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REVIEW ARTICLE

Brain death and organ and tissue donation

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Abstract

Brain death is a product of technological advances. It is possible to artificially keep the heart rate, pulmonary ventilation, blood pressure, temperature and biochemical homeostasis, even after stopping the brain functions.

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INTRODUCTION

The definition of death has important medical and legal consequences, such as: the absence of a legal requirement to provide resuscitation or life-sustaining technologies; loss of personhood and individual rights; potential organ donation and autopsy; execution of the individual's legal will and property; payment of life insurance; and body disposal by burial or cremation.

There are three physiological mechanisms of death:

a) primary cardiac arrest leading to circulatory arrest;
b) primary respiratory arrest that causes secondary cardiac arrest by hypoxemia;
c) primary brain failure that, through the interruption of respiratory control and respiratory drive, causes secondary respiratory arrest and, subsequently, cardiac arrest.

The interruption of this sequence through life sustaining technologies is the basis of assistance in ICUs, using artificial airways, mechanical pulmonary ventilation, hemodynamic support, renal replacement therapies, oxygenation by extracorporeal membranes, and artificial hearts. The aim of these procedures is to maintain the functions of vital organs in order to "gain time" so that the severe life-threatening state can be reversed.

The brain is an organ that cannot be maintained by any currently known technology, because no brain function can be replaced. Mechanical pulmonary ventilation merely interrupts the way brain failure leads to death, and neuroprotective procedures merely limit secondary brain damage.

The human brain is composed of the telencephalon, diencephalon (thalamus, hypothalamus, epithalamiums, and subthalamus), brainstem (mesencephalon, pons, and medulla oblongata), and cerebellum (Figure 1).

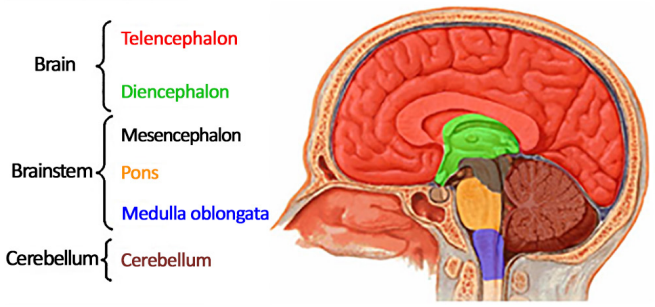

Figure 1. Human brain.

Brain death (BD) is defined as the unquestionable complete and irreversible loss of all functions of the cortex and brainstem, due to a known cause and characterized by unresponsive coma, absence of supraspinal motor response, and apnea. Although according to this definition BD is accepted as the death of a person as a citizen in most countries, this concept is not yet universal, even in some so-called developed countries, as a result of compliance with moral or religious principles characteristic of each country's culture.

BD is not to be confused with severe brain damage, with a state of persistent vegetative state, with cortical death, or with anencephaly. In these conditions, the brain damage may be catastrophic and irreversible, but it is not complete, because there is still some residual function of the brainstem.

BD is the result of technological advances that allow the artificial maintenance of heart rate, pulmonary ventilation, blood pressure, temperature, and biochemical homeostasis, even after the arrest of brain functions.

Early diagnosis of BD is of great importance. The continuation of treatment in these (already deceased) patients subjects the family to the stress of uncertainty, because it gives false hopes, it keeps material and human resources allocated to a patient that will no longer benefit from them and, for many, it is an act of disrespect toward the body.

Another important fact is that it is only after BD has been attested and the death of the individual has been declared that organs and tissues can be considered potentially suitable for donation for the purpose of transplantation, thus allowing other lives to be saved. The experience accumulated and the advances in surgical and immunosuppressive techniques have led to highly successful organ and tissue transplantation programs. One of the main limiting factors of these programs has been the difficulty in identifying potential donors. In Brazil, although the notification of BD is compulsory, only one organ donor is notified for every eight potential donors. To improve this situation, it is important to prevent a delayed diagnosis of BD, by declaring it as soon as it occurs, and then informing the family so that their permission to remove the organs and tissues for transplantation is obtained in a timely manner.

Once brain functions cease, mechanical pulmonary ventilation is necessary to maintain circulation and other vital functions. However, irreversible cardiovascular collapse occurs hours or a few days later, regardless of the intensity of the therapeutic support, because, although some organs have natural pacemakers that allow them to maintain certain functions after the diagnosis of BD, the nervous system is responsible for the unity of the human body, and without it, death occurs in a short time, even with all the artificial support systems. According to the experience of the Department of Pediatrics of the Federal University of Paraná, the mean interval between a diagnosis

of BD and irreversible cardiac arrest in children requiring mechanical pulmonary ventilation was 22 hours.

DIAGNOSIS

In 2007, Lago et al. published an article presenting a retrospective analysis of data of seven Brazilian pediatric intensive care units (PICUs), comprising four public PICUs and three private ones; two in Porto Alegre, two in São Paulo, and three in Salvador, in which 525 deaths occurred between January 2003 and December 2004. Of these deaths, 61 (11.6%) had a diagnosis of BD, of which six (9.8%) were potential organ donors.

They observed a wide geographical variation in conducts, which suggested differences in the application of protocols, without differences in patient profile.

The time until withdrawal of life support after the diagnosis of BD (measured in hours) is shown in Figure 2, and the medical conducts after the diagnosis of BD (%) are shown in Figure 3.

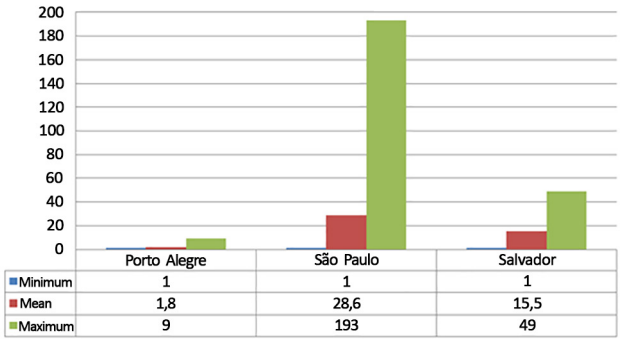

Figure 2. Time until withdrawal of life support after the diagnosis of brain death (in hours).

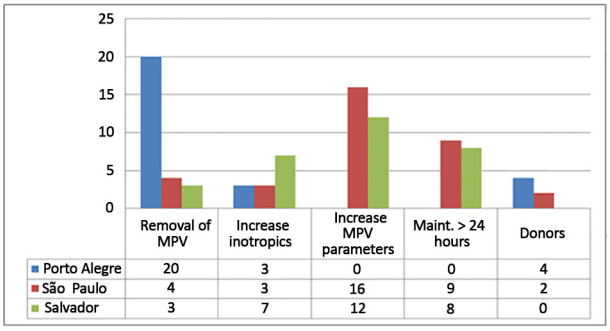

Figure 3. medical conducts after the diagnosis of brain death (%).

They concluded that the law that defines the criteria for BD in Brazil, which exists since 1997, was not being applied evenly and, as a consequence, unnecessary life support was offered to people who had already deceased. In addition, there was little involvement of pediatric ICUs in organ donation.

BD should be suspected when a patient who requires mechanical pulmonary ventilation for apnea is in an unreactive and unresponsive coma, without brainstem (supraspinal) reflexes in the absence of reversible causes, such as the use of sedative drugs, CNS-depressant drugs, or neuromuscular blockers; severe endocrine and metabolic disorders; hypotension arterial or hypothermia (rectal temperature ≤ 35°C).

The prerequisites of BD are that the etiology of the coma is known and the catastrophic brain damage is considered irreversible. Knowledge of the clinical history is essential to determine the presence of conditions that may lead to false findings in the neurological examination.

The most common causes of BD in children are head trauma, hypoxic-ischemic encephalopathy after drowning, and sudden decompensation of intracranial hypertension secondary to CNS tumors.

Clinical examination is the most important criterion to determine BD. The minimum body temperature to validate the neurological evaluation is 35ºC. Absence of cortical function is detected by the absence of somatic or autonomic response to any external stimulus. Absence of brainstem function is detected when the following brainstem reflexes are absent:

- Photomotor;
- Corneal;
- Pupillary;
- Vestibulo-ocular;
- Oropharyngeal;
- Respiratory (apnea).

Only the absence of supraspinal reactivity is considered for a diagnosis of BD. Therefore, this diagnosis does not preclude the presence of signs of infraspinal reactivity (spinal reflex activity) such as: osteotendinous reflexes (deep tendon reflexes), abdominal-cutaneous reflexes, cutaneous-plantar reflexes during flexion or extension, superficial or deep cremasteric reflex, reflex penis erection, shivering, flexor (withdrawal) reflex of the lower or upper limbs, tonic neck reflex, and the Lazarus reflex or sign.

One of the movements that most scares the family members and health professionals and which does not exclude the diagnosis of BD is the Lazarus sign. It is a sequence of movements that lasts a few seconds and that can occur spontaneously during apnea testing (passive movement of the head) or immediately after the mechanical ventilator is disconnected. First, the arms extend, then fall crossed on or touching the chest, and finally rest at the sides of the torso (flexion of the torso may also occur).

Peripheral nervous activity such as spinal reflexes may be present after BD, particularly in children. Because

of practical and legal implications, these movements should be identified and interpreted correctly. Convulsions and decorticate or decerebrate postures exclude a diagnosis of BD because they reveal activity in the brainstem or above it.

The oculocephalic or vestibulo-ocular reflex is assessed by moving the head passively in the horizontal and vertical planes. When the brainstem is intact, the eyes deviate in the opposite direction from the head's movement. In BD there is no eye movement ("doll's eyes").

When there is strong evidence of BD, after excluding potential differential diagnoses, it is essential to test the vestibulo-ocular and breathing reflexes.

The vestibulo-ocular reflex is tested using the caloric test, which consists in observing the eye movements after irrigation of the ear with cold or warm water. To conduct the test one should ensure that there is no obstruction in the auditory canal (with wax, for example), that the tympanic membranes are intact, and that there is no previous central or peripheral lesion of the ear (such as those caused by infections or the use of ototoxic drugs). The patient should be placed in a semi-seated (30º to 45º) decubitus position. 50 ml of cold saline solution (close to 0ºC) are injected into one of the external auditory canals and the patient is observed for 20 to 30 minutes to determine if there is a response. Then, the test is repeated in the other ear. When the brainstem is intact, the eyes deviate in the direction of the stimulus when cold water is used (the reverse occurs when warm water is used). In BD there are no eye movements. A unilateral response indicates localized lesion.

The breathing reflex is assessed using the apnea test. To conduct the test one should ensure good tissue oxygenation. The test requires that $PaCO_2$ reaches levels that strongly stimulate the respiratory center (above 55 mmHg), which may take several minutes between disconecting the mechanical pulmonary ventilation system and the occurrence of breathing movements (if the pontobulbar region is still intact). The test is not valid in patients with chronic pulmonary disease, who may exhibit diminished response to hypercapnia.

The following protocol should be applied to perform the apnea test:

1º Oxygenate the patient using mechanical pulmonary ventilation with 100% FiO_2 for 10 minutes, adjusting the ventilator settings to a $PaCO_2$ of approximately 40 mmHg, confirmed by arterial blood gas analysis.

2º Disconnect the mechanical ventilator, maintaning a continuous oxygen supply of 6 to 8 L/min using a T-piece or a catheter in the tracheal intubation tube.

3º Continuously observe the patient to check for breathing movements, changes in heart rate, O_2 saturation, blood pressure, or cyanosis.

4º If the patient exhibits any breathing movement or if cyanosis or hemodynamic instability occurs, reconnect the mechanical ventilator immediately.

5º If after 10 minutes of observation the patient does not exhibit breathing movements, collect another arterial blood sample for blood gas analysis and reconnect the mechanical ventilator.

Most authors consider the test to be conclusive for apnea (absence of breathing reflex, consistent with BD) if during the 10 minutes during which the mechanical ventilator is disconnected the patient does not exhibit breathing movements and $PaCO_2$ reaches values above 60 mmHg. An increase in $PaCO_2$ between 4.2 and 4.4 mmHg is to be expected during the first 5 minutes of the test and a further increase of 3.4 mmHg is expected in the subsequent 5 minutes. If at the end of the test $PaCO_2$ isless than 60 mmHg, the test is not valid and may be repeated 15 to 30 minutes later.

The apnea test should provide sufficient stimulus to eliminate the possibility of residual brain function. In general, a $PaCO_2$above 60 mmHg is used as threshold, but various protocols establish higher thresholds, up to over 90 or 100 mmHg, in disorders of the posterior fossa.

Dramatic movements caused by stimuli related to acute ischemia of the peripheral spinal motor neurons (sign of Lazarus, for example) may occur during the apnea test or when ventilation support is withdrawn. Those who witness these procedures, in particular family members, should be warned about this possibility so that they do not question the diagnosis of BD.

It should be noted that BD is the death of the individual (see legal aspects below). In this case, mechanical ventilation cannot be considered as a form of life support in a patient who has already deceased, and it should be withdrawn, albeit only after the family has been duly informed and given their consent.

Other clinical findings that may raise suspicion of BD, although not seen in all cases, are the following: significant polyuria from diabetes insipidus (38 to 88% of the cases); peripheral vasodilation (especially in the hands and feet), and hypothermia refractory to warming measures.

Ancillary tests

According to the most recent guidelines regarding the determination of BD, which are updates on the recommendations of the 1987 Task Force, complementary tests are not mandatory to establish BD, but they are useful for its diagnosis when:

- The clinical test (such as the apnea test) cannot be completed safely due to the patient's underlying medical condition;
- There is uncertainty about the results of the clinical test;
- There are doubts about the presence of effects from sedative drugs, CNS depressant drugs, or neuromuscular-blocking drugs;
- There is indication to reduce the period of observation between the clinical tests.

Complementary tests do not replace physical examination, but serve to demonstrate unequivocally the absence of intracranial blood circulation, electrical or metabolic brain activity.

According to Resolution 1480/97 of the Brazilian Federal Council of Medicine, patients who are two or more years old require one of the following complementary tests:

1. Electrical activity: electroencephalography (EEG), brainstem evoked potential.
2. Brain blood flow: cerebral angiography, transcranial Doppler, brain mapping with radioisotopes, intracranial pressure monitoring, computed tomography with xenon, SPECT (single-photon emission computed tomography).
3. Metabolic activity: PET (positron emission tomography), cerebral oxygen extraction.

EEG is recommended for patients who are less than two years old, and two examinations with an interval that varies according to age group (see below) are required.

- EEG

EEG only assesses brain cortex functions; in cases of presumed BD, maximum signal amplification should be used for a minimum period of 30 minutes, and the result should be interpreted by experienced personnel.

A flat EEG (without evidence of electrical brain activity over 2 μV between electrodes placed at a distance ≥ 10 cm) may also occur as a result of high doses of CNS depressant drugs, such as barbiturates, hypothermia (body temperature < 32 ºC), and hypotension.

It is relatively frequent to find some electrical activity of the burst-suppression type in the first EEG performed on patients with suspected BD who, 12 to 24 hours later, exhibit a flat line. On the other hand, there are reports of patients who exhibit electroencephalografic activity moments before death and whose autopsy shows cerebral liquefaction, particularly after attempts of cardiorespiratory and cerebral resuscitation (reperfusion period).

The small distances between the electrodes (in children) and the interference of other electronic devices used in ICUs sometimes hinder an adequate EEG interpretation.

- Brainstem evoked potential

It is used to assess brainstem functions, because it detects the integrity of the afferent nerve pathways, but not cortical functions. It is ideal to complement EEG. It can be performed at the bedside and is not subject to interferences from other electronic devices that are connected to the patient or from CNS depressant drugs.

Absence of auditory evoked potential has been used as a criterion for the diagnosis of BD, provided that there is viable peripheral nerve conduction (wave 1 or cochlear wave obtained after adequate sound stimulus), because the auditory nuclei are close to the vital centres of the brainstem.

If acoustic conduction is not demonstrated, the auditory evoked potential is replaced or complemented by the somatosensory potential.

- Cerebral angiography

The following findings should be present for a diagnosis of BD: bilateral absence of arterial phase both in the carotid and vertebral arteries (four vessels), carotid circulation arrest at the base of the skull, sagittal sinus not visible in the venous phase, and presence of arterial perfusion only in extracranial tissues, all for more than 10 minutes (Figure 4).

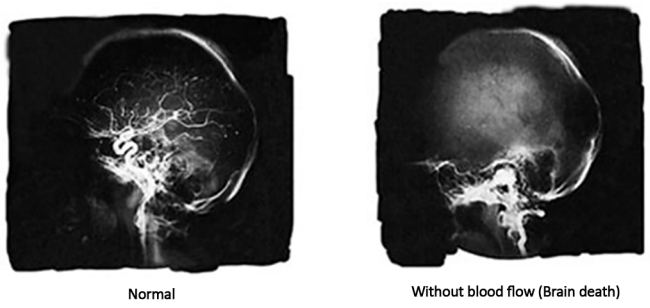

Figure 4. Cerebral angiography.

The technical difficulties of using cerebral angiography in small children and the risks associated with the transportation to radiology units hinder the use of iodinated contrasts in this test.

- Transcranial Doppler

This is a good alternative to brain angiography because it is less invasive and avoids the manifestations of hypersensitivity to iodinated contrasts. A finding of the "to and to" pattern characterizes BD (Figure 5).

Using the transorbital approach, the percentage of positive results with a definitive diagnosis of BD has increased from 79% to 88%, making it a useful addition to the diagnosis.

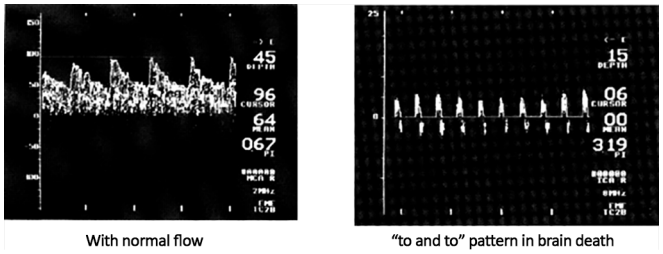

Figure 5. Transcranial Doppler.

- Brain mapping with radioisotopes

This is another good alternative to cerebral angiography. It is also little invasive and avoids manifestations of hypersensitivity to iodinated contrasts. It is performed by intravenous injection of technetium-99m, followed by the measurement of the intensity of radiation by a gamma camera, which can be portable. The results are difficult to interpret in children who are less two months old. This technique has not been used in Brazilian medical institutions and it is recommended that new-borns undergo a second mapping to confirm the diagnosis (Figure 6)

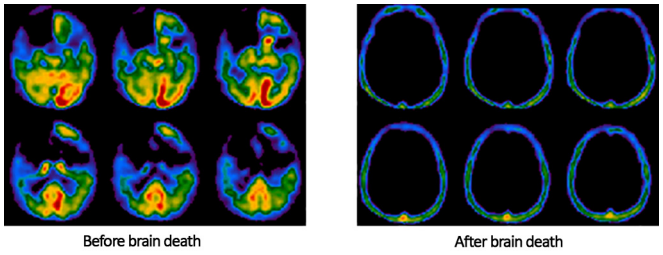

Figure 6. Brain mapping with Tc^{99m} (HMPAO SPECT)

CONDITIONS THAT MIMIC BRAIN DEATH

Situations could occur in which a diagnosis of BD was made because the brain was inactive and electrical activity was suppressed as a result of reduction of brain blood flow up to the threshold of ischemic penumbra, a state that could be reversed.

CNS depressant drugs (particularly barbiturates, benzodiazepines, opioids, and neuromuscular blocking drugs) are frequently used in PICUs and can mimic a state of brain death. Toxicology tests should be performed in all suspect cases, considering the pharmacological characteristics of each drug (absorption, distribution, half-life, metabolization routes, elimination route, and effects of the by-products). For the majority of these drugs, one should wait four half-lives before initiating the BD investigation protocol. Ideally, serum levels of the drugs should be obtained.

The drugs that are most used in ICUs are listed in Table 1 (together with the times between their interruption and the initiation of the BD investigation protocol).

Hypothermia, particularly a body temperature below 34°C (Table 2), and arterial hypotension can cause the reversible suppression of neurological activity, and therapeutic measures are required to revert their effect before initiating the investigation of BD.

Active investigation of metabolic changes that may mimic BD, such as water and electrolyte imbalances, acid-base imbalances, glucose imbalance, and endocrine imbalances (particularly of the thyroid, parathyroid, and adrenal glands) is mandatory.

IRREVERSIBILITY OF BRAIN DEATH

The irreversibility of BD is confirmed when the cause of coma is known and sufficient to explain the severity of brain impairment, and the possibility of recovery has been excluded via observation for an adequate period.

There is controversy regarding the time of observation necessary to determine the irreversibility of BD, especially in newborns, and regarding the need to confirm it via complementary diagnostic tests, which are legally mandatory in Brazil.

Resolution 1480 of the Brazilian Federal Council of Medicine, of August 1997, determines that the minimum intervals between the two clinical assessments required to determine BD are defined by age group (Table 3):

The Task Force for Determination of Brain Death in Children, formed by the Society of Critical Care Medicine, the "Sections on Critical Care and Neurology of the American Academy of Pediatrics", and the Child Neurology Society, in the *Guidelines for the determination of brain death in infants and children: an update of the 1987 Task Force recommendations*, published in September 2011, recommends that two tests be performed by different physicians and separated by an observation period (Table 4):

LEGAL ASPECTS (SEE *LEGAL FRAMEWORK* BELOW)

The diagnosis of BD is based on medical knowledge; however, it is a legal matter because the law has independent interests in the definition of BD, which may be lost when the reference is solely medical.

BD was initially regulated in Brazil through Resolution 1346 of the Federal Council of Medicine, of August 8, 1991, replaced on August 8, 1997 by Resolution 1480 of the same Council, which is reproduced below (see Annex 1).

BD, as the death of the individual, was only deemed lawful in Brazil after Law 8489, published on November 18 and 22, 1992, and replaced by Law 9434 of February 4, 1997, which concerns the removal of organs, tissues, and parts of the human body for the purpose of transplantation and treatment, amended by Law 10,211 of March 23, 2001.

Table 1. Minimum times from the interruption of CNS depressant drugs to assess brain death.

Drug	½ life	Minimum interruption time		
		Single dose or ≤ 2 doses/day	Continuous infusion or > 3 doses/day	↑ RF or LF or NB*
Barbiturates				
Phenobarbital (> 20 mg/Kg)				
• < 2 anos	130 hours			
• 2 a 12 anos	72 hours	8 days	8 days	IR e RNs
• Adults	140 hours			
Pentobarbital	24 hours	50 hours	100 hours	
Thiopental	12 hours	1 day	2 days	
Benzodayzepines				
Dayzepam				
• < 2 anos	50 hours	6 days		
• 2 a 12 anos	21 hours		2,5 days	6 days	IH e RN
• 12 a 16 anos	20 hours			
• Adults	50 hours	6 days		
Lorazepam				
• < 12 anos	17 hours	2 days	4 days	RN
• Adults	16 hours			
Midazolam				
• < 12 anos	4,5 hours	6 hours	12 hours	IR, IH e RN
• Adults	3 hours			
Opioids				
Alfentanil	2 hours	8 hours	16 hours	
Fentanyl				
• 5 m a 4,5 a	2,5 hours	9 hours	36 hours	IR e RN
• Adultos	4 hours			
Morphine				
• 1 a 3 meses	10 hours	20 hours	40 hours	RN
• < 2,5 anos	8 hours			
• < 12 anos	2 hours	10 hours	20 hours	
• Adults	4 hours			
Neuromuscular-Blocking Drugs				
Atracurium	20 min	75 min	150 min	
Cisatracurium	40 min	100 min	3,5 hours	
Pancuronium	110 min	150 min	5 hours	IR
Succinylcholine	30 min	60 min	2 hours	
Rocuronium				
• < 12 anos	1,3 hours	100 min	3,5 hours	IH
• Adults	2,5 hours			
Vecuronium	75 min	3 hours	6 hours	IR e IH
Other Drugs				
Ketamine	IM - 4 hours IV – 2 hours	10 hours	10 hours	
Droperidol	2 hours	8 hours	8 hours	
Etomidate	3 hours	7,5 hours	7,5 hours	IH
Propofol	30 min	1h15min		
• If use > 10 days	3 days		6 days	

↑ **RF or LF or NB*** = Minimum time increased in case of renal failure (RF), liver failure (LF) or in newborns (NB).
Sources: Taketomo CK, 1999; ABTO, 2014; Paraná State Government. State Health Department, 2014.

Table 2. Clinical manifestations of hypothermia.

HYPOTHERMIA		
Mild (> 34°C)	Moderate (30° a 34°C)	Severe (< 30°C)
Tachycardia	Bradycardia	Coma
Tachypnea	Bradypnea	Bradycardia
Hypertension	Hypotension	Apnea
Tremors	Hyporreflexia	Silent EEG
Confusion	Unreactive pupils	Severe arrhythmias
Hyperreflexia	Torpor or coma	
Lack of coordination	Arrhythmias	

Table 3. Minimum intervals between the two clinical evaluations necessary for the determination of BD based on age group, according to Resolution 1480/97 of the Brazilian Federal Council of Medicine.

Age group	Minimum intervals between clinical evaluations	Complementary tests*
7 to 59 days	48 hours	2 EEGs with an interval of 48 hours
2 to 12 months	24 hours	2 EEGs with an interval of 24 hours
1 to 2 years	12 hours	One of the tests; if EEG is performed, 2 EEGs with an interval of 12 hours
> 2 years	6 hours	One of the tests

* The complementary tests required for the determination of BD should demonstrate unequivocally:
- absence of electrical brain activity or
- absence of metabolic brain activity or
- absence of brain blood perfusion.

Table 4. Minimum intervals between clinical evaluations according to the American Academy of Pediatrics and the Child Neurology Society guidelines for the determination of brain death in infants and children.

Age group	Minimum intervals between clinical evaluations
Term NBs* up to 30 days	24 hours
1 month to 18 years	12 hours

- In the first examination the physician should determine if the patient meets the criteria for BD
- In the second examination another physician should confirm BD based on the inalterability and irreversibility of the condition.
- However, the evaluation performed after cardiorespiratory resuscitation manoeuvers or other severe acute cerebral injuries should be deferred for 24 hours or more if there are doubts or inconsistencies regarding the examination.

* Because of insufficient data in the literature, recommendations for premature NBs with GA < 37 weeks were not included in these guidelines.

The legal need for documentation through ancillary tests that demonstrate the absence of cerebral blood flow, electrical activity or metabolic activity to confirm the diagnosis of BD is technically questionable for individuals who are one or more years old and has been an obstacle for the timely diagnosis of BD and for the necessary procedures for organ transplantation in Brazil.

In Brazil, most centers where BD documentation with ancillary tests is possible are also transplantation centers, and it is important to observe Law 9434, which determines in Article 3 that *"The post-mortem removal of tissues, organs or parts of the human body for transplantation or treatment should be preceded by a diagnosis of brain death, determined and declared by two physicians who are not part of the organ removal and transplant teams, through the use of clinical and technological criteria defined by a resolution of the Federal Council of Medicine,"* and in Clause 3 of said article that "The presence of a physician trusted by the family of the deceased will be allowed at the moment of brain death verification and attestation."

Once BD is determined, a copy of the brain death declaration form must be sent to the state supervisory agency (Law 9434/97, Art. 13), indicating the complementary test that demonstrated unequivocally the absence of intracranial blood flow, brain electrical activity, or brain metabolic activity, with a report with the identification of the responsible physician attached to it (see Annex 2).

Once BD is confirmed, the patient is legally declared dead, even if his/her cardiorespiratory conditions are being artificially maintained. In the death certificate, the time of death should be the time BD was determined (legal opinion 29,650/95 of the State of São Paulo Regional Council of Medicine).

A patient who is a victim of violent death can be an organ donor. In this case, the body should be sent to the coroner's office (in Brazil, the locality's Medical Legal Institute - IML) for autopsy after organ removal. It should be noted that, in these cases, the coroner (at the IML) is the person who provides the death certificate.

At present, Brazilian law states that BD in children younger than seven days cannot be considered as the death of the individual, although other countries have criteria for this age group, provided the gestational age is greater than 32 weeks.

CARE PLAN

All clinical findings and complementary tests must be thoroughly documented, including date, hour, technical description of the method that was used, and results. The protocol used must be approved by the Medical Ethics Commission of the institution in which the patient is hospitalized.

It is an ethical principle (although not a legal requirement) that more than one physician be responsible for the diagnosis, preferably an intensivist physician and a neurologist who are not part of transplant teams.

The suggested plan is the following:

1. Exclude reversible causes of coma (see *Conditions that mimic brain death*, above)
2. Verify the absence of brainstem reflexes (see above);
3. Repeat items 1 and 2 after 6, 12, 24 and/or 48 hours, depending on the patient's age;
4. Perform the complementary tests that are necessary to confirm the diagnosis, especially if the patient is a potential organ donor, to shorten the observation period and comply with legal aspects.

ORGAN AND TISSUE DONATION

Organ transplantation is today considered a routine procedure (Table 5). Improved results increasingly stimulate its practice, which has led to an increasing shortage of organs for donation. This represents a serious threat to the expansion of this benefit. In the mid- to long term the alternatives to solve these problems include preventive medicine, the use of animals as donors, and organ cloning, which is still in the realm of science fiction.

Contraindications for organ donation

- Organ dysfunctions that compromise the functioning of organs and tissues for donation, such as cardiac, liver, spinal cord, pancreatic, pulmonary or renal dysfunction.
- Current or past malignant tumors, except primary central nervous system tumors, basocellular carcinoma and *in situ* cervical carcinoma.
- Bacterial or fungal sepsis (localized bacterial infection, such as pneumonia or urinary tract infection) does not exclude the possibility of donation, provided that adequate antimicrobial treatment is provided as soon as possible.
- Active systemic viral infection (such as disseminated herpes) or viral encephalitis.
- Active pulmonary or extrapulmonary tuberculosis.
- Patients positive for HIV (and individuals belonging to risk groups for HIV), Chagas disease, viral hepatitis, and other diseases that are contraindications for transfusion of blood products. Serology tests for these diseases should be performed as soon as possible.
- Rare systemic infections (such as Creutzfeldt-Jakob disease and rabies).
- Chronic degenerative diseases.
- Organs and tissues that, because of an anatomic or functional anomaly or localized parenchymal infection, cannot be used (in this, case other organs can be donated).

Considering how easy it is to obtain corneas, whose removal procedure is simple, does not require a surgical center and can be performed up to 6 hours after death following cardiorespiratory arrest, it is difficult to explain the waiting time for a corneal transplant, especially in large cities (see Annex 3).

In Brazil, informed consent is the model for organ donation agreement; the potential donor's relatives are responsible for authorizing donation. In 1997, Law 9434 created the National Transplant System and a Center for Notification, Harvesting and Distribution of Organs (CNCDO in the Portuguese acronym) in each state of the federation. This law defines how donation should occur and regulates this activity, namely with the creation of Technical Registers, a unified list for distribution.

The process was decentralized with the creation of the Organ Procurement Organizations (OPOs), which are responsible for specific geographic areas.

Obtaining consent for donation after brain death

In Brazil, free and informed consent may be given by the spouse or by a first- or second-degree relative and requires two witnesses. If the potential donor is legally incapable (Articles 3 and 4 of the Civil Code), both parents (if alive) or the legal representatives can give consent. Unidentified individuals cannot be donors.

Organ and tissue donation is a noble humanitarian act; however, it is questioned by many people for a variety

Table 5. Organs that can be donated.

Organ	Indication for transplantation	Extracorporeal preservation time
Heart	Severe cardiomiopathy	4 to 6 hours
Liver	Severe liver cirrhosis, fulminant hepatitis	12 to 24 hours
Pancreas	*Insulin-dependent diabetes mellitus*	12 a 24 horas
Lungs (2)	Chronic lung disease from fibrosis or emphysema	4 to 6 hours
Kidneys (2)	Chronic kidney failure	< 48 hours

of reasons (usually religious reasons). The patient's family (both parents in the case of children or adolescents) has exclusive competence for authorizing donation. It is important that the conversation about organ donation with the family does not coincide with the moment they are notified of the death and that a trained person performs this task. The CNCDOs have personnel who are specifically trained to have this conversation in an appropriate manner and who are available to travel to the institution where the potential donor is hospitalized. This procedure has increased the families' chance of choosing to donate.

It is important that the person who communicates the news of the death:

1. Knows everything about the patient (full name, accurate age, gender, name of the mother and father, the patient's origin when he/she was hospitalized, clinical history, physical examination data, progression, treatment, tests undergone by the patient, circumstances in which death was determined).
2. Is prepared to explain what BD is, keeping in mind that he/she will probably be talking with lay persons, and avoids excessively technical expressions (such as "the patient has an isoelectric EEG") or dubious expressions (such as "the patient is now at rest").
3. Presents him/herself in an appropriate and serene manner (not wearing bloody or dirty gloves and clothes, or having disheveled hair).
4. Identifes him/hersel by name and role.
5. Does not use the cell phone and tells everyone not to interrupt him/her.
6. Talks with the family in a quiet environment where everyone is comfortable (preferably seated) and privacy is respected (never at the bedside or within the patient care area of the ICU or emergency room).
7. Allows the correctness of the diagnosis of BD to be questioned (particularly if the Lazarus sign was witnessed by a relative) and informs the family members that, if they wish so, they have the right to another opinion from a physician they trust or from a different institution.
8. Is considerate and polite toward everyone present (even those who are very hostile) and tries to identify the closest relative to whom they can offer the option of donation as well as those who are able to support the family.
9. Is completly honest and shows his/her compassion for the family's loss, but avoids expressions such as "I know what you are feeling" (because he/she really does not know).
10. Is available to listen, without expecting logical and objective behavior.
11. Is prepared to answer questions like:
    - Which organs or tissues can be donated?
    - Will the family know who the receptors are?
    - Will the body be deformed?
    - How long will it take for the burial?
12. Clarifies that the organ harvesting team is able to give further information if that is the family's decision.

Considering that the goal is to obtain a decision from the family that is based on their genuine will (and that of the deceased) rather than to give a legalistic recitation of information, it is important to assess whether the family is able to understand the content of the information that will be provided. This is particularly important because it will probably be difficult for the family to understand it in this stressful moment. The behavior of the person who communicates the news of death is fundamental for successful organ and tissue donation. It is a critical moment, and a moment of despair for the family, which demands solidarity, understanding, and emotional support.

According to the principle of informed consent, the family should receive the following information about organ donation:

1. That the diagnosis of BD was established by at least two physicians who are not part of the organ donation team.
2. The probability that other people's lives may be saved, or at least improved, through organ donation.
3. That there is no guarantee that the organs will be suitable for donation.

4. The family's religious convictions, if known, about organ and tissue donation (most religions support organ donation) or the possibility of seeking guidance from a religious counsellor or a priest.
5. That it is guaranteed that the family can refuse donation without any embarrassment or prejudice, or that the family can establish limits to donation (donate some parts of the body but no other parts).
6. That 24 to 36 hours may be required for the entire process to be complete and for the body to finally be released for burial.
7. That the family has no expenses to pay for donation and that in some municipalities, such as São Paulo, they will be exempt from paying the municipal funeral services any fees, charges, and duties associated with the funeral service.
8. That the body will not be deformed and that no special care is necessary for burial.

Assessment of potential donors

All patients with BD should be considered as potential organ donors and even patients who progressed to irreversible cardiorespiratory arrest can be tissue donors.

The approach to the potential organ donor requires a planned sequence of measures and procedures to allow a successful outcome.

A thorough review of the clinical history, progression and prescriptions should be performed, as well as an additional thorough physical examination to identify contraindications to donation. In addition, ancillary tests are necessary to identify potential changes that can be compensated or contraindications to donation:

- Amylase	- Blood group testing
- Bilirubins	- Transaminases and gamma GT
- CPK and CKmb	- Urea and creatinine
- Electrolytes (Na+, K+, Ca++)	- Same serology as that tested in blood donors
- Alkaline phosphatase	- Urinalysis and urine culture
- Arterial blood gas	- Culture of secretions (if they exist)
- Blood glucose	- ECG
- Blood culture	- Echocardiogram
- Full blood count	- Thorax X-ray

Maintenance of the organ and tissue donor

Organ donors are patients who require artificial systems to maintain the stability of hemodynamic parameters required for the preservation of their organs and thus ensure these are viable for transplantation.

The following procedures should be performed continuously, or at least at short intervals:

- Monitoring of heart activity, oxygen saturation, central venous pressure, arterial blood pressure, and body temperature;
- Large-caliber central venous catheter for the administration of vasoactive drugs;
- Urinary catheter for the control of diuresis;
- Open nasogastric tube.

In the management of the organ donor, the following items must be considered:

1. Mechanical pulmonary ventilation and maintenance of adequate oxygenation are always required; $PaCO_2$ should be kept between 30 and 45 mmHg, and O_2 saturation should be above 95%.
2. Hypotension is one of the most important alterations; it results from the loss of venous and arterial sympathetic tone, water loss caused by diabetes insipidus, use of diuretic drugs, water restriction, or hyperglycemia. Treatment consists in the replacement of intravascular volume to achieve a positive fluid balance and maintain normal-for-age mean arterial pressure (MAP), but avoiding a much higher than normal central venous pressure (CVP), which indicates fluid overload. If fluid replacement is not sufficient to stabilize the hemodynamic parameters, dopamine should be used. The use of norepinephrine can eventually be necessary. If diabetes insipidus occurs, desmopressin (DDAVP®) should be used.
3. Hypokalemia, hypomagnesemia, and hypocalcemia occur frequently. These conditions evolve with cardiac dysrhythmias and cardiac arrest if the patient does not receive adequate replacement for these electrolytes.
4. Metabolic acidosis is a frequent event, and its control may require the administration of sodium bicarbonate. It is important to perform arterial blood gas tests to assess the occurrence of respiratory disorders that may require adjusting the settings of the mechanical pulmonary ventilator.
5. Hyperglycemia may result from using glucose, corticosteroids, or catecholamine's. Regular and frequent glucose level testing should be performed to adjust the rate of glucose infusion, and fast-acting insulin should be used if necessary. The patient's blood glucose level should be kept between 80 and 120 mg/dL when glucose is used, to maintain metabolic support.
6. Anemia may occur in potential donors, especially in victims of polytrauma, who may have bleedings that are not always well assessed on hospital admission. Hemoglobin should be maintained at approximately 12 g/dL. Packed red blood cells should be used if necessary, but only after the patient's blood samples have been collected for serology testing. It should

be noted that some families are opposed to the use of blood products for religious reasons, and that they will also be opposed to organ donation. The ethical principle of beneficence in opposition to the autonomy principle that is used for minors is not applicable in such cases.

7. Hypothermia can also lead to dysrhythmia and cardiac arrest. Treatment requires the use of warm fluids in fluid replacement therapy, increasing the temperature of the air provided by the mechanical ventilation system to 38°C, and the use of thermal blankets. If these are not available, lights can be placed close to the patient's thorax and abdomen (at a distance of ± 40 cm) to maintain the body temperature above 35°C. The use of incubators should be considered in small children.
8. The prophylactic use of antibiotics is advisable. The most common practice is to use a third-generation cephalosporin, but the most adequate antibiotic for the local bacterial flora should be used whenever possible, according to the institution's infection control department. Infections identified via X-rays, blood count, urinalysis, etc. (with or without positive cultures) should be treated according to the institution's protocols.
9. The patient's eyelids should remain closed with appropriate adhesive bands and covered with damp gauze to avoid corneal ulcers, which would invalidate the use of corneas for transplantation.
10. If cardiac arrest occurs, resuscitation should be provided because, if successful, donation may still be possible.

Donation of tissues after the determination of death from irreversible cardiorespiratory arrest

Some tissues are viable for transplantation provided that they are removed in a timely manner and stored in tissue banks, as described in Table 6.

When a potential tissue donor is identified, the recommended plan is that shown in Figure 7.

Living donor

In 2001, Brazilian Law 10,211 redefined living-donor transplants, in which relatives up to the fourth degree can

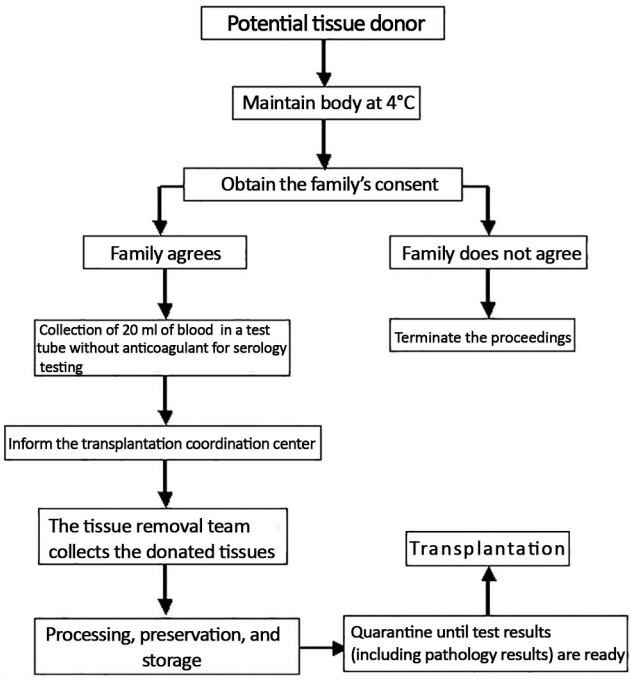

Figure 7. Plan to be followed when a potential tissue donor is identified.

be donors, a spouse can donate organs to the other spouse, and non-relatives can be donors only if they have judicial authorization. Living donors must be legally capable citizens (Article 5 of the Civil Code).

Brazilian law (articles 1594 and 1595 of the Civil Code) only deems collateral relatives those up to the fourth degree (each degree is counted from the number of intermediaries between the two persons, including their latest common ancestor) (Table 7).

Organs and tissues that can be obtained from a living donor:

- Bone marrow (via bone aspiration or peripheral blood collection),
- Part of the liver,
- Part of the pancreas,
- Part of one lung,
- One kidney.

Donation of a kidney or part of the liver, pancreas, or lung is only permitted if removal does not compromise the

Table 6. Tissues that can be donated.

Organ	Time for removal after CRA*	Contraindication to donation	Storage time
Corneas	6 hours	Corneal ulcer, eye infection, and traumatic lesion	7 days
Bones and tendons	12 hours	> 60 years, long-term corticotherapy, and fractures	5 years
Skin	≤ 12 hours	Dermatitis, dermatosis, and malnutrition	2 a 5 years
Heart valves	≤ 4 hours	> 55 years and heart diseases	5 years
Blood vessels	≤ 4 hours	Hypertension and vascular diseases	2 a 5 years

* CRA = Cardiorespiratory arrest

Tabela 7. Graus de Parentesco.

1st DEGREE	Parent	Child			
2nd DEGREE	Grandparent	Sibling	Grandchild		
3rd DEGREE	Great-grandparent	Uncle/Aunt	Nephew/Niece	Great-grandchild	
4th DEGREE	Great-great-grandparent	Great-uncle/aunt	First cousin	Sibling's grandchild	Great-great-grandchild

donor's vital functions and physical or mental capacities, and does not lead to deformity. The removal will only be allowed if it meets a therapeutic need, proven to be indispensable and urgent to the receptor.

It is mandatory that the donor is previously informed about the consequences and potential risks of removing tissues or organs for donation, via a document read and signed by him/her and two other witnesses. The donor should specify in a written document which tissue or organ he/she will be donating for transplantation into a person he/she knows. All participants (donor, witnesses, and receptor) must be duly identified (name, identity card number, address, etc.). As a condition for the donation to go through, two copies of this document must be issued, one of which is sent to the agency of the Prosecution Service that is responsible for the donor's area of residence, and the receipt of its delivery must be affixed to the second copy.

The donation may be cancelled by the donor at any moment before the procedure of tissue or organ removal has been initiated.

LEGAL FRAMEWORK

In Brazil, brain death and organ and tissue transplantation are regulated by the following laws, decrees, and resolutions:

FEDERAL LAW 9434, of February 4, 1997.

Regulation that concerns the removal of organs, tissues, and parts of the human body for the purpose of transplantation and treatment, and includes other provisions.

FEDERAL DECREE 2268, of June 30, 1997.

Regulates Law 9434, of February 4, 1997, which concerns the removal of organs, tissues, and parts of the human body for the purpose of transplantation and treatment, and includes other provisions.

FEDERAL LAW 10,211, of March 23, 2001.

Amends provisions of Law 9434, of February 4, 1997, which concerns the removal of organs, tissues, and parts of the human body for the purpose of transplantation and treatment.

FEDERAL LAW 10,406 (CIVIL CODE), of January 10, 2002.

Articles 3, 4, 5, 1594, and 1595 are relevant to this chapter.

RESOLUTION 1480, of August 8, 1997.

(Published in the Brazilian federal government's Official Gazette on August 21, 1997, Section 1, pages 18,227-8)

Revokes CFM Resolution 1346/91 and characterizes brain death through the conduction of clinical and complementary tests for varying time intervals, specific to different age groups.

RESOLUTION 1.826 OF THE FEDERAL COUNCIL OF MEDICINE (CFM), of December 06, 2007.

(Published in the Brazilian federal government's Official Gazette, of December 6, 2007, Section I, page 133)

Rules on the legality and the ethical nature of suspending therapeutic support procedures when brain death of a non-donor individual is determined.

MUNICIPAL LAW 11,479 (Municipality of São Paulo) of January 13, 1994.

Regulations on funeral aid in the municipality of São Paulo that concern the exemption from paying the Municipal Funeral Service any fees, charges, and duties associated with the funeral.

MUNICIPAL DECREE 43.560 (Municipality of São Paulo) of July 31, 2003.

Regulates law 11479 of January 13, 1994, as amended by law 13,568, of April 29, 2003, that concerns the exemption from paying the funeral services of the municipality of São Paulo any fees, charges, and duties associated with the funeral.

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Annex 1

RESOLUTION 1480/97 OF THE BRAZILIAN FEDERAL COUNCIL OF MEDICINE

The Federal Council of Medicine, in the exercise of the powers conferred by Law 3268 of September 30, 1957, regulated by Decree 44,045, of July 19, 1958 and,

WHEREAS Law 9,434, of February 4, 1997, which concerns the removal of organs, tissues and parts of the human body for the purpose of transplantation and treatment, determines in Article 3 that the responsibility of defining the criteria for the diagnosis of brain death lies with the Federal Council of Medicine;

WHEREAS the complete and irreversible arrest of brain functions is equivalent to death, according to criteria long established by the world scientific community;

WHEREAS prolonging the use of extraordinary resources to sustain vegetative functions in patients with complete and irreversible arrest of brain activity causes psychological and material burdens;

WHEREAS judicious indication is needed to interrupt the use of these resources;

WHEREAS criteria need to be adopted for the unquestionable determination of death;

WHEREAS there is still no consensus on the applicability of said criteria in children younger than seven days of age and premature infants,

DETERMINES:

Art. 1. Brain death shall be determined through the conduction of clinical and complementary tests for varying time intervals appropriate for certain age groups.

Art. 2. Clinical and complementary data obtained during the determination of brain death shall be recorded in the "brain death declaration form" annexed to this Resolution.

Single Clause. Hospital institutions may make additions to said form, which shall be approved by the Regional Council of Medicine of the institution's state, but shall not suppress any of its items.

Art. 3. Brain death must be a consequence of an irreversible process of known cause.

Art. 4. The following clinical parameters must be met for the determination of brain death: unresponsive coma with absence of supraspinal motor activity and apnea.

Art. 5. The minimum intervals between the two clinical evaluations required to determine brain death are defined based on age group, as specified below:

a) 7 days to less than 2 full months - 48 hours

b) 2 months to less than 1 full year - 24 hours

c) 1 year to less than 2 full years - 12 hours

d) above 2 years - 6 hours

Art. 6. The complementary tests required for the determination of brain death should demonstrate unequivocally:

a) absence of electrical brain activity or,

b) absence of metabolic brain activity or,

c) absence of brain blood perfusion.

Art. 7. The complementary tests shall be used based on age group, as specified below:

a) above 2 years – one of the tests mentioned in Art. 6, paragraphs "a", "b" and "c";

b) 1 year to less than 2 full years: one of the tests mentioned in Art. 6, paragraphs "a", "b" and "c". When it is chosen to perform an electroencephalogram, 2 tests separated by a time interval of 12 hours are required;

c) 2 months to less than 1 full year - 2 electroencephalograms separated by a time interval of 24 hours;

d) 7 days to less than 2 full months - 2 electroencephalograms separated by a time interval of 24 hours.

Art. 8. The brain death declaration form, duly completed and signed, and the complementary tests used for the diagnosis of brain death shall be archived in the patient's medical record.

Art. 9. Once brain death is diagnosed and declared, the clinical director of the institution, or a delegate, shall communicate the fact to the patient's legal representatives, if any, and to the Center for Notification, Harvesting and Distribution of Organs to which the hospital unit where the patient was hospitalized is affiliated.

Art. 10. This Resolution shall come into effect on the date of its publication and revokes CFM Resolution 1346/91.

Brasília, Federal District, August 8, 1997.

WALDIR PAIVA MESQUITA - President

ANTÔNIO HENRIQUE PEDROSA NETO - Secretary General

(Published in the Brazilian federal government's Official Gazette on August 21, 1997, onpage 18,227)

Annex 2

BRAIN DEATH DECLARATION FORM
(Federal Council of Medicine Resolution 1480 of August 8, 1997)

HOSPITAL IDENTIFICATION: _____

NAME: _____

FATHER: _____

MOTHER: _____

AGE: _____ years _____ months _____ days _____ DATE OF BIRTH _____/_____/_____

GENDER: ( )M ( )F ETHNICITY: _____ Hospital Record: _____

A. CAUSE OF COMA

A.1. Cause of Coma: _____

A.2. Causes of coma that must be excluded during the test

Hypothermia ( )YES ( )NO

Use of central nervous system depressant drugs ( )YES ( )NO

(If the answer is YES for any of the two items, discontinue the protocol)

B. NEUROLOGICAL EXAMINATION

Check the minimum required interval between the clinical evaluations in the table below:

AGE	INTERVAL
7 days to less than 2 full months	48 hours
2 months to less than 1 full year	24 hours
1 year to less than 2 full years	12 hours
Above 2 years	6 hours

Select one of the two options (YES or NO) for all the items below (mandatory):

ELEMENTS OF THE NEUROLOGICAL EXAMINATION

Results	First examination	Second examination
Unresponsive coma	( )YES ( )NO	( )YES ( )NO
Fixed and unreactive pupils	( )YES ( )NO	( )YES ( )NO
Absence of corneal reflex	( )YES ( )NO	( )YES ( )NO
Absence of oculomotor reflex	( )YES ( )NO	( )YES ( )NO
Absence of vestibulo-ocular reflex	( )YES ( )NO	( )YES ( )NO
Absence of coughing reflex	( )YES ( )NO	( )YES ( )NO

D. COMPLEMENTARY TEST – Indicate which test was performed and attach report with the physician's identification

1. EEG ( )
2. Cerebral angiography ( )
3. Radioisotope scintigraphy ( )
4. Transcranial Doppler ( )
5. Intracranial pressure monitoring ( )
6. Computed tomography with xenon ( )
7. Single-photon emission tomography ( )
8. Positron emission tomography ( )

Annex 3

CORNEA DONATION AUTHORIZATION FORM
Pursuant to Law 10,211 of March 23, 2001:

Art.4 – The removal of tissues, organs, and body parts of a deceased person for transplantation or other therapeutic purposes will depend on the signed authorization of the spouse or relative, of legal age, according to the direct or collat-eral line of succession, up to the second degree, which shall be attested by two witnesses.

Art.2 – Manifestations of will regarding the post mortem removal of tissues, organs, and body parts, as specified on the Identity Card and Driver's License cease to be valid on December 22, 2000.

I(we) authorize, out of my(our) own free will, without any coercion, inducement, or influence, in view of the provisions of article 4 of Law 10,211/01, the removal of the corneas of:

_____,
(full name of the deceased)

Identity Card no. _____, under the responsibility of the undersigned, by the medical team of:

_____
(name of the responsible Cornea Procurement Organization)

for transplantation, for therapeutic purposes, for the sake of the health of the person who is in need of such provision.

_____

Full name: _____

Identity Card no. _____

Kinship: _____

_____
Witness

Full name: _____

Identity Card no. _____

_____
Place

Date: _____/_____/_____

Time: _____:_____

_____

Full name: _____

Identity Card no. _____

Kinship: _____

_____
Witness

Full name: _____

Identity Card no. _____

_____
Physician who requested the donation

Full name: _____

Identity Card no. _____