device produces, as well as the primary and secondary variables analyzed to evaluate safety and effectiveness. Study endpoints and study success must be defined.

Animal toxicity studies should be conducted according to the International Standard ISO–10993, "Biological Evaluation of Medical Devices Part-1: Evaluation and Testing." Specifically:

(1) The selection of material(s) to be used in device manufacture and its toxicological evaluation should initially take into account full characterization of the material, for example, formulation, known and suspected impurities, and processing.

(2) The material(s) of manufacture, the final product and possible leachable chemicals or degradation products should be considered for their relevance to the overall toxicological evaluation of the device.

(3) Any in vitro or in vivo experiments or tests must be conducted according to recognized good laboratory practices followed by an evaluation by competent informed persons.

(4) Any change in chemical composition, manufacturing process, physical configuration or intended use of the device must be evaluated with respect to possible changes in toxicological effects and the need for additional testing.

(5) The toxicological evaluation performed in accordance with the guidance should be considered in conjunction with other information from other nonclinical studies and postmarket experiences for an overall safety assessment.

Examples of questions to be addressed by the clinical studies may include the following:

1. What morbidity (irritation of the oral cavity soft tissues, monilial infection, unusual hard and soft tissue changes, sensitization, or allergic response) is associated with the subject device in the patient population and how does this compare to the control?

2. What impact does the device have on the vertical dimension of the occlusion?

3. What are the long term effects of the device on the oral tissue?

4. What changes in physical characteristics (hardness, dimensional stability, etc.) of the materials take place over time?

5. Does the device provide a functional level of retention for the user?

6. Does the device allow sufficient comfort for the user?

7. Does the partially fabricated denture provide adequate strength for the denture to function properly?

8. What criteria are used to select the correct size of partially fabricated denture for an individual patient?

9. Because the teeth are preset, how is the individual occlusal plane determined to avoid traumatic occlusion?

10. Does the device allow the patient to be able to masticate food, insofar as oral and psychologic conditions will permit?

11. Does use of the device result in the patient presenting a normal individual appearance that satisfies esthetic requirements?

Statistically valid investigations should include a clear statement of the objectives of the study. Appropriate rationale, supported by background literature on previous uses of the device and proposed mechanisms for its effect, should be presented as justification for the questions to be answered, and the definitions of study endpoints and success. Clear study hypotheses should be formulated based on this information.

B. Study Sample Requirements

The subject population should be well defined. Ideally, the study population should be as homogeneous as possible in order to minimize selection bias and reduce variability. Otherwise, an unusually large population may be necessary to achieve statistical significance. Independent studies producing comparable results at multiple study sites using identical protocols are necessary to demonstrate repeatability. Justification must be provided for the sample size used to show that a sufficient number of completely edentulous patients were enrolled to attain statistically and clinically meaningful results. Eligibility criteria for the subject population should include the subject's potential for benefit, the ability to detect a benefit in the subject, the absence of both contraindications and any competing risk and assurance of subject compliance. In a heterogeneous sample, stratification of the patient groups participating in the clinical study may be necessary to analyze homogeneous subgroups and thereby minimize potential bias. All endpoint variables should be identified, and a sufficient number of patients from each subgroup analysis should be included to allow for stratification by pertinent demographic characteristics.

The investigation should include an evaluation of comparability between treatment groups and control groups (including historical controls). Baseline (e.g., age, gender, etc.) and other variables should be measured and compared between the treatment and control groups. The baseline variables should be measured at the time of treatment assignment, not during the course of the study. Other variables should be measured during the study as needed to completely characterize the device's safety and effectiveness.

C. Study Design

All potential sources of error, including selection bias, information bias, misclassification bias, comparison bias, or other potential bias should be evaluated and minimized. The study should clearly measure any possible placebo effect. Treatment effects should be based on objective measurements. The validity of these measurement scales should be shown to ensure that the treatment effect being measured reflects the intended uses of the device.

Adherence to the protocol by subjects, investigators, and all other individuals involved is essential and requires monitoring to assure compliance by both patients and physicians. Subject exclusion due to dropout or loss to followup greater than 20 percent may invalidate the study due to bias potential; therefore, initial patient screening and compliance of the final subject population will be needed to minimize the dropout rate. All dropout must be accounted for and the circumstances and procedures used to ensure patient compliance must be well documented.

Endpoint assessment cannot be based solely on a statistical value. Instead, 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 significance and effectiveness 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.

Observation of all potential adverse effects must be recorded and monitored throughout the study and the followup period. All adverse effects must be documented and evaluated.

D. Statistical Analysis Plan

The involvement of a biostatistician is recommended to provide proper guidance in the planning, design, conduct, and analysis of a clinical study. There must be sufficient documentation of the statistical analysis and results including comparison group selection, sample size justification,