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

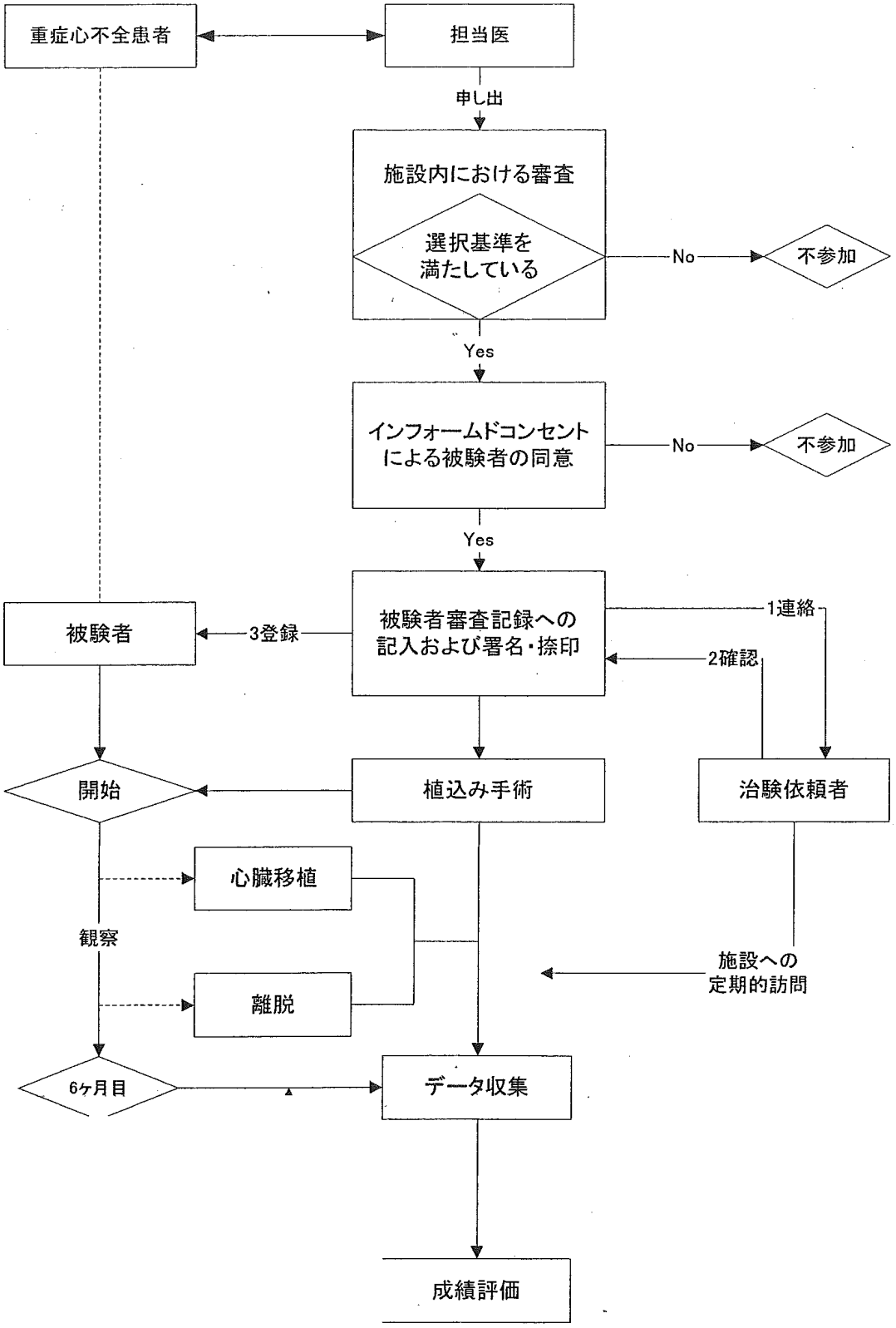
臨床試験計画書は、臨床試験依頼者と臨床試験担当医師の間で合意された文書でなければならない。試験の目的を達成するために、臨床試験計画書は、最新の臨床知識及び臨床

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。

(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

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・PDE Ⅲ 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。

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。

- 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。

*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

Date: 2005-11

ISO/CDV 14708-5

ISO /TC 150/SC 6 NXX

Secretariat: ANSI

Implants for surgery — Active implantable medical devices — Part 5: Particular requirements for circulatory support devices

Élément introductif — Élément central — Partie 2-X : Titre de la partie

Document type: International Standard
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Document language: E

Contents

Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 3.

Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this part of ISO 14708 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 14708-X was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 6, *Active implants*.

ISO 14708 consists of the following parts, under the general title *Implants for surgery — Active implantable medical devices*:

— *Part 1: General requirements for safety, marking and for information to be provided by the manufacturer*

— *Part X: Circulatory support devices*

Introduction

Heart failure is a major public health problem. According to recent statistics from the American Heart Association, about 5 million Americans have heart failure, and in 2001, over 52,800 Americans died of this disease. The number of new cases is around 400,000 per year (Schocken, 1992). Further, heart failure is implicated as a contributing factor in more than 250,000 deaths each annum (Yusuf, 1992). Overall heart failure hospital admissions have increased tenfold since 1970 (Lorell, 1994). Particularly at risk for heart failure are the elderly (≥ 60 years), who account for 70% of heart failure patients (Haldeman, et al, 1998), and for whom congestive heart failure is the leading cause of hospitalization. While the prevalence of heart failure increases with age, almost one third of patients – 1.6 million Americans – contract the disease before the age of 60. The economic costs are enormous, $21.0 billion is the estimated United States cost for treating this condition (AHA, 1999).

Despite recent developments of pharmacologic agents developed specifically to treat advancing heart failure, the 1-year actuarial survival rate for class IV heart failure patients is only 40_50 percent (Mancini, 1994), and about 25 percent at two years. For the vast majority of these patients, cardiac replacement therapy in the form of cardiac transplantation is the only viable treatment option. According to recent statistics provided by the United Network for Organ Sharing (UNOS), cardiac transplant patients have an in-hospital mortality of <5 %, a 1-year actuarial survival rate approaching 85%, and 5-year survival rates >70%. Yet the success of cardiac transplantation remains limited by the complications of chronic immunosuppressive therapy, the development of accelerated allograft atherosclerosis, and most importantly by the continuing serious shortage of donor organs. There remains an enormous difference between the number of Americans annually who might benefit from cardiac transplantation (~15,000 – 70,000) versus those who actually receive transplants (2427 in 1997, UNOS). And, since the number of cardiac transplants is not expected to increase appreciably in the foreseeable future, there is considerable interest in developing new therapies for patients suffering from end-stage heart failure.

The Institute of Medicine evaluated the Artificial Heart Program of the National Heart, Lung, and Blood Institute in 1991 (Hogness, 1991). The panel concluded that by the year 2010, there could be an annual pool of 35,000 to 70,000 candidates for mechanical circulatory support or some other form of treatment. Surgical procedures such as left ventriculectomy and cardiomyoplasty have not led to clinical benefit in the majority of patients. Xenotransplantation using non-human hearts is under active investigation. Areas of concern include immunological response of the host, inadequate performance of the non-human heart, and the possibility of transferring infectious organisms to the host. These agents sometimes have long incubation periods (10-20 years) as seen with HIV-AIDS. An additional patient group with acutely failing hearts numbering in the tens to one hundred thousand annually may also benefit from artificial heart therapy.

Active implantable medical devices — Circulatory support devices

1 Scope

This part of ISO 14708 specifies requirements for safety and performance of active implantable circulatory support devices. Excluded from this scope are intra-aortic balloon pumps, external corporeal perfusion devices and cardiomyplasty.

This standard specifies type tests, animal studies and clinical evaluation requirements that are to be carried out to show compliance with this standard.

NOTE The device that is commonly referred to as an active implantable medical device may in fact be a single device, a combination of devices, or a combination of a device or devices and one or more accessories. Not all of these parts are required to be either partially or totally implantable, but there is a need to specify main requirements of non-implantable parts and accessories if they could affect the safety or performance of the implantable device.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 14708. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 14708 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ASTM F1841-97

IEC 60300-3-2, *Dependability management — Part 3-2: Application guide — Collection of dependability data from the field*

IEC 60601-1, *Medical electrical equipment — Part 1: General requirements for safety and essential performance*

IEC 60601-1-2, *Medical electrical equipment — Part 1-2: General requirements for safety — Collateral standard: Electromagnetic compatibility — Requirements and tests*

IEC 60601-1-6, *Medical electrical equipment — Part 1-6: General requirements for safety — Collateral standard: Usability*

IEC 60601-1-8, *Medical electrical equipment — Part 1-8: General requirements for safety — Collateral standard: Alarms*

IEC/TR 60878, *Graphical symbols for electrical equipment in medical practice*

IEC 62304, *Medical device software — Software life-cycle processes*

ISO 5198, *Centrifugal, mixed flow and axial flow pumps — Code for hydraulic performance tests — Precision grade*

ISO 5840, *Cardiovascular implants — Cardiac valve prostheses*

ISO 7198, *Cardiovascular implants —Tubular vascular prostheses*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

ISO 10993-4, *Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood*

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14155-1, *Clinical investigation of medical devices for human subjects — Part 1: General requirements*

ISO 14155-2, *Clinical investigation of medical devices for human subjects — Part 2: Clinical investigation plans*

ISO 14708-1, *Implants for surgery — Active Implantable medical devices — Part 1: General requirements for safety, marking and for information to be provided by the manufacturer*

ISO 14971, *Medical Devices — Application of risk Management to medical devices*

3 Terms and definitions

For the purposes of this standard, the terms and definitions given in ISO 14708-1 and the following apply.

3.1
accessory device
separate part of a circulatory support system that is not essential to the primary function of the circulatory support system. Examples would be programming units, monitoring units, alternative power supply units, etc.

3.2
artificial/prosthetic valve
component of the circulatory support system that directs the unidirectional flow of the blood into and out of the pump.

3.3
atrial cuff
[NOTE: Definition will be drafted by Prof. Imachi.]

3.4
cavitation
the sudden formation and collapse of low pressure bubbles in the blood by means of mechanical forces.

3.5
clinical study
evaluation of a device in humans.

3.6
clinical utility
figure of merit for a medical device that includes consideration of all factors which leads to the decision of a medical practitioner to select the device. The factors would include safety, effectiveness, performance, ease of use, cost effectiveness, and other practical considerations.

NOTE Clinical Utility is defined in the working draft of IEC 60601-1-2. It is only relevant with respect to interference and degradation of performance.

3.7
conduit
component of the circulatory support system that connects the pump to the patient's circulation.

NOTE Conduit(s) is generally used interchangeably with cannula(e). The specific definition for cannula(e) is: Connection to/from the patient's circulation and the device.

3.8
continuous flow
characteristic of the output of a pump where the steady flow component is predominant.

3.9
controller
component of the circulatory support system containing the logic, circuitry and/or software to control the driving mechanism that enables the system to perform its primary function.

3.10
diastolic pressure
arithmetic average of diastolic blood pressure (when the left ventricle is not contracting), over a sufficient number of cycles to filter out cyclic variation, of the minimum aortic pressures in a pulsatile pressure waveform.

3.11
volume displacement pump
pump that imparts its pumping action by changing the volume of the pumping chamber, e.g. by displacement of a diaphragm or pusher plate.

3.12
dP/dt
time derivative of pressure giving the rate of change of pressure with respect to time. dP/dt has the units of millimeters of mercury per second, mmHg/sec (kiloPascal per second [kPa/sec] in SI units).

3.13
dQ/dt
the time derivative of flow giving the rate of change of flow with respect to time. dQ/dt has units of liters per minute per second.

3.14
drive line
tube that connects a driver or energy source to the pump (e.g., the tube that connects a pneumatic console to a pneumatically driven pump).

3.15
durability
ability of an item to perform a required function under given conditions of use and maintenance, until a limiting state is reached.

NOTE *A limiting state of an item should be characterized by the end of the useful life, unsuitability for any economic or technological* reasons, or other relevant factors.

3.16
dynamic stroke volume
performance measure for a circulatory support system indicating the volume pumped into the host circulatory system per beat by a pump with pulsatile flow. The dynamic stroke volume has the units of milliliters.

3.17
extracorporeal component
component or subsystem of the circulatory support system that is kept external to the patient (outside of the body).

3.18
failure
termination of the ability of an item to perform a required function.

NOTES
1 After failure the item has a fault.
2 "Failure" is an event, as distinguished from "fault", which is a state.
3 This concept as defined does not apply to items consisting of software only.

3.19
fault
state of an item characterized by inability to perform a required function, excluding the inability during preventive maintenance or other planned actions, or due to lack of external resources.

NOTE A fault is often the result of a failure of the item itself, but may exist without prior failure.

3.20
filling pressure
arithmetic average pressure required during filling of a pump.

3.21
fully implantable
implanted circulatory support system with no skin penetrations (i.e. percutaneous lead).

3.22
hazard analysis
identification of hazards and their initiating causes.

3.23
H-Q
pressure head (H) versus flow (Q) relationship, typically for a steady flow pump at a specific cycle.

3.24
***in vitro* simulated circulation**
also known as a mock loop (a fixture that is used in laboratory testing to simulate human circulation for testing the performance of a circulatory support system)

3.25
labeling (marking)
any written, printed, or graphical matter affixed to a medical device or any of its containers or wrappers, or accompanying the medical device related to identification, technical description and use, but excluding shipping documents.

3.26
monitor
component of the circulatory support system that allows data pertaining to the operation of the system to be displayed.

3.27
peak flow
maximum flow rate during ejection of blood from a pump into the host circulatory system.

3.28
percutaneous lead
a lead (electrical or otherwise) that crosses the patient's skin to connect implantable parts of a circulatory support system to extracorporeal parts of the system.

3.29
power supply
source of energy.

3.30
pulsatile flow
characteristic of the output of a pump where the flow is time-dependent (flow varies with time during one beat).

3.31
pump ejection
term used to describe the ejection phase of a pump with pulsatile flow.

NOTE Systole is used to describe only the pumping phase of the host's native ventricle(s).

3.32
pump fill
term used to describe the filling phase of a pump with pulsatile flow.

NOTE Diastole is used to describe only the filling phase of the host's native ventricle(s).

3.33
pump output
performance measure for a circulatory support system indicating the volume of blood pumped into the host circulatory system per minute. The pump output has the units of liters per minute or its equivalent in other units.

3.34
pump/pulse rate
performance measure for a circulatory support system indicating the number of complete pump cycles per minute. The pump rate has the units of beats per minute. Pump rate is not relevant to non-pulsatile pumps.

3.35
pump volume
volumetric capacity of the pump. The pump volume has the units of milliliters.

3.36
reliability
probability that an item can perform a required function under given conditions for a given time interval (t1, t2).

NOTES
1 It is generally assumed that the item is in a state to perform this required function at the beginning of the time interval.
2 The term "reliability" is also used to denote the reliability performance quantified by this probability [see 191-02-06 of IEC 50(191) definition of reliability (performance)].

3.37
remote access device
component of the circulatory support system that allows modification to the controller of the operation of the system.

3.38
risk
combination of the probability of occurrence of harm and the severity of that harm.

[ISO/IEC Guide 51:1999, definition 3.2]

3.39
risk analysis
systematic use of available information to identify hazards and to estimate the risks.

[ISO/IEC Guide 51:1999, definition 3.10]

3.40
rotary pump
pump that imparts its pumping action by hydrodynamic forces, imparted by a rotating impeller.

3.41
safe and effective
reasonable assurance that a device will not induce harm to the recipient and that it will provide clinical benefit for the recipient for its conditions of use (Code of Federal Regulation title 21 part 860 section 860.7 Determination of safety and effectiveness).

3.42
safety
freedom from unacceptable risk.

[ISO/IEC Guide 51:1999, definition 3.1]

3.43
safety hazard
potentially detrimental effect on the patient, other persons, animals, or the surroundings, arising directly from the circulatory support system.

3.44
sales packaging
packaging that protects and identifies the device during storage and handling by the purchaser.

NOTE The sales packaging should be enclosed in further packaging, for example, a "shipping package", for delivery.

3.45
S/D (systolic/diastolic) ratio
the ratio between the fill time period and the eject time period of the blood pump cycle.

3.46
stroke volume
the amount of blood pumped by the ventricle of the heart in one contraction.

3.47
systolic pressure
arithmetic average, over a sufficient number of cycles to filter out cyclic variation, of the peak aortic pressures in a pulsatile pressure waveform.

3.48
TETS
[NOTE: Definition will be drafted by Prof. Imachi.]

3.49
total artificial heart
circulatory support system that replaces a patient's native heart.

3.50
ventricular assist system/device (VAS/VAD)
circulatory support system that augments the function of either one or both ventricles of the native heart of a patient by capturing blood from the atrium(a) or ventricle(s) and providing work to pump blood into the pulmonary and/or systemic circulation.

4 Symbols and abbreviations (optional)

This clause of ISO 14708-1 applies.