DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Date September 13, 2016

Michael A. Arata, M.D.
President
Synergy Health Concepts, Inc.
4501 Birch Street, Suite B
Newport Beach, CA 92660

Dear Dr. Arata:

Between November 16, 2015 and January 28, 2016, Ms. Diane C. Van Leeuwen, representing the U.S. Food and Drug Administration (FDA) (hereafter referred to as the "agency"), conducted an inspection at your clinical site as a follow up to your Warning Letter of September 5, 2012. This inspection was conducted as part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Van Leeuwen presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We acknowledge receipt of the March 4, 2016 written response to the Form FDA 483 from Benjamin L. England & Associates, LLC.

We have reviewed the FDA inspection report, the documents submitted with that report, and the written response to the Form FDA 483. We do not find your response to be acceptable in addressing the matters under complaint, which are described below.

Based on our evaluation of information obtained by the Agency, we believe that you, as a sponsor-investigator, have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products, as published under Title 21, Code of Federal Regulations (CFR), Part 812, Investigational Device Exemptions (copy enclosed), and Part 50, Protection of Human Subjects (copy enclosed).

This letter provides you with written notice of the matters under complaint and offers you an opportunity to explain the matter in writing or in an informal conference. This letter also initiates an administrative disqualification proceeding, described below, to determine whether you should be disqualified from eligibility to receive test articles as set forth under 21 CFR 812.119, and disqualified from eligibility to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, food, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

A listing of the violations follows, and the applicable provisions of 21 CFR Part 812 and Part 50 are cited for each violation.

1. **You repeatedly failed to submit an application to the FDA and obtain institutional review board (IRB) and FDA approval prior to allowing subjects to participate in an investigation [21 CFR 812.20, 812.40, and 812.42]**

   In its September 5, 2012 Warning Letter sent to you, FDA explained that a sponsor must submit an Investigational Device Exemption (IDE) for a significant risk device to the FDA (21 CFR 812.40) and shall not begin an investigation, or part of an investigation, until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation (21 CFR 812.42). In the 2012 Warning Letter, we notified you of your failure to obtain such approval prior to allowing subjects to participate in your significant risk device investigation of treatment for Chronic Cerebrospinal Venous Insufficiency (CCSVI) with devices not approved for that use. However, despite having received the 2012 Warning Letter, you have continued to conduct similar research without FDA and IRB approval.

   Specifically, as you did before with CCSVI, you studied the use of a device, the Bard ATLAS® Percutaneous Transluminal Angioplasty Balloon Dilation Catheter, as part of the Transvascular Autonomic Modulation (TVAM) investigation, and did not comply with applicable FDA requirements. Namely, you did not have an Investigational Device Exemption (IDE) or obtain IRB and FDA approval to conduct an investigation using the Bard ATLAS® catheter, which is not approved for dilation of jugular, azygos, renal and iliac veins. Nevertheless, from April 18, 2013 through September 11, 2013, you treated b(subjects with this device as part of the TVAM investigation.

   From your description, the use of the angioplasty balloon device is similar to one used to study CCSVI. There are different terms for the description of the disease as well as indications for treatment, but the intended population is the same, namely, patients diagnosed with ‘autonomic dysfunction’ and other neurological disease conditions including multiple sclerosis. Medical devices used for balloon angioplasty as described in your work are not approved as a treatment modality for autonomic dysfunction or multiple sclerosis. Autonomic dysfunction is ill-defined and could encompass a wide range of situations. You wrote about the TVAM treatment in the following publications and claimed safety and effectiveness for the treatment. The medical device identified in the literature is similar to one used in a CCSVI research clinical study in which you participated. Examples of the

publications in which you made claims of safety and effectiveness for unapproved treatment include, but are not limited to, the following:

Phlebology (2013;0(0)1-8) Blood Pressure Normalization in Post-jugular Venous Balloon Angioplasty

In this publication, you stated the following:

- "This study is the first in a series…"
- "In addition, venous dilation angioplasty to correct venous obstruction, although controversial, has been shown to have an acceptable safety profile and clinical efficacy."
- "The study involved MS patients who visited the Endovascular Clinic (Synergy Health concepts, Newport Beach, CA) between 2011 and 2012."
- "It should be noted that authors are engaged in additional studies aiming to show the close association between CCSVI and ANS dysfunction."

Journal of Endovascular Therapy (2014; 21:417-428) Transvascular Autonomic Modulation: A Modified Balloon Angioplasty Technique for the Treatment of Autonomic Dysfunction in Multiple Sclerosis Patients

In this publication, you stated the following:

- "The safety and efficacy of TVAM in MS patients observed in this pilot study…"
- "We propose extending the angioplasty procedure beyond dilation of obstructing lesions."
- "In this pilot study, we detail the technique of TVAM and compare the safety of this approach with traditional balloon angioplasty in MS patients."

Endocrine Care (2015) Neuroendocrine Responses to Transvascular Autonomic Modulation: A Modified Balloon Angioplasty in Multiple Sclerosis Patients

In this publication, you stated the following:

- "Balloon angioplasty is a treatment modality to correct vascular lesions in multiple sclerosis (MS) patients who present with chronic cerebrospinal insufficiency."
- "The study involved MS patients who visited the Endovascular Clinic (Synergy Health concepts, Newport Beach CA, USA."

In your investigations you continued to collect data from b(subjects between April 18, 2013 and September 11, 2013 with TVAM, a modified balloon angioplasty technique, using percutaneous transluminal angioplasty balloon dilation catheters in the internal jugular veins, azygos veins (vascular lesions).

As a result, you have continued to place subjects at increased risk of serious harm, despite having received the 2012 Warning Letter.

2. **You deliberately allowed subjects to participate in a study before obtaining approval from the reviewing IRB prior to initiation of the study [21 CFR 812.100 and 812.110(a)]**

In the 2012 Warning Letter, FDA noted that, as an investigator, you failed to ensure that informed consent was obtained from subjects and documented in accordance with 21 CFR Parts 50 and 56. Subsequent to the 2012 Warning letter, you failed to use an IRB-approved written consent form. An investigator is responsible for obtaining IRB approval prior to allowing any subject to participate in an investigational study. Moreover, an investigator must obtain IRB and FDA approval (21 CFR 812.100 and 812.110(a)) prior to obtaining written informed consent from subjects and allowing subjects to participate in research. You applied for and received IRB approval for a retrospective chart review. However, the Journal of Endovascular Therapy describes in detail the elements of a prospective clinical research investigation (e.g. the name of the device and identification of a treatment and control group).

3. **You deliberately failed to ensure that IRB-approved informed consent was obtained from study subjects and adhere to informed consent requirements [21 CFR 50.20, 50.25(a)(l), 50.27(a), and 812.100]**

In the 2012 Warning Letter, FDA noted that, as an investigator, you failed to ensure that informed consent was obtained from subjects and documented in accordance with regulatory requirements. Subsequent to the 2012 Warning Letter, you failed to obtain the legally effective informed consent, approved by an IRB (21 CFR 50.27(a), that contains the required elements set forth in 21 CFR 50.25. For example, b(subjects were not provided with an IRB-approved informed consent. Rather, different treatment consent documents were identified in subject records. For example, the physician medical record note stated that:

> "Risks and benefits of the procedure were discussed with the patient including 'off-label' use of a device. The risks include, but are not limited to vessel rupture, re-stenosis, thrombosis, recurrence of symptoms and post-operative bleeding including death. The expectations of the result of the procedure were also discussed. The patient understands that results cannot be guaranteed and those improvements of Dysautonomia symptoms are more commonly seen. Knowing these risks, potential benefits and possible lack of improvement of symptoms, the patient wishes to proceed with the procedure."

This statement in the physician medical record does not substitute for a consent form that describes research, nor does it contain the required elements, such as "[a] disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject" and "[a]n explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject" (21 CFR 50.25). Therefore, the statement written in the medical record cannot substitute for a written research informed consent that a subject signs to indicate his or her understanding of participation in research. Moreover, as we explained in the 2012 Warning Letter,

informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or subject's legally authorized representative at the time of consent. There is no evidence that the subjects understood and agreed to participate in research to determine safety and effectiveness using a device that was not approved for the indication of use (e.g., there is no evidence that the subjects or their representatives signed and dated any IRB-approved written consent form).

In addition, some subject records contained a "Physician-Patient Arbitration Agreement" that states "both parties to this contract, by entering into it, are giving up their constitutional rights to have any such dispute decided in a court of law before a jury and instead are accepting the use of arbitration." This language expressly waives the subject's legal rights and thereby releases, or appears to release, the investigator, the institution or its agents from liability for negligence. An investigator is required to obtain and have written documentation of informed consent by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative (21 CFR 50.27(a)). Moreover, "[n]o informed consent, whether oral or written, may include exculpatory language through which the subject of the representative is made to waive or appear to waive any of the subjects' legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence" (21 CFR 50.20).

4. **You deliberately represented a device as safe and effective for the purpose of treating various diseases other than those for which FDA has approved them. [21 CFR 812.7(d)]**

   Under 21 CFR 812.7(d), a sponsor-investigator is prohibited from representing that an investigational device is safe or effective for the purposes for which it is being investigated. However, as a sponsor-investigator, you have deliberately represented in the following publications that the use of balloon angioplasty devices to treat TVAM and CCSVI in what you explicitly designated as studies is safe and effective for the purpose of investigating various diseases other than those for which FDA has approved them:

   - *Phlebology (2013;0(0)1-8) Blood Pressure Normalization in Post-jugular Venous Balloon Angioplasty*
   - *Journal of Endovascular Therapy (2014; 21:417-428) Transvascular Autonomic Modulation: A Modified Balloon Angioplasty Technique for the Treatment of Autonomic Dysfunction in Multiple Sclerosis Patients*
   - *Endocrine Care (2015) Neuroendocrine Responses to Transvascular Autonomic Modulation: A Modified Balloon Angioplasty in Multiple Sclerosis Patients*

   These representations violate 21 CFR 812.7(d).

5. **You repeatedly failed to maintain accurate and complete records of receipt, use, and disposition of devices [21 CFR 812.140(a)(2)]**

> In the 2012 Warning letter, FDA informed you that you are responsible for maintaining accurate, complete, and current records relating to the shipment and disposition of devices. You failed to maintain records of receipt, use, and disposition of the devices. The Journal of Endovascular Therapy publication identifies a specific device; however, there are no records maintained to show receipt (e.g., shipment record), use, and disposition of the device (e.g., there are no specifics about the type and quantity of the device, dates of receipt and batch number or code mark for the catheters used for the TVAM Venous Balloon Dilation Therapy investigation).

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of TVAM. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above-listed violations, FDA asserts that you have repeatedly and deliberately failed to comply with the cited regulations and failed to comply with the conditions of the exempting regulations and FDA proposes that you be disqualified as a clinical investigator. You may reply to the above-stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 812.119.

Within fifteen (15) working days of your receipt of this letter, write or call Adam Donat at 301-796-5316 to arrange a conference time or to indicate your intent to respond in writing. Should you choose to respond in writing, your written response should be forwarded within thirty (30) working days of your receipt of this letter.

Your reply should be sent to:

James F. Saviola, O.D., CAPT USPHS
Director, Division of Biomedical Research
Office of Compliance
Center for Devices and Radiological Health,
Food and Drug Administration
10903 New Hampshire Avenue
WO 66, Room 3516
Silver Spring, MD 20993

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the violations listed above. You should bring with you all pertinent documents, and a representative of your choice may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request. At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

FDA's Center for Devices and Radiological Health ("the Center") will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or if we cannot come to terms on an Agreement with Respect to Use of Investigational Products with FDA, or if you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (copy enclosed), 21 CFR 50 (copy enclosed) and 21 CFR 812.119 (copy enclosed). Before such a hearing, FDA will provide you with notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer who has not participated in this matter will conduct the hearing. After such hearing, the Commissioner will determine whether you will remain entitled to receive test articles and to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

To enter into the enclosed Agreement with Respect to Use of Investigational Products with FDA thereby terminating this disqualification process, you must:

(1) Initial and date each page of this agreement;
(2) Sign and date the last page of this agreement; and
(3) Return this agreement initialed, signed, and dated to the signer below.

A copy of the fully executed agreement will be mailed to you.

Sincerely yours,

Robin W. Newman MSN EdD
Director
Office of Compliance
Center for Devices and
Radiological Health

Enclosures:
#1: Agreement with Respect to Use of Investigational Products with FDA
#2: 21 CFR 16
#3: 21 CFR 812.119
#4: 21 CFR 50