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## A review of brain death protocols across the globe and need for brain death guideline for Pakistan.

Mohammad Wasay  
*Aga Khan University Hospital, Karachi*

Syeda Batool Mujtaba  
*Aga Khan University, Stadium Road, Karachi, Pakistan*

Mughis Sheerani  
*Sindh Institute of Urology and transplantation*

Saleem Barech  
*Bolan Medical University, Quetta*

Rashid Jooma  
*Aga Khan University, Karachi*

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# A REVIEW OF BRAIN DEATH PROTOCOLS ACROSS THE GLOBE AND NEED FOR BRAIN DEATH GUIDELINE FOR PAKISTAN.

Mohammad Wasay<sup>1</sup>, Syeda Batoool Mujtaba<sup>1</sup>, Rashid Jooma<sup>1</sup>, Mughis Sheerani<sup>2</sup>, Saleem Barech<sup>3</sup>

<sup>1</sup>Aga Khan University, Karachi. <sup>2</sup>Sindh Institute of Urology and transplantation, Karachi. <sup>3</sup>Bolan Medical University, Quetta

**Correspondence to:** Mohammad Wasay Email: Mohammad.wasay@aku.edu

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## ABSTRACT:

**INTRODUCTION:** The concept of brain death was first formally presented in United States of America in 1968 (Ad Hoc Committee of the Harvard Medical School to examine the definition of Brain Death, 1968) in part to facilitate organ donation. It is a widely accepted term in most countries but some like Japan do not consider it as death. According to AAN, brain death is defined as death due to irreversible loss of function of the entire brain — comparable to circulatory death, which is defined as irreversible loss of function of the circulatory system. The purpose of our study is to review brain death protocols from various parts of the world to ultimately formulate a concise brain death protocol for Pakistan.

**Methods:** In this study, a secondary research design was used, comparing the different brain death protocols of Muslim and non-Muslim countries. This study was conducted at Aga Khan University Hospital, an urban tertiary care hospital. A convenient purposive sampling technique was used in which countries were selected on the basis of being either developed or non-developed and Muslim or Non-Muslim. In short, a total of 13 countries and their brain death protocols were selected and compared over a 6 month period from October 2019 to March 2020.

**Results:** Thirteen countries were selected on the basis of religion and whether or not they had a brain death protocol made to be followed within their countries and their protocol documents were compared. Of these countries, 4 were Muslim and 9 Non-Muslim. Some of these did not have their own particular protocol fashioned but rather had one molded on the pattern of other developed countries for e.g., Bangladesh and Pakistan following the AAN, India following the UK and Japan do not consider brain death as death. Variations exist across countries over definition and protocols. In the absence of a national guideline or protocol in Pakistan, some centers have devised their own protocol. The Transplantation of Human Organs and Tissues Act 2010 of Pakistan provide the definition of brain death only for organ transplantation but no protocol is annexed with this law. This comparative study of brain death protocols across the globe clearly identifies a need for a national guideline related to brain death from health care authorities in Pakistan. Based on this study it is feasible to devise a culturally and ethically acceptable scientific protocol which fulfills current and future needs of the country.

**Conclusion:** There is no official brain death protocol for Pakistan. Different institutions and hospitals have published their own protocols but with significant variation between those as well. Hence, the need arises for a standardized national brain death criterion for Pakistan that is approved by the medical regulatory institutions such as The Pakistan Health and Research Council, the Pakistan Medical and Dental Council and The Ministry of Health Services.

**Key words:** Brain death, death, protocol, countries, Pakistan, transplant,

## Appendix: Abbreviation:

BD= brain death

CT=Computed Tomography

TCD=Transcranial Doppler

AAN=American Academy of Neurology

MRA=Magnetic Resonance Angiogram

MRI=Magnetic Resonance Imaging

CTA=Computed Tomography Angiography

EEG=Electroencephalogram

SSEP=Somatosensory Evoked Potential

BAEP= Brainstem Auditory Evoked Potential

SLSEP=Short-latency somatosensory evoked potential

COPD=Chronic Obstructive Pulmonary Disease

PaCO<sub>2</sub>=Arterial partial pressure of Carbon dioxide / PCO<sub>2</sub>= partial pressure of Carbon dioxide

JPMC=Jinnah Postgraduate Medical Centre

UK = United Kingdom

## Introduction

The idea about brain death was first introduced in 1954 by Robert Schwab, a neurologist at Massachusetts General Hospital, who was the first to recognize it while evaluating a comatose patient on a respirator following a massive brain hemorrhage. In 1959, Wertheimer and Jouve; two French neurologists, reported "Diagnosis of Death of the Nervous System in Comas With Respiratory Arrest Treated by Artificial Respiration". REFA decade later, brain death was formulated in an influential report –A Definition of Irreversible Coma.<sup>[1]</sup> The concept of brain death was first formally presented in United States of America in 1968 (Ad Hoc Committee of the Harvard Medical School to examine the definition of Brain Death, 1968) in part to facilitate organ donation. "Brain death" is the term used for the irreversible cessation of all clinical brain functions. It is a widely accepted term yet some ambiguity remains in its acceptance by some countries due to cultural and religious point of views.<sup>[2]</sup>

According to our literature search, the countries who have modeled their brain death criteria on the other well-developed countries are Bangladesh and Pakistan (AAN) and India (UK). Japan is the only one among the 13 countries selected that doesn't consider brain death as death except for when a transplant is performed and hence doesn't have a set brain death protocol to follow.<sup>[3]</sup> Pakistan doesn't have an official brain death criterion and there are no governing bodies which oversee the laws regarding brain death yet hospitals more or less follow AAN to diagnose brain death in the comatose or those with severe brain injury. Recently, Shifa International Hospital Ltd, Islamabad, has come up with a brain death criteria formulated on AAN and Islamic laws and jurisprudence regarding brain death.

[4]In 2010 Pakistan adopted a transplantation law, namely The Transplantation of Human Organs and Tissues Act 2010. In this law, the definition of brain death is given but only in the context of organ transplantation.<sup>[5]</sup>

Jurists of the Islamic World, first brought the issue of brain death under consideration at the 2nd International Conference of Islamic Jurists held in Jeddah in 1985 but without a definite conclusion. However, that the 3rd Conference in Amman the following year, a resolution was passed incorporating the concept of brain death into the legal definition of death in Islam. REF 2. This was reaffirmed in 1987 at the 10 Fiqh Academy Conference in Makkah. Malaysia recognized it in 1992, Singapore in 1994 whereas Indonesia did so in 1996.<sup>[6]</sup>

Despite the practicality of brain death, the laws and regulations regulating brain death in Pakistan have not been formulated and the only information available is hospital-based protocols. To fill this gap with valid and well-researched data from religious, ethical and internationally accepted viewpoints, we decided to approach this problem by re-evaluating the brain death criteria presented by previous researches in Pakistan as most physicians do not have a clear idea regarding the concept of brain death as reported by Sheerani et al and the matters are made worse by the lack of a governing body to legislate on brain death and its criterion<sup>[7]</sup>

## Methodology

A systematic study design where data was obtained via secondary research method was used for this study because it provides an accurate account of the characteristics required. It was done so by comparing

and collating it with a larger pool of data available from all over the world including various Muslim and non-Muslim countries. In the protocols reviewed, the minimum observation period before clinical testing, medical personnel able to confirm death, repetition of tests, apnea test, role of confirmatory investigation and recommended confirmatory testing were compared to form a concise and easy to use brain death protocol for Pakistan. In this study, the information was collected via previously existing data for the brain death protocol of a variety of countries with especial comparison for the Muslim and Non-Muslim countries as Pakistan is a Muslim country and the rules regarding brain death from an Islamic Shariah point of view are different from that of the Non-Muslim countries. Inclusion Criteria: Adults (Males and Females); Muslim and Non-Muslim Countries; Research papers from the years 2000 till 2020; Developed and Developing Countries.

Exclusion Criteria: Below 18 year old (Males and Females); Research papers before 2000; Countries without any protocol or guidance (however vague) for brain death and organ transplantation. A convenient purposive sampling technique was used in which countries were selected on the basis of being developed or non-developed and Muslim or Non-Muslim in total amounting to 13 countries whose brain death protocols were selected and compared over a 6 month period from October 2019 to March 2020. These 13 countries were randomly selected out of 37 countries where brain death protocols were published in English.

The study was aimed at gaining a comparison and a common ground between the 13 countries selected with the focus on the concept ,etiology , minimum observation period before clinical testing, medical personnel who can confirm death, repetition of tests, apnea test, role of confirmatory investigation and recommended confirmatory investigation of the countries selected by the Principal Investigator. This was done in order to make comprehensive yet concise brain death criteria for Pakistan.

**Literature search strategy:** Following key words were used to identify manuscripts for review; Brain Death, Brain death Criteria for (insert\*country name), Brain death/Brain death AND Country; Braindeath/Brain death OR country; Braindeath/Brain Death Criteria For (insert name of the required) Country; Brain? Death protocol for (insert name of the required Country); Brain\* Death protocol for (insert name of the required Country); Brain Death and Islam; Brain Death Criteria NOT Death; "Brain Death"; BrainDeath AND (Country name OR Criteria); Braindeath \*N3 Criteria Following data bases were searched: Google Scholar, PubMed,

Cochrane, FHSLibrary (<http://portal/akulibrary/>), Medline, and Ovid Medline. A total of 154 articles were identified out of which 72 manuscripts were selected for review. Articles selection was based on availability in English and if protocols were endorsed by national authorities or professional organizations.

## Results

In this section we provide details of available data from each of the thirteen countries. This information is partly provided in tabulated form for comparison. (Table 1-3) Pakistan has no official brain death criteria, majority of hospitals either follow the pattern of the AAN (American Academy of Neurology) guidelines or have their own brain death criteria formulated more or less on AAN. Specifically, discussing Shifa and JPMC brain death criteria, there are some differences among them. The criterion formed by Shifa International Hospital Islamabad (Punjab) is based almost entirely on AAN guidelines. According to it; brain death is the total cessation of cardiac, respiratory, and cerebral functions .To diagnose brain death two confirmation tests which are carried out six hours apart are required to be performed by two qualified physicians, something which it shares with its American counterpart. Shifa's brain death criteria doesn't specify minimum observation time and requires apnea testing as part of the confirmatory testing with readings for PaCO<sub>2</sub> being  $\geq 60$  mm Hg or an increase by  $\geq 20$  mm Hg over baseline normal PaCO<sub>2</sub>. But if the readings are  $< 60$  mm Hg or an increase is seen that is  $< 20$  mm Hg over baseline normal for PaCO<sub>2</sub> than the results are indeterminate. For indeterminate results, ancillary confirmation tests along with repeat confirmation exam and apnea tests are considered mandatory after the recommended waiting period. These tests include EEG and one of either, that is cerebral angiography, radionuclide angiography and transcranial Doppler. According to WHO document for IRIS, Apnea test should be the last test to administer contrary to the Pakistani brain death protocol. <sup>[8]</sup> Jinnah Postgraduate medical Centre, the largest government operated hospital in Karachi (Sindh), on the other hand has a criteria currently in place which differs from that practiced in Shifa Hospital. The criteria differs in more than one ways as it considers brain death as the irreversible cessation of all brain functions including those of brain stem. It requires four medical personnel namely an anesthesiologist, neurologist, neurosurgeon and a general practitioner to diagnose death after each one examining the patient again and again amounting to a total of four times at 0 hours, 6 hours, and 18 hours and 24 hours. The person examining has to first

rule out the reversible causes of coma and conditions mimicking brain death namely hypothermia, metabolic disorders, and drug overdoses etc. This is followed by examination of the patient and any abnormal posturing, spontaneous movements, shivering, seizures or any response to verbal and noxious stimuli is ruled out as well. After this pupillary reflex, corneal reflex, oculovestibular reflex and occulocephalic reflex is checked as well as gag or cough reflex is also examined depending on whether or not an ETT is in place or not. Reflexes are succeeded by apnea testing (readings for which are: PaCO<sub>2</sub> ≥ 60 mm Hg or an increase by ≥ 20 mm Hg over baseline normal PaCO<sub>2</sub>). After this, to further confirm the case, ancillary tests are performed with EEG reigning supreme followed by CT, MRI and MRA depending on the situation and the patient's family's affordability as the patients coming to JPMC mostly belong to lower middle or lower socioeconomic class and cannot afford expensive testing modalities. [Ref to Table 3]

**India's** brain death criteria differ from Pakistan as it follows UK's brain death criteria. India's brain death criteria has to have a panel of four doctors to diagnose brain death and the clinical and apnea tests have to be repeated twice in order to be considered brain dead. It doesn't consider ancillary tests to be mandatory but the apnea test readings are same when considering brain death in a patient. [Ref to Table 3]

**Bangladesh** follows AAN entirely. There is a dearth of literature on the Bangladeshi brain death criteria. [Ref to Table 3]

**China's** brain death criteria does not mention minimum observation period like Pakistani criteria. It also demands that there should be two physicians who have passed a standardized training as well as have five years of clinical experience to make any diagnosis regarding brain death. Its test repetition duration is 12 hours whereas Pakistani Shifa criterion calls for six hours duration and JPMC criterion calls for repeat testing at 0,6,18 and 24 hrs. The apnea test readings are the same as that of Pakistan's criteria. When considering ancillary tests, EEG is considered the initial ancillary confirmatory test after it the preferred tests and their sequences are different, with China mentioning SSEP (somatosensory evoked potentials) and TCD (transcranial doppler) as the preferred choice of tests in the sequence mentioned whereas Pakistani Shifa criterion mentions cerebral angiography, radionuclide angiography and transcranial doppler in no particular order and JPMC calls for EEG primarily followed by CT MRI or MRA depending on patient's family's affordability. [Ref to Table 3]

**Malaysia's** brain death criteria calls for two specialists with at least three years of post graduate experience and special training in assessing /diagnosing brain death with special preference for anesthesiologists, neurologists or neurosurgeons. It doesn't allow organ transplantation doctors to diagnose brain death something which Pakistani Shifa and JPMC criterion doesn't call for. The assessment is to be repeated twice six hours apart like its Pakistani Shifa counterpart. The apnea test rulings are the same except where Malaysian criterion specifies it for COPD patients. For them, their baseline PaCO<sub>2</sub> may well be over 40mmHg, so no respiratory effort at 20mmHg is considered a positive apnea test. Malaysian criteria consider brain death a clinical diagnosis hence confirmatory tests are to be done only if need arises. These tests include conventional angiography, transcranial Doppler ultrasonography and EEG. [Ref to Table 3]

**Kingdom of Saudi Arabia's** brain death criteria, minimum observation time isn't listed and it also calls for two examiners to diagnose brain death but Saudi Arabia's brain death criteria specifies the physician qualification and expertise. For it, the minimum standard is not to be a part of the patient care team or the organ retrieval teams, similar to Malaysian criterion. The apnea test rulings are the same as Pakistani one and confirmatory tests, only required when clinical assessment isn't accurate or incomplete. The ancillary tests include TCD, MRA, CTA, cerebral angiography, EEG, SSEP, BAEPs and nuclear medicine. [Ref to Table 3]

**Turkey** recommends a minimum observation period of 24 hours supported with tests evaluating cerebral blood flow and also calls for either a neurologist/neurosurgeon or intensivist and anesthesiologist to diagnose brain death something which it differs in from its Pakistani equivalents. But it's similar when considering the number of physicians diagnosing brain death (that is two) and in its apnea test ruling. Turkish criteria employs EEG, cerebral angiography, radionuclide angiography and transcranial Doppler something which is similar to Pakistani Shifa criteria. Although it also employs different ancillary tests like SEPs, CT angiography and radionuclide cerebral scintigraphy to diagnose brain death in potential patients. [Ref to Table 3]

**United State of America's** brain death criteria leaves minimum observation time up to the discernment of the of the physician involved, although six hours is the recommended time period as well as all the physicians are allowed to make the diagnosis of brain death in most states with only one neurological exam needed.

This differs from Pakistani criteria (Shifa and JPMC) which require at least two physicians to pronounce the patient brain dead. Apnea test specifications are the same as Pakistani one. The ancillary tests are the same as the Pakistani ones with the exception of nuclear scan. American brain death criteria recommends ancillary tests when apnea test can't be performed or when there is uncertainty about the reliability of the neurological exam or to shorten the duration of observation period, something which the Pakistani criteria doesn't specify. [Ref to Table 3]

**United Kingdom's** brain death criteria requires minimum observation to be left for the discernment of the physicians like the American criteria with the exception that it requires two physicians like Pakistani Shifa criteria but who are present at both times the test is conducted and have been registered for more than five years. One of them should be a consultant with special training in the conduct and interpretation of brainstem testing. UK's brain death criteria is different from Pakistani criteria in apnea testing ruling where it recommends PaCO<sub>2</sub> to be >45mmHg before disconnection followed by five minutes of observed time where PaCO<sub>2</sub> is supposed to be risen by more than 4mmHg instead of readings for PaCO<sub>2</sub> ≥ 60 mm Hg or an increase by ≥ 20 mm Hg over baseline normal PaCO<sub>2</sub> like Pakistani brain death criteria. Ancillary tests are only recommended in specific cases like when a comprehensive neurological case can't be done or when a primary metabolic or pharmacological derangement can't be ruled out or in the cases of high cervical cord injury other than that they aren't specifically recommended. [Ref to Table 3]

**Australian** criteria recommend minimum observation time to be four hours or 24 hours in case of acute anoxic-ischemic brain injury subsequent to cardiopulmonary arrest. Like its Pakistani Shifa counterpart it calls for two physicians to make the diagnosis but it differs in the criteria for their qualification which varies between different states. Each doctor is to implement the examination separately and the tests not done simultaneously but rather consecutively. Apnea test ruling are the same as that of Pakistan (Shifa and JPMC) and the recommended ancillary tests include four-vessel angiography, radionuclide imaging, contrast CT, contrast CT angiography and MRI. [Ref to Table 3]

**German** criteria require a monitoring period ranging between 12-72 hours depending upon injury type. It requires the diagnosing physicians not to be a part of the transplantation team and to make their observations separately. German criteria differ from

Pakistani (Shifa and JPMC) ones where it recommends ancillary confirmatory tests on the basis of the type of the brain injury. Apnea test ranges are the same as that of Pakistani (Shifa and JPMC) ones. Ancillary tests specifically aren't mentioned but commonly used are EEG and TCD like its Pakistani (Shifa and JPMC) counterparts. Other tests in routine use, different from Pakistani criteria (Shifa and JPMC) are brain nuclear scan, four vessel catheter angiography, brain perfusion scintigraphy, duplex ultrasound and SSEPs. [Ref to Table 3]

**Canadian** criteria recommend a 24 hour observation period following cardiopulmonary arrest with the physicians required to perform two clinical tests at no fixed particular interval regardless of the type of brain injury. Like USA and UK but unlike Pakistani criteria (Shifa and JPMC) ancillary tests are only recommended when it's impossible to complete the minimum clinical criteria. The tests included are cerebral angiography and TCD like Pakistani criteria but differs where EEG is no longer recommended by the Canadian criteria but MRI and radionuclide imaging technique are included. Apnea test ranges are the same as that of Pakistan's (Shifa and JPMC) criteria. [Ref to Table 3]

**Japanese** criteria entails the physicians to belong to six academic societies and the number of doctors involved in diagnosing brain death has to be two or more unlike Pakistani Shifa criteria which recommends only two physicians to make the diagnosis of brain death but more like JPMC one which calls for 4 doctors to make brain death diagnosis. Apnea test range to be considered positive is the same as that of Pakistan (Shifa and JPMC) and no specific ancillary tests have been recommended. [Ref to Table 3]

## Discussion

According to the Harvard Ad Hoc Committee of 1968 to Examine the Definition of Brain Death brain death was agreed to be unresponsiveness or lack of reactivity, the absence of movement and breathing followed by absence of brainstem reflexes and coma whose cause has been identified. [9] The views regarding brain death vary across different scientific bodies. According to the Punjab Transplant Act 2010 brain death can be described as an irreversible cessation of the entire function of the brainstem. [5] whereas according to paragraph 21.2 of the code of ethics (2001-2002) of the Pakistan's Medical And Dental Council: "Prior to considering transplant from the dead donor brain death should be diagnosed, using currently accepted criteria, by at least two independent and appropriately qualified

clinicians, who are also independent of the transplant team".<sup>[10]</sup> Historically, brain death has been controversial and from an Islamic point of view even more so, where according to different school of thoughts consensus has been reached with quite difficulty in this matter. There have been some differences regarding accepting brain death among the Sunni and Shia school of thoughts. Ayatollah Khomeini passed the edict regarding organ transplantation from brain dead patients in 1964, four years before the Harvard Ad Hoc committee formed the official brain death definition as mentioned by Padela et al in their review regarding brain death and applied Islamic bioethics.<sup>[11]</sup> A more in-depth review is presented by MM Golmakani on this topic.<sup>[12]</sup> Our study was aimed at gaining a comparison and a common ground between the 12 countries selected with that of Pakistan's criteria so that a comprehensive yet concise brain death protocol, which is kept in view with the Islamic ideology as well as the medical requirements for the Islamic Republic of Pakistan, is made. Pakistan as a Muslim country doesn't have a set brain death criteria nor does it accept brain death in the conventional sense like the other countries of the world which is also mentioned by Dariusch Atighetchi in his book *Islamic Bioethics: Problems and Perspectives* where he mentions a case of transplant undertaken by SIUT, Pakistan, following AAN's brain death criteria in 1998 and 2005 even though there was a lack of laws regarding brain death at that time.<sup>[10]</sup> The systematic review conducted found that brain death criteria made by Shifa International for Pakistan has been formulated on the United State of America's brain death protocol [4] and in many places AAN recommended criteria is in use whereas some places make use of a combination of book recommended criteria and Islamic bioethics. However, Pakistan's criteria developed by Shifa International Hospital has made a few changes in the criteria keeping in pace with the Islamic Ideology. Changes made, include the number of physicians required for making the diagnoses of brain death, observation time and additional ancillary confirmatory tests. If considered in detail, the criteria proposed by Shifa, changes the criteria requirement to two doctors in accordance with the PMDC code of ethics (2001-2002). [4] Shifa's brain death criteria also doesn't specify minimum observation time and requires apnea testing as part of the confirmatory testing with readings for PaCO<sub>2</sub> ≥ 60 mm Hg or an increase by ≥ 20 mm Hg over baseline normal PaCO<sub>2</sub>. But results are considered indeterminate if the readings are < 60 mm Hg or an

increase is seen that is < 20 mm Hg over baseline normal for PaCO<sub>2</sub>. For indeterminate results, ancillary confirmation tests along with repeat confirmation exam and apnea tests are considered mandatory after the recommended waiting period. These tests include EEG and one of either, that is cerebral angiography, radionuclide angiography and transcranial Doppler. [4] The differences between the brain death criteria proposed by Shifa International's (Islamabad, Pakistan) and the one used in JPMC (Sindh; Pakistan) demonstrates the usage of different criteria in use for declaring brain death in Pakistan and the need of imposing uniformity in declaring brain death among patients to ease the health care, social and transplant burden as countries like Japan and Pakistan where brain death criteria are either vague, not formed or followed precisely present a risk as the number of organ transplants increase.<sup>[13]</sup> Significant differences exist among criteria of various countries. India requires four physicians to be involved for the diagnosis whereas Bangladesh adds CTA, MRI and MRA to the list of confirmatory tests. China on the other hand, requires a specific sequence of ancillary tests to be performed starting from EEG than SSEP followed finally by TCD. Kingdom of Saudi Arabia adds MRA, CTA, SSEP and BAEP to the list of confirmatory test but without a specific sequence in which they have to be conducted. Turkey calls for an observation period of 24 hours along with addition of SSEP and CTA. USA interestingly considers one physician to be sufficient whereas it considers the observation time to be either six hours or leaves it up to the discretion of the physician in charge. USA's criteria also adds CTA, MRA and MRI to the list of ancillary tests in addition to the ones that are in Pakistani Shifa criterion whereas Pakistani JPMC criteria considers EEG, CT, MRI and MRA to be appropriate ancillary tests with EEG is given preference much like Japanese criteria. UK like USA leaves the observation time up to the physician and its unique to notice, that it doesn't specifically recommends confirmatory tests to diagnose brain death. Australia considers four hours ample observatory period whereas 4-vessel angiography and radionuclide imaging are the preferred tests for brain death diagnosis. Germany on the other hand, specifies observation time to be 12 or 72 hours and like UK but unlike Pakistan it doesn't specifically recommend confirmatory tests. Canada differs from Pakistan as it considers a 24 hour observation time to be a good reason for brain death diagnosis. It's interesting to note that EEG isn't the recommended ancillary test. Japan on the other

hand, is quite similar to Shifa's proposed brain death criteria for Pakistan except for the fact; it considers EEG and CT to be sufficient for confirming brain death among prospective patients where it is closer to its Pakistani JPMC counterpart. An important area needs exploration is utilization of brain death protocols. Traditionally these protocols are used to evaluate further need of ventilatory support or artificial respiration and for organ harvesting for transplant patients. [33,34]. Use of mechanical ventilation is spreading in Pakistan and centers for transplants. A national official brain death protocol is a need for today and future.

In short, this review highlights the need of a national and standardized brain death criterion for Pakistan approved by Pakistan Health and Research Council, Pakistan Medical and Dental Council and The Ministry of Health Services. This protocol should be drafted with consultation of neurologists, neurosurgeons, critical care experts and anesthesiologists and disseminated amongst stakeholders of the medical community to get buy-in and wider adoption.

**Table1: Brief overview of the important variables for the brain death study**

| Countries  | Guideline | Apnea Test | No. of physicians | Observation time ,(hr) | Confirmatory Test            |
|------------|-----------|------------|-------------------|------------------------|------------------------------|
| Pakistan   | Present   | PaCO2      | 2                 | 6                      | Yes                          |
| India      | Present   | PCO2       | 4                 | 6                      | No                           |
| Bangladesh | Present   | PaCO2      | 2                 | 6                      | Yes                          |
| China      | Present   | PaCO2      | 2                 | 12                     | Yes                          |
| Malaysia   | Present   | PaCO2      | 2                 | 6                      | Yes                          |
| KSA        | Present   | PaCO2      | 2                 | 6                      | Yes                          |
| Turkey     | Present   | PaCO2      | 2                 | 24                     | Yes                          |
| USA        | Present   | PaCO2      | 1                 | 6/ Up to physician     | Yes                          |
| UK         | Present   | PaCO2      | 2                 | Up to physician        | NIL specifically Recommended |
| Australia  | Present   | PaCO2      | 2                 | 4                      | Yes                          |
| Germany    | Present   | PaCO2      | 2                 | 12 / 72                | NIL specifically Recommended |
| Canada     | Present   | PaCO2      | 2                 | 24                     | Yes                          |
| Japan      | Present   | PaCO2      | 2                 | 6                      | Yes                          |

| Countries  | Apnea Test | No. of Physicians | Observation time ,(hr) | Confirmatory Test            | Confirmatory Test Types   |
|------------|------------|-------------------|------------------------|------------------------------|---|
| Pakistan   | PaCO2      | 2                 | 6                      | Yes                          | EEG and one of either:<br><ul style="list-style-type: none"> <li>• Cerebral Angiography</li> <li>• Radionuclide Angiography</li> <li>• Transcranial Doppler.</li> </ul> |
| India      | PCO2       | 4                 | 5                      | No                           | No  |
| Bangladesh | S          | S                 | S                      | S                            | Same in addition to:<br>CTA, MRI, MRA.  |
| China      | S          | S                 | 12                     | S                            | Same but in a specific sequence i.e. EEG, SLSEP and TCD.  |
| Malaysia   | S          | S                 | 5                      | S                            | Same  |
| KSA        | S          | S                 | 5                      | S                            | Same in addition to:<br>MRA, CTA, SSEPs, BAEPs.   |
| Turkey     | S          | S                 | 24                     | S                            | Same in addition to sensory evoke potentials and CT angiography.  |
| USA        | S          | 1                 | 6/ Up to physician     | S                            | Same in addition to CTA, MRA, MRI   |
| UK         | S          | S                 | Up to physician        | NIL specifically Recommended | NIL specifically Recommended  |
| Australia  | S          | S                 | 4                      | S                            | Four-vessel angiography and radionuclide imaging are preferred. Other tests include:<br>Contrast CT/CT angiography & MRI.   |
| Germany    | S          | S                 | 12 / 72                | NIL specifically Recommended | NIL specifically Recommended  |
| Canada     | S          | S                 | 24                     | S                            | Same but without EEG, other additional test include MRI.  |
| Japan      | S          | S                 | S                      | S                            | EEG and CT scan only.   |



S= same as Pakistan.

**Table2: differences and similarities among the different variables with those of Pakistan's criteria.**

| Country/Language                    | Minimum Ethical, Medical, Technical, Regulatory/ Law Requirements  | Approved / Status of Regulatory Body   | Confidence's Test  |  |
|-------------------------------------|--|--|--|--|
| <b>Pakistan [16]</b>                | <b>IDEA INTERNATIONAL CRITERIA</b><br>Total cessation of all cardiac, respiratory and cerebral functions.<br><b>IDEA CRITERIA</b><br>Brain death is the irreversible cessation of all brain functions including those of brain stem.<br><b>IDEA CRITERIA</b><br>A physician must observe patient, examine and certify that there is total and irreversible cessation of all brain functions including those of brain stem. | <b>IDEA INTERNATIONAL CRITERIA</b><br>Total cessation of all cardiac, respiratory and cerebral functions.<br><b>IDEA CRITERIA</b><br>Brain death is the irreversible cessation of all brain functions including those of brain stem.<br><b>IDEA CRITERIA</b><br>A physician must observe patient, examine and certify that there is total and irreversible cessation of all brain functions including those of brain stem. | <b>IDEA INTERNATIONAL CRITERIA</b><br>Total cessation of all cardiac, respiratory and cerebral functions.<br><b>IDEA CRITERIA</b><br>Brain death is the irreversible cessation of all brain functions including those of brain stem.<br><b>IDEA CRITERIA</b><br>A physician must observe patient, examine and certify that there is total and irreversible cessation of all brain functions including those of brain stem. | <b>IDEA INTERNATIONAL CRITERIA</b><br>Total cessation of all cardiac, respiratory and cerebral functions.<br><b>IDEA CRITERIA</b><br>Brain death is the irreversible cessation of all brain functions including those of brain stem.<br><b>IDEA CRITERIA</b><br>A physician must observe patient, examine and certify that there is total and irreversible cessation of all brain functions including those of brain stem. |
| <b>India [15]</b>                   | Irreversible cessation of all brain functions including brain stem.  | Ministry of Health and Family Welfare, Government of India.  | Not mentioned  |  |
| <b>Bangladesh [16]</b>              | Brain death is a state of irreversible cessation of all brain functions including those of brain stem.   | Ministry of Health and Family Welfare, Government of Bangladesh.   | Not mentioned  |  |
| <b>China [17][18]</b>               | Brain death is a state of irreversible cessation of all brain functions including those of brain stem.   | Ministry of Health and Family Welfare, Government of China.  | Not mentioned  |  |
| <b>Malaysia [19]</b>                | Brain death is a state of irreversible cessation of all brain functions including those of brain stem.   | Ministry of Health and Family Welfare, Government of Malaysia.   | Not mentioned  |  |
| <b>Kingdom of Saudi Arabia [20]</b> | Brain death is a state of irreversible cessation of all brain functions including those of brain stem.   | Ministry of Health and Family Welfare, Government of Saudi Arabia.   | Not mentioned  |  |
| <b>Turkey [21]</b>                  | Brain death is a state of irreversible cessation of all brain functions including those of brain stem.   | Ministry of Health and Family Welfare, Government of Turkey.   | Not mentioned  |  |
| <b>USA [22][23]</b>                 | Brain death is a state of irreversible cessation of all brain functions including those of brain stem.   | Ministry of Health and Family Welfare, Government of USA.  | Not mentioned  |  |
| <b>SIN [22]</b>                     | Brain death is a state of irreversible cessation of all brain functions including those of brain stem.   | Ministry of Health and Family Welfare, Government of Singapore.  | Not mentioned  |  |
| <b>South Africa [24][25]</b>        | Brain death is a state of irreversible cessation of all brain functions including those of brain stem.   | Ministry of Health and Family Welfare, Government of South Africa.   | Not mentioned  |  |
| <b>Germany [26][27][28]</b>         | Brain death is a state of irreversible cessation of all brain functions including those of brain stem.   | Ministry of Health and Family Welfare, Government of Germany.  | Not mentioned  |  |

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