B. BUSINESS PROPOSAL

ORIGINAL* AND 10 COPIES TO:

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*THE ORIGINAL PROPOSAL MUST BE READILY ACCESSIBLE FOR DATE STAMPING.

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STATEMENT OF WORK

INTRODUCTORY STATEMENT

The purpose of the RFP is to solicit proposals for research, development, and evaluation of tether-free, miniature, implantable, electrically energized total artificial heart replacement systems. INNOVATIVE AND STATE-OF-THE-ART CONCEPTS WILL BE CONSIDERED; HOWEVER, SIGNIFICANT FEASIBILITY DATA MUST BE PROVIDED.

A two-phased program is planned. Phase I (October 1, 1993 through September 30, 1996) comprises design completion for a five year Total Artificial Heart (TAH) life, demonstration of manufacturability, short term performance testing in animals and short term bench testing of several TAH systems to demonstrate the contractor's capability to begin readiness (reliability) testing. It is anticipated that fewer than four contracts will continue into Phase II. The decision to continue each of the contract programs into Phase II will be based on successful completion of Phase I and the Government's judgment of merit for both the Phase I work and the planned program to be performed in Phase II. It is anticipated that technical merit will be evaluated at that time by means of the same criteria listed in Part 17 below for the initial technical review with an emphasis placed on the results of the Phase I work.

Phase II (October 1, 1996 through September 30, 2000) will consist of *in vitro* formal reliability and *in vivo* animal testing of implantable total artificial heart systems. *In vitro* testing and evaluation of a sufficient number of TAH systems will establish the required reliability, and animal performance testing in a series of animal experiments will establish that TAH performance can be maintained in an *in vivo* environment. It is recognized that real-time evaluation of the integrated TAH over 5 years is not feasible, and thus the device readiness testing for reliability is required for at least two years. However, the offeror must describe any components of the TAH which have already been life tested for five years or which are amenable to accelerated life testing to be performed during this phase.

The proposed TAH systems must be designed and developed specifically for human use. *In vivo* testing will of necessity be performed in animals, but the device should not be specifically designed for animals. **THIS SOLICITATION EXCLUDES CLINICAL TESTING AND THE DEVELOPMENT OF A SINGLE VENTRICLE ASSIST DEVICE.** Proposals which offer to develop only portions of the TAH will be considered unacceptable.

Phase II is predicated on the assumption that one or more TAH systems developed in Phase I have progressed to a point where the establishment of device and team readiness guidelines is warranted. These devices will eventually provide permanent circulatory support in patients with forms of ventricular failure not amenable to medical or surgical treatment.

A Steering Committee including the principal investigators of each of the contractors and the NHLBI Project Officer will make the major scientific decisions regarding the development of the study protocol and manual of operations during Phase II and will be responsible for governing the conduct of the study thereafter. The Chairperson will be appointed by the NHLBI. During Phase I, the Steering Committee will meet six (6) times over the three (3) year period. During Phase II,

it is anticipated that the Steering Committee will meet ten (10) times over the four (4) year period.

A Technical Review Committee (TRC) composed of experts in relevant medical, engineering, ethical, and statistical fields will be established by NHLBI to review periodically the progress of the study during Phase II. Relevant Federal agencies will have ad-hoc observers. The TRC will advise the NHLBI regarding progress and direction of the efforts of the contractors.

Proposal Guidelines

Each proposal submitted in response to the RFP must offer to perform research and development on a single system concept. The offeror must provide clear rationale for the selection of major system components. The offeror must provide supportive data using its prototype TAH to demonstrate that it is able to achieve the goals and timetable established in this solicitation. The following provides guidelines for information to be included in the scientific proposal and amplifies the review criteria which will be used to evaluate each proposal.

The TAH must be capable of supporting the full cardiac output as described below. Although pulsatile pumps need not mimic the "normal" ventricular pulse or arterial pressure waveforms, they should generally produce a substantial pulsatile component in the arterial pressure. Offerors must provide evidence that the rate of pressure rise and fall in the pump emulates the natural heart and does not cause premature failure or wear of the pump components (e.g., inlet or outlet valves) or excessive turbulence, or hemolysis of blood. Pump designs without a pulsatile output are not excluded from this solicitation; however, the rationale and justification of the design with appropriate feasibility studies must be presented. PHYSIOLOGICAL TESTING OF PULSATILE VERSUS NON-PULSATILE PUMPING OF BLOOD IS EXCLUDED FROM THE RFP.

It is recognized that in an implantable TAH system, a variable volume will occur between the blood pump actuator piston (or similar mechanism) and the electrical energy converter. Appropriate techniques must be provided to prevent the buildup of pressure in the variable volume which would inhibit or prevent pump filling. Left and right atrial pressures must mimic normal physiology. The design must avoid "venting" to the body surface, and must be capable of adjusting to atmospheric pressure changes. The issue of leakage across membranes must be addressed, e.g., pump bladder, variable volume device. An overall system fluid leakage rate (gas with SF_6 or liquid) of 10^{-7} cc/s at 30 Torr shall be a design goal.

Consideration should be given to the overall efficiency of the TAH, over its anticipated operating range. Efficiencies of 20 percent or greater are desirable. System efficiency as used here is the work output of the blood pump divided by the electrical energy provided to the system from an extracorporeal power source/battery pack.

It is required that the implantable TAH be specifically designed for a selected anatomical position in the human and that the appropriate dimensions, configuration, and weight be physiologically compatible. Offeror must describe system limitations of the TAH with regard to body habitus, age, and gender (excluding morbid obesity -- Body Mass Index ≥ 43.0 Kg/m^2). Incorrect positioning or surgical attachment of the

replacement TAH system may be injurious to neighboring tissues. Obstruction to venous return and/or compromise of nearby organ systems must be avoided.

It is desirable that control of the systems emphasize auto-regulation (e.g., Frank-Starling mechanism). Ideal pump systems should present minimal resistance to inlet blood flow and consistently deliver a major fraction of the volume of blood received into the arterial system in an efficient fashion. Appropriate control techniques must be developed to account for the flow differences between the right and left ventricles. The TAH control system must also adapt to ambient pressure changes. The system must not stall under any operational mode.

It is necessary that potential catastrophic failure mechanisms be eliminated from the TAH design. Potential failure mechanisms should result in only reduced or degraded performance which is not life threatening and allows sufficient time for corrective action.

Since the determinants of blood-material interactions are not fully understood at the present, choice of materials (natural or synthetic) for the blood- and tissue-contacting surfaces of the pumping chambers must be carefully documented, and the physical and chemical properties of the materials must be characterized. The choice of biologically quiescent or bioactive materials must be justified. The transfer of water across blood-contacting material could damage certain energy converter components. Methods to eliminate or minimize fluid transfer across these surfaces must be included in the design. Pertinent implanted material specimens should be carefully retrieved, preserved, and evaluated to determine their interaction with blood or tissue components. **PRIMARY AND SECONDARY SOURCES MUST BE IDENTIFIED FOR ALL MATERIALS TO BE USED FOR BLOOD AND/OR TISSUE CONTACTING SURFACES.**

The protocols for characterization shall include techniques with the sensitivity and specificity to detect changes which may occur as a result of fabrication procedures, sterilization and storage. In choosing which tests to use, the offeror shall consider the environmental changes which may alter surface properties during the fabrication of a device and identify the types of analysis which could detect changes induced by such variables as curing rate, casting surface properties, light exposure, sterilization, storage, etc. The materials shall be evaluated before, after, and where possible, during in vivo testing. **RESEARCH ON MECHANICAL PROPERTIES AND BASIC MECHANISMS OF BLOOD-MATERIAL INTERACTIONS ARE EXCLUDED FROM THE RFP.**

Research on electrochemical batteries is not excluded in this RFP, although the development of internal and external power sources using state-of-the-art batteries is a more practical approach since research support is limited. The proposed system must provide for the transfer of energy from the external battery pack in a fail-safe manner through or across the intact skin to power the implanted system components. The device must provide for emergency, hygienic, and other short-term personal needs using an internal battery pack or other means.

The performance of the TAH must be evaluated in animals prior to clinical use. The contractor should discuss the advantages and disadvantages of the particular animal model selected, including any design alterations that may be necessary for animal testing as compared with the design configured for human use.

a. Performance Goals

Typically, an implantable TAH should:

- Be capable of supporting the failed ventricles with an output of eight liters per minute.
- Provide for five years of tether-free operation.
- Include a reliable control system which is responsive to varying circulatory demands.
- Be associated with little or no infection, hemolysis, thrombosis, clots, or emboli and require little or no antithrombotic therapy.
- Be capable of operation in the presence of electric, magnetic, and electromagnetic fields encountered in typical home, work, social, and recreational environments.
- Be compatible with the body following initial implantation response (e.g., non-toxic, non-inflammatory, non-corrosive, etc.), impervious to body fluids, stable in the biologic environment and free of leakage of device fluids into surrounding tissues.
- Avoid thermal management problems and operate reliably at body temperature without localized "hot spots" or causing local tissue injury.
- Provide rechargeable external electrochemical energy storage to support the TAH for at least 8 hours and means for alerting the patient for replacement of the power source.
- If the offeror chooses to provide implantable rechargeable electrochemical energy storage to support the TAH for emergency and hygienic purposes, sufficient energy should be provided for a continuous output of 6 liters per minute for 30 minutes.

b. Human Factors

The device is to be used only in a situation in which it offers at least as likely benefit as any known accepted technique or any experimental technique which is available for clinical trial. **Consideration of patient quality of life is paramount.**

The TAH should:

- Be capable of reliable operation in any orientation, in the presence of typical environmental vibration (e.g., airplane, auto, etc.), mechanical shocks (e.g., falls, auto accident, etc.) and muscle movement. It should also be easily started, should not produce adverse gyroscopic effects and should safely dissipate excess heat.

- Have system packaging parameters such as shape, weight, volume, attachments, and edges, which are compatible with both internal and external human anatomy (minimize organ displacement and cosmetic deformities), and minimize potential for pressure necrosis or mechanical erosion. The system should avoid bulky or heavy extracorporeal components.

- Provide psychologically and physiologically acceptable noise and vibration characteristics to the recipient and observers.

c. Design Reliability and Performance in Animals

- The expected reliability of the device over its intended period of life must be established, using generally accepted practices.

- The functioning and the effects of the device must be characterized in bench testing and in experimental animals.

- The device must be fully described as to quality, materials, and methods of use.

- There must be evidence of reasonable safety against potential ordinary hazards of devices such as electrical shocks, as well as against any special hazards which may be associated with the device; the device must not fail catastrophically and whenever feasible, the device shall be failsafe.

- The medical-surgical team must have specific and extensive familiarity and actual experience with the device.

- The consequences and courses of action if the device fails must be considered and a plan of action outlined.

NOTE FOR FUTURE CONSIDERATION

A goal of this work is to develop a device for use with humans. It is anticipated that future work using this device with humans will be undertaken after the completion of this program. Offerors are reminded that an Investigational Devices Exemption must be obtained from the Food and Drug Administration before human investigation is initiated. However, **CONTRACT AWARDS MADE UNDER THIS RFP WILL NOT INCLUDE HUMAN USE OF TAH DEVICES.**

d. Design and Manufacturing Documentation

System and component design, materials used, methods of manufacture and operating procedures must be described and illustrated in detail. Second sources for critical and subcontracted components must be documented.

Offerors are encouraged to consider all applicable FDA laws and regulations when planning their research program such as "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 Congressional Federal Registry (CFR) Part 58) and the "Good Manufacturing Practice Regulation" (21CFR, Part 820).

Additionally, post-award planning should consider regular visits with FDA personnel to exchange information.

e. Quality Control and Quality Management (QC&QM)

The International Organization for Standardization has published guidelines for quality management. These guidelines shall be used by TAH contractors (ISO 9000, Attachment 16).

The purpose of this quality control and management program is to ensure requisite quality among the systems, including those under test and those that will be available for animal testing. Processes and process control must be detailed and fully described. There shall be no "blind" processes or procedures.

In instances of proprietary technology or components, these procedures must demonstrate that the quality of these components is invariant. Both new and refurbished components must pass the same QA/QC procedures.

f. Packaging and Labeling

Offerors must define the packing procedures for shipment of the devices for future clinical use. The package to be included with each device must contain general information, operating instructions, precautions and descriptions of all procedures and tests which have to be completed before device implantation.

Protocols for device sterilization must be defined and tests performed to demonstrate the stated shelf life of the device and components (e.g., internal and external power packs).

Recommended shipping and handling procedures must be described, including any special precautions required to assure the safety and integrity of the device.

g. Mock Loop and Characterization of System Performance

The operation of the system must be characterized in a mock circulation loop under varied conditions with the intent of documenting the operational domain, device parameters and limits of system performance. Test procedures should be documented in sufficient detail, including the viscosity of the blood analog and the test temperature, so that different investigators can achieve substantially the same results with the same device and mock circulatory loop. It is recommended that a mock loop be used for these tests having characteristics equivalent to those described by a 1990 Artificial Heart Committee (see Attachment 17).

The test procedures should cover both transient and steady state evaluation of the TAH. Steady state performance evaluation should include three specific points: (1) 8 L/min at 110 mm Hg average aortic pressure; (2) 5 L/min at 100 mm Hg average aortic pressure; and (3) the maximum cardiac output that corresponds to a left atrial filling pressure of 15 mm Hg and an average aortic pressure of 120 mm Hg. For points (1) and (2), the lowest filling pressure consistent with the above output points should be utilized, the goal being a

filling pressure just ahead of the left atrial inlet valve of 15 mm Hg or less (right atrial pressure less than or equal to 10 mm Hg).

Transient operation defines the system response to rapid changes in beat rate, stroke volume and systemic pressure. Transient operation test points should include: (1) varying the beat rate rapidly from 70 to 100 BPM and similarly back to 70 BPM; and (2) rapidly changing pump flows by approximately 40%. The parametric rate of change should be documented.

Leakage across components that separate different fluids must be measured periodically, including variable volume devices, pump bladders, and hydraulic or pneumatic lines. The total TAH system leakage rate should not exceed 10^{-7} cc/s at 30 Torr with SF_6.

h. Device Readiness

The objective of the Device Readiness Testing Program is to demonstrate that the TAH can function safely, effectively and with a high degree of reliability.

1) Planned Reliability and Documentation

Along with the Phase I demonstration tests the developer shall document the readiness of the TAH for the initiation of these tests. A plan outlining achieved TAH reliability at a specified milestone, including planned number of devices and success/failure criteria, shall be prepared. The in vitro tests shall demonstrate a reliability of at least 80% with 80% confidence. The initial plan to demonstrate reliability must be provided in the proposal and may include trade-off studies showing number of test devices and operating test time or test effort versus reliability and associated confidence levels. All changes in the plan prior to initiation of reliability demonstration shall be documented. No change may be made in the conduct of the plan without prior approval of the NHLBI Project Officer.

2) Sample Size

Current knowledge of medical device reliability precludes accelerated testing and suggests that the expected reliability be tested for the intended period of use. For the purpose of this RFP, reliability testing is planned for 8 systems with zero (0) failure for two years (80% Reliability, 80% Confidence Level).* At least four of these systems will be recharacterized on the mock-loop and disassembled for inspection and analysis. Therefore, the reliability, including confidence level, should be extrapolated to five years of use.

* Offerors may propose alternative experimental designs for Device Readiness Testing to achieve the minimum 80% reliability and 80% confidence levels.

3) System Testing

Simulated use tests must be performed to establish the engineering reliability of the implantable TAH system. These tests may be performed in vitro as described in Attachment 18, or using an in vivo approach recently described for muscle powered ventricles.** Specific guidelines for performing system reliability tests are provided in this section, including test conditions, parameters and a test plan. Systems undergoing reliability tests should include all components. A finalized TAH prototype design must be established before initiation of tests. In preparation for device readiness testing in Phase II, at least two hermetically sealed TAHs must be tested for at least three months during Phase I.

High reliability for their period of use must be demonstrated for external and periodically replaceable components, such as external batteries. Based on sufficient engineering justification, this demonstration may be performed separately from implanted system tests.

a) Test Conditions

System tests should be conducted using mock loops with physiological flows and pressures. System inputs should simulate those that would normally be available in vivo. Positioning of the TAH in the mock loop shall approximate its anticipated position in the standing human. The tests should be conducted with all components at physiologic temperatures (37°C±1°C), and the subsystems to be implanted should be immersed in a bath of normal saline (0.15M NaCl). The test environment should be monitored on a regular basis and parameters documented.

Offerors must discuss methods of coping with contamination of the fluid and chamber of the mock loop over the period of testing. The use of blood in a mock loop is usually not feasible. However, the TAH may perform differently when pumping blood as compared to other fluids. Offerors must discuss this issue.

b) Test Parameters

Systems should be operated at a mean aortic pressure of 100-120 mm Hg, and a mean flow of 6-8 L/min for approximately 50% of the time. For the remainder of the time, the system should be operated within the flow and pressure ranges of 4-6 L/min, 80-100 mm Hg mean aortic pressure. The lowest filling pressure consistent with those operational points should be used. Periodically, as per the test plan, flow should be recorded, with mean outflow and inflow pressures maintained at 120 and 15 mm Hg, respectively. Input current and power must be continuously monitored.

** Pochettino, A, et al. Skeletal muscle ventricles with improved thromboresistance: 28 weeks in circulation. Ann Thorac Surg 53:1025-32, 1992.

c) TAH In Vitro Failure Criteria

If maximum TAH flow rates fall to less than 3.0 L/min over a period of 30 seconds with inflow pressures of 20 mm Hg and/or if the TAH cannot maintain a mean outlet pressure greater than 60 mm Hg, then it shall be considered a system failure. If this reduced flow occurs for less than a 30 second period but recurs more frequently than every 60 minutes, this shall also be considered a failure.

4) Monitoring; Progress and Event Reporting

During reliability testing in Phase II, each TAH will be monitored continuously for a set of parameters which characterize status and performance, e.g., inflow and outflow pressures, input current and power, output flow rate. Events will be communicated immediately and automatically, in real time, to the NHLBI Program Office. Weekly status reports to the Program Office will include performance data on selected parameters.

5) Post-Reliability TAH Evaluations

TAHs removed from reliability testing shall be examined, inspected, and analyzed with regard to system performance and integrity. Examination and documentation of mechanical electrical, electronics (including software), and physiochemical integrity of all components shall be performed on all system components. A detailed failure mode and effects analysis shall be performed to determine the root cause for all failed components.

i. In Vivo Characterization

Animal implant studies should be designed to demonstrate TAH performance *in vivo*. Device reliability should be demonstrated separately by *in vitro* tests, using guidelines described above.

The consistent response of the TAH to various physiologic and transiently unphysiologic states must be demonstrated *in vivo* in at least six (6) studies with the TAH in its finalized prototype configuration. Six individual systems must be evaluated during various steady state conditions over a reasonable range of physiologic variables, and during transient unphysiologic conditions. These studies are intended to establish the range of responses of the devices and to demonstrate the reproducibility of responses from device to device. Studies may be performed in acute or chronic animal experiments.

1) Operating conditions to be evaluated include: control modes, power system (internal and external, including charging and switching system) start-up sequence, and back-up mode of operation.

2) The ranges of steady state physiologic conditions include: Heart rate (60-120 beats per minute), arterial pressures (60-120 mm Hg), pump flow (4-8 L/min), left ventricular end-diastolic or atrial pressure (0-15 mm Hg).

3) A variety of conditions will be evaluated by changing preload, afterload, rhythm, and various states of ventricular failure. These conditions may be induced by volume load and unloading, by the use of drugs or by surgical intervention. They must be demonstrated in at least six experimental animals. These studies are intended to identify the limitations of the system.

j. Chronic In Vivo TAH Performance

The proposal must include a discussion of animal models, justification of the choice of a specific model, projected realistic test time for an implanted TAH in that model, and the specific aims which are expected to be achieved from these tests.

In Phase I, two hermetically sealed TAHs must be evaluated in animals over at least a two month period. During Phase II, reliable operation of the TAH in its final prototype configuration, and evidence of safe operation with minimal adverse effects on the experimental animal, must be demonstrated in a series of chronic five-month animal studies. Even though the in vitro studies may qualify the design for initially two and eventually five years of clinical use, limitations presently imposed by animal models are such that requirements for animal studies in excess of five months duration may not be realistic. All animal studies must conform to DHHS policy on animal experimentation as explained in Attachment 19. In order to qualify for clinical use of the TAH, the following studies must be performed during Phase II:

1) Chronic studies shall be undertaken in at least eight animals but no more than twelve animals.

   a) Eight (8) animals shall be studied with acceptable TAH function for five months (mean) of continuous pumping. The goal is to complete at least 40 animal-months of testing, with each animal completing a minimum of four months.

   b) Up to three (3) experiments can be terminated prior to four months due to failures unrelated to the TAH and one experiment with a TAH related failure.

   c) These non-TAH related exclusions are of biological origin and include infections, accelerated calcification or physical growth which are more directly a consequence of the specific animal model. If the TAH delivers less than 2.0 L/min pump flow, or if other complications arise and continue despite all corrective efforts, the test shall be terminated.

   d) All animals, excluding operative deaths, are to be included in the number of experiments above. Operative deaths are defined as animal deaths not traceable to TAH function occurring within 48 hours of the implant procedure.

2) The general condition of all animals is to be evaluated. In addition, appropriate hematologic, microbiologic, clinical chemistry and circulatory

parameters are to be measured to determine whether there are hazardous consequences due to the TAH implantation. Therapeutic regimens must be detailed.

3) It is necessary to document the proper function of the TAH during the course of the experiment (including during exercise). Documentation of pump flow, power consumption, and leakage rate across the variable volume device (if part of the design) is essential. Leakage rates should be measured across other membranes which separate different fluids, such as the pump bladder.

4) All animals (including early terminations) must have a complete autopsy including both gross and microscopic examination. Particular attention shall be paid to the anastomotic connections of the TAH to the cardiovascular system, to evidence of thromboembolic events and evidence of thermal damage in tissue adjacent to the TAH.

5) Biweekly reports shall be transmitted to the NHLBI Program Office regarding animal status. The reports will include the hematology profile, prothrombin time, and antithrombotic regimen for each animal with an implanted TAH.

k. Post-Explant TAH Evaluations

Each post-explant TAH shall be examined and documented in detail regarding system performance and component integrity.

1) Each TAH subjected to chronic studies shall have proper fixation of the blood contacting surface upon explanation for histopathological analysis. Internal pump surfaces including conduits and valves shall be examined both macroscopically and microscopically.

2) The pathology protocol used to evaluate the host-device interactions, in addition to specifying the standard gross and microscopic examination techniques to be used, should specify in detail any special additional studies that are planned. For example, an investigator could propose studying the local and/or systemic effects of tissue heating or vibration. Retrieval techniques for implanted materials and preservation of retrieved materials should be fully addressed. The implant must be retrieved and evaluated for its interaction with blood and tissue components. The manner in which the implant is preserved should maximize the possibility for future additional studies. Evaluation of the retrieved implant might include qualitative and quantitative description of the biological components adherent to the TAH (pump housing, bladder, valves) or which have penetrated the bulk of material (for example, lipids or calcium in a blood pump bladder).

3) Examination and documentation of mechanical, electrical, electronic and physiochemical integrity of all system components including software, shall be performed.

4) A detailed failure mode and effects analysis shall be performed on all failed components.

Summary of Contract Deliverable Items

(1) Phase I

Phase I accomplishments will be a major factor in determining which contractors will receive funding for Phase II. These demonstrated accomplishments must include, as a minimum:

A TAH design for five year life.

Two hermetically sealed TAH systems tested in vitro for at least three (3) months.

Two hermetically sealed TAH systems evaluated in animals over at least a two (2) month period.

A completed test fixture appropriate for performing device readiness testing for at least two TAH systems.

A Quality Control and Quality Management program in place.

One completely operational TAH system to NHLBI, packaged and labelled.

(2) Phase II

Deliverables required at the end of Phase II include:

A minimum of eight hermetically sealed TAH systems in their final "clinical" configuration tested over at least a two year period in vitro, and/or in vivo with no failures.

A minimum of 40 animal months of operation of implanted hermetically sealed TAH systems in eight animals, achieving at least four months duration in each animal.

One complete operational TAH system to NHLBI, packaged and labeled.

There is considerable overlap in the tasks which are required for Phases I and II. The table below summarizes requirements with references to sections a thru k, above:

		Phase I	Phase II
a.	Performance Goals	X	X
b.	Human Factors	X	X
c.	Design Reliability; Animal Performance	X	X
d.	Design, Manufacturing Documentation	X	X
e.	QC&QM	X	X
f.	Packaging		X
g.	Mock Loop and Characterization	X	X

h.	Device Readiness		X
i.	In Vivo Characterization	X	
j.	Chronic In Vivo Performance		X
k.	Post-Explant Evaluation	X	X

SCOPE OF WORK

Independently and not as an agent of the Government, the Contractor shall furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the Government as needed to perform the Statement of Work below:

PHASE I--October 1, 1993 through September 30, 1996

Task 1. Design

1. Using Quality of Life as the guiding factor, a reliability-based TAH design shall be developed that addresses quality, surface integrity, corrosion, control, software, flow, performance, materials, tissue and blood contacting surface configuration, biocompatibility, environmental compatibility, hemolysis, thromboembolism, intimal hyperplasia, infection, and manufacturing. Manufacturing design shall address computer aided reliability, process modeling, and systems engineering. The design model must be based upon five years of failure free life. It shall be updated and modified based upon test data and reported results.

   a) Blood Pump

      The contractor shall complete research, development, and evaluation of the blood pump component of the TAH. This effort includes fabrication and development of individual elements. Areas of study include, but are not limited to, materials evaluation and selection, bladder development and testing, inlet and outlet valve configurational studies, improved grafts, pump and housing development, hemodynamic studies, biologic studies, corrosion studies, and life testing of all components. Where appropriate, accelerated component life testing shall be performed to complement the real time testing. Manufacturability under QC&QM shall be demonstrated.

   b) Energy System

      The contractor shall complete development of the energy system selected to actuate and control the blood pump chambers. This effort includes in vitro characterization testing, component accelerated life testing, real time life testing, and energy system optimization studies. Manufacturability of this subsystem under QC&QM shall be demonstrated.

   c) System Integration

      Under QC&QM, the contractor shall integrate each element of the system into a TAH. Typical components included are the blood pump, energy converter, variable volume mechanism, power conditioning hardware and software, external and internal power sources, and diagnostic instrumentation.

Appropriate interface studies, which include both hardware and software testing of the electrical, mechanical, and chemical integrity of the entire TAH must be completed. System integration and optimization studies shall address areas such as the anatomical location of the TAH, thermal management, control modes, orientation effects, variable volume mechanism, and manufacturability.

Task 2. Quality of Life

An estimate shall be made of the expected Quality of Life based on actual performance of the TAH. Indices of Quality of Life shall be enumerated, modified, and finalized.

Task 3. Quality Control and Quality Management (QC&QM)

The contractor shall develop and implement a program for Quality Control and Quality Management which includes all phases of manufacturing, procurement of components, assembly, testing, and post-test evaluation of the TAH. The contractor shall have a discrepancy reporting system, configuration control of the TAH design, and a procedure for incorporating any modifications which are introduced during the design or testing phases. The program shall involve subcontractors and alternate sources. The program, including human resource development, shall be updated and evaluated periodically as necessary based on test or other information. The ISO 9000 International Standard or equivalent will be employed.

Task 4. Documentation

The contractor shall develop a plan and shall provide documentation for all phases of design, production, and evaluation of the TAH. The preparation of design and manufacturing documentation shall be completed to meet FDA requirements.

Task 5. System Fabrication and Manufacturing

This task includes the fabrication of systems to meet development and testing requirements. Demonstration of system manufacturability, including raw material processing, workpiece fabrication, joining and assembly, test and inspection, and machining and tooling technologies, shall be completed. One operational system shall be delivered to NHLBI at the end of the Phase I contract period of performance.

Task 6. Test Equipment Fabrication and Documentation

All test equipment and test fixtures, including hardware and software, to be used for testing and evaluation shall be identified. Documentation shall be provided regarding the accuracy and precision of the test equipment. At least two fully operational test fixtures intended for use during Phase II device readiness testing must be completed by the end of Phase I.

Task 7. In Vitro Testing

TAHs shall be tested in mock loops (laboratory and/or animal) to verify performance, using at least two fully operational and independent TAH systems over a period of at

least three months each. The TAHs shall be hermetically sealed and leakage measurements will be made for components such as bladders, variable volume devices, and hydraulic chambers. These tests shall simulate physiological environments as a prelude to Device Readiness Testing.

Task 8. Animal Testing for In Vivo Characterization

Animal experiments shall be performed with implanted TAHs. A major goal of this task will be to achieve two month survival in two animals, each supported with an implanted hermetically sealed TAH. The TAH shall be configured to conform to its ultimate configuration as a "clinical" system. Leakage rates of fluids shall be determined for components such as pump bladders, variable volume devices, and chambers containing hydraulic or other nonphysiologic fluids. The overall leakage rate of the implanted TAH shall be determined for each animal study.

Task 9. Biological Effects

The contractor shall perform studies to determine biological and physiological effects on animals with implanted TAHs for both acute and chronic experiments, and shall provide documentation of these effects.

Task 10. Anatomical Studies

The geometric suitability of intracorporeal components shall be determined using human cadaver fittings. The positioning of the TAH must be ascertained as feasible and as adaptable to such positional changes as may be expected in a mobile patient. The contractor shall demonstrate the TAH application in a range of cadaver sizes and extrapolate the sizes of living humans in whom the TAH would be appropriate.

Task 11. Device Retrieval and Evaluation

The contractor shall develop a plan, provide documentation, and implement device retrieval and evaluation after explanation from animals.

Task 12. Failure Mode and Effects

The contractor shall develop a plan and documentation for evaluating failure modes and making root cause determinations, and shall perform such evaluations for failures which occur during various phases of fabrication, assembly, manufacturing, and testing.

Task 13. FDA Requirements

The contractor shall develop and implement a program for interactions with FDA regarding manufacturing and testing practices as a prelude to preparation and submission of an application for an Investigational Device Exemption (IDE).

Task 14. Reports and Technical Data Packages

Quarterly, annual, and final technical reports shall be prepared. Financial reporting will also be required. In addition, a technical data package shall be prepared which fully documents the TAH design, including engineering drawings.

Scientific papers appropriate for publication in refereed journals are anticipated. The contractor shall collaborate with other contractors and the NHLBI in these efforts.

Task 15. Meetings

The contractor shall meet periodically with other contractors and NHLBI staff to interchange information regarding research findings and progress. Meetings with staff shall be scheduled at least twice annually, on site and at the National Institutes of Health in Bethesda. It is anticipated that areas of mutual interest will be identified during these meetings and that cooperation and collaboration among contractors will be recommended by NHLBI.

PHASE II--October 1. 1996 through September 30, 2000

Task 1. Common Protocol Development

In vitro and in vivo protocols shall be developed and finalized to test and evaluate the TAH. This task shall be performed in cooperation with the Government Project Officer and other NHLBI selected contractors in this program. It is anticipated that this effort shall require six to nine months to complete.

Task 2. Quality Control and Quality Management

The contractor shall continue implementing the program developed in Phase I, with modifications as necessary.

Task 3. Documentation

The contractor shall provide documentation for all phases of design, production and evaluation of the TAH. The FDA Good Manufacturing Practices will be observed.

Task 4. System Fabrication and Manufacturing

As in Phase I, and using Quality Control and Quality Management procedures, TAH systems shall be fabricated to meet the demands of in vitro and in vivo evaluations. One operational system, packaged and labeled, shall be delivered to NHLBI at the end of the contract period.

Task 5. Device Readiness Testing

TAH reliability shall be established by testing hermetically sealed systems in their final configuration in mock test loops. As per the protocol developed in Task 1, TAHs shall be tested to establish, as a minimum, 80% reliability with 80% confidence, over a minimum period of two years real time testing. A monitoring system shall be implemented to provide information on a timely basis to NHLBI regarding problems and progress during testing.

Task 6. TAH Performance in Chronic Animal Experiments

TAH performance shall be evaluated in animals with hermetically sealed implanted systems configured for "clinical" use, as per the protocol developed in Task 1. At least 40 animal months of failure-free operation shall be demonstrated in eight animals for an average of five (5) months with a minimum of four months each. No more than twelve animals shall be utilized for this set of experiments, one of which may be excluded for a device problem and three of which may be terminated due to failures unrelated to the TAH. A monitoring system shall be implemented to provide information on a timely basis to NHLBI regarding problems and progress during animal studies.

Task 7. Biological Effects

The contractor shall perform studies to determine biological effects on animals wit implanted TAHs for all animal experiments, and shall provide documentation of these effects.

Task 8. Device Retrieval and Evaluation

The contractor shall implement and document device retrieval and evaluation after explantation from animals in accordance with the protocol.

Task 9. Failure Mode Analyses and Corrective Action

The contractor shall document failures and failure mode analyses for failures which occur during fabrication, assembly, manufacturing, and in vitro and in vivo evaluations. Root cause determination shall be performed. Restart, redesign, retooling, corrective action, or new verification studies of TAH design shall not b initiated prior to receipt of written authorization from the Contracting Officer.

Task 10. FDA Requirements

The contractor shall continue interactions with FDA regarding manufacturing and testing practices.

Task 11. Reports and Technical Data Packages

Quarterly, annual, and final technical reports shall be prepared. Financial reporting shall also be required. In addition, a technical data package shall be prepared which fully documents the TAH in vitro and in vivo evaluations.

Scientific papers appropriate for publication in refereed journals are anticipated. The contractor shall collaborate with other contractors and the NHLBI in these efforts.

Task 12. Meetings

The contractor shall meet periodically with other contractors and NHLBI staff to develop protocols and exchange research and evaluation information. During protocol development in the first year of Phase II, four (4) meeting are anticipated. Meetings shall be scheduled at least twice annually thereafter, on site and at the National Institutes of Health in Bethesda. Contractors may cooperate and collaborate with one another in certain areas, as recommended by NHLBI.

重症心不全に対する治療機器の臨床試験ガイドライン（案）

日本人工臓器学会

Ⅰ．緒言

医療機器の開発に関する臨床試験の実施に当たっては、医薬品と同様に、倫理性、科学性および信頼性の確保が必要であることから、「医薬品の臨床試験の実施の基準（GCP:Good clinical practice)」が定められ、またその後も、臨床試験を円滑に推進するための具体的な方策について検討が進められてきている。本ガイドラインは、重症心不全に対する治療機器の臨床試験を、臨床試験の本来の目的である安全性と有効性の評価を科学的かつ効率的に、かつ倫理面からも配慮することにより、円滑に遂行することができるように、考慮する事項についてまとめたものである。医療機器は医薬品に比べて多くの構成要素ならなっており、また、日進月歩の技術革新がその性能が大きく向上されていく可能性が高い。それらの点も踏まえて、本ガイドラインの利用に当たっては、決して硬直した利用をするのではなく、技術の進歩が患者治療の改善に早急に結びつくよう、機動的な運用が望まれる。

Ⅱ．非臨床試験

1．総論

臨床試験の実施にあたっては、各種の安全性試験や動物での適切な非臨床試験が既に行なわれていることが前提であり、その機器がヒトにおいて許容される安全性と有効性を示唆する成績が得られていなければならない。

臨床試験計画書には、当該機器をヒト被験者に使用することを正当化するために今まで実施された非臨床試験と、その試験結果の評価を要約しなければならない。この要約には非臨床試験データを含めるか引用しつつ、設計基準、in vitro 試験、機械的及び電気的試験、信頼性チェック、ソフトウエアの検証等を含めなければならない。更に、GLP に基づいて、性能試験、ex-vivo 試験、毒性試験および動物による安全性試験、必要に応じて慢性動物実験などの結果を含むこととし、試験の適切性と試験履歴を含めなければならない。

2．機械的循環補助装置について

機械的循環補助装置については以下のような試験項目の中から必要とされる項目を選択する。

物理的化学的性能

ポンプ性能

システムの耐久性

流入出コンデュイットの機械的性状、人工血管の性状

装置のシール性能