		MCT	MCT
Week 3	ALA-PDT	MCT	ALA-PDT+MCT
Week 4		MCT	MCT
Week 5	ALA-PDT	MCT	ALA-PDT+MCT

6. Conduct remaining assessments according to the following table using measures described above

	Arm 1	Arm 2	Arm 3
Week 1	Baseline	Baseline	Baseline
Week 2			
Week 3	Intermediary assessment	Intermediary assessment	Intermediary assessment
Week 4			
Week 5	Intermediary assessment	Intermediary assessment	Intermediary assessment
Week 6	Intermediary assessment	Intermediary assessment	Intermediary assessment
Week 9	Follow-up I	Follow-up I	Follow-up I
Week 12	Follow-up II	Follow-up II	Follow-up II

7. The lottery will be conducted when all the follow-up assessments have been completed.
8. A computer program will be used to generate the three winners of the lottery based on the individual identification number.
9. The winners of the lottery will be notified and asked to provide a mailing address where we can send the $150 money order.
10. We will clean and prepare the final data set and conduct the outcome analysis using SPSS.
11. We will prepare the manuscript and submit to a peer-review journal.

Part 4 – Sources of Data Information

Are you using questionnaires, tests, instruments, or forms?

Yes	No
X	

If "Yes", list them below and include a copy of each as appendices.

Data for this study will be derived from following:

- Sebumeter SM 815 will be used to estimate the amount of sebum produced
- Dermatology Life Quality Index (DLQI)
- Liebowitz Social Anxiety Scale
- Hospital Anxiety and Depression Scale (HADS)
- Rosenberg Self-Esteem Scale

Do you plan to use any data from records or archives?

Yes	No
	X

If "Yes", please describe (such as data originally created for non research purposes or data created as a result of a previous study).

Do you plan to use any de-identified data?

Yes	No
-	X

If "Yes", please describe the data and how it will be de-identified.

3. Additional Study Information

3.A. Clinical Testing

Food and Drug Administration

Investigational Drugs and Devices

	Yes	No
Does the study involve the use of an investigational drug?		X
If "Yes", has an Investigational New Drug application been submitted for the drug?		
Does the study involve the use of an investigational device?		X
If "Yes", has an Investigational Device Exemption (IDE) been, or will be, secured prior to the start of the study?		
Does the study use any device (either as a part of the experiment or to collect data) that has not received FDA approved for clinical/medical use or is being used in a manner not consistent with its cleared/marketing status?	X	

If "Yes", please describe the device and how its use differs from its approved status by the FDA.

ALA-PDT treatment is approved by U.S. FDA for actinic keratosis and it has been used off label for a wide range of dermatologic conditions including acne.

Clinical Procedures

	Yes	No
Does the study involve the use of any procedure that is not used in routine clinical practice? MCT has been widely used in wound healing and routinely used in aesthetics.		X

If "Yes", please list the procedures.

3.B. Sensitive Information

	Yes	No
Are you asking questions about sensitive issues, such as illegal activity, sexual history, or anything else that, if made public, could jeopardize a person's reputation, employability, safety, or quality of life?		X

If "Yes", please describe the information.

	Yes	No
Does the study involve the collection of data from voice, video, digital, or image recordings made for research purposes?	X	

If "Yes", please describe the procedures associated with these recordings.

We will take digital photographs of the affected areas of participant's face to determine acne severity and track changes over the course of treatment. Digital photographs will be taken 3 times over the period of 17 weeks, at baseline and at the 2 follow-up assessments. The photographs will be identified exclusively by study ID and will be kept in a password protected file in a secure NSU computer. We are seeking permission from participants to use their photographs in the manuscript or at scientific meetings as

routinely done in dermatological studies. We will explain that their participation in the study is not contingent upon their giving permission to use the photographs. All photographs, except those that were selected for use in the manuscript or scientific meetings, will be electronically deleted after three years.

3.C. Non-English Speaking Participants

Will the study involve non-English speaking participants? Yes [ ] No [X]

Will the study require translation of consent forms? Yes [ ] No [X]

If you answered "Yes," please specify the language(s) that the consent forms will be translated in to:

If you are including non-English speaking participants, when you complete section III.H., please discuss how you will ensure that the participants understand the study, including the use of a qualified translator to provide oral consent information.

3.D. Subject Compensation

Will your subjects receive any payments, incentives, or gifts? Yes [X] No [ ]

If "Yes," please indicate the types of compensation. Otherwise move on to section E.

Monetary Payment [X] | Gift [ ] | Extra credit (Students) or Workplace Incentive (Employees) [ ]

Other incentive [ ]

Please describe:

$150 check or money order to 3 participants determined by lottery.

Describe the payment(s)/gift(s)/incentive(s), and if it is a gift, estimate its monetary value. Indicate whether all participants are given the payment/gift/incentive, or if only some are eligible. (Note: the value of the payment/gift/incentive should not be so significant that it might compromise the subject's good judgment.)

Following completion of all study activities, participant will be entered into a lottery for a chance to win one of three awards to the amount of $150. Three participants will be randomly selected using a computer program. The winners of the lottery will receive $150 check to the address they provide when notified.

Describe when the subject will receive the payment/gift/incentive, and whether the amount differs depending upon whether different portions of the study are completed or is limited if the subject discontinues participation during the study.

The lottery will be conducted after all of the follow-up data has been collected. The winners of the lottery will be notified and asked to provide a mailing address where we can send the $150 money order.

3.E. Inclusion / Exclusion Criteria for Subjects

Describe the inclusion and exclusion criteria for the proposed subjects. Please list the criteria in bullet or outline format rather than narrative. If the study limits participation based on gender, age or race, please justify the exclusion criteria. (Subject protection and appropriate study design may require specific inclusion or exclusion criteria, but the IRB does not permit subject selection that is not equitable or prevents a subpopulation from benefiting from the scientific discoveries of the

3.G. Potential for Coercion in Subject Recruitment		
Are any of the subjects a student or advisee of the PI or a Co-I?	Yes	No X
Does the PI or a Co-I serve in any capacity (e.g., administrative, therapeutic) that might affect a subject's willingness to participate?	Yes X	No

If "Yes" to either of the above, then describe the relationship of the subjects and investigator.

Dr. Faxreau is the Chairperson of the Department of Dermatology and she directs the residency program and sees patients at the dermatology clinic.

If you answered yes, please read the NSU policy about use of students in research. http://www.nova.edu/irb/manual/forms/research_students_subjects.pdf

Are any of the subjects employees of, or report to, the PI or a Co-I?	Yes	No X
Are any of the subjects a patient of the PI or a Co-I? It is possible	Yes X	No
Are any of the subjects a patient within a PI or a Co-I's clinical practice? It is possible	Yes X	No
Are any of the subjects informed about the study by their doctor / clinician?	Yes X	No

If you answered "yes" to any of the questions in this section (3.G.), please describe how you will ensure that the subjects will feel free to decline participation without fear of reprisal. If the subjects are patients, how will you prevent "therapeutic misconception" (the mistaken belief that when a care provider provides information about a study, it means that the provider thinks that study participation will benefit the patient).

Physicians will be referring potential participants to the study, they will not be conducting the screening and enrollment. Our recruiters will be trained and will work diligently to ensure that the potential participant fully understands that participation is voluntary and their decision to participate or not to participate will not influence the care they receive at the clinic.

If you are providing any incentive to the student/employee subjects, discuss whether there is a mechanism for students / employees to receive the incentive by doing something other than participating in the research project (see http://www.nova.edu/irb/manual/forms/research_students_subjects.pdf).

3.H. Informed Consent

Part 1 – Consent Process

Another situation involving waiver or alteration of the requirement to obtain a signed consent form is when the research only entails conducting anonymous surveys that are not intrusive. If there is no way that the subjects' responses could be linked to them, then waiving the requirement for a signed consent form would minimize a risk to their confidentiality and privacy because the only record linking the subject and the research would be the consent form. If the principal risk would be potential harm resulting from a breach of confidentiality and the research presents no more than minimal risk to subjects and involves no procedures for which written consent is normally required outside of the research context, then the elements of informed consent are put into the survey itself. The person indicates his/her voluntary participation by completing the survey after being advised about the study and voluntary nature of his/her participation.

If you think this applies in your study, please describe your rationale.

There may be other cases where you would wish to ask for a waiver or alteration of informed consent or signed consent documentation.

If you are seeking a waiver or alteration, please describe your rationale.

Part 3 – Consent and Assent Document Information

Typically, you are asked to use the NSU format consent and assent forms. However, if this is cooperative research, or sponsored research that requires the use of a different template or model, you may use their format.

I will use NSU format consent/assent forms	X
I will be using another institution's format for consent/assent forms (NOTE: Please review the other institution's consent forms and the NSU requirements to be sure that all of the NSU requirements are present. You may also want to discuss the consent forms with your college/center representative)	
As noted above, I am requesting a waiver/alteration of consent and/or signed consent form requirements	

If you have different procedures for different groups of subjects, you will need a separate consent and/or assent form for each group. If the reading level of different groups of subjects differs, this may also require you to have different consent and/or assent forms (e.g. young children vs adolescents). If your subjects are children, you will also need parental consent.

What is the total number of consent/assent form types that you plan to use?

1

If using more than one consent form, create a list below that describes the different forms that you will be using (e.g. 1. Teacher consent form, 2. Parent consent form, 3. Assent form for children age 7-12, 4. Assent form for adolescents).

Include copies of the consent / assent forms. When you attach the consent forms, put them in this order. Please note that the IRB prefers that the consent document be written using the simplest

language possible, and strongly recommends the question and answer format (see Document Model #1 for Adult/General Consent Form [Readability Score: Grade 6]).

3.I. Protected Health Information Use

	Yes	No
Are you obtaining any data from the subject's medical record?		X
Are you asking the subject about his or her health information, and doing so in a clinic or entity that would normally be subject to HIPAA regulations on protected health information?	X	

If you answered "Yes" to either question, continue. Otherwise go on to section 3.J.

Please review the NSU HIPAA research policies available at (http://www.nova.edu/irb/manual/policies.html for more information.

Please note that effective 12/10/2009 the NSU IRB no longer reviews separate HIPAA authorizations for research. It is the principal investigator's responsibility to use the correct HIPAA authorization as outlined in the aforementioned policy. In instances where the HIPAA authorization must be a part of the informed consent form for research, the NSU IRB will review the compound consent.

Specify the exact data to be gathered (e.g., weight, blood pressure, IQ score, diagnosis, depression rating, number of treatments, etc.).

1) number of acne lesions; 2) amount of sebum produced; and 3) degree of acne severity.

Which procedure are you proposing to use? (Check)

I will obtain the subject's authorization to obtain the protected health information via the NSU Authorization for Use and Disclosure of Protected Health Information in Research (research activities will be occurring at an NSU clinic).	X
I will obtain the subject's authorization to obtain the protected health information via the authorization for use and disclosure of protected health information in research provided by the non-NSU covered entity.	
The protected health information data are a fully de-identified data set (data obtained without recording any patient information, with the data accessed by an employee of the institution).	
The data are part of a limited data set agreement as defined by the Office of Human Research Protections. (Attach a copy of the agreement.)	

If part of a limited data set agreement, what is the justification that confidentiality is protected?

I have a waiver provided by a duly constituted privacy board. (Attach a copy of the waiver.)

HIPAA Research Authorization

If the research is to be conducted at an NSU clinic, have you created a HIPAA authorization form as outlined in the HIPAA Research Policy No. 1 (http://www.nova.edu/irb/manual/policies.html) and in keeping with the Instructions for Preparing the Authorization For Use and Disclosure of Protected Health Information in Research Form and the model form provided (http://www.nova.edu/irb/manual/forms.html)?

Yes	No
X	

Please note, do NOT submit a copy of the HIPAA authorization form if you are following the model noted in the aforementioned policy.

If the research is to be conducted at a non-NSU covered entity, have you reviewed the HIPAA Research Policy No. 6: Guidance on Research at Outside Entities (http://www.nova.edu/irb/manual/policies.html)?

Yes	No

Researchers are advised to discuss the proposed research with the applicable HIPAA privacy officer at the non-NSU covered entity.

Does the researcher sponsor or cooperating agency require the incorporation of the HIPAA authorization within the consent document (Compound Consent)? N/A

Yes	No

If yes, please briefly indicate who requires that this be in the informed consent document.

Please note, consent forms that include the HIPAA authorization may need approval from the university Office of Corporate Compliance.

3.J. Student/Academic Information Use

Are you obtaining any data from the subject's academic records?

Yes	No
	X

If you answered "Yes", continue. Otherwise go on to section K.

Specify the exact data to be gathered (e.g., GPA, standardized test score, IQ score, medical/psychological information stored in academic files, attendance records, disciplinary records, etc.).

Specify how you will obtain the data.

Which procedure are you proposing to use? (Check all that apply)

I will obtain the subject's consent to obtain the academic information. ☐

The academic information will be a part of a fully de-identified data set (data obtained without recording any subject information, and provided to you in keeping with the institution's policies and the Federal Educational Rights and Privacy Act [FERPA]). ☐

3.K. Risks, Discomforts, & Inconveniences

In this section, discuss all potential risks (physical, economic/financial, legal, psychological, social, etc.), discomforts, or inconveniences to the subjects.

- All studies using identifiable subject information must address the issue of possible loss of subject confidentiality
- Some possible risks include physical, psychological or emotional harm, breach of confidentiality, and invasion of privacy.
- Discomfort includes anticipated risk for mild physical or emotional pain.

- Study inconveniences include loss of time or pay.

Each risk, discomfort and inconvenience should be addressed individually in the following format (use the tables provided and copy if the study presents more than 3).

- List each item individually
- Discuss likelihood: How likely is it that this risk/discomfort or inconvenience will occur? This is usually classified as minimal, moderate, or high.
- Discuss magnitude/duration: How dire is the risk/inconvenience/discomfort, and if it occurs, how long do you expect that the subject will be affected?
- Discuss risk minimization: Describe the procedures undertaken to minimize the risk that this specific risk/discomfort/inconvenience will occur.

Risk/Discomfort	Potential side effects associated with ALA-PDT include postinflammatory hyperpigmentation, pain and burning sensation. These side effects are typically associated with longer incubation periods of 3 hours or longer.
Likelihood	Minimal likelihood
Magnitude/Duration	Low magnitude/duration
Risk Minimization	To minimize this risk, we are proposing to use 1 hour incubation period, the shortest time possible to obtain the desired sensitization.

Risk/Discomfort	Another side effect of ALA-PDT treatment is short-term sensitivity to sunlight.
Likelihood	Moderate to high likelihood
Magnitude/Duration	Low magnitude/duration
Risk Minimization	This risk is minimized by the brief incubation period we selected and the careful instructions we will provide to participants regarding the need to protect themselves from exposure to sunlight.

Risk/Discomfort	Some participants may temporarily experience fatigue, nausea, sleepiness and flu-like symptoms 60 to 90 minutes after MCT, similar but slightly stronger than those that some people experience after a massage.
Likelihood	Minimal likelihood
Magnitude/Duration	Low magnitude/duration
Risk Minimization	To minimize this risk, we will strongly encourage participants to stay maximally hydrated to mitigate the possibility of this side-effect.

Risk/Discomfort	Some participants may experience psychological distress from responding to some of the questions in our assessment battery. They may be sensitive about reporting their feelings regarding how acne affects their daily activities and social interactions or how sad, anxious or depressed they feel as a result.
Likelihood	Minimal likelihood
Magnitude/Duration	Low magnitude/duration
Risk Minimization	To minimize this risk we will ensure that our research staff is well trained and prepared to identify distress in our participants. Our staff will remind participants that they have the option of refusing to continue with the treatment or not answer any question that makes them feel uncomfortable or anxious.

Risk/Discomfort	Potential for a breach of confidentiality from study materials being accessed by non-authorized individuals or staff inadvertently divulging confidential

	information.
Likelihood	Minimal likelihood
Magnitude/Duration	Low magnitude/duration
Risk Minimization	The risk is minimized by our extensive staff training regarding confidentiality protections and the strict procedures we have in-place for storing, de-identifying, and protecting all study materials. All study materials and data will be identified with a unique identification number not the participant's name and stored in password protected files and secure computers. File linking participants' IDs with their names will be stored in a separate password protected and secure computer.

One way in which confidentiality is partially protected is to destroy study documents containing identifiable information when they are no longer needed. The IRB requires that study materials be kept for a minimum of three years from the end of the study to permit study auditing; you may elect to keep them for a longer period of time and study sponsors may have their own data retention requirements. Please indicate when and how you plan to destroy data that contains identifiable subject information, such as consent forms, lists that link subject identity to data coding, or raw data containing subject names.

Any identifying information or documents will be shredded and/or electronically deleted after three years.

3.L. Benefits to Subjects

In this section, discuss all direct benefits of the study to participants. This does not include "helping research" or other generalities, nor does it include compensation for participation. Some examples of benefits include receiving free treatment, receiving a list of reputable local services, or obtaining tutoring. The value of any such benefits should be listed as well. If there are no direct benefits to the participants, this should be indicated.

Are there any direct benefits to the research participants?

There are no direct benefits to study participants [X]

This study provides benefit to, or is likely to benefit, the participants [ ]

List/describe each benefit

While participating in this study may not directly benefit all participants, it is likely that some participants will experience improvement in their acne.

3.M. Data Analysis Plan

Please describe preliminarily proposed data analysis procedures.

Data from the physiological and psychosocial assessments will be transferred into SPSS or other data analysis package for analysis. We will use means and other measures of central tendency to describe the characteristics of the sample and present count variables and safety information. If the assumptions of equal variance are met, we will use repeated measures analysis of variance to compute the main and interaction effects of our trial over time. If not, we will conduct the outcome analysis using parametric statistics.

3.N. Scientific Benefit

Briefly discuss how generalization of the information obtained from this study will be scientifically useful, or useful to your research site.

The study has the potential to generate new knowledge that may be used for the treatment of a debilitating, prevalent condition. It will provide valuable information about safety and preliminary efficacy of using MCT in treating acne as well as preliminary evidence on the use of a new combination therapy ALA-PDT with MCT. Additional knowledge to be gained from this study derives from the use of psychosocial measures. Not only are we documenting the physiologic outcomes of treatment, but we will also be able to describe patients' reactions and feelings prior to, during and post treatment. Furthermore, if the results of this trial are promising, we will have the necessary preliminary evidence to launch a large efficacy scale trial of a new therapeutic treatment for acne.

3.O. Risk/Benefit Ratio

To be approved, a study needs to have greater benefits than risks. Why do you believe this study has a positive benefits-to-risks ratio?

Based on the evaluation of the potential risks associated with this study, the steps we will take to minimize these risks, and the potential benefits to the individual and society, the risks seem reasonable in relation to the anticipated benefits stated above.

3.P. Safety Monitoring Plans

All researchers are required to report adverse events and unanticipated problems in keeping with the NSU IRB policy (http://www.nova.edu/irb/manual/forms/adverse_events.pdf).

Studies that entail significant risk to subjects, such as randomized controlled drug trials, may warrant safety monitoring by an outside safety board. Does your study utilize a Data Safety Monitoring plan?

Yes	No
	X

If "Yes," please describe the safety monitoring plans. Please specify if the study will be monitored by the investigators, sponsors (if applicable), or a Data Safety Monitoring Board (DSMB). Sponsored studies may reference an attached Investigator Brochure.

3.Q. Other Information

If there is other information about this study that is required in order for those reviewing the study to fully understand the study, its risks and benefits, please describe below.

3.R. Principal Investigator Assurance and Obligations

I certify that all information provided in this submission (including any supporting documents) is a complete and accurate description of the proposed study. I agree to the following:

This study will be conducted in the manner described in this submission and will not be implemented (including subject recruitment or consenting) until all applicable IRBs have granted permission to conduct the research. No changes to this study will be implemented until an amendment form has been submitted and approved by the IRB.

PI Initials SA

If the IRB approves this study via expedited or full procedure, I will submit for continuing review as stipulated in the approval letter. If the study or data analysis will exceed the approval period, I will submit a Submission Form for Continuing Review of IRB Approved Studies in a timely manner (well in advance of the renewal date). I understand that study activities may not continue past an approval period.

PI Initials SA

I will provide a copy of the signed consent form to the subject or patient, if applicable.

PI Initials SA

I will retain all signed informed consent documents and study-related records for a minimum of three (3) years (or longer as stipulated by funding agencies) from the date the study is concluded.

PI Initials SA

I will report in writing any serious adverse events to the IRB within 24 hours and all other adverse events and unanticipated problems within 5 working days.

PI Initials SA

I will provide participants with any significant new information obtained during the course of the study and submit reports of new information to the IRB as a Study Amendment.

PI Initials SA

If my study has been approved at the Expedited or Full Review levels, I will report to the IRB when this study has closed (no further data collection or analysis). This report will be provided no later than 30 days after the end of the study via the IRB Closing Report Form.

PI Initials SA

Principal Investigator's Signature: Sergey Arutyunyan Date: 8/26/14

3.S. Co-Investigator Assurance and Obligations (for Student PIs)

If this study is for the completion of a degree requirement, the thesis adviser or dissertation chair must sign the attestation below.

- All departmental approvals by the student's committee (if applicable) and chair or thesis adviser have been completed.
- I accept that the University and IRB consider the faculty advisor's responsibility to be equal to that of the student in regard to
  - The quality of the research design AND the accuracy of the protocol
  - The appropriateness of the recruitment methods, the design of the process for informing the subjects about the nature of the study, and the process of obtaining informed consent
  - The readability, accuracy, and format of the informed consent/assent document(s) and the explanation of all informed consent procedures.

My signature below attests that I have read this submission in its entirety and believe that it is accurate, complete, appropriate, and adheres to the principles of the Belmont report and that all departmental approvals by the student's committee have been completed.

Chair/Adviser's Signature: [signature] Date: 8-26-2014

NOVA SOUTHEASTERN UNIVERSITY

Consent Form for Participation in the Research Study Entitled "Safety and preliminary efficacy of combination photodynamic therapy with 5-aminolevulinic acid and microcurrent therapy for the treatment of acne vulgaris"

IRB protocol #:

Principal Investigator
Sergey Arutyunyan, M.S.
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Co-investigator
M. Isabel Fernandez, Ph.D.
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Co-investigator
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Co-investigator
Michael A. Carranza, M.S.
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Miami, FL 33133
(305) 860-8710
mc2423@nova.edu

For questions/concerns about your research rights, contact:
Human Research Oversight Board (Institutional Review Board or IRB)
Nova Southeastern University
(954) 262-5369/Toll Free: 866-499-0790
IRB@nsu.nova.edu

Nova Southeastern University
Division of Dermatology, General, Cosmetic Dermatology and Cutaneous Surgery
3200 South University Drive, Ziff Clinic
Davie, Florida 33328
(954) 262-4104
Nova Southeastern University
Behavioral Health Promotion Program
2000 South Dixie Highway, Suite 108
Miami, FL 33133
(305) 860-8710

What is the study about?
You are invited to participate in a research study involving facial acne. The goal of this study is to conduct an initial trial of a new combination therapy to treat acne and to examine if this new treatment is as effective as more traditional treatments.

Initials: _____ **Date:** _____

Why are you asking me?
We are inviting you to participate because you have mild to moderate facial acne and are 18 to 30 years of age. There will be up to 60 participants in this research study.

What will I be doing if I agree to be in the study?
You will receive one of 3 treatments conditions. If you are assigned to the first condition, you will receive 3 treatments with photodynamic therapy with aminolevulinic acid (Levulan). At each treatment, we will apply Levulan to the areas of your face affected by acne. We will ask you to wait up to 60 minutes -- this is the time needed for medication to become effective. After 60 minutes, the affected areas will be exposed to a light source using photodynamic machine. Each treatment will take approximately 90 minutes.

If you are assigned to the second condition, you will receive 5 sessions of microcurrent therapy. Microcurrent is a non-invasive therapy that sends electrical currents into the tissues, mimicking your body's electric energy. This therapy will be applied to your face and will be stimulating your body's natural healing mechanisms by improving blood, lymphatic drainage, etc. Similar therapy is widely used in spas and aesthetics. Each treatment will take approximately 45 minutes.

If you are assigned to the third condition, you will receive a combination of both of these treatments over five weeks. You will receive 3 sessions of combined photodynamic therapy with aminolevulinic acid and microcurrent therapy and 2 sessions of microcurrent therapy alone. Each of these combined sessions will last approximately 135 minutes and the microcurrent therapy will last approximately 45 minutes. Chance will determine which treatment option you receive.

At 6 points in time during the course of 17 weeks, you will complete a computer-assisted self-interview. Three of these interviews will be longer and the other 3 are much shorter. In these interviews, you will report how much your acne problem has affected your life, how much has your acne affected your activities and self-esteem, and how anxious you feel in social situations. In addition, staff will count the number of acne lesions and measure the amount of sebum present. As part of the longer interviews, we will take digital pictures of your face so we can determine the severity of your acne. It will take approximately 45 minutes to complete the longer activities and approximately 15 to complete the shorter activities.

Is there any audio or video recording?
This research project will include digital photographs of the affected areas of the face that will be used to determine the severity of your acne. Digital photographs will be taken 3 times over the period of 17 weeks. These digital photographs will be available to be reviewed by the researchers and the IRB. The digital photographs will be kept securely in a password protected file in an NSU password protected computer. Photographs are identified with a unique number not your real name. The digital photographs will be kept for 36 months and destroyed after that time by deleting the file unless you have given us permission to include them in the publication or presentation of the study findings. Because your digital pictures will be potentially identifiable by anyone who sees them, your confidentiality cannot be guaranteed although the researcher will try to limit access to the digital photographs as described in this paragraph.

Why might we want to use your photographs?
Dermatological studies typically include before and after pictures of the affected areas when the study results are published or presented at scientific meetings. When photographs are published, necessary steps are taken to protect the participant's privacy. Eyes and unaffected areas are blocked with black boxes to ensure that participant's identity remains unknown. Any facial features such as birthmarks, tattoos, etc. that might reveal your identity are also blocked with black boxes. Photographs will not be linked to your real name.

What are the dangers to me?
Risks to you are associated with the side effects that may result from the treatments. You may experience mild pain, burning sensation, darkening of the skin and short-term sensitivity to sun light. We will provide instructions on how to protect your skin after the treatment to avoid sensitivity to sun light. You may also experience fatigue, nausea, sleepiness and flu-like symptoms 60 to 90 minutes after the treatment. We will council you to stay hydrated to avoid onset of these symptoms. You may feel upset/anxious when answering questions regarding how acne affects your daily activities and social interactions. If this happens, staff will try to help you. If you need further help, we will suggest someone you can see but you will have to pay for it yourself. Taking digital photographs of parts of your face may compromise your confidentiality. If you have questions about the research, your research rights, or if you experience an injury because of the research please contact Mr. Arutyunyan or Dr. Fernandez at (305) 860-8710. You may also contact the IRB at the numbers indicated above with questions about your research rights.

Are there any benefits for taking part in this research study?
There are no direct benefits to you for participating in this study. Some participants may benefit from the acne treatments being tested in the study.

Will I get paid for being in the study? Will it cost me anything?
There are no costs to you for participating in this study. You do not need health insurance to participate in this study. If you agree to participate in this study, you will be offered the opportunity to be entered into a lottery for a chance to win one of three awards to the amount of $150. After all of the study data have been collected, three winners will be randomly selected using a computer program and a check will be mailed to the address they provide when notified.

How will you keep my information private?
We will assign a unique number to you. We will not put any identifying information in the study materials. All study materials and data will be stored in password protected files and secure computers. Printed materials will be kept in a locked cabinet. Digital photographs will be identified exclusively by study ID and not your name. They will be kept in a password protected file in a secure NSU server for 36 months. At this point, they will be destroyed. Only research staff will have a password to the files and a key to the cabinet. All information collected in this study is strictly confidential to the extent allowed by law. If you reveal information that you may harm yourself, we are required by law to notify the authorities. The IRB, regulatory agencies, or the study investigators may review research records.

What if I do not want to participate or I want to leave the study?
You have the right to leave this study at any time or refuse to participate. If you do decide to leave or you decide not to participate, you will not experience any penalty or loss of services you have a right to receive. If you choose to withdraw, any information collected about you before the date you leave the study will be kept in the research records for 36 months from the conclusion of the study and may be used as part of the research.

Other Considerations:
If significant new information relating to the study becomes available, which may relate to your willingness to continue to participate, this information will be provided to you by the investigators. If the results of this trial show promise, we may conduct a study to assess the longer term effects of this treatment. If we do this, we may re-contact you to invite you to participate in the follow-up study.

Voluntary Consent by Participant:
By signing below, you indicate that

- this study has been explained to you
- you have read this document or it has been read to you
- your questions about this research study have been answered
- you have been told that you may ask the researchers any study related questions in the future or contact them in the event of a research-related injury
- you have been told that you may ask Institutional Review Board (IRB) personnel questions about your study rights
- you are entitled to a copy of this form after you have read and signed it
- you voluntarily agree to participate in the study entitled "Safety and preliminary efficacy of combination photodynamic therapy with 5-aminolevulinic acid and microcurrent therapy for the treatment of acne vulgaris"

Participant's Signature: _____ Date: _____

Participant's Name: _____ Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

By checking the box, you give us permission to use your photographs in scientific publications or presentations? ☐ Yes

INSTITUTIONAL REVIEW BOARD FOR RESEARCH WITH HUMAN SUBJECTS
Outline of Research Protocol

DESCRIPTION OF THE STUDY

A. Protocol Title.

Safety and preliminary efficacy of combination photodynamic therapy with 5-aminolevulinic acid and microcurrent therapy for the treatment of acne vulgaris.

B. Principal Investigator and Co-Investigators

Principal Investigator
Sergey Arutyunyan, M.S.
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Co-Investigator(s):
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C. Funding/Sponsor of the Study

Nova Southeastern University College of Osteopathic Medicine Research Fellowship Program.

D. Purpose and Potential Benefits

The goal of this study is to conduct a small randomized control trial (RCT) to test the safety and preliminary efficacy of a novel combination therapy to treat acne vulgaris. We will also explore the effects of the treatments on psychosocial factors (Dermatology Life Quality Index (DLQI), social anxiety, depressive symptomatology, and self-esteem). The RCT will have 3 arms: 1) Standard treatment: photodynamic therapy with 5-aminolevulinic acid (ALA-PDT); 2) Microcurrent therapy (MCT); and 3) combination therapy (ALA-PDT + MCT). The main outcomes will be: 1) number of acne lesions; 2) amount of sebum produced, 3) degree of acne severity; and 4) improvement in dermatologic quality of life. The specific aims of the study are:

Aim 1: To examine the safety and preliminary efficacy of MCT for the treatment of acne vulgaris

Ho1: MCT will be as safe and effective as ALA-PDT in the treatment of acne vulgaris.

Aim 2: To examine the safety and preliminary efficacy of combination therapy (ALA-PDT + MCT) for the treatment of acne vulgaris

Ho2: Combination therapy (ALA-PDT + MCT) will be as safe and effective as ALA-PDT in the treatment of acne vulgaris.

Aim 3: To determine if combination therapy is a more effective treatment (fewer number of acne lesions, decreased amount of sebum produced, lesser degree of acne severity and greater improvement in dermatologic quality of life) for acne than either type of monotherapy.

Ho3a: Combination therapy (ALA-PDT + MCT) will be more effective than standard therapy in the treatment of acne vulgaris.

Ho3b: Combination therapy (ALA-PDT + MCT) will be more effective than MCT in the treatment of acne vulgaris.

Ho3c: Participants in the combination therapy arm will exhibit less side-effects than those in the standard treatment arm.

Aim 4: To explore the effects of the three therapeutic modalities on psychosocial factors (social anxiety, depressive symptomatology, and self-esteem).

Ho4: Participants in the combination therapy arm will report greater improvement in psychosocial factors than those in either monotherapy arm.

The benefits: Acne is debilitating disease that impacts life of an individual in physical, emotional, and psychosocial way. This study will provide data regarding the safety and preliminary efficacy of an innovative approach for acne treatment and will add to the existing literature on acne treatments. If the results of this study show promise, we will have the necessary data to support launching a larger, fully powered clinical trial to test the efficacy of this new treatment modality for acne vulgaris.

E. Justification for the Study

Acne vulgaris is one of the most common problems in dermatology affecting almost 80% of adolescents and young adults 11–30 years of age. [1, 2] It is estimated that acne affects 45 million people in the United States. [3] Acne is a multifactorial disease of the pilosebaceous unit, involving abnormalities in sebum production, follicular epithelial desquamation, bacterial proliferation, and inflammation. [4-6]. Acne results in physical symptoms such as scarring, soreness, itching, and pain, [7] but most importantly it manifests as comedones, papules, pustules and erythematous skin on highly visible areas of the body, including the face – a vital area of social display.

Because of its physical manifestations, individuals with acne often suffer from a wide range of psychological manifestations such as depression, social anxiety, low self-esteem and reduced quality of life. [8-11] "There is no single disease which causes more psychic trauma and more maladjustment between parents and children, more general insecurity and feelings of inferiority and greater sums of psychic assessment than does acne vulgaris" [12]. Retrospective examination of the association between acne and depression showed that depression was two to three times more prevalent in acne patients than in the general population, with a reported 8.8% of acne patients having clinical depression. The majority of acne patients suffering from depression and/or utilizing antidepressants were 18 years of age or older. [1]

In a study of dermatological patients with conditions associated with cosmetic disfigurement, 5.6% of patients with acne reported having had acute suicidal ideations, the highest among all participants. [13] Not only do acne patients have the highest prevalence of acute suicidal ideation among all dermatological patients, but also their prevalence is higher than the 3.3%, 2.6%, and 2.4% reported in 3 studies focused on medical patients. [14-16] Individuals with acne have, on average, worse academic functioning and higher unemployment rates compared to those without acne. [17] It is estimated that consumers spend $100 million per year in over-the-counter remedies. Coupled with loss of productivity and unemployment, the direct cost of acne may exceed $1 billion per year in the United States. [3]

A variety of therapeutic options to treat acne are currently available. Traditional treatments of acne include retinoids and antibiotics administered either topically or systemically. Although effective, these treatments are not without side-effects. For instance, retinoids often produce dryness, erythema, exfoliation, teratogenicity and depressed mood while antibiotics are associated with gastrointestinal irritation and bacterial resistance. Furthermore, widespread use of antibiotic therapy has resulted in increased bacterial resistance to antibiotics especially in *P. acne,* the major bacteria associated with acne vulgaris, leading clinicians to utilize various combinations of retinoids, benzoyl peroxide and antibiotics. It is now widely accepted that combination therapy is more effective than any single therapy alone.

More recently, photodynamic therapy using aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) have become part of the treatment armamentarium. Photodynamic therapy (PDT) is based upon the interaction of a photosensitizer, a light source and oxygen. [18] The photosensitizer is applied topically and is activated upon its exposure to visible light. As the photosensitizer absorbs energy of light, it becomes activated from a "ground state" to an "excited state". [19] As it returns to the ground state, energy is transferred to oxygen to form singlet oxygen ($^1O_2$), a subset of reactive oxygen species, which then oxidizes various substrates and thus mediates selective cell killing. [19, 20] There are currently only two photosensitizers approved by the US FDA for dermatologic indications: 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL). Both ALA and MAL act as prodrugs and are metabolic precursors of protoporphyrin IX (PpIX) – an active photosensitizer. Once applied to the skin, ALA and MAL are preferentially taken up by the pilosebaceous unit and augment the response to light therapy. [19] Although traditional pharmacological

therapy (i.e. antibiotics, retinoids, etc.) remains the gold standard for treatment of acne, use of ALA-PDT to treat acne and other dermatological conditions has increased significantly due to its tremendous success.

Figure 1. Mechanism of Photodynamic Therapy*

*Clinical, Cosmetic and Investigational Dermatology 2014:7 145–163

Microcurrent therapy is a non-invasive therapeutic modality that has successfully been used to promote wound healing among other applications. Microcurrent therapy transmits gentle, electrical currents into the tissues, mimicking endogenous electric energy of the human body and stimulating body's natural healing mechanisms by improving blood flow and lymphatic drainage, stimulating ATP production [21], and promoting faster tissue repair and growth. [22, 23] It has been successfully used to enhance soft tissue healing and to treat fracture nonunion [24-26]. Study by Whitcomb demonstrated a 45.4% faster, and more robust healing of wounds with the use of the MCT, when compared to standard of care in a rehabilitation center environment. [27] It has been shown that microcurrent therapy accelerates the natural anti-inflammatory "cascade" to significantly reduce edema and pain, while decreasing both recovery time and the use of pain medication and other pharmacologic agents. [28] In addition, it has been shown that MCT stimulates dermal fibroblasts and U937 cells to secrete transforming growth factor-β1, a major regulator of cell-mediated inflammation and tissue regeneration. [29] Since acne patients experience inflammation, pain, edema, tissue damage and scarring, it is possible that microcurrent therapy may be a promising approach for the treatment of acne vulgaris. However, we found no evidence in the published literature reporting the use of microcurrent therapy to treat acne vulgaris.

Given the prevalence of acne and the deleterious impact it has on mental health and quality of life, coupled with the efficacy of existing combination treatment approaches, development of more effective and innovative treatment combination that may promote healing and reduce side effects, such as microcurrent therapy, are warranted. The proposed study is designed to assess the safety and preliminary efficacy of combination photodynamic therapy with aminolevulinic acid and microcurrent therapy for the treatment of acne vulgaris.

F. Location of Study

The majority of the study activities will be conducted in the Division of Dermatology, General, Cosmetic Dermatology and Cutaneous Surgery. The research directors will be Dr. M. Isabel Fernandez and Dr. Tracy Favreau, located at 3200 South University Drive, Fort Lauderdale, Florida 33328. Data

entry, analysis and associated activities may be conducted at offices of the Behavioral Health Promotion Program located at 2000 South Dixie Highway, Suite 108, Miami, FL 33133.

G. Dates of Study

We plan to initiate the study as soon as we obtain approval from the IRB. We anticipate completing all study activities by March 2016.

H. Subjects/Participants

H1. Sample Size, Composition and Eligibility Requirements

We are planning to recruit up to 60 males and females with mild to moderate facial acne to participate in this study. (Mild to moderate acne is operationally defined as being acne severity grade 2-4 on the Leeds grading system) To be eligible, participants must: 1) be ages 18 to 30; 2) have mild to moderate facial acne; 3) have skin type II-V as measured in the Fitzpatrick Scale; 4) be able to understand written and/or spoken English; and 5) be able to provide written informed consent.

Individuals who: 1) have been treated with oral retinoids in the past 6 months; and/or 2) have been treated with oral antibiotic within the last 30 days; and/or 3) have received topical acne treatment (i.e. retinoids, antibiotics and anti-inflammatory agents or chemical peeling) within the last 30 days; 4) are pregnant or lactating; 5) have history of photo-sensitive dermatitis; 6) are taking oral contraceptive pills (OCP); and 7) have pacemaker will not be eligible to participate.

H2. Subject Selection and Recruitment.

We will use both active and passive recruitment approaches. Active recruitment will primarily consist of direct referrals from physicians at NSU Ziff Clinic Division of Dermatology, General, Cosmetic Dermatology and Cutaneous Surgery or other dermatology providers in South Florida. To complement our active recruitment strategies we will also engage in passive recruitment which will include: 1) e-mail announcements distributed via list-serves; and 2) distributing and/or posting project flyers at bulletin boards, community organizations etc.

H2.1 Active recruitment approaches

NSU Physician Referral. We will provide study related recruitment materials to NSU affiliated physicians and ask them to refer potential participants to research staff. We anticipate that the primary source of patient referral will come from Ziff Clinic Division of Dermatology. All new patients presenting with acne will be informed about the study. Interested individuals will be referred to research staff for screening and enrollment. Information about the study will be distributed to existing patients with acne through a variety of sources including but not limited to e-mail, telephone, or face-to-face at their regularly scheduled clinic appointments.

Other Referral. We will contact practicing dermatologists within Broward, and Miami-Dade counties and provide information about the study. We will ask if they would be willing to refer participants to our study and/or display our IRB approved recruitment materials in their offices. Recruitment materials will be attractive, include a brief description of the study and how to contact research staff. We will also accept self-referrals. We will also ask participants to encourage other individuals with acne vulgaris who might be interested in participating to contact our research staff.

H2.2 Passive recruitment approaches

We will distribute recruitment materials via e-mail list-serves to the NSU students inviting them to contact research staff for additional study information and procedures for screening and enrollment.

We will post recruitment materials throughout NSU campus as well as in different venues throughout the community.

H2.3 Procedures for Screening and Enrollment

Research staff will briefly describe the study and requirements for participation. Interested individuals will be invited to complete the eligibility screener. If permission is granted, staff will administer the eligibility screen and invite all eligible individuals to enroll in the study. We will obtain written informed consent from all eligible individuals wishing to participate in the study. After obtaining informed consent, we will complete the locator/enrollment form, select the randomization envelope (See section *I*), and inform participants of their condition assignment. Research staff will ascertain whether the participant has sufficient time available at the current visit to complete the baseline assessment and receive the initial treatment. This is important because the time required to complete the treatment varies by condition (See Table 1). Participant who have sufficient time will complete the baseline assessment and will be given first treatment immediately following the informed consent process. Those who do not, will be scheduled to complete these activities at a subsequent visit. Individuals who do not wish to proceed through any point described above and those who screen not eligible, will be thanked for their interest and encouraged to seek treatment at the Ziff Clinic or any other dermatology provider.

Although we anticipate that the majority of screeners will be completed face-to-face, it is possible that some individuals may contact research staff via telephone. In this case, staff will describe the study and obtain permission to conduct a preliminary eligibility screen over the telephone using the above referenced procedures. If the potential participant is eligible, we will make an in-person appointment where we will confirm eligibility by re-administering the screening questionnaire, obtain informed consent, complete locator/enrollment form, assign to treatment conditions, and administer the baseline assessment along with the first treatment. As part of the scheduling process, we will explain that the duration of the study visit will be contingent upon their condition assignment and the maximum time that may be required for the initial visit will be approximately 4 hours. Consequently, we will schedule their initial appointments at a time during which they have 4 hours available for the visit.

H3. Informed Consent Procedures.

Written informed consent will be obtained in person at NSU Ziff Clinic or at a safe and private space. Trained research staff, all of whom have completed CITI Course for the Protection of Human Subjects, will obtain informed consent. The informed consent process will begin with a thorough explanation of the study and its procedures. Great attention will be placed on ensuring that the potential participant understands any and all potential risks and benefits associated with participation. We will describe the lottery system we will use as an incentive for their time and participation and obtain their permission to be entered into the lottery. Ample time will be provided to insure that all questions and/or concerns are addressed and have been fully understood by the participant prior to enrollment and completion of the study. All interested individuals will be informed that participation is strictly voluntary, that he/she may withdraw from the study at any time for any reason and that he/she will be eligible to participate in a lottery as compensation for his/her time and effort. Interested individuals who wish to participate will be asked to sign and date the consent form. Research staff will witness and, as proof, will sign and date the consent form. A copy of the consent form will be given to the participant.

I. Methods and Procedures

I1. Overview

We propose to conduct a small randomized control trial to determine the safety and preliminary

efficacy of combination photodynamic therapy with 5-aminolevulinic acid and microcurrent therapy for the treatment of acne vulgaris. We will recruit up to 60 males and females and randomly assign them to one of 3 treatment arms (*photodynamic therapy with 5-aminolevulinic acid (ALA-PDT); microcurrent therapy (MCT); and combination therapy (ALA-PDT and MCT*). (See Table 1.) All participants will complete a baseline assessment prior to initiating treatment and two follow-up assessments at 4 weeks and 12 weeks post termination of treatment. During the treatment phase, we will conduct intermediary assessments to help us track the progression of the treatment over time at weeks 3 and 5 as well as 1 week post the termination of the treatment (week 6). We will conduct both physiological and psychosocial assessments; the content of the intermediary assessment will be much less than the other 3 assessments to reduce participant data. The most comprehensive assessments will be conducted at baseline and the 2 follow-up points and will consist of all of the physiological and psychosocial factors as well as demographic factors that will be collected exclusively at the baseline assessment. At the intermediary assessments we will collect the number of acne lesions, amount of sebum produced and dermatologic quality of life. Psychosocial data will be collected via computer-assisted self-interviews (CASI). Physiological data will be entered into the computer program by research staff.

Table 1. Frequency and duration of study visits (assessment(s) and treatment(s))

	ALA-PDT	MCT	ALA-PDT+MCT
Week 1	√	√	√+√
Week 2		√	√
Week 3	√	√	√+√
Week 4		√	√
Week 5	√	√	√+√

I2. Description of the ALA-PDT treatment arm

In this arm participants will receive 3 ALA-PDT treatments at 2 week intervals. The duration of each treatment will be approximately 2 hours. At each treatment, we will apply a formulation of ALA called Levulan® Kerastick (manufactured by Dusa Pharmaceuticals, MA, USA) to the affected areas of the participant's face (See Figure 2). After 1 hour incubation, the affected areas will be exposed to a light source using photodynamic machine between 15 to 20 minutes. (See Figure 2). Each treatment will take approximately 90 minutes. At the completion of each treatment session, participants will be counseled to follow the photo-protection measures.

Figure 2. Levulan® Kerastick and Photodynamic Therapy Machine*

*http://www.dermacaremedical.com/acne-treatment.php

I3. Description of the MCT treatment arm

In this arm participants will receive 5 MCT treatments at 1 week intervals using MCT machine (See Figure 3). The duration of each treatment will be approximately 45 minutes. Trained staff will place one electrode in one of the regional areas of the lymph nodes or affected area (i.e. the forehead) and move the second electrode systematically from the affected area towards the stationary electrode. Once the entire affected area has been covered, the staff will move the first electrode to another regional area of the lymph nodes or affected area and the process will be repeated. This will continue until all of the affected areas have been treated.

Figure 3. Microcurrent Therapy Machine* and Application in a Cosmetic Procedure**

*http://www.laserbodyandskincare.com/product.php?productid=17517
**http://labellelula.com/microcurrent-therapy

I4. Description of the combination (ALA-PDT + MCT) treatment arm

In this arm participants will receive 3 ALA-PDT treatments at 2 weeks intervals and 5 MCT treatments at 1 week intervals. At week 1, 3 and 5 participants will receive MCT treatment as described in *I3* followed by ALA-PDT treatment as described in *I2*. These visits will last approximately 135 minutes. In weeks 2 and 4, participants will only receive MCT treatment as described in *I3*.

I5. Assignment to Treatment Conditions

Using block randomization procedures, we will randomize participants into the three conditions in blocks of 6 using a computerized randomization program. The data manager will prepare a set of sealed envelopes containing the condition assignment as determined by the randomization program and place the envelopes into a box in sequential order. The box will be stored in a secure place accessible only to the research staff enrolling participants. After obtaining informed consent and completing the enrollment procedures, staff will remove the first envelop from the box to ascertain the condition assignment of the newly enrolled participant. We have used these procedures successfully in a number of previous studies. We will monitor the randomization procedures and adjust if necessary to ensure equivalence in the number of participants assigned to each condition.

I6. Assessment Procedures

We will assess both physiological parameters and psychosocial factors. The physiological parameters will be: 1) number of acne lesions; 2) amount of sebum produced; and 3) degree of acne severity. The psychosocial factors will be: 1) dermatologic quality of life; 2) social anxiety; 3) depressive symptomatology; and 4) self-esteem. For our main outcome variables, we selected a combination of all of the physiological and 1 psychosocial factor (dermatologic quality of life).

Assessment of the main outcome variables and psychosocial factors will be conducted at baseline, at 4 weeks and 12 weeks after completing the treatment. We will conduct intermediary assessments consisting of the number of acne lesions, amount of sebum produced and dermatologic quality of life on week 3 and week 5 prior to administering the scheduled treatment and at 1 week post the termination of treatment. Our assessment schedule is summarized in Table 2.

Table 2. Schedule of assessments

	ALA-PDT	MCT	ALA-PDT+MCT
Week 1	Baseline	Baseline	Baseline
Week 2			
Week 3	Intermediary assessment	Intermediary assessment	Intermediary assessment
Week 4			
Week 5	Intermediary assessment	Intermediary assessment	Intermediary assessment
Week 6	Intermediary assessment	Intermediary assessment	Intermediary assessment
Week 9	Follow-up I	Follow-up I	Follow-up I
Week 17	Follow-up II	Follow-up II	Follow-up II

I6.1 Procedures for collecting psychosocial data:

All assessments will be conducted using computer-assisted self-interviews (CASI). Participants will be assigned a unique study identification number (ID) that will be used to track data. Computer-assisted self-interviews are more effective than other tools for measuring sensitive and socially stigmatized behaviors. This mode of data collection eliminates interviewer bias, standardizes questionnaire administration, and reduces skip pattern errors. Using CASI, the participant responds to the questions using the computer keyboard or mouse. Selection of CASI for data collection decreases costs and error of entry, cleaning data, and publication lag, as well as enhances interviewer efficiency. Our team has extensive experience in programming and using CASI in community-based and clinic-based studies, transferring, and managing the data. Our data manager has used NOVA Research Company's Questionnaire Development System (QDS) to program the instruments, collect and manage the data for 6 protocol approved by the NSU IRB. Our research associates have participated in bench-testing and piloting of CASI. She has also developed quality assurance and tracking protocols with multiple feedback loops that flag potential errors rapidly and efficiently (e.g., missing or skipped ID number).

The laptop computers we use for data collection have been set up with two different log-in screens, one for participants and one for an administrator. The screen used by participants only contains the icon to access the CASI system. No other files appear or are available on this screen. Research staff access the CASI for participants by clicking the icon and filling in the assigned participant ID number (not participant name) completing all set up procedures. The staff member then provides a brief training on using the laptop and completing the CASI. As part of this training, the participant will complete a brief set of practice questions illustrative of the type of questions and the responses contained in the assessment. The staff member remains with the participant during the practice session to answer questions or to provide additional instructions. Participants will be encouraged to seek assistance, if needed, as they complete the interview. At this point, the interview starts and the participant completes the interview on their own. Once the participant completes the interview, he/she comes upon a screen instructing him/her to contact staff so that the file may be saved correctly.

I6.2 Procedures for collecting physiological data:

Research staff will conduct visual inspection of the affected areas and systematically count the number of acne lesions present on the face. At baseline and the two follow-up assessments we will also take high quality digital photographs of the affected areas that will be used to compute the degree of acne severity following the procedures developed by Hayashi et al, (2008). The photographs will be identified exclusively by study ID and will be kept in a password protected file in a secure NSU computer. The Sebumeter® SM 815 sebum meter will be used to estimate the amount of sebum produced. Staff will bring the mat tape of the meter in contact with the affected areas. This instrument uses a non-invasive probe placed on the affected area and the instrument then calculates the amount of sebum produced.

I7. Lottery Procedures

The lottery will be conducted when all the data have been collected. Participant IDs will be entered into an excel spreadsheet. A computer program will be used to generate the three winners of the lottery based on the row number on the excel spreadsheet. Each winner will receive a check for $150. The winners of the lottery will be notified and a check sent to the address they provide when notified.

I8. Data Management, Analysis and Quality Assurance Procedure

We employ strict data management and quality assurance procedures. Data from the physiological and psychosocial assessments will be transferred into SPSS or other data analysis package for analysis. Database management, writing, graphics preparation, and statistical analyses are completed on a secure computer. Data cleaning through consistency, logic, and outlier checks will be conducted throughout the data-gathering period, so that analyses can proceed quickly. We will use means and other measures of central tendency to describe the characteristics of the sample and present count variables and safety information. If the assumptions of equal variance are met, we will use repeated measures analysis of variance to compute the main and interaction effects of our trial over time. If not. we will conduct the outcome analysis using parametric statistics.

J. Measure

J1. Physiologic assessments

Acne Lesions. We will conduct a systematic count of acne lesions (papules and pustules) present in all of the affected areas of the face.

Amount of Sebum Produced. We will use the Sebumeter® SM 815 manufactured by CK Electronic to estimate the amount of sebum. The measurement is based on grease spot photometry. The mat tape of the Sebumeter® SM 815 is brought into contact with facial skin. It becomes transparent in relation to the sebum on the surface of the measurement area. Then the tape is inserted into the aperture of the device and the transparency is measured by a photocell. The light transmission represents the sebum content. http://www.courage-khazaka.de/index.php/en/products/scientific/129-sebumeter

Acne Severity. We will use the acne counts and the digital photographs of the affected areas to compute the acne severity level following the procedures established by Hayashi et al. (2008). We will not print the digital photographs. Trained research staff will visually inspect the digital photographs and assign a preliminary severity score to each half of the face using the following classification guide: 0–5 papules and/pustules for mild acne; 6–20 for moderate acne, 21–50 for severe acne; and more than 50 for very severe. Staff will examine each half of the face separately. The most severe classification obtained for either side of the face will be the assigned severity score.

J2. Psychosocial assessment

Demographic Variables. Participants will report their age, gender, race/ethnicity, education, employment, income, and zip code.

Dermatologic Quality of Life. We will use the Dermatology Life Quality Index (DLQI) developed by A. Y. Finlay and G. K. Khan (1992), one of the most widely used, dermatologic specific quality of life measures in the published literature to assess quality of life. The DLQI consists of 10 Likert type items; 9 of these items have 4 response categories scored from 0 to 3 with "very much" being "3" to "not at all" being "0". Item 7 *"Over the last week, has your skin prevented you from working or studying"* uses dichotomous responses; where "yes" is scored as a "3" and a "no" requires answering an additional sub-question, *"Over the past week how much has your skin been a problem at work or studying"*. Responses for this sub-question range from "a lot" coded a "2", to "not at all" coded a "0." The DLQI is calculated by summing the response to each question; the maximum score is "30" and the minimum score is "0". The higher the score, the lower the dermatologic quality of life. Guidelines for interpreting the index are that the dermatologic condition has: 0-1 = no effect at all on patient's life; 2-5 = small effect on patient's life; 6-10 = moderate effect on patient's life; 11-20 = very large effect on patient's life; 21-30 = extremely large effect on patient's life.

Social Anxiety. Symptoms of social anxiety will be assessed using the Liebowitz Social Anxiety Scale (Liebowitz, 1987), one of the most widely used scales to measure social anxiety. It consists of 24 items designed to assess fear and avoidance in different situations that are likely to produce social anxiety such as going to a party or speaking in public. For each situation, participants are first asked to state how fearful or anxious they feel in that situation using a Likert scale that ranges from "none" (0) to "severe" (3). Then they are asked to state how often they avoid that same situation using a Likert scale that ranges from "never" (0) to "usually" (3). Responses are summed to create an overall anxiety score. The scale is highly reliable ($\alpha > .70$) and has discriminant and convergent validity when administered by a clinician or through participant self-report (Cox, Ross, Swinson, & Direnfeld, 1998).

Depressive Symptomatology. We will assess depressive symptomatology using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983), one of the most widely used screening tools to identify symptoms of depression, anxiety and emotional distress amongst patients being treated for a variety of clinical problems. It consists of 14 items, 7 of which assess generalized symptoms of anxiety and the remaining 7 assess depressive symptomatology. Although the specific wording of the item responses vary in accordance to the item, all responses are coded using a Likert format ranging from "0" to "3" where the most positive response is coded a "0" and the most negative response a "3". The maximum score for each subscale is 21; higher scores are reflective of more symptoms of anxiety or depression. HAD has good psychometric properties. It is internally consistent and has good reliability, convergence and discriminant validity (Herrmann 1997; Beck et al., 1997; Herrero et al., 2003; Whelan-Goodinson et al., 2009; www.abiebr.com/node/410 downloaded 8/15/2014).

Self-esteem will be assessed using the Rosenberg Self-Esteem Scale (Rosenberg, 1965), one of the most widely-used self-esteem measures in social science research. It consists of ten items designed to assess respondent's self-satisfaction, self-respect and other general feelings about himself/herself. The response format is a four point Likert scale ranging from "strongly agree" to "strongly disagree". For items 1, 2, 4, 6, 7: Strongly Agree=3, Agree=2, Disagree=1, and Strongly Disagree=0. For items 3, 5, 8, 9, 10: Strongly Agree=0, Agree=1, Disagree=2, and Strongly Disagree=3. The scale ranges from 0-30, higher scores indicating higher self-esteem. The scale has been used extensively and across a number of different populations and it can be used as a unidimensional or a multi-dimensional scale with two factor-structures, self-confidence and self-deprecation. It has high test-retest reliability with estimates

ranging between .82 and .88 and Chronbach's apha ranging between .77 and .88 (see Blascovich and Tomaka, 1993 and Rosenberg, 1986 for further detail).

K. Potential Risks to Participants

Some participants may experience postinflammatory hyperpigmentation, pain and burning sensation as a result of being treated with ALA-PDT, but these side-effects occur rarely and when they do they are typically associated with longer incubation periods of 3 hours or longer. To minimize this risk, we are proposing to use 1 hour incubation period, the shortest time possible to obtain the desired sensitization. Consequently, we consider the risk level for this concern is of low magnitude and duration. Individuals treated with ALA-PTA will experience short-term sensitivity to sunlight. This risk is minimized by the brief incubation period we selected and the careful instructions we will provide to participants regarding the need to protect themselves from exposure to sunlight. Thus, the risk is of low magnitude and duration.

Some participants may temporarily experience fatigue, nausea, sleepiness and flu-like symptoms 60 to 90 minutes after MCT, similar but slightly stronger than those that some people experience after a massage. Although these side-effects rarely occur, they are the by-product of the lymphatic system flushing toxins from the body and they resolve within 24 hours. To minimize this risk, we will strongly encourage participants to stay maximally hydrated to mitigate this side-effect. Thus, the risk is of low magnitude and duration.

Some participants may experience psychological distress from responding to some of the questions in our assessment battery. They may be sensitive about reporting their feelings regarding how acne affects their daily activities and social interactions or how sad, anxious or depressed they feel as a result. We have taken steps to minimize this risk by ensuring that our research staff is well trained and prepared to identify distress in our participants. Our staff will remind participants that they have the option of refusing to continue with the treatment or not answer any question that makes them feel uncomfortable or anxious. The risk level for this concern is of low magnitude and duration.

Another risk is the potential for a breach of confidentiality from study materials being accessed by non-authorized individuals or staff inadvertently divulging confidential information. The risk is minimized by our extensive staff training regarding confidentiality protections and the strict procedures we have in place to storing, de-identifying, and protecting all study materials. All study materials and data will be identified with a unique identification number not the participant's name and stored in password protected files and secure computers. Thus, this concern is of low magnitude and duration.

L. Potential Benefit of the Research to Participant and Others

While participating in this study may not directly benefit all participants, it is likely that some participants will experience improvement in their acne. The study has the potential to generate new knowledge that may be used for the treatment of a debilitating, prevalent condition. It will provide valuable information about safety and efficacy of using MCT in treating acne as well as preliminary evidence on the use of a new combination therapy ALA-PDT with MCT. Additional knowledge to be gained from this study derives from the use of psychosocial measures. Not only are we documenting the physiologic outcomes of treatment, but we will also be able to describe patients' reactions and feelings prior to, during and post treatment. Furthermore, if the results of this trial are promising, we will have the necessary preliminary evidence to launch a large efficacy scale trial of a new therapeutic treatment for acne.

M. Risk/Benefit Ratio

Based on the evaluation of the potential risks associated with this study, the steps we will take to minimize these risks, and the potential benefits to the individual and society, the risks seem reasonable in relation to the anticipated benefits stated above.

N. Consent Forms

Consent form is attached.

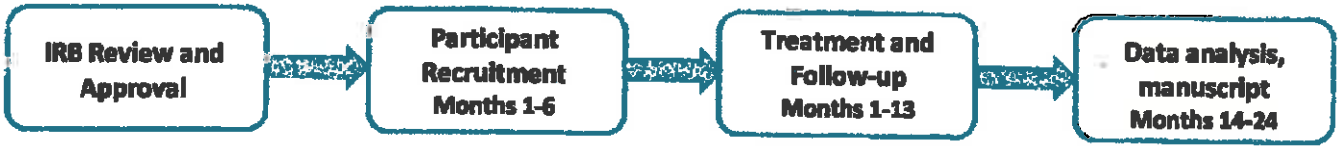
O. PHI

Because this study is being conducted in a clinical setting, it has PHI.

P. Qualification of Investigators

The CVs of Investigators are attached to this protocol.

Q. Timeline



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Data Collection Forms and Measures

LOCATOR INFORMATION FORM

1. Name _____
   First Middle Last

2. What would you prefer to be called _____

3. Address _____ _____
   Street Apt. #

   _____ _____ _____
   City State Zip Code

4. Email _____

5. Home Telephone Number _____ Can we leave a message ☐ Yes ☐ No

6. Cell Telephone Number _____ Can we leave a message ☐ Yes ☐ No

7. What is the best time to contact you? _____

DEMOGRAPHICS SECTION

What is your date of birth? mm/dd/yyyy

How old are you?

18 - 30 = Years old
98 = Refuse to Answer

What is you gender?

1=Male
2=Female

What is your race/ethnicity?

1= White, Caucasian, European not Hispanic
2 = Hispanic or Latino
3 = Black or African American
4 = Asian or Oriental
5 = Native American
6 = Other _____
98= Refuse to Answer

What is your highest level of formal education?

1 = Less than high school
2 = Some high school
3 = High School Diploma/GED
4 = Some college or vocational school
5 = Vocational Degree
6 = College degree
7 = Some graduate work
8 = Master's degree
9 = Doctoral degree
10 = Other _____
98 = Refuse to Answer

What best describes your current employment status?

1 = Working full-time
2 = Working part-time
3 = Working equivalent of full-time job through part-time jobs
4 = Unemployed and looking for work
5 = Unemployed and not looking for work
6 = School full-time
7 = School part-time
8 = Both work and school
9 = Other _____
98 = Refuse to Answer

Thinking about the last 12 months, on average, after taxes, how much was your total net (take home) income per MONTH? Include all your sources of income (workers comp, student loan,Social Security, etc.).

1 = Less than $500
2 = Between $501 & $1000
3 = Between $1001 & $1500
4 = Between $1501 & $2000
5 = Between $2001 & $2500
6 = Between $2501 & $3000
7 = Between $3001 & $3500
8 = Between $3501 & $4000
9 = Between $4001 & $6000
10 = Between $6001 & $8000
11 = More than $8000
98 = Refuse to Answer

What is the zip/postal code where you currently live? _____

Screener

Safety and preliminary efficacy of combination photodynamic therapy with 5-aminolevulinic acid and microcurrent therapy for the treatment of acne vulgaris

Date: _____ **Screener:** _____

Recruitment Source: _____

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1. How old are you?

   _____ *(If **less than 18** INELIGIBLE and HALT screener; If **older than 30**, INELIGIBLE but continue screener)*

2. Are you pregnant or do you suspect being pregnant?
   Yes No *(If **yes**, INELIGIBLE but continue screener)*

3. Are you actively trying to get pregnant?
   Yes No *(If **yes**, INELIGIBLE but continue screener)*

4. Are you planning to get pregnant in the next 3 months?
   Yes No *(If **yes**, INELIGIBLE but continue screener)*

5. Are you taking oral contraceptive pills?
   Yes No *(If **yes**, INELIGIBLE but continue screener)*

6. Are you breastfeeding/lactating?
   Yes No *(If **yes**, INELIGIBLE but continue screener)*

7. Are you taking any medication for your acne?
   Yes No

   If ***yes*** what kind of medication? * _____

   When was the last time you took your medication? _____

   If oral retinoids in the past 6 months (*INELIGIBLE but continue screener)*

   If oral antibiotic within the last 30 days (*INELIGIBLE but continue screener)*

   If have received topical acne treatment (i.e. retinoids, antibiotics and anti-inflammatory agents or chemical peeling) within the last 30 days (*INELIGIBLE but continue screener)*

   * If respondent does not remember their medication ask the following probes:
   - can you describe the medication… is it a pill? Is it a cream or lotion that you put on your skin? How often do you use it? If the respondent still cannot remember explain that this information is important and ask them to provide it by contacting the research team, asking their provider, or other reasonable steps.

   (Continue screening but do not enroll because eligibility cannot be determined)

8. Do you have history of photo-sensitive dermatitis?
   Yes No *(If **yes**, INELIGIBLE but continue screener)*

9. Do you have a pacemaker?
   Yes No *(If **yes**, INELIGIBLE but continue screener)*

Eligible and enrolled _____ Eligible not interested _____ Ineligible

Particpant ID	Lesions 1	Lesions 3	Lesions 5	Lesions 6	Lesions 9	Lesions 17