参考資料

(1)資料1:重症心不全に対する治療機器の臨床試験ガイドライン
（日本人工臓器学会）
(2)資料2:NEDO人工心臓プロジェクト実験プロトコル(2001)
(3)資料3:NHLBI-HV-92-28 (1992). TAH Request for Proposal.
(4)資料4:FDA Guideline, F89-33838(1987)
(5)資料5:ASAIO/STS, Long-term mechanical circulatory support system reliability recommendation(1998).

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）

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

機械的安全性

発熱
制御性能
駆動状況表示部の性能
警報の作動状況
Computational Fluid Dynamics ／ Flow Visualization

安定性
搬送、保存、保存期間

電気的安全性
漏れ電流試験
耐電圧試験
電磁波障害
電源管理

生物学的安全性
生体適合性
抗血栓性
溶血性能
使用材料の安全性
その他
Human Factors

Ⅲ．臨床試験

Ａ．臨床試験の実施にあたって

１．「医療機器の臨床試験の実施の基準」(GCP)の遵守

臨床試験はヒトを対象として行なわれるものであり、被検者の安全と人権の保護に対する倫理的配慮のもとに、科学的に適正に実施されなければならない。具体的には医療機器の GCP を遵守して行なわれるべきである。

２．臨床試験の進め方

臨床試験の実施にあたっては、以下のような臨床試験計画書に従って進めなければならない。また、その結果は臨床試験総括報告書としてまとめなければならない。

３．臨床試験計画書

臨床試験計画書は、臨床試験依頼者と臨床試験担当医師の間で合意された文書でなければならない。試験の目的を達成するために、臨床試験計画書は、最新の臨床知識及び臨床経験などをよく勘案し、試験の結果の科学的妥当性と再現性を適切に確保出来るように設計されなければならない。試験プロトコル作

成にあたっては、（１）文献レビュー、（２）非臨床試験、（３）リスク分析、（４）予備試験や医学的経験等から有効性および安全性の両面から十分な検討をおこない、ヒトを対象とした試験を実施することの妥当性を明記すべきである。

４．臨床試験総括報告書

臨床試験総括報告書は試験結果が明確に判るようにまとめる必要がある。その構成と内容としては、まず簡潔なサマリーである「概要」に続き、「倫理」、「組織」、「緒言」、「目的」、「計画」、「対象患者」、「有効性の評価」、「安全性の評価」、「考察と全般的結論」、「文献」の順でまとめることが望ましい。

B．機械的循環補助装置の臨床試験

1．臨床試験計画書の構成例

1　はじめに

2　治験の目的

3　治験用具

3.1　治験用具の型式名、形状、性能および仕様
3.1.1　治験用具の型式名
3.1.2　治験用具の形状
3.1.3　治験用具の性能および仕様
3.2　治験用具の使用方法
3.2.1　装着手術手技
3.2.2　操作方法
3.2.3　抗凝固療法

4　対象疾患及び選択・除外基準

4.1　対象疾患
4.2　選択基準
4.3　除外基準
4.4　実施目標症例数
4.4.1　実施目標症例数
4.4.2　根拠

5　治験の方法（適用手順）

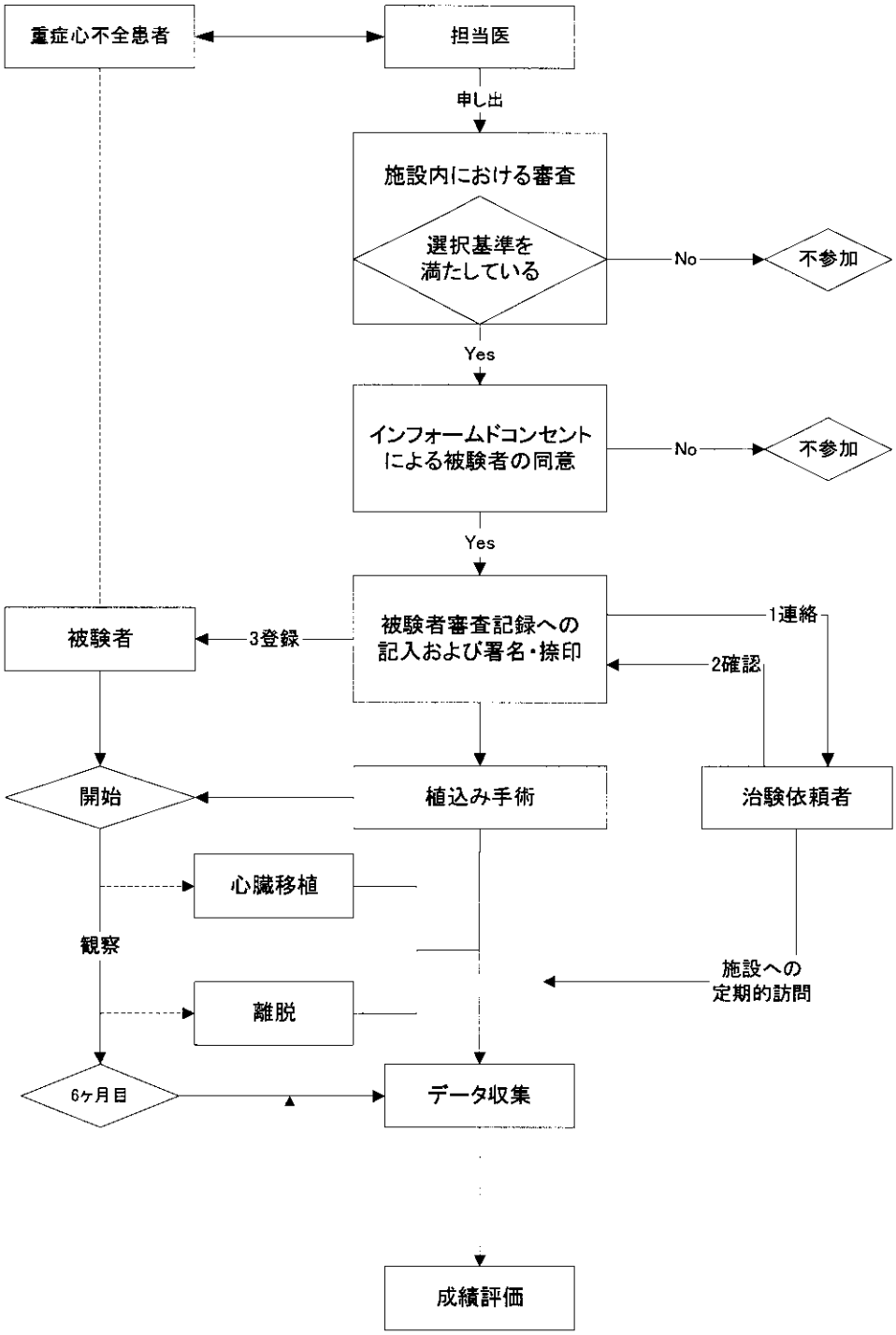
5.1　被験者の登録
5.1.1　各治験実施施設内における審査
5.1.2　被験者の同意（インフォームドコンセント
5.1.3　被験者の登録
5.2　植込み手術
5.3　植込後の管理
5.3.1　術後管理
5.3.2　抗凝固療法
5.3.3　日常管理
5.3.4　リハビリテーション
5.4　治験の終了
5.4.1　観察期間
5.4.2　ポンプの摘出
5.5　被験者の登録から終了
5.6　緊急事態の対応
5.6.1　治験用具の動作不良による緊急事態
5.6.2　治験用具の動作不良以外による緊急事態
5.6.3　治験依頼者の連絡先およびその対応
5.6.4　緊急事態の対応の流れ

２．機械的循環補助装置の臨床試験で検討すべき事項

(1)臨床試験のデザイン

機械的循環補助装置の臨床試験では Randamized Control Trial を行うことは必ずしも適切ではない。探索的臨床試験と検証的臨床試験の２段階試験、市販後臨床調査の積極的活用、承認後の一部変更の奨励のための非臨床試験の活用などが望まれる。

(2) 治験の方法（適用手順）


重症心不全患者
担当医
申し出
施設内における審査
選択基準を
満たしている
No
不参加
Yes
インフォームドコンセント
による被験者の同意
No
不参加
Yes
被験者
3登録
被験者審査記録への
記入および署名・捺印
1連絡
2確認
開始
植込み手術
治験依頼者
心臓移植
観察
施設への
定期的訪問
離脱
6ヶ月目
データ収集
成績評価

(3) 対象疾患及び選択・除外基準

1．対象疾患

長期使用循環補助装置は心臓移植待機中の極めて重症な心不全患者で、心不全が増悪した症例に対して使用することを原則とする。適応となる疾患は従来の治療法では救命ないし延命の期待がもてない以下の重症心疾患である。

1. 拡張型心筋症、および拡張相の肥大型心筋症
2. 虚血性心筋疾患
3. その他（日本循環器学会および日本小児循環器学会の心臓移植適応検討会で承認する心臓疾患）

2．選択基準

原則として被験者は以下の選択基準Aに該当し、かつ選択基準Bに該当しなければならない（項目4はa, b, cのいずれか1つ）。

ただし、選択基準Aに該当しないが、選択基準Bに該当し、長期使用循環補助装置以外に救命ないし延命の期待がもてない患者を被験者として登録する場合には、心臓移植の適応者として（社）日本臓器移植ネットワーク心臓移植待機リストへの登録手続きを速やかに行うものとする。

選択基準A

1. (社)日本臓器移植ネットワークの心臓移植待機リストに登録されていること。

選択基準B

1. 高度心不全状態が持続し、かつNYHA分類クラスIV[2)]の心不全症例。ただし、ジギタリス・利尿薬・アンギオテンシン変換酵素(ACE)阻害薬・硝酸塩・β遮断剤など最大限の薬物治療によっても効果が見られないこと。
2. 年齢は原則として15歳以上であること。
3. 原則として体表面積(BSA)が1.5m^{2}以上の症例。
4. 以下の項目(a)、(b)、(c)いずれかを満足している症例。
   (a) 内科治療にても収縮期圧80mmHg以下あるいは心係数(CI)が2.0 l/min/m^{2}以下でかつ肺動脈楔入圧が20mmHg以上である症例。
   (b) 下記の強心剤に依存している症例。

ドブタミン・ドーパミン・エピネフリン・ノルエピネフリン・PDEⅢ Inhibitor 等

(c) 下記の機械的循環補助に依存している症例。

IABP・PCPS・国産型補助人工心臓等

5. 被験者が本治験の意義を十分理解し、被験者本人からの文書によるインフォームドコンセントが得られていること。被験者が未成年である場合は、被験者の親権者または実質的保護者からも同意が得られていること。被験者が意識を喪失している等、被験者本人の判断が不可能な場合であって、かつ本治験用具の使用が被験者の生命予後によって不可欠と考えられる場合には、代諾者による同意が得られていること。

2) NYHA (New York Heart Association) 心機能分類

クラス Ⅰ	器質的心疾患があるが、身体的活動には制限が無い。普通の身体的労作では疲労、動悸、呼吸困難または狭心痛を起こさない。	クラス Ⅲ	器質的心疾患があり、身体的活動は著明に制限される。安静時には自覚症状はないが、普通の軽い身体的労作でも疲労、動悸、呼吸困難または狭心痛を起こす。
クラス Ⅱ	器質的心疾患があり、身体的活動は軽度制限される。安静時には自覚症状はないが、普通の身体的労作で疲労、動悸、呼吸困難または狭心痛を起こす。	クラス Ⅳ	器質的心疾患があり、どんな身体的労作でも自覚症状を伴う。心不全徴候または狭心症が安静時にも認められ、わずかな身体的労作でも、症状が悪化する。

3. 除外基準

以下の基準に 1 つでも該当している場合は長期使用循環補助装置被験者として認められない。

1. 重症感染症を有する症例。
2. 不可逆性多臓器不全を有する症例。
3. 妊娠中の症例。
4. 重度の慢性閉塞性肺疾患を合併した症例。
5. 最近 30 日以内に顕著な肺動脈塞栓症の徴候をみた症例。
6. 高度の肺高血圧症を有する症例。
7. 開心術後早期（2 週間程度）の症例。
8. 重度の肝臓疾患を合併した症例。
9. 重度の中枢神経障害を有する症例。

10. 治療不可能な腹部動脈瘤や重度の末梢血管疾患を合併した症例。

11. 重度の出血傾向、慢性腎不全、癌など生命予後不良な悪性疾患を合併した症例。

12. 著しい肥満のある症例。

13. 薬物中毒またはアルコール依存の既往がある症例。

14. プロトコールに従えない、あるいは理解不可能と判断されるほどの精神神経障害の既往歴がある症例。

15. その他担当医師が不適当と判断した症例。

4．実施目標症例数

○症例　(施設は○グループ最大○施設)

(4) エンドポイント、成績評価

エンドポイントの例
（参考資料1　Table 6）

1　成績評価

長期使用循環補助装置の成績評価を、次の通り評価することとする。

1.1　機器の有効性（1）

長期使用循環補助装置を用いることにより被験者の心臓を充分に補助する血液ポンプとしての機能を有するかどうか、下記評価基準に対する適合の可否を評価する。

評価項目	評価基準	適合する
平均ポンプ係数（計算値）	観察期間中における平均ポンプ係数が2.0 l/min/m²以上であること。	はい／いいえ

1.2　機器の有効性（2）

心臓移植待機中に長期使用循環補助装置を装着することによる被験者の状態として下記評価項目を観察し、被験者の治験前臨床所見と治験観察期間中の臨床所見とを比較し、下記評価基準に対する適合の可否を評価する。

評価項目	評価基準	適合する

循環維持機能	全身循環が改善するもしくは増悪しないこと。	はい／いいえ
肝 機 能	総ビリルビン、GOT、GPT が改善するもしくは増悪しないこと。	はい／いいえ
腎 機 能	BUN、クレアチニンが改善するもしくは増悪しないこと。	はい／いいえ
右心機能	右心機能が改善するもしくは増悪しないこと。	はい／いいえ
呼吸機能	呼吸不全が改善するもしくは増悪しないこと。	はい／いいえ
強心剤投与	投与されている強心剤の種類が軽減したこと、および／または投与量が軽減したこと。	はい／いいえ
NYHA 心機能分類	NYHA 心機能分類が改善するもしくは増悪しないこと。	はい／いいえ

1.3 安全性

1.3.1 判定基準

有害事象の有無に関して長期使用循環補助装置に直接起因する有害事象の程度から下記の 4 段階で安全性を判定する。なお有害事象は長期使用循環補助装置装着後新たに発生したものとし、有害事象の程度は重症度、持続期間および回復度から治験責任医師または治験分担医師が判断する。

判定項目	判 定 基 準
極めて安全	長期使用循環補助装置に直接関連した有害事象を認めなかった。
安 全	長期使用循環補助装置に直接関連した軽微な有害事象を認めたが、処置を施すことによって完全に改善し得た。
安全性にやや問題あり	長期使用循環補助装置に直接関連した有害事象を認め、いかなる処置を施しても完全には改善され

	なかったが、被験者に重篤な影響を与えなかった。
安全性に重大な問題あり	長期使用循環補助装置に直接関連した有害事象を認め、いかなる処置を施しても改善し得ず、被験者に重篤な影響を与えた。

1.3.2 有害事象の定義

予測され得る主な有害事象とその定義を以下に示す。

- **感染症**
  白血球数の上昇、発熱、および抗菌剤治療を伴い、血液、尿、痰、または組織の培養結果が陽性であること。

- **出血**
  手術（例えば、心タンポナーデのように）が必要な大量出血または死に至るような大量出血。

- **血栓塞栓症**
  装置挿入中または摘出後の突発的な神経、肺、腎臓、肝臓または末梢血管等の疾患の臨床的兆候。もし被験者が死亡すれば、1つまたは複数の臓器に血栓または梗塞の存在が病理解剖により明らかにされる場合。

- **溶血**
  遊離ヘモグロビン値が2回続けて40 mg/dlより大きい場合。なお、2回目の測定は1回目の測定から24時間以内に行うことが望ましい。

- **装置植込み後の手術**
  装置植込み後や取り外し後の装置に関連しない理由による手術（例えば、虫垂切除）。

- **装置誤作動**
  システムの構成品が意図した通り動かない場合、誤作動とみなされる。装置によるディスプレイの非表示、バッテリでの作動不可、および、一時的な生命維持の欠落は誤作動と考える。

- **装置故障**
  装置故障は多くの外部バックアップ部品や機器類を含め、長期使用循環補助装置が被験者の生命の維持をできないこととして定義される。

1.3.3 治験用具に起因する有害事象および起因しない有害事象の判定指針

上記有害事象が発生した場合に、その有害事象が長期使用循環補助装置に起因して発生したものか、もしくは被験者やその他の要因によるものなのか判定しなければならない。以下にその判定基準を示す。

- **感染症**

  装置関連　術前に特定の菌が同定されなかった場合にLVAS装着中に生じる感染症。経皮ドライブラインの感染症とは抗菌治療を必要とする皮膚貫通部周辺部より採取した陽性培養の感染として定義される。

  被験者関連　　術前に特定の菌が存在した場合に生じる感染症。（除外基準である重症感染症とは異なり、適応前に発見された症状を伴わない排菌もしくは症状があっても軽微な感染症の場合は、短期間に治癒が可能とみなされ治験の対象である。）

  その他　記録された陽性培養が装置からではなく、カテーテル、胸腔ドレーンチューブ、気管チューブから分離された明らかな感染症。

- **出血**

  装置関連　コネクタやグラフトといった装置から、または植込み部位や装置取り付け位置からの出血。装置からの出血が見られる場合の挿入後における心タンポナーデは装置関連の出血の一例である。

  被験者関連　　装置ではなく手術操作あるいは確認された血液疾患による出血。装置からの出血が全く見られない場合の挿入後における心タンポナーデは被験者関連の出血の一例である。

- **血栓塞栓症**

  装置関連　装置植込み時または摘出による血栓塞栓症。血栓塞栓症は装置の補助中または摘出時に発生する。例えば、装置内血栓はコネクターから外れたり、または、摘出中に起こる低流量状態により遊離される。装置摘出中または摘出後すぐに見られる装置に由来する（装置内に塞栓の残りが見受けられるところの）血栓塞栓症は、装置関連の血栓塞栓症と見なされる。

  被験者関連　　摘出時における装置ではなく、装置摘出後の血栓塞栓。血栓塞栓は被験者関連の理由によりポンプ摘

出時に生じることがある。例えば、血栓は吻合部から生じるし、あるいはドナー心臓の細動により発生する塞栓。

その他　補助中、装置摘出時、または摘出後 24 時間以内の血栓塞栓症は、もし血栓が装置に起因しているかわからないならば、疑装置関連として分類される。血栓塞栓症が起き、しかしそれが装置と関連しているかどうかはっきりしないならば、その血栓塞栓症の発現は疑装置関連と見なされる。

- **溶血**

  装置関連 植込み後 3 日以降に見られる溶血。

  被験者関連　　植込み後 3 日以内の溶血。

- **装置植込み後の手術**

  装置関連 ヘルニア、癒着、腸閉塞または他の装置に帰する医学的な問題を治すための装置植込み後の手術。

  被験者関連　　装置植込み後や取り外し後の装置に関連しない理由による手術（例えば、虫垂切除）。

1.4 データの収集

長期機械的循環補助装置の有効性及び安全性を評価する為に以下のデータを収集する。

1.4.1 用具の有効性（1）に関わるデータ

- 用具の状態（モニタからの読み取り）
  - ポンプ拍出量
  - 駆動モード(Auto/Fixed Rate)
  - ポンプ流量
  - ポンプ拍動数

1.4.2 用具の有効性（2）に関わるデータ

- 心機能等（心電図血圧モニタ、心エコー、胸部 X 線）
  - 心拍数(H.R.)
  - 血圧(AoP)
  - 心拍出量(CO)*
  - 左室拡張期径(LVDd)
  - NYHA 分類
  - 中心静脈圧(CVP)*
  - 肺動脈圧(PAP)*
  - 心胸郭比(CTR)
  - 肺動脈楔入圧(PCWP)*
- 血液検査（血液学、血液生化学、血液ガス*）
  - 白血球(WBC)
  - コレステロール
  - 総ビリルビン
  - 尿素窒素(BUN)
  - クレアチニン(CRE)

(T-Bil)
- 中性脂肪(Trig)
- 総蛋白(T-Protein)
- アルブミン(ALB)
- GOT
- GPT
- LDH
- CPK
- PaO2(動脈血酸素分圧)
- 尿酸
- Na
- K
- Cl
- Ca
- P
- FDP
- PaCO2(動脈血炭酸ガス分圧)

*心拍出量、肺動脈楔入圧、中心静脈圧、肺動脈圧および血液ガスは術前、術後 1 日およびこれ以降カテーテルを抜去するまで観察を実施する。カテーテル抜去後は治験責任医師又は治験分担医師が必要と判断した場合に観察を実施する。

1.4.3 安全性評価に関わるデータ

- 血液検査（血液学）
  - 赤血球(RBC)
  - 血小板(PLTC)
  - 遊離ヘモグロビン(PFHb)
  - プロトロンビン時間(PT)
  - ヘモグロビン(Hb)
  - ヘマトクリット(Ht)
  - 活性化部分トロンボプラスチン時間(APTT)

1.5 項目別観察検査周期

項目別観察検査周期は下表に示すとおりとする。

項目		植込前	体外循環終了時	植込み後					
				1 日	1 週	2 週	3 週	1 ヶ月	2, 3, 4, 5, 6,12 ヶ月目
既往症		○							
現病歴		○							
ポンプの状態				毎日					毎月
心機能等	心拍数	○		○	○	○	○	○	毎月
	血圧	○		○	○	○	○	○	毎月
	心拍出量*	○		○	*				
	左室拡張期径	○						○	毎月
	肺動脈楔入圧*	○		○	*				
	中心静脈圧*	○		○	*				

	肺動脈圧*	○		○	*				
	心胸郭比	○		○	○	○	○	○	毎月
	NYHA 分類	○		○	○	○	○	○	毎月
血液検査	血液学	○	○	○	○	○	○	○	毎月
	血液生化学	○	○	○	○	○	○	○	毎月
	血液ガス*	○	○	○	*				
強心剤の使用状況		○		○	○	○	○	○	毎月
有害事象の有無				有害事象発生時					

*心拍出量、肺動脈楔入圧、中心静脈圧、肺動脈圧および血液ガスは術前、術後一日およびこれ以降カテーテルを抜去するまで観察を実施する。カテーテル抜去後は治験責任医師又は治験分担医師が必要と判断した場合に観察を実施する。

心移植移行後については、術後 1 週目、2 週目、3 週目、1 ヶ月目、2 ヶ月目および 1 年目に長期機械的循環補助装置装着中と同様の検査を行う。

長期機械的循環補助装置 離脱症例（心移植移行以外の場合）に関してはフォローアップとして、離脱後 1 週目、1 ヶ月目、2 ヶ月目および 1 年目に長期機械的循環補助装置 装着中と同様の検査を行う。

また、12 ヶ月以降長期機械的循環補助装置による補助循環治療が継続している場合は、各治験実施施設で 1 ヶ月毎にそれまでと同様の観察および臨床検査を継続する。

7.7 有用性の評価

7.7.1. 2.0L/min/m2 平均ポンプ係数が得られ、患者が長期機械的循環補助装置装着前に陥っていた多臓器不全を含む末期的循環不全から回復し、以下の結果が得られた場合、当該デバイスによる治療有効症例と評価する。

①長期機械的循環補助装置補助により 12 ヶ月以上生存した場合

②心臓移植手術が実施された場合

③心機能の回復により長期機械的循環補助装置離脱した場合(離脱後 1 か月以上生存)

④海外で心移植を受けるために渡航した場合

7.7.2. 7.7.1 の基準で 6 例中 3 例以上の治療有効症例が得られた場合、長期機械的循環補助装置の臨床的有用性を認める。6 例中 2 例の治療有

効症例が得られた場合、更に有用性を明確にする目的で 4 例追加して治験を続行し、10 例中 4 例(40%)の有効例が得られた場合、長期機械的循環補助装置の臨床的有用性を認める。

ガイドライン作成委員会委員名簿

参考文献

臨床応用に向けた体内埋め込み型人工心臓システム
総合評価実験プロトコール（NEDO プロジェクト）

構　成

1）基本方針

2）慢性動物実験プロトコール

3）耐久試験プロトコール

〈基本方針〉

1.　本プロジェクトで開発する人工心臓システムの性能が基本計画に掲げた目標仕様を達成しているかどうかの評価、あるいは目標達成及び改良のために必要な、性能の評価をするための科学的なデータに基づいた総合評価実験プロトコールを作成する。

2.　本プロトコールの第一の目標は本プロジェクトで開発する人工心臓システムの臨床応用の可能性を証明するためのものである。そのためにはシステムの有効性、安全性、信頼性、および耐久性を動物実験及び耐久試験をもって証明する事が必要である。ここでは、上記に示す実験を行うために規定しておくべき実験条件を定める。また、評価のために必要な記録項目、注目して観察すべき項目を定める。

3.　この人工心臓および両心バイパスシステムは適応とされる成人の両心機能の代替を行ったことが立証できる実験手法を用いる必要がある。また、生理的な要求に対して満足する流量制御ができるシステムであることを証明する必要もある。

4.　基本的に、全システムについて動物実験を行い、また全システムについて耐久試験を行うこととする。但し、完成した要素から順次、実験を行うことを妨げない。

〈慢性動物実験プロトコール〉

1. ポンプユニット(血液ポンプ、駆動装置およびコントローラ)

1) 規定しておくべき実験条件

ア. 使用する動物の埋め込み時の体重を明記。

イ. 周術期を除いて経口抗凝固剤、経口抗血小板剤を使用、不使用。術中および周術期はヘパリンを用いても構わない。尚、経口抗凝固剤、ワーファリンを使用する場合、PT の測定値には信頼性の高い INR を用いる。

2) 評価のために必要な記録事項

ア. 埋め込み方式

・同所性置換か、異所性埋め込みか？ 異所性の場合、埋め込み場所は？

イ. 動物種

ウ. 体重

エ. 手術記録(麻酔、体外循環記録含む)

オ. 術後経過記録(表1)

カ. 生理学的パラメータの記録(流量、左右心房圧、大動脈・肺動脈圧等)(表1)。尚、各種生体モニターラインの故障はそれが、実験の継続に支障を来さない限り、それをもって実験を中止する必要はない。

キ. デバイスパラメータの記録(入力電力、デバイス温度(生体接触面)、その他モータ電流、電圧、モータ回転数等必要に応じてモニター)(表1)

ク. 血液・生化学検査(表2)

ケ. 経口抗凝固剤、経口抗血小板薬、抗生物質、輸血、輸液を含む投薬記録(表1)

コ. 合併症の記載(出血、血栓塞栓症、感染症、多臓器不全、デバイス不具合等)(表1)

サ. 解剖所見(血栓塞栓症、熱傷の有無、感染、装置近傍組織所見)

シ. 摘出デバイスの分析(血栓形成、石灰沈着、感染、機能劣化、体液の侵入等)

＊尚、各種パラメータ記録におけるサンプリング法に関しては、各自の方法で連続モニターが可能なシステムを用いる。

2. TET

1) 規定しておくべき実験条件

特になし。

2) 評価のために必要な記録事項

ア. 動物種、埋め込み部位、実験期間
イ. 装置温度(生体との接触表面の最高温度)
ウ. 入力電力、伝送効率
エ. 人工心臓システムや模擬負荷などへの出力電力
オ. 合併症(出欠、感染、機械の故障等)
カ. 解剖所見(熱傷、感染、装置近傍の病理組織所見等)
キ. 摘出デバイスの所見(感染、体液の侵入等)及び機能維持度

3. 情報伝送部

1) 規定しておくべき実験条件

特になし

2) 評価のために必要な記録事項

ア. 伝送する情報の明記
イ. 動物種、埋め込み部位、実験期間
ウ. 伝送速度、認識率
エ. 許容偏心距離
オ. 合併症(出血、感染、機械の故障等)
カ. 解剖所見(熱傷、感染、装置近傍の病理組織所見等)
キ. 摘出デバイスの所見(感染、体液の侵入等)及び機能維持度

4. 体内バッテリー

1) 規定しておくべき実験条件

特になし

2) 評価のために必要な記録事項

ア. 充放電頻度(時間)
イ. 動物種、埋め込み部位、実験期間
ウ. 人工心臓システムや模擬負荷などへの出力電力、駆動可能期間
エ. 充放電時表面温度
オ. その他の合併症(出血、感染、機械の故障等)
カ. 解剖所見(熱傷、感染、装置近傍の病理組織所見等)
キ. 摘出デバイスの所見(感染、体液の侵入等)及び機能維持度

5. 運動負荷試験

ア. 動物種
イ. 運動負荷時体重
ウ. 運動負荷の条件(トレッドミルの場合には、速度、負荷時間など)
エ. 血行動態や生理学的パラメータの変化

オ. 人工心臓駆動パラメータの変化

6. 構造・被覆材料

A. 抗血栓性の評価

1) 規定しておくべき実験条件

周術期を除いて経口抗凝固剤、経口血小板剤を使用、または不使用。

2) 評価のために必要な記録事項

ア. 動物種、埋め込み部位、実験期間

イ. 経口抗凝固剤、経口抗血小板剤の種類、量、期間

ウ. 血液・生化学検査

エ. 合併症(出血、感染、機械の故障等)の記録

オ. 解剖所見(熱傷、感染、装置近傍の病理組織所見等)

カ. 摘出デバイスの所見(血栓、感染、劣化、体液の侵入等)

キ. 血液接触面の表面解析(光学および電子顕微鏡等による解析)

B. 組織適合性

1) 規定しておくべき実験条件

特になし。可能ならば ISO 10993-6 に準じて評価を行う。

2) 評価のために必要な記録事項

ア. 動物種、埋め込み部位、実験期間

イ. 合併症(出血、感染等)

ウ. 解剖所見(感染、材料近傍臓器の病理組織所見等)

エ. 摘出デバイスの所見(感染、劣化、体液による侵入等)

オ. 表面の解析(光学、電子顕微鏡等による解析)

〈耐久試験プロトコール〉

本プロトコールは、基本計画に示された、人工心臓システムについての埋め込み模擬環境下における機械的耐久性を検証するための、2年間の耐久試験に関するものである。拍動流型および連続流型の人工心臓に関する試験条件および記録項目は、別表に示すとおりとする。

耐久試験プロトコール比較表

項目			試験条件等	
			（拍動流）	（連続流）
供試品	対象システム		体内埋込み全システム	
	目標個数		8 セット	
試験期間			2年以上	
試験条件	環境	温度	37±2℃	
		使用液	生理食塩水	
	負荷条件*	平均前負荷	5mmHg～15mmHg	左心バイパス：100±20mmHg 右心バイパス：40±10mmHg
		平均右心後負荷	20mmHg～40mmHg	
		平均左心後負荷	100mmHg～120mmHg	
	平均流量		5L/min 以上	5L/min±20%
	駆動条件		規定した負荷に対して規定した流量を得られるよう駆動条件を設定。	
	試験装置		生体内使用条件を模擬したモック回路を使用する。 体内システムは生理食塩水に浸す。	
	エネルギー供給、貯蔵		1日1回30分のバッテリー駆動および充電	
判定基準 （継続不可）	流量		・30秒間平均流量3l/min 以下または、平均後負荷60mmHg を維持できない場合 ・3l/min 以下の流量（平均）の低下が60分に2回以上頻回に発生	
モニター項目	人工心臓システム		流量	
			TET 入力電力	
			モーター電流、電圧（または電力）	
			人工心臓拍動数	—
			モーター回転数(左右)	回転数
	試験環境		温度	
			塩分濃度 前後負荷圧力	
その他	性能試験		試験前後に実施	
	試験終了後		全数分解調査	
	連続試験の定義		停電等外的要因による中断は許容	

注*：連続流において前負荷、後負荷として規定するのではなく、圧較差を導入する。

表1　　慢性動物実験術後経過表

実験＃　　動物種：　　体重：　　埋込み場所：

項目		実験前（日時）	POD：　（日時）	POD：　（日時）	POD：　（日時）
抗凝固剤	薬剤（量）				
投与薬剤 輸液･輸血	薬剤（量）				
生理パラメータ	大動脈圧（mmHg） 肺動脈圧（mmHg） 右心房圧（mmHg） 左心房圧（mmHg） 右心流量（L/min） 左心流量（L/min）				
デバイス パラメータ	温度：モータ 温度：コントローラ モータ電流 入力電力				
合併症等					
その他特記事項					

表 2　　慢性動物実験データシート（血液・生化学）

実験#　　デバイス:　　シート#

項目	正常値	実験前 Date:	POD:	POD:	POD:	POD:	POD:	POD:	POD:
Ht(%)									
Hb(g/dl)									
RBC($x10^4$/ 1)									
WBC(/ 1)									
Platelet($x10^4$/ 1)									
Platelet Aggregation									
Free Hb(mg/dl)									
PT　　(sec)									
(INR)									
PTT(sec)									
ACT*(sec)									
Fibrinogen(mg/dl)									
FDP(g/ml)									
ALT**(IU/L)									
AST***(IU/L)									
LDH(IU/L)									
Creatinine(mg/dl)									
BUN(mg/dl)									
Na(mEq/l)									
K(mEq/l)									
Total Protein(g/dl)									
Albumin(g/dl)									
Total Billirubin(mg/dl)									
Urine　　潜血									
タンパク									
Blood Gas　PH									

PO2 (mmHg)									
PCO2 (mmHg)									
$HCO3^-$(mmol/L)									
BE (mmol/L)									

*ACT: Activated Clotting Time,

**ALT: L-alanine:2-oxoglutarate aminotransferase = GPT,

***AST: L-asparate:2-oxoglutarate aminotransferase = GOT

OMB NO. 0990-0115

SOLICITATION

SECTION A - SOLICITATION/CONTRACT FORM

1. Purchase Authority: Public Law 95-83 as amended

2. REQUEST FOR PROPOSAL (RFP) NUMBER: NHLBI-HV-92-28	3. ISSUE DATE: October 8, 1992	4. SET ASIDE: X NO ___ YES See Part IV Section L

5. TITLE: Phased Readiness Testing of Implantable Total Artificial Hearts

6. ISSUED BY:	7. SUBMIT OFFERS TO:
HLVD Contracts Section National Heart, Lung, and Blood Institute National Institutes of Health Federal Building, Room 4C04 9000 Rockville Pike Bethesda, Maryland 20892	See Part III, Section J, "Packaging and Delivery of the Proposal," ATTACHMENT I of this Solicitation

8. Proposals for furnishing the supplies and/or services in THE SCHEDULE will be received at the place specified in, and in the number of copies specified in Attachment 1 until 4:00pm local time on January 28, 1993.

9. THIS SOLICITATION REQUIRES DELIVERY OF PROPOSALS TO TWO DIFFERENT LOCATIONS. THE OFFICIAL POINT OF RECEIPT FOR THE PURPOSE OF DETERMINING TIMELY DELIVERY IS THE ADDRESS PROVIDED FOR THE RESEARCH CONTRACTS BRANCH AS STATED IN ATTACHMENT 1. IF YOUR PROPOSAL IS NOT RECEIVED BY THE CONTRACTING OFFICER OR HIS DESIGNEE AT THE PLACE AND TIME SPECIFIED FOR THE RESEARCH CONTRACTS BRANCH, THEN IT WILL BE CONSIDERED LATE AND HANDLED IN ACCORDANCE WITH PHS CLAUSE 352.215-10 ENTITLED, "LATE PROPOSALS, MODIFICATIONS OF PROPOSALS AND WITHDRAWALS OF PROPOSALS" LOCATED ON PAGE 132 OF THIS SOLICITATION.

10. Offeror must provide full name, address, TIN, and, if different, the address to which payment should be mailed.

FOR INFORMATION CALL: Joan E. O'Brien
PHONE: (301) 496-6838
COLLECT CALLS WILL NOT BE ACCEPTED.

12. Table of Contents on following page.

Joan E. O'Brien
Contracting Officer
HLVD Contracts Section
National Heart, Lung, and Blood Institute

DETAILED TABLE OF RFP CONTENTS

PART I - THE SCHEDULE

THE CONTRACT SCHEDULE SET FORTH IN SECTIONS B THROUGH H, HEREIN, CONTAINS CONTRACTUAL INFORMATION PERTINENT TO THIS SOLICITATION. IT IS NOT AN EXACT REPRESENTATION OF THE PROPOSED CONTRACT DOCUMENT. CONTRACTUAL PROVISIONS PERTINENT TO THE OFFEROR (I.E., THOSE RELATING TO THE ORGANIZATIONAL STRUCTURE [E.G., NON-PROFIT, COMMERCIAL] AND SPECIFIC COST AUTHORIZATIONS UNIQUE TO THE OFFEROR'S PROPOSAL AND REQUIRING CONTRACTING OFFICER PRIOR APPROVAL) WILL BE DISCUSSED IN THE NEGOTIATION PROCESS AND WILL BE INCLUDED IN THE RESULTANT CONTRACT. HOWEVER, THE ENCLOSED CONTRACT SCHEDULE PROVIDES ALL THE NECESSARY INFORMATION FOR THE OFFEROR TO UNDERSTAND THE TERMS AND CONDITIONS OF THE RESULTANT CONTRACT.

SECTION B - SUPPLIES OR SERVICES AND PRICES/COSTS

ARTICLE B.1. BRIEF DESCRIPTION OF SUPPLIES OR SERVICES

The objectives of the solicitation are to complete the development of electrically powered, totally implantable artificial heart (TAH) system and establish the reliability, performance and manufacturability of these TAH systems.

ARTICLE B.2. PRICES/COSTS

The final contract will contain the price/cost provisions agreed upon during negotiations.

ARTICLE B.3. PROVISIONS APPLICABLE TO DIRECT COSTS

This article will prohibit or restrict the use of contract funds, unless otherwise approved by the Contracting Officer for: 1) Acquisition, by purchase or lease, of any interest in real property; 2) Special rearrangement or alteration of facilities; 3) Purchase or lease of any item of general purpose office furniture or office equipment regardless of dollar value; 4) Travel Costs; 5) Patient Care Costs; 6) Accountable Government Property; and 7) Research Funding.

ARTICLE B.4. ADVANCE UNDERSTANDINGS

Specific elements of cost, which normally require prior written approval of the Contracting Officer before incurrence of the cost (e.g., foreign travel, consultant fees, subcontracts) will be included in this Article if the Contracting Officer has granted his/her approval in the preaward negotiation process.

SECTION C - DESCRIPTION/SPECIFICATIONS/WORK STATEMENT

ARTICLE C.1. STATEMENT OF WORK

a. Independently and not as an agent of the Government, the Contractor shall be required to 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, SECTION J, ATTACHMENT 2, dated October 8, 1992, attached hereto and made a part of this Solicitation.

ARTICLE C.2. REPORTING REQUIREMENTS

a. Technical Progress Reports

In addition to the required reports set forth elsewhere in this Schedule, the preparation and submission of regularly recurring Technical Progress Reports will be required in any contract resulting from this solicitation. These reports will require descriptive information about the activities undertaken during the reporting period and will require information about planned activities for future reporting periods. The frequency and specific content of these reports will be determined during negotiations.

For proposal preparation purposes only, it is estimated that three copies of these reports will be required as follows:

(X) Quarterly
(X) Annually (with a requirement for a Draft Annual Report)
(X) Final - Upon final completion of the contract (with a requirement for a Draft Final Report)

b. Summary of Salient Results

The Contractor will be required to prepare and submit, with the final report, a summary (not to exceed 200 words) of salient results achieved during the performance of the contract. This report will be required on or before the expiration date of the contract.

c. Program Plan

The Contractor shall prepare a program plan comprised of anticipated completion dates of key milestones. This report will be required on or before thirty (30) dates from the date of award in Phase I and on or before thirty (30) days from the beginning of Phase II.

d. In Vivo Reports

The Contractor shall prepare a report which will contain the important measurements that indicate the physiological status of the animals as well as device performance. This report will be required biweekly during chronic in vivo TAH performance tests.

e. Final Technical Report - Phase I

Ninety days before the end of Phase I, the contractor shall prepare and submit a final technical report of progress of activities, specifically describing accomplishments on a task by task basis. The demonstrated accomplishments shall include, at a minimum, a TAH design for five year life, two hermetically sealed TAH systems tested in vitro for at least 3 months two hermetically sealed TAH systems evaluated in animals over at least a two 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, etc. An operational TAH system shall accompany the Final Technical Report.

f. Final Technical Report - Phase II

Ninety days before the end of Phase II, the contractor shall prepare and submit a final technical report of progress of activities, specifically describing accomplishments on a task by task basis. The accomplishments shall include, at a minimum, the results of the in vitro device readiness testing over a two year period and the results of the chronic animal testing to achieve 40 animal months of failure free operation. An operational TAH system shall accompany the Final Technical Report.

SECTION D - PACKAGING, MARKING AND SHIPPING

All deliverables required under this contract shall be packaged, marked and shipped in accordance with Government specifications. The Contractor shall guarantee that all required materials shall be delivered in immediate usable and acceptable condition.

SECTION E - INSPECTION AND ACCEPTANCE

a. The Contracting Officer or the duly authorized representative will perform inspection and acceptance of materials and services to be provided.

b. For the purpose of this ARTICLE, the Project Officer is the authorized representative of the Contracting Officer.

c. Inspection and acceptance will be performed at:

National Heart, Lung, and Blood Institute
National Institutes of Health
Federal Building, Room 4C04
7550 Wisconsin Avenue
Bethesda, Maryland 20892

Acceptance may be presumed unless otherwise indicated in writing by the Contracting Officer or the duly authorized representative within 30 days of receipt.

d. This contract incorporates the following clause by reference, with the same force and effect as if it were given in full text. Upon request, the Contracting Officer will make its full text available.

FAR Clause No 52.246-8, INSPECTION OF RESEARCH AND DEVELOPMENT - COST REIMBURSEMENT (APRIL 1984)

SECTION F - DELIVERIES OR PERFORMANCE

ARTICLE F.1. DELIVERIES

a. Satisfactory performance of the final contract shall be deemed to occur upon delivery and acceptance by the Contracting Officer, or the duly authorized representative, of the following items in accordance with the stated delivery schedule:

(1) The items specified below as described in SECTION C, ARTICLE C.1 and C.2 will be required to be delivered F.O.B. Destination as set forth in FAR 52.247-35, F.O.B. DESTINATION, WITHIN CONSIGNEES PREMISES (APRIL 1984), and in accordance with and by the date(s) specified below [and any specifications stated in SECTION D, PACKAGING AND MARKING, of the contract]:

Phase I

Item	Description	Quantity	Delivery Schedule
(a)	Program Plan	3	30 days from the date of contract award.
(b)	In Vivo Report	3	Biweekly during chronic in vivo TAH performance tests.
(c)	Quarterly Reports	3	15 days following the end of each three-month interval after the date of award.
(d)	Draft Annual Report	3	90 days before the anniversary dates of the award.
(e)	Annual Reports	3	Yearly, on anniversary dates of award.
(f)	Final Phase I Technical Report	3	90 days before the completion of Phase I.
(g)	Operational TAH system	1	Completion date of Phase I.

Phase II

Item	Description	Quantity	Delivery Schedule
(a)	Program Plan	3	30 days from the beginning day of Phase II.
(b)	In Vivo Report	3	Biweekly during chronic in vivo TAH performance tests.
(c)	Quarterly Reports	3	15 days following the end of each three-month interval after the start date of Phase II.
(d)	Draft Annual Report	3	90 days before the anniversary dates of the start of Phase II.

(e)	Annual Reports	3	Yearly, on anniversary dates of the start of Phase II.
(f)	Draft Final Phase II Technical Report	3	90 days before contract expiration.
(g)	Final Phase II Technical Report, summary of salient report	3	Contract expiration date.
(h)	Operational TAH System	1	Contract expiration date.

The above items shall be addressed and delivered to:

Phase I

Addressee	Deliverable Item No.	Quantity
Project Officer National Heart, Lung and Blood Institute National Institute of Health Bethesda, MD. 20892	(a) Program Plan (b) In Vivo Report (c) Quarterly Reports (d) Draft Annual Report (e) Annual Report (f) Final Phase I Technical Report (g) Operational TAH system Phase I	2 2 2 2 2 2 1
Contracting Officer HLVD Contracts Section National Heart, Lung and Blood Institute National Institute of Health Bethesda, MD. 20892	(a) Program Plan (b) In Vivo Report (c) Quarterly Reports (d) Draft Annual Report (e) Annual Report (f) Final Phase I Technical Report	1 1 1 1 1 1

Phase II

Addressee	Deliverable Item No.	Quantity
Project Officer National Heart, Lung and Blood Institute National Institute of Health Bethesda, MD. 20892	(a) Program Plan (b) In Vivo Report (c) Quarterly Reports (d) Draft Annual Report (e) Annual Report (f) Draft Final Phase II Technical Report (g) Final Phase II Technical Report (h) Operational TAH system Phase II	2 2 2 2 2 2 1 1

Contracting Officer HLVD Contracts Section National Heart, Lung and Blood Institute National Institute of Health Bethesda, MD. 20892	(a) Program Plan (b) In Vivo Report (c) Quarterly Reports (d) Draft Annual Report (e) Annual Report (f) Draft Final Phase II Technical Report (g) Final Phase II Technical Report	1 1 1 1 1 1 1

ARTICLE F.2. STOP WORK ORDER

Any contract resulting from this RFP will contain the following:

This contract incorporates the following clause by reference, with the same force and effect as if it were given in full text. Upon request, the Contracting Officer will make its full text available.

FEDERAL ACQUISITION REGULATION (48 CFR CHAPTER 1) CLAUSE: 52.212-13, STOP WORK ORDER (AUGUST 1989) with ALTERNATE I (APRIL 1984)

SECTION G - CONTRACT ADMINISTRATION DATA

Any contract awarded from this RFP will contain the following:

ARTICLE G.1. PROJECT OFFICER

The following Project Officer(s) will represent the Government for the purpose of this contract:

[To be specified during negotiations]

The Project Officer is responsible for: (1) monitoring the Contractor's technical progress, including the surveillance and assessment of performance and recommending to the Contracting Officer changes in requirements; (2) interpreting the statement of work and any other technical performance requirements; (3) performing technical evaluation as required; (4) performing technical inspections and acceptances equired by this contract; and (5) assisting in the resolution of technical problems encountered during performance.

The Contracting Officer is the only person with authority to act as agent of the Government under this contract. Only the Contracting Officer has authority to: (1) direct or negotiate any changes in the statement of work; (2) modify or extend the period of performance; (3) change the delivery schedule; (4) authorize reimbursement to the Contractor any costs incurred during the performance of this contract; or (5) otherwise change any terms and conditions of this contract.

The Government may unilaterally change its Project Officer designation.

ARTICLE G.3. KEY PERSONNEL

The personnel specified in this contract are considered to be essential to the work to be performed hereunder. Prior to diverting any of the specified individuals to other programs, the Contractor shall notify the Contracting Officer reasonably in advance and shall submit justification (including proposed substitutions) in sufficient detail to permit evaluation of the impact on the program. No diversion shall be made by the Contractor without the written consent of the Contracting Officer; provided, that the Contracting Officer may ratify in writing such diversion and such ratification shall constitute the consent of the Contracting Officer required by this article. The contract may be amended from time to time during the course of the contract to either add or delete personnel, as appropriate.

The following individuals are considered to be essential to the work being performed hereunder:

NAME	TITLE
[To be specified during negotiations]	

ARTICLE G.4. INVOICE SUBMISSION

a. Invoice/Financing Request Instructions for NIH Cost-Reimbursement Type Contracts, NIH(RC)-1, are attached and made part of this contract. The instructions and the following directions for the submission of invoices/financing requests must be followed to meet the requirements of a "proper" payment request pursuant to FAR 32.9.

Invoices/financing requests shall be submitted concurrently as follows:

(1) An original and two copies to the following designated payment office:

National Institutes of Health
Division of Financial Management
Chief, Contracts Section, FAAB
Building 31, Room B1B05A
9000 Rockville Pike
Bethesda, Maryland 20892

(2) Three copies to the following approving officer:

Contracting Officer
HLVD Contracts Section
National Heart, Lung and Blood Institute, NIH
Federal Building, Room 4C04
Bethesda, Maryland 20892

Inquiries regarding payment of invoices should be directed to the designated payment office, attention of Chief, Contracts Section, FAAB, (301) 496-6452.

ARTICLE G.5. CONTRACT FINANCIAL REPORT

a. Financial reports on the attached Form NIH-2706, Financial Report of Individual Project/Contract, shall be submitted by the Contractor in accordance with the Instructions for Completing Form NIH-2706, which accompany the form, in an original and two copies, not later than the 30th working day after the close of the reporting period. The line entries for subdivisions of work and elements of cost (expenditure categories) which shall be reported within the total contract are listed in paragraph e., below. Subsequent changes and/or additions in the line entries shall be made in writing.

b. Unless otherwise stated in that part of the Instructions for Completing Form NIH-2706, "Preparation Instructions," all columns A through J, shall be completed for each report submitted.

c. The first financial report shall cover the period consisting of the first full three calendar months following the date of the contract, in addition to any fractional part of the initial month. Thereafter, reports will be on a quarterly basis.

d. The Contracting Officer may require the Contractor to submit detailed support for costs contained in one or more interim financial reports. This clause does not supersede the record retention requirements in FAR Part 4.7.

e. The following are examples of expenditure categories to be reported:

Expenditure Category A	Percentage of Effort/Hours
(1) Direct Labor	
(a) Principal Investigator	
(b) Co-Principal Investigator	
(c) Key Personnel	
(i)	
(ii)	
(iii)	
(2) Professional Personnel - Other	
(3) Personnel Other	
(4) Fringe Benefits	
(5) Materials/Supplies	
(6) Travel	
(7) Equipment	
(8) Indirect Cost	
(9) G&A	
(10) Premium Pay	
(11) Computer Costs	
(12) Consultant Costs	
(13) Subcontract Costs	
(14) Fee	
(15) Total	

ARTICLE G.6. INDIRECT COST RATES

In accordance with Federal Acquisition Regulation (FAR) (48 CFR Chapter 1) Clause 52.216-7(d)(2), Allowable Cost and Payment incorporated by reference in this contract in Part II, Section I, the cognizant Contracting Officer responsible for negotiating provisional and/or final indirect cost rates is identified as follows:

Chief, Financial Advisory Services Branch
Division of Contracts and Grants
Building 31, Room 1B43
National Institutes of Health
Bethesda, Maryland 20892

These rates are hereby incorporated without further action of the Contracting Officer.

ARTICLE G.7. GOVERNMENT PROPERTY

If this RFP will result in the acquisition or use of Government Property provided by the contracting agency or if the Contracting Officer authorizes in the preaward negotiation process, the acquisition of property (other than real property), this ARTICLE will include applicable provisions and incorporate the DHHS Publication (OS) 686, entitled, Contractor's Guide for Control of Government Property, (1990).

ARTICLE G.8. GOVERNMENT SUPPLY SOURCES

Any contract resulting from this RFP will incorporate the following clause by reference, with the same force and effect as if it were given a full text. Upon request, the Contracting Officer will make its full text available.

FEDERAL ACQUISITION REGULATION (48 CFR CHAPTER 1) CLAUSE: 52.251-1, GOVERNMENT SUPPLY SOURCES (APRIL 1984)

SECTION H - SPECIAL CONTRACT REQUIREMENTS

ARTICLE H.1. SUBCONTRACTING PROVISIONS

a. Small Business and Small Disadvantaged Business Subcontracting Plan

(1) The Small Business and Small Disadvantaged Business Subcontracting Plan, dated is attached hereto and made a part of this contract.

(2) The failure of any Contractor or subcontractor to comply in good faith with the Clause entitled "Utilization of Small Business Concerns and Small Disadvantaged Business Concerns" incorporated in this contract and the attached Subcontracting Plan, will be a material breach of such contract or subcontract and subject to the remedies reserved to the Government under FAR Clause 52.219-16 entitled, "LIQUIDATED DAMAGES - SMALL BUSINESS SUBCONTRACTING PLAN."

b. Subcontracting Reports

(1) The Contractor shall submit the original and 1 copy of Subcontracting Report for Individual Contracts, SF-294 in accordance with the instructions on the report as referenced in Public Law 95-507, Section 211. Regardless of the effective date of this contract, the Report shall be submitted on the following dates for the entire life of this contract:

April 30th
October 30th

The Report shall be sent to the following address:

Contracting Officer
HLVD Contracts Section
National Heart, Lung and Blood Institute, NIH
Federal Building, Room 4C04
Bethesda, Maryland 20892

(2) The Contractor shall submit 1 copy of Summary Subcontract Report, SF-295 in accordance with the instructions on the report as referenced in Public Law 95-507, Section 211. The Summary Contracting Report shall be submitted annually on the following date for the entire life of this contract:

October 30th

The first report shall be submitted after the first full year of this contract in addition to any fractional part of the year in which this contract became effective. This Report shall be mailed to the following address:

Office of Small and Disadvantaged Business Utilization
Department of Health and Human Services
Hubert H. Humphrey Bldg., Room 517-D
200 Independence Avenue, S.W.
Washington, D.C. 20201

ARTICLE H.2. SALARY RATE LIMITATION IN FISCAL YEAR 1992*

Pursuant to Public Law (P.L.) 102-107, no NIH Fiscal Year 1992 (October 1, 1991 - September 30, 1992) funds may be used to pay the direct salary of an individual through this contract at a rate in excess of $125,000 per year (direct salary is exclusive of Overhead, Fringe Benefits and General and Administrative Expenses). The $125,000 per year salary limit also applies to individuals proposed under subcontracts. If this is a multi-year contract, it may be subject to unilateral modification by the Government if an individual's salary rate exceeds any salary rate ceiling established in future DHHS appropriation acts. P.L. 102-107 states in pertinent part:

"None of the funds appropriated in this title for the National Institutes of Health and the Alcohol, Drug Abuse and Mental Health Administration shall be used to pay the salary of an individual through a grant or other extramural mechanism at a rate in excess of $125,000 per year."

*Legislation is pending for salary rate limitation for Fiscal year 1993. This article will be modified when the public law has been signed.

ARTICLE H.3. RESTRICTION FROM USE OF LIVE VERTEBRATE ANIMALS

UNDER GOVERNING POLICY, FEDERAL FUNDS ADMINISTERED BY THE PUBLIC HEALTH SERVICE (PHS) SHALL NOT BE EXPENDED FOR RESEARCH INVOLVING LIVE VERTEBRATE ANIMALS WITHOUT PRIOR APPROVAL BY THE OFFICE FOR PROTECTION FROM RESEARCH RISKS (OPRR) OF AN ASSURANCE TO COMPLY WITH THE PHS POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS. THIS RESTRICTION APPLIES TO ALL PERFORMANCE SITES WITHOUT OPRR-APPROVAL ASSURANCES, WHETHER DOMESTIC OR FOREIGN.

PART III

LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACHMENTS

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PART III - LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACHMENTS

SECTION J - LIST OF ATTACHMENTS

	TITLE	DATE	# of PAGES
1.	Packaging and Delivery of Proposal	Dec., 1988	2
2.	Statement of Work	Oct., 1992	17
3.	Invoice/Financing Request Instructions for NIH Cost-Reimbursement Type Contracts, NIH(RC)-1[5]	Jan., 1991	5
4.	HHS 646, Financial Report of Individual Project/Contract[5]	Jan., 1981	1
5.	Instructions for Completing Form HHS-646[5]	Dec., 1990	4
6.	Subcontract Plan Format[2] or [3]	May, 1991	8
7.	Procurement of Certain Equipment, NIH(RC)-7 (OMB Bulletin 81-16)[5]	Apr., 1984	1
8.	Disclosure of Lobbying Activities, OMB Form SF-LLL[2]	Dec., 1989	3
9.	Proposal Summary and Data Record, NIH-2043 (Rev. 6/82)[2]	June, 1982	2
10.	Technical Proposal Cost Information[1]	Dec., 1988	1
11.	Contract Pricing Proposal, SF 1411[2]	July, 1987	1
12.	Breakdown of Proposed Estimated Cost (plus fee) and Labor Hours[2]	Dec., 1988	2
13.	Summary of Related Activities[1]	March, 1984	1
14.	Proposal Intent Response Sheet	March, 1984	1
15.	Government Notice for Handling Proposals[1]	Apr., 1984	1
16.	International Standard ISO 9000.	ISO 9000:1987	9
17.	Rosenberg, G, et al. report.	June, 1990	8
18.	NIH Publication No. 1 85-2723,	Oct., 1983	5
19.	Public Health Service Policy on Humane Care and Use of Laboratory Animals.	N/A	1

Footnotes:

1. These forms must be completed (where applicable) and submitted with the Technical Proposal.
2. These forms must be completed (where applicable) and submitted with the Business Proposal.
3. These forms are for informational purposes only.
4. If applicable, this form is to be completed and submitted with the Technical Proposal. ALL INSTITUTIONS MUST HAVE THE FORM REVIEWED AND APPROVED BY THEIR INSTITUTIONAL REVIEW COMMITTEE.
5. These forms will be attached to any contract resulting from this RFP.

PACKAGING AND DELIVERY OF THE PROPOSAL

Your proposal shall be organized as specified in Section L.2., "Instructions to Offerors" - General Instructions. Shipment and marking shall be as indicated below.

EXTERNAL PACKAGE MARKING

In addition to the address cited below, mark each package as follows:

"RFP NO. 92-28

TO BE OPENED BY AUTHORIZED GOVERNMENT PERSONNEL ONLY"

NUMBER OF COPIES

PLEASE NOTE - THE TECHNICAL PROPOSAL SHALL BE SENT IN SPLIT SHIPMENTS TO TWO LOCATIONS. PLEASE READ THE FOLLOWING INFORMATION CAREFULLY.

A. TECHNICAL PROPOSAL ONLY

ORIGINAL* AND 25 COPIES TO:

If hand-delivered or delivery service

Joan E. O'Brien
Contract Specialist
HLVD Contracts Section
National Heart, Lung, and
Blood Institute, NIH
Federal Building, Room 4C04
7550 Wisconsin Avenue
Rockville, Maryland 20814

If using U.S. Postal Service

Joan E. O'Brien
Contract Specialist
HLVD Contracts Section
National Institutes of Health
National Heart, Lung, and
Blood Institute
Federal Building, Rm. 4C04
Bethesda, Maryland 20892

COPIES TO:

If hand-delivered or delivery service

Review Branch
Division of Extramural Affairs
National Heart, Lung and
and Blood Institute, NIH
Westwood Building, Room 5A14
5333 Westbard Avenue
Bethesda, Maryland 20816

If using U.S. Postal Service

Review Branch
Division of Extramural Affairs
National Institutes of Health
National Heart, Lung, and
Blood Institute
Westwood Building, Room 5A14
Bethesda, Maryland 20892

B. BUSINESS PROPOSAL

ORIGINAL* AND 10 COPIES TO:

If hand-delivered or delivery service

Joan E. O'Brien
Contract Specialist
HLVD Contracts Section
National Heart, Lung, and
Blood Institute, NIH
Federal Building, Room 4C04
7550 Wisconsin Avenue
Bethesda, Maryland 20814

If using U.S. Postal Service

Joan E. O'Brien
Contract Specialist
HLVD Contracts Section
National Institutes of Health
National Heart, Lung, and
Blood Institute
Federal Building., Room 4C04
Bethesda, Maryland 20892

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

NOTE: The U.S. Postal Service's "Express Mail" does not deliver to the Bethesda, Maryland address. Any package sent to the Bethesda address via this service will be held at a local post office for pick-up. The Government is not responsible for picking up any mail at a local post office. If a proposal is not received at the place, date, and time specified herein, it will be considered a "late proposal."

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 $\geq$ 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 with 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 be 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.

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PRELIMINARY DRAFT

GUIDELINE FOR THE PREPARATION AND CONTENT OF APPLICATIONS TO THE FOOD AND DRUG ADMINISTRATION FOR VENTRICULAR ASSIST DEVICES AND TOTAL ARTIFICIAL HEARTS

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Patient Management
Definition of Adverse Events
Pathology Studies and Device Analysis
Deviations from the Protocol
Follow - up Plan
Training
Participants
Content
Continuing Education
Investigators Manual
Monitoring
Reports

1.0 PURPOSE

This guidance is intended to address the specific information that must be collected to support the safety and effectiveness of a ventricular assist device (VAD) or total artificial heart (TAH). This guidance was written to cover both temporary and permanent use including partial support, biventricular support, and total replacement devices. Because of the broad scope intended for this document, there may be instances where the information requested may not be applicable or alternative information may be more suitable. Some of these instances are discussed in this document, but any questions will be addressed by the Division of Cardiovascular Devices (DCD) at (301) 427-7594.

This guidance is intended to complement, but not replace, the general information necessary for an investigational device exemption application (DE) or a premarket approval application (PMA). These and additional requirements such as the Good Laboratory Practice Regulation, Current Good Manufacturing Practice Regulations, etc., are referenced in Appendix I. For your convenience, a glossary of terms is provided in Appendix II.

To evaluate the safety of a device in an IDE application, information describing the device, the manufacturing process, and performance data from in - vitro, in - vivo, and clinical tests are required. Some of the requirements have been explicitly stated, but many requirements have not. Instead, some general considerations, particularly in the clinical investigation section, are presented that must be addressed.

At this time, this document is still in draft and under revision. A copy of this guidance, as well as other guidance documents, is available on an electronic bulletin board. Through this electronic bulletin board, you can download copies of the guidance documents, and enter your comments, suggestions, or questions. The electronic bulletin board can be accessed on (301) 443-7496. If you do not have access to a computer and communication equipment, please contact DCD.

2.0 SYSTEM DESCRIPTION

2.1 DETAILED DESCRIPTION

Provide a detailed description of the system (pump and controller) including design, dimensions, and materials. Diagrams, engineering drawings, and photos can be used to clarify details of the system and each component of the system.

2.1.1 Pump Placement

Describe the placement of the pump in the body (internal or external) and how it is connected to the circulatory system. How is fit determined? Is implantation limited to patients of certain anatomical dimensions?

2.1.2 Design Features

Describe features of the device designed to modify or lessen the incidence of clinical complications generally attributed to heart pump devices, i.e., thromboembolism, hemolysis, bleeding, infection, calcification, device failure, immune deficiency, neurological

deficiencies, etc.

2.1.3 Operation

Describe the algorithm or modes of operation. Indicate whether VAD operation will be synchronous or asynchronous with the natural heart, and whether adjustment of beat rate and flow is automatic or manual.

2.1.4 Safety Factors

Describe anticipated loads, transvalvular pressures, power requirements, and design safety factors. Discuss the worst case conditions under which the pump can operate and compare to physiological conditions expected.

2.1.5 Alarm Systems

Describe alarm systems. What physiological conditions or control system states is the software designed to detect?

2.1.6 Materials

Provide a complete listing of all materials used in the fabrication of the pump and leads that are implanted in the body. Include the chemical generic name or biological source. Indicate the thermal/mechanical/chemical condition of all constituent materials in both the raw material and finished product form (e.g., for metals - cast, solution annealed, percent cold - worked, etc.; for polymers - degree of crystallinity, molecular weight distribution, etc.).

Provide information on the relevant properties of all materials in the condition of the finished product. Test samples shall have undergone sterilization by the process described in Section 3.3, subjected to the recommended maximum number of resterilization cycles using the worst case method and/or conditions specified. Include the effects of the service environment, as appropriate.

2.1.7 Environmental Assessment

Provide an environmental assessment as described by 21 CFR 25.31(a), or claim a categorical exclusion from this requirement by stating that approval of this IDE or PMA will not result in release of substances that, at the expected levels of exposure, may be toxic to organisms in the environment as provided in 21 CFR 25.24(e).

2.2 SYSTEM DESIGN

Provide a description of the engineering considerations that went in to the design specifications for the device. Include a description of the loads applied to all critical structural members throughout the entire cardiac cycle. Consideration of worst - case, within - tolerance conditions for geometry, material properties, configuration of placement, power system, etc., should be included, as well as an evaluation of the effects of all forming, joining, and other manufacturing processes of each component on the design life of the device.

2.2.1 Design Qualifications

Provide the design qualification for the console including mechanical tests, electrical tests, component tests, pressure tests, and environmental tests. If the console will be used to transport patients, the entire system must be qualified for this purpose.

2.2.2 Performance Specifications

Provide performance specifications including tolerance of error. This information must be included in the labeling. See Appendix II for the definition of labeling.

2.2.3 Accuracy

Document the accuracy and range of the console in estimating blood flow and other control parameters. Provide a description of the methods used to verify the accuracy of the controller including assurance that the test equipment has been accurately calibrated or standardized. Describe potential causes of controller failure and the intended response of backup systems.

2.2.4 Limits of Operation

Describe conditions under which the pump or pump components will fail and compare this with worst case physiological conditions expected in order to calculate a safety margin.

2.2.5 Software Validation

Describe the validation of your system software including:

o the numerical input boundaries of the software.

o an overview of the software algorithm and the methods used to verify its performance.

o a description of safety features and an analysis of possible errors and failures (i.e., a failure mode and effects analysis) for both the software alone and the total system. This analysis should indicate the conditions that may lead to erroneous information and/or cause patient injury, the steps taken to minimize these occurrences, and the steps the user should take in the event of failure. The results of this analysis should be consistent with indications, warnings, and precautions in the labeling.

2.2.6 Heat Generation

If the pump is implanted, quantify the amount of heat generated that will be transferred to body tissues. Discuss the physiologic heat absorption capacity in the area in which the device will be implanted comparing heat generation to dissipation capacity. Under worst case conditions (i.e., maximum heat generation), what is the safety factor of heat output to heat absorption capacity?

3.0 MANUFACTURING

3.1 PROCESS DESCRIPTION

Identify the critical components of the system, describe the steps involved in manufacture of the device including components, subassemblies, system integration, key equipment, testing, packaging, and the layout and location of your manufacturing facility.

3.2 PROCESS VALIDATION

Provide documentary evidence that establishes a high degree of assurance in the processing and quality assessment procedures used in the manufacture of the device. Guidance in the establishment of the documentation of process validation as outlined below is provided in the 'Principles of Manufacturing Process Validation' in Appendix III.

3.2.1 Quality Control

Specify acceptance/rejection criteria for critical quality control tests. Explain the rationale behind the test and why the criteria were chosen. Specify the schedule of quality control tests (e.g., 100% test, lot testing, periodic, etc.). If an automated inspection or test system is used, information demonstrating validation of the system must be provided.

3.2.2 Specification Tolerance

Demonstrate that the window of specification tolerances and test acceptance criteria is adequate to consistently produce a device of life supporting quality. See Appendix III for a general discussion of process validation.

3.2.3 Records (PMA Applications)

The manufacturer must certify that adequate records are maintained to comply with Current Good Manufacturing Practices.

3.3 STERILIZATION

For any implanted device, a sterilization assurance level of 10(SUP -6) must be accomplished. See Appendix IV for references.

3.3.1 Procedure

Specify in detail the sterilization procedure including cycle parameters, corrective action levels, and indicator use and placement. Specify residue levels after aerating (when a gas sterilant such as

ethylene oxide (ETO) is used) or rinsing (when a liquid sterilant is used) as specified in the labeling, the worst case size and configuration of the device. Appendix IV contains a copy of the Federal Register notice that specifies the allowable limits of ETO residuals. Include procedures and sampling requirements for sterility testing done for lot release.

3.3.2 Resterilization

Discuss provisions for resterilizing returned or failed goods, if applicable. Provide results of physical and performance testing that show resterilization does not affect the properties of the device. If resterilization or disinfection by the user will be recommended, specific instructions must be given in the labeling including maximum number of times the device may be resterilized. If resterilization is not recommended, a contraindication must appear in the labeling.

3.3.3 Validation

Supply data used to validate the sterilization process, including the sterility assurance level achieved, chemical or biological indicators used, product functionality tests performed, and results of testing. Specify any standards followed to validate the sterilizer and cycle.

3.4 SHELF LIFE

Provide results of testing or a protocol describing testing to be performed to establish a sterile shelf life date which is to appear in the labeling. Testing must include exposure of an adequate sample size of may be subjected
during shipment, handling, and storage. Testing should include, but is not limited to, exposure to dropping, vibration, humidity, atmospheric pressure changes, temperature extremes, and shock. Provide a rationale for all parameters chosen. After stress, aging, and exposure, testing must demonstrate the package and product integrity. FDA recommends that a protocol be submitted prior to testing and aging.

4.0 TESTING

4.1 IN VITRO TESTING

The following is needed to document bench testing done before clinical trials are initiated. All final testing must be done with final design devices, using devices sterilized by the method described in Section 3.3.

4.1.1 Preliminary Studies

Report the results from any performance characterization studies done with prototypes claimed to simulate the final design. Discuss changes made to the prototype device that have lead to the current configuration.

4.1.2 System Characterization

Operation of the device/system must be demonstrated to characterize the operating domain and limits of performance. Demonstrate the device performance on a mock circulatory system in all modes of operation under a full range of steady state conditions under which the device is expected to clinically operate. Demonstrate the full range of cardiac outputs that the device will provide under varying operating conditions such as fill pressure, drive pressure, cycle rate, stroke volume, and any other applicable parameters that affect device output. Characterize the device's response under transient conditions that include rapid changes in systemic pressure and flow, beat rate, and when applicable, changes in stroke volume and switching between synchronous and asynchronous modes. Demonstrate system response to simulated cardiogenic shock, i.e., AOP (LESS THAN) 20 mmHg, fill pressure (GREATER THAN) 20 mmHg, CO (LESS THAN) 2-3 L/min. For a VAD, with the jock ventricle in a passive state, characterize the VAD response to simulated ventricular fibrillation.

4.1.2.1 Test conditions

Describe the mock loop, test fluid, operating temperature range, measurement instrumentation, and calibration equipment. Define a range of

beat rates and cardiac outputs including the upper and lower limits of expected physiological conditions of operation as described above. Explain the rationale for these limits.

4.1.2.2 Test results

Provide output flow data for the device as a function of all loop and control parameters that determine this flow and for the modes of operation described above including the norms and extremes of steady state flow, simulated cardiogenic shock, and ventricular fibrillation where applicable. Report peak pressure gradients (dP/dt) across each valve and peak outlet pressure for the range of flows and modes described above.

For battery operated devices, report the electrical power consumption per unit time for the device in operation in each mode.

4.1.3 Durability and Reliability Testing

Describe the experimental protocol for durability and reliability testing of the final clinical model of the pump and console.

4.1.3.1 Test apparatus

Provide a detailed description of the durability test loop and its ability to simulate physiological pressures and flows. Describe the instrumentation used to test the system. Specify the actual flow conditions during the tests, the role of the mock ventricle, if one is used, and the duty cycle for each operating mode.

Where applicable, describe the number and duration of each internal battery run and the pressure/flow conditions during each run.

Describe the environmental conditions under which the test was conducted and the instrumentation used to monitor inlet/outlet and drive pressures, flows, pressure gradients, temperature, viscosity, run time, (electrical) power consumption, and other relevant parameters.

At this time, it is expected that durability testing be done in real time. At some point in the future, however, testing done at an accelerated rate may be accepted if it can be shown that equivalent wear will occur.

4.1.3.2 Failure criteria

Define the failure criteria used to evaluate reliable performance of the system over a specified short or long term (permanent) duration. These criteria should not be limited to simple component failure but should extend to circumstances when, for any reason, the system is unable to meet specified clinical pressure and flow requirements. When applicable, failure criteria must also be specified for an implantable battery in terms of the system's ability to provide minimum periods of operation, at specified clinical pressures and flows, without an external power source.

4.1.3.3 Reliability objectives

Depending on the proposed indications for use, the device must meet the following objective:

Short term: At least ---- devices must be run under the specified test conditions with no more than ---- failures over a period of at least twice the intended clinical implant duration.

Long term: At least ---- devices must be run under the specified test conditions with no more than ---- failures over a period of at least ---- years.

4.1.3.4 Results and documentation

Provide a tabular description of the overall test results including run times, down times, operational conditions, duty cycles, cycle rates, input/output flows, pressures, pressure gradients, and for battery operated devices, electrical power consumption. If a failure occurred, identify the failure and indicate the time of occurrence.

For those devices that did not fail, compare the results of functional performance tests over the full range of system operating parameters, with similar results obtained before durability testing. Provide the results

from a detailed examination of all components for wear and fatigue using SEM, thermal imaging, or other high resolution examination methods with emphasis on the blood sac or diaphragm and valves, and where application, the energy converter. Discuss the performance of the controller/console used in the durability testing, noting all failures.

4.1.4 Biocompatibility/Toxicity

Describe testing and results to ensure the biocompatibility, non - pyrogenicity and non - toxicity of the implantable components of the system.

4.2 IN VIVO TESTING

4.2.1 Summary of Literature

Summarize the results of animal studies published in scientific journals using the device proposed for this study or similar devices. Discuss definitive findings from these studies and questions posed by the results that require further investigation.

4.2.2 Summary of Prototype Studies

Describe the animal tests that were done to develop your prototype model and subsequent studies leading to your final design for clinical evaluation. Include all evaluations of the device in animal failure models such as artery ligation or induced fibrillation.

4.2.3 Protocol

A scientific study of the final clinical design is expected to accompany the application for the investigational device exemption (IDE). In - vivo testing is expected to demonstrate both durability and performance of the system as a complement to in - vitro testing. The device must be tested in animals for at least twice the expected duration of implantation for intended for permanent implant
must demonstrate operation in - vivo for a minimum of five months. The following are minimum protocol expectations for this study:

A. Provide standardized procedures and data collection techniques.

B. Discuss the rationale for the choice of animal(s) selected in the study.

C. Provide the rationale for the number of animals to be studied and the duration of the studies (a minimum of eight animals for each model is expected).

D. Describe the implant techniques and the post operative care procedures.

E. Submit a complete evaluation of system effects including all of the following:

1. a discussion of the anticoagulation regimen(s) tested and a coagulation profile for the study;

2. a discussion of hemolysis in the animal model accompanied by a profile of relevant studies (hematocrit, hemoglobin, plasma hemoglobin, reticulocytes, LDH); and

3. blood chemistry profiles including blood gases, electrolytes, SGPT, bilirubin, creatinine, and BUN.

The test data requested above are suggested as the minimum test data needed to evaluate the system effects.

F. Provide an evaluation of the safety of the weaning protocol.

G. Describe and evaluate all of the device - related and non - device - related adverse events.

H. Submit all of the pathology studies for all animals that expire on the device or are sacrificed. The information that is submitted must include:

1. a description and photos of the device in situ;

2. a gross necropsy examination with conventional histologic studies of major organs; and

3. histological evaluation of all areas of grossly evident pathology.

I. Provide an evaluation of the explanted device including:

1. a description and pictures of the total explanted device and its individual parts;

2. a detailed examination for wear and fatigue at susceptible areas; and

3. a gross and microscopic evaluation of any tissue attached to the device or any damaged material.

4.2.4 Data Analysis

Data analyzed should be presented in a systematic way to facilitate assimilation of the results. Laboratory data should include normal values for the type of animal in that laboratory, and data points on charts should indicate the number of animals represented by each data point. Device analysis results should be presented in a manner that compares the results for animals by date and should include other relevant information such as anticoagulation and adverse events.

4.2.5 Relationship To Clinical Studies

The results of this study must be discussed in relationship to the proposed clinical study. Discuss the purpose of animal studies using your device including your hypotheses for use of the intervention.

5.0 CADAVER STUDIES

Provide a summary of the cadaver studies that were performed to arrive at the optimum configuration for the device. Discuss the variables that were studied, the basis for your conclusions, the specific limitations on the size of the patient, and the specific recommendation for insertion.

6.0 CLINICAL INVESTIGATION

to
call or write the Division of Cardiovascular
Devices (DCD), and to discuss
their plans and ideas before submitting an IDE or PMA application.

6.1 PROTOCOL DEVELOPMENT FOR THE CLINICAL TRIAL

The accrual of a sufficient number of subjects into a heart pump study requires the inclusion of more centers than are ordinarily required in a clinical trial. This section of the guidance includes minimum requirements to facilitate a scientific study of a complicated device within a limited patient population in a large number of institutions. For scientifically valid conclusions to be drawn from the study, the study must have clear objectives with a fully developed protocol that is developed by both the investigators involved in the study and the sponsors of the study. From the experience of past clinical investigations, if the clinical investigators have participated in development, or agree to adhere to the protocol, conduct of the investigation will be uniform.

Note: FDA encourages the sponsor of a multi - center investigation to establish an investigation steering committee composed of the investigators involved in the investigation.

6.1.1 Objectives

The purpose of the study including the specific objectives and the specific study design are the first considerations. Based on the study objectives, discuss the following:

A. How you intend to demonstrate success or failure to meet the objectives of the investigation, and

B. How the data collected during the investigation will be used to determine whether the criteria for success have been met.

6.1.2 Study Size

A proposal for the size of the study with a rationale for the number of patients and institutions required to draw statistically valid conclusions about the safety and efficacy of the device and its indications for use should be submitted. If you anticipate evaluating several patient groups (i.e., post - cardiotomy, post acute myocardial infarction, chronic

degenerative heart disease), the proposal should reflect the effect of multiple patient subgroups in study size. The time frame should be outlined taking into consideration planning time, center recruitment, patient entry, data analysis and the preparation of a final report.

6.1.3 Preliminary Investigations

It may be beneficial to do a preliminary IDE study of five to ten patients at one or two centers to test the device, study design, procedures (implant, patient management, weaning, follow - up, etc.), to determine the feasibility of extending the study to multiple centers. In order to get meaningful data from such a study, characteristics discussed below should be incorporated. Based on the results of this study, the design may be modified for the final study design.

Note: If a preliminary investigation is conducted, the investigation should be designed to reduce as many variables and confounding factors as possible, e.g., a single system configuration, strict limits on patient selection, etc.

6.2 CHARACTERISTICS OF INVESTIGATIONAL CENTERS

6.2.1 Investigational Center

Special attention should be given to the characteristics of an investigational center to assure that the center is a viable study participant. For instance, what is the annual cardiovascular caseload and does it support the projected annual rate of patient entry into the study? Are the surgeons, the surgical team, and the hospital sufficiently experienced in cardiac transplant procedures and the management of transplantation patients? Are the facilities adequate? Can the laboratory perform the required testing and can the pathology department carry out the autopsy and device evaluation protocols? How committed is the center to participation in this multicenter study? Are there sufficient qualified people that can be assigned to the study for data management, operation and maintenance of the equipment, and patient care? Include this information in the IDE application. The wholehearted commitment of the investigator and the center will facilitate your progress. A monitoring plan which addresses all of these issues should be included with the clinical protocol. For bridge to transplant studies, the investigational center must be an established heart transplant center (Section 6.2.3).

6.2.2 Principal Investigator

IDE submissions should include pertinent information on the principal investigator's background and characteristics of the center that make them an appropriate combination for inclusion in the investigation.

6.2.3 Established Heart Transplant Center

An established center is one that has performed a minimum of 12 heart transplants in the 12 months prior to submission with an overall success rate (survival) of 70 percent or better at the time of the submission. All submissions must include:

A. the number of heart transplants at an institution in the last 12 months and the number of patients alive in that group,

B. the total number of heart transplants performed at the center to date and the overall success rate at 12 months, 2 years, etc.,

C. whether the heart transplant surgeon is the same person as the investigator for the proposed study, and

D. the experience of the heart transplant surgeon.

6.2.4 Institutional Review Board

Heart pumps are complex devices that have stimulated considerable public debate concerning their use in humans. FDA therefore requires that an institutional review board (IRB) considering that institution's participation in a TAH/VAD study must have at least:

A. one member or consultant who is knowledgeable about the engineering -

related aspects of the device development and who is not directly associated with the study; and

B. one member who is considered to be an expert in regard to the moral and ethical issues concerning artificial implantations, organ transplants, etc.

6.2.5 Permanent Dependence

FDA also requires that the IRB of each study center certify its understanding that patients implanted for temporary use may become permanently dependent upon the device and that the center is prepared, should such dependence occur, to provide for the needs of such patients. Based on experience with the permanent implant study, the needs of these patients would include full time availability of cardiac surgeons and TAH/VAD technicians, additional backup equipment, adaptation of the hospital environment to patient's needs, transportation, housing for the patient's family, social and psychiatric services for patients and their families, nutritional, physical and occupational therapy services, on - going medical consultations, and continued staff training.

6.2.6 Cost and Reimbursement

A study center policy must also make clear who will pay for the care associated with continued implantation of the device.

6.2.7 Backup System

Each center must have at least one complete backup system that is available and ready to be used in the event of a failure of the system in use.

6.3 STANDARDIZATION OF PROCEDURES

A critical element in a manufacturer - sponsored clinical trial is the elimination of conflicting issues that might arise during the progress of the study. Obtaining agreement early in protocol development among centers on the conduct of the study (i.e., methodologies, judgments, and data collection procedures) facilitates an unbiased multi - center study. When planning a multi - center study, it is useful to have a steering group that includes several investigators plus investigator committees to develop different aspects of the protocol. In any case, procedures must be standardized for use at each study center. This requires a written description of procedures, specific data collection formats, with instructions for use. Study personnel at each center must be trained in the use of methods and form completion and must be monitored on a regular basis. The following are areas in which study management agreement must be reached.

6.3.1 Data Collection Forms

Uniform assessment criteria and data collection forms for pertinent pre - op, on study, and post - op information should be in place, (i.e., past history, operative assessments, post - op procedures). As the study population increases, this information will foster an insightful analysis.

6.3.2 Patient Selection

Patient selection criteria and patient exclusion criteria should be sufficiently specific to allow for a valid analysis of who may and who may not benefit from the intervention. Particular attention should be given to the development of TAH/VAD implant criteria for bridge to transplant patients that can be implemented at each center and are also consistent with each center's heart transplant criteria. A theoretical or empirical rationale for each criterion must be given.

6.3.3 Control Group(s)

There must be a control group(s) for the study. The ideal group would be subjects similar to the study group in all ways except that they do not receive the intervention. Prospective or retrospective patient groups as well as morbidity and/or mortality statistics may be appropriate. A

rationale for the choice of control group must be included in the submission.

6.3.4 Consent Form

In addition to the requirements of 21 CFR part 50, the following items must be added when appropriate for your protocol:

A. a statement of the center's experience in obtaining a donor heart (i.e., longest wait, average wait, and recent experience for patients in the most urgent category);

B. situations that might cause the waiting period to be extended;

C. complications arising from use of the device that could preclude transplantation;

D. that the study center is prepared to care for the needs of patients shouldthey become permanently dependent upon the device; and

E. whether the study center, the manufacturer, the patients or other will bear the cost of the patient's extended care as a permanent implantee.

6.3.5 Operative Procedures

In order to decrease potential bias in study results, variations in operative technique must be kept to a minimum. The operative procedures should be described in detail in the investigator manual and training manual, and should be fully reported on the appropriate patient forms.

6.3.6 Laboratory Procedures

Reliability of the data depends on standardization of results across study sites. A methodology should be specified for standardizing results among centers in order that data between centers can be compared and combined. The selection, assessment, and schedule of testing should be standard among centers.

6.3.7 Patient Management

Based upon experience to date, specific areas that warrant systematic evaluation in studies of these devices include infection control, hemodynamic control, management of bleeding, the anticoagulation regimen, renal, hepatic, pulmonary, neurological, metabolic, nutritional, and immune system function. Procedures for the assessment of these issues must be included in the submission.

6.3.8 Definitions of Adverse Events

Standard definitions of adverse events must be developed for use at each study site. Consideration should be given and criteria developed for use in the evaluation of each adverse event in terms of its severity, its significance, its relationship to the device being tested, the outcome of the event, and whether the subsequent death of the patient was related to the event. For instance, in the event that a transplanted patient develops an acute episode of rejection or infection, it should be evaluate as to whether implantation of the bridging device caused or contributed to the occurrence. Procedures should be developed for following up on the occurrence of all adverse events.

6.3.9 Pathology Studies

Submit all of the pathology studies on all patients who expire. Precise procedures including location of samples, number of samples, type of photographs, number of photographs, etc., must be included in protocols for use at each study site. The information that is submitted must include:

A. a description and photos of the device in situ;

B. a gross necropsy examination with conventional histological studies of major organs; and

C. histological evaluation of all areas of grossly evident pathology.

6.3.10 Device Analysis

Provide an evaluation of the explanted device including:

A. a description and pictures of the total explanted device and its individual parts;

I. pertinent information on other centers participating in the study (names, addresses, telephone numbers).

6.6 MONITORING

Frequent and close monitoring of subject recruitment, adherence to protocols, the quality of data collection and processing, and the quality of laboratory procedures is required. Monitoring concerns when preparing for a multicentered trial are: the number of monitors, the qualifications of the monitors, types of monitoring (telephone, site visit), frequency of site visits, monitoring report forms, and resolving problems.

IDE submissions for TAH/VAD multicenter trials should include a proposed monitoring plan that takes all areas mentioned above into consideration. Site visits must be scheduled prior to start - up and as soon as possible following the first implant. A schedule should be proposed for subsequent visits.

6.7 REPORTS

6.7.1 Adverse Events

A complete description of all adverse events must be reported.

6.7.2 Investigator List

A list of each investigator and clinical center participating in the investigation must be provided every 6 months from the date of the original approval of the IDE application.

6.7.3 Annual Report

The annual progress report must provide a comprehensive picture of what has occurred in each center and in the study as a whole at the time of the report. A summary is required for each new case entered into the study in the current report year, accompanied by a presentation of the data for all patients entered in to the study to date. It should be formatted in such a way that the information is readily assimilated by the reader, readily updated at regular intervals, and readily developed into a final report or PMA application.

6.7.3.1 Content

The annual report must address experience as discussed in section 6.3.7 with the patients entered into the study, with the performance of the entire system and components (number of failure/error free operations, description of failures or problems, etc.), and with the investigators and investigational team (evaluation of the training program, etc.). Documentation such as patient case report forms (CRFs) and raw data must be submitted unless specifically exempted by FDA.

6.7.3.2 Analysis

In addition to the CRFs on all patients, raw data must be provided on specific analyses. An analysis for each individual center and aggregated multicenter data should include, but need not be limited to, the following:

A. descriptive statistics on demographic data and summary data on patient characteristics (i.e., age, sex, etiology, device size, NYHA, hematology studies, blood chemistries, device evaluation, autopsy results, complement activation, etc.);

B. survival analysis (comparison of control and study groups and/or subgroups of interest);

and nondevice related

adverse events;

D. examination of the similarities and differences among patients in the control and study groups; and

E. analysis of additional hypotheses (relationships of disease etiology versus outcomes of interest, complication rate profiles versus outcomes, waiting times versus outcomes, etc.).

6.7.3.3 Summary and conclusions

The report generated as a result of this aggregation and analysis should

B. detailed examination of the device for wear and fatigue; and

C. a gross and microscopic evaluation of any tissue attached to the device or any damaged material.

6.3.11 Deviations from the Protocol

Any deviations from established clinical plan must be noted on the appropriate patient record and all reasons for the deviations provided.

6.3.12 Follow - up Plan

This plan should include standardized assessments, e.g., at one month, six months, and one year. A rationale must be included for timing of assessments and the type of data to be collected at each assessment. Patients should be seen at follow - up by the principal investigator or other members of the investigational team. Followup exam by a non - study physician is not recommended unless the physician has been oriented to the study test and data protocols.

6.4 TRAINING

Training is an essential element in promoting standardization and quality in a multi - center study. IDE submissions must include a detailed training protocol that assures the proper training and retraining of study participants.

6.4.1 Participants

The principal investigator and all staff associated with the investigation should receive training appropriate to their level of involvement. Trainees should include the following types of participants: physicians (surgeons, cardiologists, anesthesiologists), biomedical engineers, perfusionists, OR nurses, ICU nurses, laboratory personnel, data managers, etc.

6.4.2 Content

The content of the training and the location of the training should be appropriate to the needs of the trainees. Some items that have been included are: theory and practice (lecture); practical experience (implanting and explanting animals; setup, running, and trouble shooting; overview of clinical protocol; data collection and management; inservice education; dry run; etc.). All trainees should receive adequate instruction regarding the clinical protocol, standardization of procedures, and data collection methods.

6.4.3 Continuing Education

The use of periodic evaluation and the retraining of study participants should be considered in the overall plan for assuring safety and quality. This issue should probably be addressed by the steering committee of participating physicians or another committee of center participants.

6.5 INVESTIGATOR'S MANUAL

A manual that contains all information about the clinical trial must be site. Some of the items that should be included are:

A. a description of the study;

B. the investigator's responsibilities (21 CFR, 812.100);

C. the protocol (information on control groups, patient selection criteria, preoperative history/assessments, operative procedures, laboratory procedures, patient management procedure, adverse event reporting, autopsies and device analysis, deviations from the protocol, and follow - up procedures);

D. data management (data collection forms and instructions for use);

E. maintenance/repair of equipment (routine procedures, contacts);

F. procedures for updating/maintaining the skills of participants (physicians, nurses, lab technicians, etc.);

G. approved consent form;

H. emergency guidelines; and

be disseminated for in - depth review by the investigator steering committee and follow - up discussion at investigator meetings. It should also be submitted to FDA and each reviewing IRB annually, along with the general information in the attached 'Suggested Format for IDE Progress Reports' (Appendix V).

APPENDICES

I. Federal Regulations
II. Glossary
III. Process Validation
IV. Sterilization
V. IDE Report Format
PRELIMINARY DRAFT

END OF DOCUMENT

Long-Term Mechanical Circulatory Support System Reliability Recommendation

American Society for Artificial Internal Organs and The Society of Thoracic Surgeons: Long-Term Mechanical Circulatory Support System Reliability Recommendation

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