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GUIDANCE FOR CLINICAL DATA TO BE SUBMITTED FOR PREMARKET APPROVAL APPLICATION FOR CRANIAL ELECTROTHERAPY STIMULATORS

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- **While this guidance document represents a final document, comments and suggestions may be submitted at any time for Agency consideration to the Restorative Devices Branch, 9200 Corporate Blvd., HFZ-410, Rockville, MD 20850.**
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U.S. Department of Health and Human Services

Food and Drug Administration

Center for Devices and Radiological Health

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1. INTRODUCTION

This document presents requirements for the type of clinical data to be submitted in support of applications for premarket approval for cranial electrotherapy stimulators (CES) introduced into interstate commerce after the enactment of the 1976 Medical Device Amendment to the Food, Drug and Cosmetic Act.

This document supplements and explains, but does not take the place of, the requirements of the regulation "Premarket Approval of Medical Devices" 21 CFR Part 814. Sponsors of PMA applications are advised to also obtain a copy of the Premarket Approval Manual and Premarket Approval Manual Supplement issued by the Center for Devices and Radiological Health, as a general guide on the procedural aspects, format, and contents of a PMA application.

A submission of a premarket approval application requires the sponsor to provide valid scientific evidence which could support a conclusion that their device is safe and effective for its intended use. Valid scientific evidence, in accordance with 21 CFR 860.7, is evidence from well-controlled investigations from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Therefore, clinical data are needed from controlled clinical studies at multiple independent sites with identical protocols to provide reasonable assurance of the safety and effectiveness of the cranial electrotherapy stimulator for the uses for which it is intended.

The basic elements of the plan for any clinical study will be set long before the first patient is enrolled. The medical claims for the device must be well thought out when planning a clinical study. If it is unclear what the actual medical claims are it would be advantageous to conduct a pilot study to pinpoint the potential effect of the device and determine the primary and secondary variables. If the medical claims are known then it is important to limit the scope of the study to objectives which can be scientifically demonstrated. The clinical study must be designed, conducted, and analyzed to definitively demonstrate the safety and effectiveness of the device for its intended use and medical claims.

It is important with CES devices that the optimum parameters of the device be determined prior to a clinical study. It should be clearly demonstrated what are the most effective operating parameters and electrical characteristics with respect to the intended use. For example, number of treatments, duration of treatment, frequency of treatment, and electrical output, i.e., waveform, amplitude, pulse width, monophasic vs. biphasic, etc.

2. PROTOCOL

The foundation of a clinical study is the study protocol. The clinical protocol(s) should be described in sufficient detail to indicate whether the protocol(s) meet the criteria deemed necessary by FDA to provide reasonable assurance of the device's safety and effectiveness for its intended use.

2.1 The study protocol for a cranial electrotherapy stimulator must contain a clear definition of the hypothesis to be tested, including:

2.1.1. An identification of the stages of the disease or condition, based on a recognized classification, so that an improvement or deterioration can be measured. The disease or

condition must be described in sufficient detail and supported with valid scientific evidence either through historical data, currently recognized scientific literature, or valid experimental results.

2.1.2 An indication of whether the device is intended as a sole or adjunctive treatment for the condition it is intended. If the device is intended as an adjunctive treatment the clinical study must be designed to include the whole treatment plan and measures implemented to isolate the effect of the device in the overall outcome of the treatment plan.

2.1.3 The protocol should be supported by background literature on previous uses of the device and proposed mechanisms for its effect. This includes a determination of physiological effects which the device produces from valid scientific evidence. When making a medical claim with a device, particularly a CES device, it is essential to identify and explain with valid scientific evidence the physiological relationship(s) between the use of the device and specific physiological changes in the body. Once a relationship is identified substantial evidence must then be provided to explain the logical connection between those physiological changes and their effect on the treatment of the medical claim of the device.

2.1.4 An identification of the primary and secondary variables analyzed to demonstrate effectiveness. Primary variables or the endpoint variables used for measurement of safety and effectiveness of the device for its intended use should be clearly defined. The secondary variables should be identified and defined as either independent variables or influencing variables. Again, pilot studies are recommended to characterize the primary and secondary variables associated with the use of the device.

2.2 One of the most common errors in conducting a clinical study is the failure to follow the protocol. It is important to implement a monitoring mechanism to reasonably assure patient and physician compliance to the protocol. Although some protocol deviations or changes may have legitimate reasons, all protocol deviations or changes must be described in detail in order to assess the effect of those changes on the study's outcome.

2.3 Clinical Utility. The protocol should address the clinical utility in terms of the risk to benefit ratio of the device for its intended use. Endpoint assessment cannot be based solely on a statistical value, the clinical outcome must be carefully defined to distinguish between the evaluation of the proper function of the device versus its benefit to the subject. Statistical and clinical utility of the device must be demonstrated by the statistical results. However, under certain restricted circumstances, a clinically significant result may be acceptable without statistical significance.

3. PHASES OF STUDY

The study should consist of four phases: enrollment, baseline, treatment, and follow-up and each phase must be clearly presented.

3.1 Enrollment. During enrollment the sampling methods and intervals must be pre-determined and kept constant and identical for all patients at all sites. Patients are

screened to assure they conform to inclusion criteria and assure that their medication and other forms of therapy are stabilized.

3.2 Baseline. Once patients are enrolled, multiple baseline measurements should be obtained for all variables to be examined.

3.3 Treatment. The treatment phase should incorporate standard measures for each study variable. The primary study variables should be collected using several standard methodologies. Multiple measurement throughout the treatment phase may be necessary to determine sample variance.

3.4 Follow-up. During each follow-up interval the variables are again collected and analyzed for treatment effect. Follow-up must be complete and of sufficient duration to reasonably assure safety and effectiveness. There should be a minimum of one year follow-up for at least 80% of the study population. Any imbalances and exclusions must be thoroughly explained and justified.

4. STUDY SAMPLE REQUIREMENTS

The subject population must be well defined. Ideally, the study population should be made as homogeneous as possible to minimize selection bias and reduce variability. Otherwise, an excessively large population may be necessary to achieve statistical significance. Independent studies which give comparable results at multiple study sites using identical protocols are necessary to demonstrate repeatability. All endpoint variables must be identified and a sufficient number of patients for each subgroup analysis must be included to allow for stratification by pertinent demographic characteristics. Justification must be provided of the sample size to show that a sufficient number of patients are enrolled to attain statistically and clinically meaningful results.

The criteria for patient inclusion or exclusion into the study should be formulated based on the subjects demographics and eligibility criteria. Eligibility criteria of the subject population should be based on the subjects potential for benefit, the ability to detect a benefit in the subject, no known contraindications, the absence of any competing risk, and subject compliance. A detailed eligibility criteria should be developed by experts and monitored so that compliance to the protocol is never violated.

It is not always possible to attain a completely homogeneous subject population, therefore, all influencing variables must be stratified. Stratification of patients groups participating in the clinical study is necessary for a heterogeneous sample to analyze homogeneous subgroups and minimize potential bias. It is important to include and describe in sufficient detail all concurrent drug or psychiatric/psychological therapy for the indication(s) under study or other existing conditions.

5. STUDY DESIGN

The clinical study design must be of good power and size to adequately answer the important questions associated with the device claims. Use the best measurement variables and appropriate statistical analysis.

An essential function and key objective of a clinical study design is to control sources of error and bias. Error is recognized as the inability to measure a variable accurately, whereas, bias is any characteristic of the investigator, study population, or study conduct which interferes with the ability to measure a variable accurately. Potential sources of error can be eliminated through proper clinical design and the effects of potential bias can be minimized through balance. The important elements of a good clinical design, in addition to a design with good power and size to control sources of error and bias include:

5.1 Randomization study population. The study should be a randomized double-blind design where all subjects of the study population are assigned concurrently by a method of randomization to an active group and a placebo control group. The preferred method for subject enrollment into a study is randomization by a central monitor.

5.2 Verification of balance. It is essential to attain and verify a balance in the study population in important factors regarding demographics including disease/condition status, age, sex, concomitant medication and any other influencing variables in the population.

5.3 Inclusion/exclusion criteria. Inclusion and exclusion criteria should be formulated and developed by experts in order to have a sample population with a minimum number of influencing variables. Without good criteria for eligibility to the study the effect of exclusion for non-compliance or loss to follow-up will bias the study and void the advantages of randomization.

5.4 Blinding. The individuals responsible for the analysis and interpretation of the data obtained from the study should not have any pre-exposure to the study population. Blinding, therefore, is needed both of the subject population and of those individuals where their function requires interaction with the subject population. Blinding is particularly important in studies for CES devices when the assessment of the outcome may be subjective. Blinding incorporates methods to minimize the effects of bias.

5.5 Control. In order to demonstrate efficacy of a device the effect of the device must be compared to a control. CES devices have been known to demonstrate a strong placebo effect therefore, the study must clearly measure any possible placebo effect. It is important then to design a study to incorporate a placebo control group to be compared with an active treatment group.

5.6 Objective endpoint measures. Treatment effects should be based on objective measurements. The validity of these measurement scales must be provided to insure that the treatment effect being measured reflects the intended use of the device.

5.7 Patient Accountability. Adherence to the protocol by subjects, investigators, and all other individuals involved is essential and requires monitoring to assure patient compliance, physician compliance, and blinding. Subject exclusion due to drop-out or lost to follow-up greater than 20% may invalidate the study due to bias potential; therefore, initial patient screening and intensive compliance of the final subject population will be needed to minimize the drop-out rate. All drop-outs must be accounted for and the circumstances and procedures used to ensure patient compliance must be well documented.

5.8 Adverse effects. Observation of all potential adverse effects must be recorded and monitored throughout the study and through the follow-up period. All adverse effects must be well documented and evaluated.

6. DOCUMENTATION OF STATISTICAL ANALYSIS AND RESULTS

The involvement of an expert in biostatistics is necessary to provide proper guidance in the planning, design, conduct, and analysis of a clinical study to estimate the required number of patients based on the number of variables to be examined, the subgroup analyses to be conducted, and the expected treatment effect.

The study should be designed to obtain statistical and clinical significance of the primary and secondary variables at the alpha level of 0.05 and a beta of 0.20 for each primary variable. Non-parametric tests may be required when analyzing data if the basic assumptions for parametric tests cannot be met.

Study analysis must correspond to the protocol used and it is essential that adherence to the protocol is conducted. All patients must be accounted for and all exclusions from the study or analysis must be explained including those that may be lost to follow-up. Any other deviations or changes in the protocol must also be well documented and explained in detail.

It is important when presenting the statistical analysis and results of a clinical investigation that certain key points be clearly identified and supported with valid evidence:

6.1 The control group for the clinical study must be defined and justified to demonstrate that any placebo effect is clearly measured.

6.2 The study sample size must be determined and its justification be statistically calculated before the start of the clinical study. A sufficient sample size must be determined to demonstrate a reasonable assurance of detecting a clinically significant outcome.

6.3 The hypothesis test statement must be clearly outlined.

6.4 An evaluation of all potential bias must be outlined and discussed which demonstrates how bias has been minimized. Key issues of randomization, blinding techniques, and descriptive analysis of patient demographics, the investigator(s), and investigational site must be addressed.

6.5 If pooling data across clinical sites is chosen in order to satisfy the minimal sample size requirements a clear justification must be demonstrated. Pooling requires a clear demonstration of identical protocols at each site and that the study sites are sufficiently similar in protocol adherence, population demographics, and other factors to assure that the study sites are truly representative of a single clinical study.

6.6 The statistical test selected to demonstrated a statistical significance of the clinical outcome of the investigation must be presented including a justification why this test is appropriate and the statistical procedures completely described and referenced.

6.7 All data and statistical results must be provided in a clear presentation and the statistical conclusions drawn from the results and their clinical significance must be provided. The clinical outcome must be carefully defined to distinguish between evaluation of the proper function of the device versus its benefit to the subject.

In addition to this generalized guidance, the investigator is expected to incorporate additional requirements necessary for a well-controlled scientific study. These additional requirements are dependent on what the investigator is intending to measure or what is the expected treatment effect based on the intended use.